SECTION 4

The patient with interstitial disease

CHAPTER 83

Acute tubulointerstitial nephritis: overview

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Introduction

Acute tubulointerstitial nephritis (ATIN) is a clinical syndrome, usually associated with the development of acute kidney injury (AKI), which is characterized by the presence of inflammatory cells (and often oedema) within the renal interstitium. Some of these cells may cross the tubular basement membrane (TBM) to invade the tubules, resulting in tubulitis. The glomeruli and blood vessels are usually unaffected or only minimally abnormal. Notably, this definition of ATIN excludes both pyelonephritis, due to direct bacterial invasion (see Chapter 177), and AKI secondary to glomerular or vascular diseases, which may both display prominent interstitial infiltrates (see Section 11). Since ATIN is a morphologically defined process, the diagnosis can only be confirmed by renal biopsy. The characteristic interstitial and tubular inflammation do not always leads to AKI, but sometimes to milder forms of renal disease such as asymptomatic urinary abnormalities.

The exact incidence of ATIN is difficult to define, since indications for performing a renal biopsy vary according to local practice and, furthermore, patients are often treated presumptively, without a biopsy-based diagnosis. In a study of Finnish army recruits who underwent biopsy for the evaluation of urinary abnormalities, the incidence of ATIN was approximately 1% (Pettersson et al., 1984). However, in another series of 109 renal biopsies performed in a large centre because of unexplained AKI, this incidence reached 27% (Farrington et al., 1989). A similar study from the United States described 259 older patients (age ≥ 60 years) who were biopsied for AKI and ATIN was found to be responsible for 18.6% of cases (Haas et al., 2000). Data extracted from two large European registries suggests that the diagnosis of ATIN constitutes approximately 11% of renal biopsies performed for the evaluation of AKI (Schena, 1997; Lopez-Gomez et al., 2008). It is in this latter context that ATIN is particularly important, since it represents a relatively common and potentially reversible cause of AKI, which requires prompt and specific treatment. There is some evidence that early therapy leads to a quicker and more complete recovery of renal function.

ATIN is sometimes called 'acute interstitial nephritis'; however, since the tubulitis is often a prominent feature, the term 'ATIN' is preferred. This entity was first described by Councilman in 1898 at Harvard Medical School, in a series of 42 autopsies from patients dead of diphtheria and scarlet fever, all of whom had typical renal 'cellular and fluid exudation in the interstitial tissue' (Councilman, 1898). The inflammation within the kidneys was characterized by an exudate that was not purulent and the tissue itself was sterile. He speculated that the cells might accumulate because 'soluble substances may exert a positive chemotaxis'. Crucially, he made the observation that the tissue damage was not due to direct microbial invasion, but secondary to an allergic-type phenomenon. In 1946 a series of patients with similar histological findings was described, all of whom had been treated with sulphonamides, but it was not clear at the time whether the inciting agent was the drug itself or the underlying infection (More et al., 1946). During the 1960s the first reports emerged of ATIN associated with penicillins, particularly methicillin (Hewitt et al., 1961; Baldwin et al., 1968), and over the ensuing decades links with other drugs (e.g. phenindione, rifampicin, and azathioprine) were established, confirming drug allergy as a common cause of ATIN (Hewitt et al., 1961; McMenamin et al., 1976; Ditlove et al., 1977; Nolan and Abernathy, 1977; Galpin et al., 1978; Linton et al., 1980). With the burgeoning use of percutaneous renal biopsy throughout the 1950s and 1960s, ATIN became increasingly recognized as a cause of AKI. The exact pathophysiology of ATIN is unclear, but there are a number of observations, predominantly derived from patients with drug-related ATIN, which suggest that the renal injury is immune-mediated in an allergic-type reaction.

Aetiology

Drugs

Approximately 80% of ATIN cases are related to the administration of drugs (Chapter 84), with antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) being the two main culprits (see Tables 83.1 and 83.2) (Rossert, 2001; Izzedine et al., 2007; Perazella and Markowitz, 2010; Praga and Gonzalez, 2010). However, the list of agents that may cause ATIN continues to grow, and ongoing vigilance is required, as new drugs are constantly being involved, including levetiracetam, etanercept, sorafenib, and highly active antiretroviral therapy (HAART) among the most recent ones (Izzedine et al., 2007; Said et al., 2007; Schmid et al., 2007; Sugimoto et al., 2008). Although reported series are currently dominated by drug-related ATIN (see Chapter 84), the causative agent is often difficult to pinpoint precisely, for a number of different reasons. Firstly, antibiotics are often being used to treat infections and, in such cases, it is not always clear, in retrospect, whether it was the infection itself or the antibiotic that caused the ATIN. Secondly, although the latent period between exposure to a neoantigen and the development of a primary immune response is usually approximately 10 days, there are numerous exceptions in clinical practice. For example ATIN may develop after short exposure to drugs such as rifampicin, especially on re-exposure (Covic et al., 1998, 2004; Muthukumar et al., 2002; Schubert et al.,

Table 83.1 Agents causing ATIN from seven published series including 237 patients

Causative agent	%	Common examples
Antibiotics	39.7	β-lactams, sulphonamides, rifampicin, macrolides, aminoglycosides, chloramphenicol, quinolones, tetracyclines
NSAIDs	22.4	Indomethacin, ketoprofen, fenoprofen, naproxen, ibuprofen, diclofenac
Other drugs	16.8	Diuretics, H_2-antagonists, proton pump inhibitors, anticonvulsants, allopurinol, analgesics, warfarin
Infections	5.9	*Pneumococcus, Streptococcus, Mycobacteria, Leptospira, Legionella*, syphilis
Other	15.2	Idiopathic, TINU, sarcoidosis

2010), and after much longer periods, between 6 and 18 months after NSAIDs (Pirani et al., 1987). Finally, patients suffering from ATIN are often on multiple drugs and, in this case, clinicians usually attribute causality to the most commonly associated agent, thus generating a self-fulfilling prophecy, whereby NSAIDs and antibiotics will continue to be the commonest drugs associated with ATIN. Drug-related ATIN is covered in more detail in Chapter 84.

Infection

Infectious disease constitutes the second major group of causes for ATIN. As mentioned above, ATIN was originally described in association with diphtheria and scarlet fever. Once again, the list of causal agents is a long one, with new associations continually evolving. For example, there have been recent descriptions of ATIN associated with hydatid disease and histoplasmosis in native kidneys, and BK virus and adenovirus in renal allografts (Randhawa et al., 1999; Dall et al., 2008; Nickavar et al., 2011; Qian et al., 2011; Storsley et al., 2011). It should be emphasized that these infectious diseases cause interstitial and tubular tissue injury by an indirect mechanism, not by direct microbial invasion, as in ascending infection of the urinary tract (see Chapter 177). In ATIN the interstitium is sterile, as originally described by Councilman, the damage resulting from immunological and inflammatory mechanisms.

The link between tuberculosis and ATIN is an intriguing one (see Chapter 196). Classically, renal tuberculosis has been associated with lower urinary tract calcification and scarring. Renal parenchymal involvement consists of caseating granulomas, and mycobacteria can often be cultured from early morning urine samples. More recently, histological changes of ATIN have been reported in patients with extrarenal tuberculosis (Chapagain et al., 2011; Eastwood et al., 2011). In these cases, urine cultures did not grow mycobacteria and, where available, molecular testing of renal tissue (e.g. polymerase chain reaction) was negative. Since end-stage renal disease (ESRD), particularly due to interstitial nephritis, is overrepresented in immigrant Asian populations in the United Kingdom, it has been speculated that ATIN secondary to tuberculosis could evolve into a chronic form of nephropathy, contributing to the increased incidence of ESRD amongst these populations (Clark et al., 1993; Lightstone et al., 1995; Ball et al., 1997, 2001).

Table 83.2 Causes of ATIN

Drug-related

Antibiotics:
- β-lactams—methicillin, ampicillin, benzylpenicillin, flucloxacillin, cephalosporins
- Sulphonamides, co-trimoxazole
- Gentamicin
- Tetracycline
- Vancomycin, teicoplanin
- Quinolones—ciprofloxacin, levofloxacin
- Macrolides—erythromycin, clarithromycin, azithromycin
- Chloramphenicol
- Rifampicin, ethambutol, isoniazid

Antivirals:
- Aciclovir, HAART (indinavir),

NSAIDs:
- Fenoprofen, indomethacin, ketoprofen, naproxen, ibuprofen, diclofenac, phenylbutazone, tolmetin, aspirin, celecoxib, rofecoxib, and most others

Antiulcer medications:
- Omeprazole, lansoprazole, famotidine, ranitidine, cimetidine

Diuretics:
- Furosemide, thiazides, triamterene

Anticonvulsants:
- Carbamazepine, phenytoin, levetiracetam, valproate

Anticoagulants:
- Warfarin, phenindione

Analgesics

Others:
- Allopurinol, mesalazine, propranolol, amlodipine, azathioprine, etanercept, sorafenib, captopril, clofibrate, cocaine, creatine, diltiazem, pranlukast, propylthiouracil, quinine

Infectious

Bacterial:
- *Streptococcus, Staphylococcus, Pneumococcus, Legionella, Corynebacterium diphtheriae, Yersinia, Brucella, Campylobacter, Escherichia coli, Salmonella, Mycobacterium tuberculosis*

Viral:
- *Cytomegalovirus*, Epstein–Barr virus, herpes simplex virus, Hantavirus, hepatitis A, hepatitis B, hepatitis C, HIV, measles, mumps, Polyoma (BK) virus, adenovirus

Other:
- *Leptospira, Treponema, Mycoplasma, Rickettsia, Toxoplasma, Chlamydia, Leishmania*

Systemic autoimmune disease

Connective tissue disease
- Systemic lupus erythematosus, Sjögren syndrome, cryoglobulinaemia, ANCA-associated small vessel vasculitis

Tubulointerstitial nephritis and uveitis (TINU)

IgG4-related disease

Sarcoidosis

Idiopathic:
- With anti-TBM antibodies
- Without anti-TBM antibodies

Secondary:
- Associated with glomerular disease
- Associated with light chain nephropathy
- Associated with vascular disease

Systemic diseases

Numerous systemic diseases are also associated with ATIN, but this is usually secondary to extensive glomerular involvement. For example, ATIN is often present on biopsies of patients with systemic lupus erythematosus (SLE) (see Chapter 161) or in myeloma (see Chapter 153). Occasionally, isolated primary ATIN may occur in SLE with absent or only minor glomerular changes (Cunningham et al., 1978; Gur et al., 1987; Mori et al., 2005).

Sarcoidosis

Renal involvement in sarcoidosis (see Chapter 156) has been described in a minority of patients, manifested by nephrocalcinosis and tubulointerstitial nephritis, with or without granulomas on renal biopsy (Bergner et al., 2003). Conversely, approximately 90% of patients with renal sarcoidosis will have extrarenal symptoms (Hannedouche et al., 1990; Robson et al., 2003; Rajakariar et al., 2006; Joss et al., 2007; Mahevas et al., 2009).

ATIN has also been described in patients with Sjögren syndrome (see Chapter 93), although this disorder more commonly presents with chronic tubular dysfunction (Goules et al., 2000). ATIN associated with both sarcoidosis and Sjögren syndrome has been reported to show a good response to corticosteroids.

IgG4-related TINU

IgG4-related TIN occurs in association with autoimmune pancreatitis. The association between autoimmune pancreatitis and hypergammaglobulinaemia was first described in 1961 and later on these antibodies have been characterized as of IgG4 isotype (Sarles et al., 1961). Furthermore, tissue deposition of IgG4-positive plasma cells has been demonstrated in a number of different organs (Cornell, 2010; Saeki et al., 2010). The condition is described further in Chapter 93.

Studies suggest that most patients are men over the age of 50 and they present with either acute or chronically progressive renal failure, often with hypocomplementaemia. Approximately 80% of patients will have multiorgan involvement (especially lymphadenopathy, adenitis, and pancreatitis), 80% have radiological renal abnormalities (enlarged kidneys or patchy hypoattenuated lesions) and 80% have either total IgG or IgG4 raised serum levels (Raissian et al., 2011). Histological examination reveals a plasma cell-rich infiltrate, sometimes accompanied by prominent eosinophils. Diffuse interstitial fibrosis and deposition of immune complexes along the TBM is common. Immunostaining for IgG4 appears to be highly suggestive of the diagnosis and a good response to steroids has been described.

Tubulointerstitial nephritis with uveitis (TINU syndrome)

TINU was first reported in 1975 as an association between ATIN and anterior uveitis, sometimes with additional bone marrow granulomas (Dobrin et al., 1975). A number of such patients have now been described (Mandeville et al., 2001). Although associations with both *Chlamydia* and *Mycoplasma* infections have been suggested, the aetiology remains obscure (Stupp et al., 1990). The uveitis may occur several weeks before or up to 3 months after the ATIN. The TINU syndrome commonly occurs in adolescence and early adulthood, with a preponderance of females (3:1). Patients generally suffer from weight loss, myalgia, fever, and anaemia. Elevated serum inflammatory markers are common and prolonged steroid therapy usually leads to improvement in both renal function and uveitis, though the latter may relapse (Rodriguez-Perez et al., 1995; Mackensen and Billing et al., 2009). Curiously, a relapse of TINU with both renal an ocular involvement has been described after renal transplantation, despite ongoing immunosuppression (Onyekpe et al., 2011).

Idiopathic

Occasionally ATIN will occur without any precipitant or associated factors and these cases are termed idiopathic. Only rarely will such cases have evidence of anti-TBM antibodies (Bergstein and Litman, 1975; Rakotoarivony et al., 1981).

Pathogenesis

The pathogenesis of ATIN is poorly understood, but there are a number of features that suggest that the disease is triggered by an immune hypersensitivity reaction to either drugs or infectious agents:

1. Drug reactions are idiosyncratic and occur only in a small percentage of patients.
2. Older series that were dominated by antibiotic-associated ATIN commonly described clinical features associated with allergic-type phenomena, for example, arthralgia, rash, fever, and eosinophilia (Ditlove et al., 1977; Galpin et al., 1978; Linton et al., 1980; Rossert, 2000). These associated manifestations are much less frequently seen now.
3. ATIN often occurs within 10–14 days of antigen exposure, the archetypal timing of a primary immune response.
4. Inadvertent rechallenge with a drug that previously caused ATIN leads to a rapid recrudescence of disease, suggesting a classical memory response (Sloth and Thomsen, 1971; Saltissi et al., 1979; Pusey et al., 1983; Covic et al., 2004; Schubert et al., 2010).
5. The histology of ATIN is dominated by lymphocyte infiltration, with the formation of granulomas in some cases, the hallmark of a delayed-type hypersensitivity (DTH) reaction.
6. In infection-related ATIN, the renal parenchyma is sterile, with relatively rare neutrophils, as originally described by Councilman (1898).
7. Some patients show a DTH-like reaction on intradermal injection of the offending drug (Border et al., 1974; Baldwin et al., 1977).
8. A proliferation of autologous lymphocytes *in vitro* after exposure to the culprit drug has been demonstrated (Joh et al., 1990; Shibasaki et al., 1991; Spanou et al., 2006).
9. Animal models of ATIN, like the kd/kd mouse, develop spontaneous interstitial nephritis, the expression of which is dependent on a finely tuned balance between nephritogenic and regulatory T cells (Neilson et al., 1984; Kelly and Neilson, 1987; Kelly, 1990).
10. Immunization of animals with renal proteins, such as the Tamm–Horsfall protein or components of the normal human TBM, like glycoprotein H3M-1 and TIN-antigen, can induce ATIN (Clayman et al., 1986; Neilson, 1989; Butkowski et al., 1990; Wilson, 1991).

The nature of the actual antigens involved in clinical ATIN is unknown. Drugs themselves are relatively small molecules, which are capable of generating only weak immune responses. For this reason, it has been proposed that they may act as haptens to alter the immunogenicity of associated proteins. According to this model, drugs

are filtered in the kidney and become associated either with residual renal proteins or with other antigens that have become entrapped in the kidney. This mechanism is supported by the occasional demonstration of anti-TBM antibodies in human drug-related disease (Border et al., 1974; Bergstein and Litman, 1975). Interestingly, in patients with rapidly progressive glomerulonephritis associated with anti-GBM antibodies, the subgroup who also develop anti-TBM antibodies have the most florid interstitial inflammation, suggesting a possible pathogenic role (Andres et al., 1978). The isolation of anti-TBM antibodies from patients with ATIN has led to the identification of a 48kD antigen, R3M-1, which is the target of these antibodies (Clayman et al., 1986). However, the evidence for a major humoral component in the pathogenesis of ATIN is lacking, since the vast majority of the patients have no anti-TBM antibodies, normal complement levels, and no evidence of immune deposits, either by immunofluorescence or electron microscopy. An alternative explanation could involve molecular mimicry, whereby an immune response to a pathogen or drug results in cross-reactivity against renal antigens. One experimental model of ATIN has shown nephritogenic T cells cross-reactive to heat shock proteins (Weiss et al., 1994) and another demonstrated the development of ATIN after immunization with *Escherichia coli* in adjuvant (Sherlock, 1977).

The characteristic pathological features of ATIN are found in a number of different circumstances (e.g. allograft rejection and BK virus nephropathy), suggesting that the histological picture probably represents the outcome of a common downstream inflammatory pathway. It is certainly possible that mechanisms other than priming of the adaptive immune system exist to induce this pattern of inflammation. For example, it has been shown that highly conserved lipoproteins (LipL32) in the outer membrane proteins of pathogenic strains of *Leptospira* can trigger interstitial inflammation via Toll-like receptor-2 (TLR-2) on renal tubular cells (Yang et al., 2002; Yang, 2007). Indeed, it has been demonstrated that renal inflammation can be triggered by both damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) via Toll-like and other receptors, thus triggering renal inflammation independent of upstream adaptive immune responses (Anders et al., 2004; Anders, 2010). Such a mechanism has been demonstrated in ATIN caused by BK virus in renal allografts (Anders et al., 2004; Ribeiro et al., 2012). It is likely that these mechanisms (and probably others) act in concert to bring about the histological picture that characterizes ATIN.

Under the influence of chemotactic stimuli, inflammatory leucocytes, which are predominantly mononuclear in nature, leave the circulation from the peritubular capillaries. They cross the vascular endothelium and capillary basement membrane to infiltrate the interstitial space, pushing apart the tubules which are normally juxtaposed. From here, some cells continue to cross the TBM and inflict injury to the tubular epithelial cells (tubulitis). Following the acute phase, the inflammation may resolve, with return to baseline renal function; however, in some cases the inflammatory infiltrates persist and evolve into a more fibrotic phenotype, associated with deposition of extracellular matrix, leading to progressive renal disease (Neilson, 2006; Zeisberg and Neilson, 2010).

Pathology

The normal renal tubulointerstitium consists of tubular epithelial cells attached to the TBM and surrounded by small peritubular capillaries. The tubules appear on light microscopy to be virtually back to

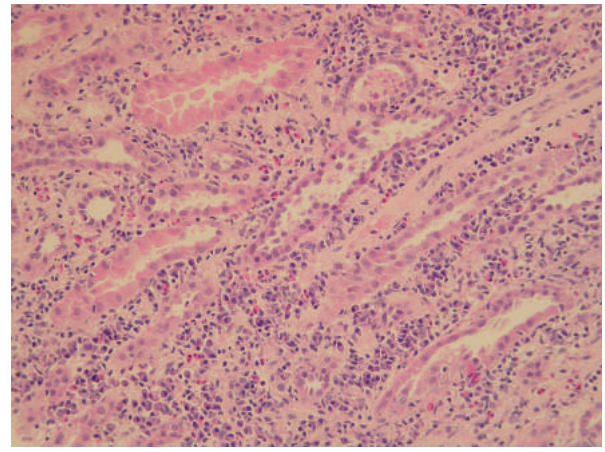

Fig. 83.1 Tubulitis in ATIN.

back, but in fact there are two types of cells normally present between the tubules and the peritubular capillaries. These are renal fibroblasts, which provide the extracellular skeleton upon which the tubules and capillaries are suspended, and dendritic cells, which are positive for class II major histocompatibility complex molecules and are thought to play a role in antigen presentation (Kaissling and Le Hir, 2008).

Macroscopically, in ATIN the kidneys are often oedematous and enlarged. Under the microscope, the normal renal architecture is disturbed by an infiltration of inflammatory cells in the renal interstitium, which cross the TBM to invade the tubules. This process, termed 'tubulitis', may cause breaks in the TBM, with necrosis and atrophy of tubular epithelial cells (Fig. 83.1) Thus, the tubular epithelial cells may appear flattened. This inflammatory process is often focal and may be accompanied by interstitial oedema. Mononuclear cells, specifically lymphocytes and macrophages, usually dominate the picture and create new space between the tubules. Immunophenotyping studies have suggested that in most cases the predominant mononuclear cell is the CD4+ T cell, but sometimes $CD8^+$ cells may be preeminent (Bender et al., 1984). Neutrophil infiltrates may be present, but if prominent they arouse suspicion of pyelonephritis. When drug allergy is implicated, there may be large numbers of eosinophils (Fig. 83.2). If the inflammation persists, then macrophages and

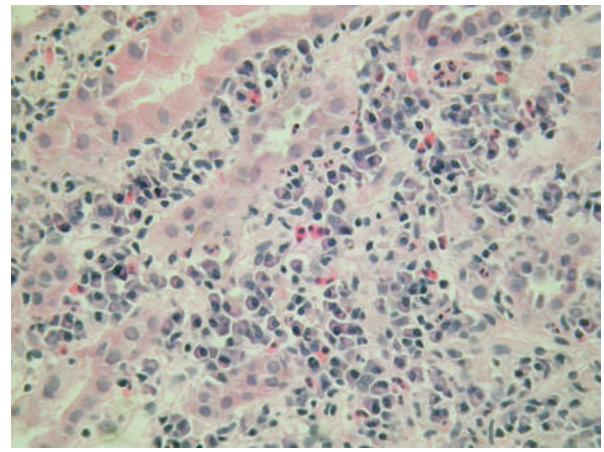

Fig. 83.2 Interstitial infiltrate in ATIN.

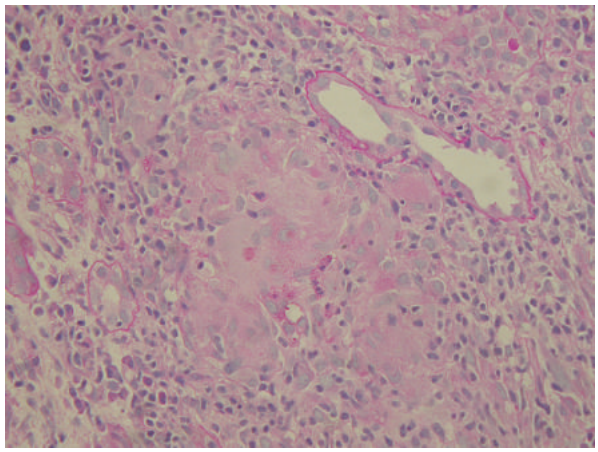

Fig. 83.3 Granuloma in ATIN.

monocytes often prevail and eventually plasma cells and histiocytes may become evident. The inflammatory process is finely balanced between repair and fibrosis (Tanaka and Nangaku, 2011). In chronic forms of the disease and with certain agents interstitial fibrosis may ensue, with proliferation of extracellular matrix and ascendancy of fibroblasts. Uncommonly, granulomas may develop, a process that is associated with certain drug reactions, tuberculosis, and sarcoidosis (Fig. 83.3) (Magil, 1983; Mignon et al., 1984; Bijol et al., 2006; Joss et al., 2007). Electron microscopy, immunohistochemical, and immunofluorescence studies are rarely helpful, except in rare cases of linear staining secondary to anti-TBM disease. The glomeruli are typically normal or have only minor abnormalities. Examination of the blood vessels may reveal evidence of ageing or hypertension, but nothing specific to ATIN. Overall, the morphology is non-specific with regards to the underlying cause and, while certain findings (e.g. eosinophils) may suggest certain aetiological agents, it is not possible to be specific.

Clinical manifestations

The renal disease associated with ATIN is variable and may range from completely asymptomatic to fulminant and irreversible AKI. However, it usually presents with slowly progressive AKI (over a few weeks). Epidemiological evidence suggests that, when there is no obvious precipitant for AKI and an ultrasound reveals normal sized kidneys, then there is a high likelihood that ATIN is the underlying cause (10–25% of cases).

The first published reports of ATIN were dominated by cases related to the use of penicillin and many of these patients had allergic-type clinical features, such as rash, arthralgia, fever, and eosinophilia (Baldwin et al., 1968; Ditlove et al., 1977; Nolan et al., 1977; Galpin et al., 1978). In recent years these features have become less common (as shown in Table 83.3), particularly in cases associated with NSAID usage (Clive and Stoff, 1984; Baker and Pusey, 2004). The classical allergic triad of fever, arthralgia, and rash is now only seen in 10% of patients. Other rare symptoms consistent with a hypersensitivity reaction that have been described include haemolysis, hepatitis and elevated serum IgE levels.

Clinical findings are inconsistent, but the history and physical examination can be guided by certain fundamental principles. A thorough history is mandatory, including enquiry about recent episodes of infection or drug exposure. Details should be sought regarding over-the-counter medications such as NSAID creams and herbal remedies. When discussing drug exposure it should be borne in mind that drug-related ATIN is an idiosyncratic reaction and not dose-related. It can occur at any time after starting drug treatment and prior tolerance of a medication does not necessarily preclude its involvement; this is particularly true for ATIN associated with NSAIDs (Kleinknecht, 1995). Symptoms such as malaise, anorexia, and fatigue are common, particularly in severe AKI. Occasionally, flank pain may be described, presumably due to renal capsular stretching. There may symptoms related to extrarenal disease, especially if the ATIN is part of a multisystem disease (e.g. TINU, IgG4-related ATIN, or sarcoidosis). The clinical examination will usually be normal, although rarely there may be evidence of a rash, swollen joints or uveitis. Most patients with ATIN are normotensive and have no peripheral oedema.

Investigations will usually yield a raised serum creatinine and biochemical evidence of tubular dysfunction may be present (e.g. renal tubular acidosis or Fanconi syndrome). The renal function is impaired severely enough to require dialysis in approximately 40% of patients. There may be a low fractional excretion of sodium. Eosinophilia is present in approximately one-third of cases and serum inflammatory markers may be raised.

Urinalysis usually reveals low-grade proteinuria (< 2 g/24 hours), but occasionally nephrotic-range proteinuria may be present, indicating the coexistence of significant glomerular disease. This may occur in the elderly, with the occasional association of anti-TBM disease with membranous glomerulopathy or in some NSAID- and methicillin-related cases (Nolan and Abernathy, 1977; Clive and Stoff, 1984; Porile et al., 1990; Katz et al., 1992; Haas et al., 2000). Microscopic haematuria is common, but macroscopic haematuria is unusual and suggests an alternative diagnosis. Sediment-free urine does not exclude the diagnosis of ATIN. White blood cells

Table 83.3 Clinical features of ATIN[a]

AKI	100%
AKI requiring renal replacement therapy	40%
Arthralgia	45%
Rash	18%
Fever	32%
'Allergic triad' (fever, rash and arthralgia)	10%
Eosinophilia	31%
Microscopic haematuria	67%
Macroscopic haematuria	5%
Leucocyturia	82%
Non-nephrotic-range proteinuria	93%
Nephrotic-range proteinuria	2.5%
Nephrotic syndrome	0.8%

[a] Data pooled from several studies (Buysen et al., 1990; Schwarz et al., 2000; Baker and Pusey, 2004; Clarkson et al., 2004; Gonzalez et al., 2008).

and white cell casts may also be present in the urine and examination for eosinophiluria (eosinophils > 1% of total urine white cells) with Hansel's stain is often positive. This test is not routinely performed in many centres and detailed analysis demonstrates a low sensitivity and low positive predictive value for the diagnosis of ATIN (Nolan et al., 1986; Landais et al., 1987; Ruffing et al., 1994; Fletcher, 2008; Kaye and Gagnon, 2008). It is possible that urinary biomarkers may prove useful in the future but they are not currently validated for the diagnosis of ATIN (Waanders et al., 2010; Chen et al., 2011).

Diagnosis

Enlarged renal bipolar length is a non-specific finding in ATIN, but it is not sensitive enough to aid diagnosis. Gallium-67 scintigraphy was originally described as a useful diagnostic test in ATIN, the tracer being taken up by the mononuclear phagocytic cells within the renal interstitium (Wood et al., 1978; Linton et al., 1985). However, subsequent reports have not confirmed these observations and this investigation is no longer considered useful (Graham et al., 1983; Kodner and Kudrimoti, 2003). The lack of any non-invasive test with a satisfactory sensitivity and specificity to make the diagnosis of ATIN means that a percutaneous renal biopsy remains the gold standard for diagnosis. If the clinical situation allows, an early biopsy is recommended, since there is some evidence that early treatment ensures both a more rapid and more complete renal recovery (see below).

Prognosis

Full recovery from AKI caused by ATIN is the usual, but by no means universal, outcome. Historical data demonstrates that the majority of patients with methicillin-induced ATIN recovered renal function after either discontinuation of the drug or steroid therapy, but other reports suggest a lower proportion of patients recovering renal function after ATIN secondary to other drugs (Galpin et al., 1978; Schwarz et al., 2000). Acute dialysis is sometimes required, but only a few patients become dialysis-dependent (Laberke and Bohle, 1980; Kida et al., 1984). Renal function does not return to baseline in up to 40% of patients with ATIN, but the final creatinine level does not correlate with its peak value (Rossert, 2001).

Attempts have been made to gain prognostic information from the renal biopsy, with inconsistent results. The degree of tubular atrophy predicted renal outcome in one series (Baker and Pusey, 2004), whereas some authors have reported that patchy cellular infiltration is associated with a better prognosis than diffuse disease (Laberke and Bohle, 1980; Kida et al., 1984; Chen et al., 2011). Other studies showed no correlation between the degree of cellular infiltration or tubulitis and outcome (Buysen et al., 1990; Ivanyi et al., 1996). The degree of interstitial fibrosis has been correlated to outcome in some studies (Bhaumik et al., 1996; Ivanyi et al., 1996; Gonzalez et al., 2008), but no such relationship has been found in others (Cheng et al., 1989). These conflicting observations may be due to the patchy nature of the disease and the random sampling on renal biopsy. This was recognized over 100 years ago by Councilman, who commented on the local nature of the histological changes (Councilman, 1898). The infiltrate is generally most prominent at the corticomedullary junction, with the medulla being relatively spared. Some authors have linked the presence of granulomas with a good response to steroids and a favourable outcome (Joss et al., 2007).

It has previously been suggested that the long-term outcome is worse if renal failure lasts for > 3 weeks (Ditlove et al., 1977; Laberke and Bohle, 1980). However, this is clearly not useful prospectively. Two series have demonstrated worse outcomes with increasing age (Ditlove et al., 1977; Kida et al., 1984).

Management

Most authors favour early treatment with steroids in most circumstances.

Unfortunately, recommendations for the management are blighted by the absence of any prospective randomized controlled studies in the treatment of ATIN. The published literature consists entirely of relatively small retrospective and uncontrolled studies, usually extracted from a single centre. Interpretation is further complicated by the transformation in aetiology that has taken place over the last five decades. Patients with antibiotic-related ATIN, in particular methicillin, dominated early series, whereas contemporary series are more heterogeneous, although still dominated by drug allergy. The following discussion is an attempt to assimilate the evidence from these studies.

Since ATIN is thought to be driven by a pathological response to an allergenic antigen, it follows that removal of the offending agent remains a cornerstone of treatment. Therefore, in drug-related ATIN it is incumbent upon the clinician to identify the most likely agent and stop it. In clinical practice the patient is often taking multiple drugs and deciding which of them to stop is based on probability derived from epidemiological data. It is perhaps prudent to stop all non-essential medications, at least in the short term. In the case of infection-related ATIN it is important to treat the primary infection, especially if it represents an indolent process such as tuberculosis.

The nature of the inflammatory infiltrate and the putative allergic-type mechanism has led clinicians to use corticosteroids to treat ATIN for many years. However, the exact role of steroids in treatment remains to be defined. Several small uncontrolled series have suggested that the administration of steroids is superior to conservative therapy alone (Galpin et al., 1978; Laberke and Bohle, 1980; Pusey et al., 1983; Buysen et al., 1990). A retrospective study of 27 patients with ATIN, by Laberke et al., demonstrated that the seven patients who were treated with steroids had a significantly better renal outcome than those who were not (Laberke, 1980). Buysen et al. (1990) described 27 patients with ATIN, 17 of whom improved spontaneously with conservative measures and drug discontinuation. The remaining 10 showed further deterioration of renal function in the 2 weeks following admission, and were then treated with steroids. In all of these patients, renal function subsequently improved, returning to baseline in 6 weeks.

More recently Clarkson et al. described a retrospective series of 60 patients from a single centre, presenting between 1988 and 2001, in over 90% of whom drugs were invoked as the aetiological agents (44% NSAIDs) (Clarkson et al., 2004). Full follow-up data was available in 42 patients (60%), of whom 26 were treated with corticosteroids and 16 were not. Treatment was not uniform, but involved daily 500 mg methylprednisone intravenously for 2–4 days, followed by tapering oral steroids for a further 3–6 weeks. Two patients died, but the remaining patients had good short- and medium-term outcomes of renal function, although

a noteworthy proportion was left with chronic renal impairment. There was no significant difference between the patients who were treated with steroids and those who were not. It is important to note that patients in the steroid group were treated at a median of 4 weeks after the onset of symptoms and had a mean creatinine of 545 μmol/L (339–1110 μmol/L) at presentation. It has been argued that this cohort of patients may have been treated too late for steroids to make any significant difference (Praga and Gonzalez, 2010).

In contrast, Gonzalez et al. have reported a retrospective series of 61 patients with drug-induced ATIN from multiple Spanish centres, presenting between 1975 and 2006 (Gonzalez et al., 2008). Fifty-six per cent of cases were ascribed to antibiotics and 37% to NSAIDs. Fifty-two patients (85%) were treated with corticosteroids. Treatment was not uniform, but most patients received methylprednisolone (250–500 mg daily for 3–4 consecutive days), followed by oral prednisone (1 mg/kg/day) tapered off over 8–12 weeks. The outcome at a median of 19 months was considerably better in the patients receiving steroid treatment, both in terms of requirement for chronic renal replacement therapy (3.8 vs 44%) and final serum creatinine (185 ± 185 vs 326 ± 255 μmol/L). There were no other significant differences at baseline between the two groups and the duration and doses of steroids were similar. However, those patients who experienced incomplete renal function recovery had a significantly longer interval between withdrawal of the offending drug and the start of steroid treatment (34 ± 17 vs 13 ± 10 days). This study suggests that steroids are indeed effective, but to gain the maximum benefit they need to be administered early. Given that up to half of the patients with ATIN will not regain their baseline renal function, most authors favour the early use of steroids (Baker and Pusey, 2004; Appel, 2008; Perazella and Markowitz, 2010; Praga and Gonzalez, 2010). Experimental data showing that fibrosis can develop within 7 days of an inflammatory stimulus also supports this approach (Neilson, 2006; Zeisberg and Neilson, 2010). Clearly, a multicentre prospective randomized trial of early versus late steroid treatment is required. Until such a study is performed, it is recommended to perform an early renal biopsy, if clinically safe, and start steroid therapy immediately following diagnosis, with a course that tapers over 8 to 12 weeks (Appel, 2008).

The duration and strength of steroid treatment is also uncertain. Most use prednisolone at 1 mg/kg/day to a maximum of 60 mg/day, tapering after 2 weeks, when the creatinine has started to fall and continuing for 2–3 months. Methylprednisolone has been used to initiate therapy in patients with severe renal impairment. Using pulsed methylprednisolone for a few days in the hospital setting may be more attractive in certain clinical situations, for example if there are questions about potential adherence or there are anxieties over the morbidities associated with steroids, such as psychosis or diabetes.

Ciclosporin has been shown to ameliorate animal models of autoimmune ATIN and might be used as a second-line agent in humans (Shih et al., 1988), although there is limited evidence that it may be effective (Zuliani et al., 2005). Both mycophenolate mofetil and cyclophosphamide have also been used as alternative agents with some success, predominantly in steroid-resistant cases (Preddie et al., 2006).

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CHAPTER 84

Drug-induced acute tubulointerstitial nephritis

Hassan Izzedine and Victor Gueutin

Introduction

Acute tubulointerstitial nephritis (ATIN) defines a pattern of renal disease usually associated with acute kidney injury (AKI), inflammation, and oedema of the renal interstitium. The incidence of ATIN remains unknown. Available estimates show ATIN in 1% of autopsies, 1% of renal biopsies for the evaluation of haematuria and/or proteinuria (Michel and Kelly, 1998), 1–3% of all cases of AKI, and 15% of renal biopsies for unexplained AKI (Farrington et al., 1989; Neilson, 1989; Kodner and Kudrimoti, 2003). Drug-induced ATIN is responsible for approximately 70% of all ATIN cases (Michel and Kelly, 1998; Kabakus et al., 1999; Nishitarumizu et al., 2000; Baker and Pusey, 2004).

Medication-induced adverse events may be classified using a qualitative study assessment, based upon the classification of causal criteria for adverse effects of medications from the World Health Organization, which rates causality as certain, probable, possible, improbable, and conditional or insufficient (Table 84.1) (Edwards and Aronson, 2000). Drug-induced ATIN was first described in 1968, when it was associated with the use of methicillin (Baldwin et al., 1968), occurring in up to 17% of patients who have been treated for > 10 days (Nolan and Abernathy, 1977; Galpin et al., 1978; Rossert, 2001), and the clinical manifestations of methicillin-induced ATIN were considered the prototypical presentation of ATIN. There are several case reports of cross-sensitivity to beta-lactam antibiotics, eliciting acute allergic TIN. Since then, many other drugs have been implicated, of which antimicrobial agents, non-steroidal anti-inflammatory drugs (NSAIDs), and, more recently, proton pump inhibitors (PPIs) have been most commonly involved. Currently, the list of drugs that can cause ATIN continues to expand. Table 84.2 summarizes the most common of these (Nessi et al., 1976; Galpin et al., 1978; Ten et al., 1988; Neilson, 1989; Allon et al., 1990; Gaughan et al., 1993; Lo et al., 1993; Neelakantappa et al., 1993; World et al., 1996; Abadín et al., 1998; Cruz and Perazella, 1998; Fang and Huang, 1998; Markowitz et al., 1998; Michel and Kelly, 1998; Schurman et al., 1998; Wai et al., 1998; Andrews and Robinson, 1999; Koshy et al., 1999; Corrigan and Stevens, 2000; Ejaz et al., 2000; Jaradat et al., 2000; Post et al., 2000; Torpey et al., 2004; Esteve et al., 2005; Audimoolam and Bhandari, 2006; Tomlinson et al., 2006; Hoppes et al., 2007; Brosnahan et al., 2008; Hunter et al., 2009; Wang et al., 2009; Chatzikyrkou et al., 2010; Korsten et al., 2010). Recently, antivascular endothelial growth factor agents (bevacizumab, sorafenib, sunitinib) used in clinical trials to treat cancer, have also been reported to cause ATIN (Barakat et al., 2007; Izzedine et al., 2007; Winn et al., 2009).

Pathogenesis

Drug-induced ATIN occurs in an idiosyncratic, dose-independent manner. The pathogenesis of ATIN involves an allergic response that is prompted by exposure to a drug. A type-IV (delayed) hypersensitivity response is often implicated in the pathogenesis of drug-induced ATIN. The presence of helper-inducer and suppressor-cytotoxic T lymphocytes in the renal interstitial inflammatory infiltrate suggests that T-cell-mediated hypersensitivity reactions and cytotoxic T-cell-induced injury are involved in pathogenesis of ATIN (Toto, 1990). While antibiotics often produce a systemic allergic reaction (including fever, skin rash, and eosinophilia), NSAIDs trigger a cell-mediated or delayed-type hypersensitivity response. A humoral response underlies rare cases of ATIN, in which a portion of a drug molecule (i.e. methicillin) may act as a hapten, bind to the tubular basement membrane (TBM), and elicit anti-TBM antibodies (Border et al., 1974; Perazella and Markowitz, 2010).

The most widely accepted theory is that drugs behave as haptens after binding either to extrarenal proteins that later will be planted in the kidney, or to renal proteins (Rossert, 2001). The reaction to the agent is presumably caused by previous sensitization, and, indeed, patients may have a history of exposure to the ingested drug or to a similar drug. The inflammation in the kidney is often part of a systemic hypersensitivity reaction, which may include fever, arthralgias, and skin rash. Eosinophils are commonly a significant component of the renal inflammatory infiltrate, and, as noted earlier, peripheral blood eosinophilia is often seen, as well. Reactions involving immune complex deposition are of two types: those with formation of immune complexes that are deposited around tubules and those owing to formation of antibodies directed against antigens of the TBM. Rarely, drug antigens may be planted in the TBM. The inciting drug may serve as a hapten, leading to antibody formation (Nadasdy and Sedmak, 2007).

Cell-mediated immunity has also been involved in the genesis of drug-induced ATIN. Reactions to antibiotics are often associated with infiltrates consisting mainly of mononuclear cells and eosinophils. Most of the mononuclear cells are CD4+ T lymphocytes (Bender et al., 1984; Pamukcu et al., 1984; Kobayashi et al., 1998).

Table 84.1 Classification of causal criteria for adverse effects of medications

Classification	Criteria
Certain	Clinical event including abnormalities in the laboratory, which occurs in a coherent temporal relation to the administration of the drug, and which cannot be explained by concurrent illness, drugs or other chemicals The response to withdrawal of the medication can be clinically demonstrated The phenomenon can be pharmacologically demonstrable, using the re-administration of the medication if necessary
Probable	Clinical event including abnormalities in the laboratory, which occurs within a 'reasonable' time period after the administration of the drug, and for which it would be improbable to explain by concurrent illness, drugs or other chemicals In clinical follow-ups there is a reasonable response upon withdrawal of the medication It is not necessary to re-administer the drug
Possible	Clinical event including abnormalities in the laboratory, occurring within a reasonable time period upon administering the medication, but which can be explained by illness, other medications, or concomitantly used chemicals Information about suspending the drug is hidden or is unclear
Improbable	Clinical event including abnormalities in the laboratory, within a reasonable time period upon administering the drug, but for which a causal relation is improbable due to the fact that other drugs, chemicals, or illness can provide a causal explanation
Conditional	Clinical event including abnormalities in the laboratory, reported as an adverse reaction to the drug but for which more essential data are necessary to make an appropriate evaluation or for which additional data are beginning to be evaluated
Insufficient	The report suggests an adverse reaction that cannot be judged because the information is insufficient or cannot be verified or corroborated

However, patients with drug-induced ATIN and nephrotic-range proteinuria were found to have a predominance of CD8+ T cells in the interstitial infiltrate (Bender et al., 1984; Pamukcu et al., 1984; D'Agati et al., 1986; Kobayashi et al., 1998). Eosinophils are commonly seen, but their absence does not exclude drug-induced ATIN (Hawkins et al., 1989). After a few days or weeks from the onset of the disease, a variable accumulation of plasma cells and histiocytes may occur. Although rare in other types of ATIN, granulomas may sometimes develop in drug-induced cases (Nadasdy, 2007); the presence of granulomas is consistent with delayed-type hypersensitivity. T-cell reactivity has been documented in some patients with drug-induced hypersensitivity reactions (Joh et al., 1990; Shibasaki et al., 1991). Cytotoxic lymphocytes reactive against autologous renal cell lines have been isolated from one patient treated with recombinant interleukin-2 (IL-2) (Vlasveld et al., 1993).

Clinical presentation

General features

The clinical presentation of ATIN is highly variable. A lag of 7–10 days typically exists between drug exposure and the development of AKI (Ten et al., 1988; Neilson, 1989), but this lag can be considerably shorter following repeated exposure (Ten et al., 1988; Neilson, 1989; Schubert et al., 2010) or markedly longer with certain drugs (e.g. up to 18 months with NSAIDs) (Clive and Stoff, 1984).

The clinical presentation may vary from isolated abnormal urinary sediment or asymptomatic elevation in serum creatinine to generalized hypersensitivity syndrome, with fever, rash, eosinophilia, and oliguric AKI. Skin rash, fever, eosinophilia, and the classic triad (including all three of the above) were observed in 21%, 30%, 36%, and < 10% of cases, respectively (Clarkson et al., 2004).

Table 84.2 Drugs associated with ATIN

Drug class	Examples
Antibiotics	Almost all agents, in particular **ampicillin**, **cephalosporins**, **ciprofloxacin**, *co-trimoxazole*, ethambutol (myambutol), isoniazid, macrolides, **penicillin G**, **rifampicin**, **sulphonamides**, tetracycline, vancomycin
NSAIDs (including salicylates and selective COX2 inhibitors)	Almost all agents, in particular **aspirin**, **fenoprofen**, **ibuprofen**, **indomethacin, naproxen, phenylbutazone, indomethacin, naproxen, phenylbutazone, piroxicam**, **tolemetin, zomepirac**
Gastric acid suppressants	**Proton pump inhibitors** (**omeprazole**, **lansoprazole**, **rabeprazole**), cimetidine, ranitidine (very rarely)
Diuretics	Chlorthalidone, ethacrynic acid, *furosemide*, *thiazides*, indapamide, *tienilic acid*, *triamterene*
Miscellaneous	Abacavir, aciclovir, adalimumab, *allopurinol*, amlodipine, anti-CD4 antibody, atazanavir, azathioprine, *bethanidine*, *captopril*, *carbimazole*, *chlorpropamide*, **cimetidine**, carbamazepine, clofibrate, *clometacin*, cocaine, creatine, deferasirox, diltiazem, famotidine, *fenofibrate*, *floctafenin*, foscarnet, *glafenin*, indinavir, interferon, interleukin-2, lenalidomide, mesalazine, phentermine, *phenindione*, *phenytoin*, pranlukast, propylthiouracil, quinine, sunitinib, sorafenib, TNF-alpha inhibitors etc.

Bold: frequent or clinically important.

Italic: with interstitial granuloma formation.

AKI can often be irreversible, resulting in chronic kidney disease (CKD) (Michel and Kelly, 1998; Kodner and Kudrimoti, 2003).

AKI is typically non-oliguric. It develops 7–10 days after drug exposure in 80% of patients (Rossert, 2001), with a slow increase in serum creatinine; however, patients with severe AKI can present with oliguria and a rapidly progressive course (Alexopoulos, 1998). Other associated symptoms may include flank pain (distension of the renal capsule by inflammation and parenchymal swelling may occur, particularly with rifampicin), gross haematuria, and other general manifestations, such as myalgias, arthralgias, and myositis. Occasionally, the kidneys are palpable, when markedly enlarged (Baker and Williams 1963; Simenhoff et al., 1968; Toto, 1990).

Drug-induced hypersensitivity syndrome (DiHS), also called 'drug rash with eosinophilia and systemic symptoms' (DRESS), is a severe drug hypersensitivity reaction involving rash, fever (38–40°C), and multiorgan failure, affecting liver, kidneys, heart, and/or lungs (Mauri-Hellweg et al., 1995; Peyrière et al., 2006; Ben M'rad et al., 2009). Debate is ongoing about the most accurate name for this syndrome, as fewer than one-half of cases show eosinophilia (whereas, for example, those caused by drugs like abacavir or lamotrigine typically do not).

Granulomatous interstitial nephritis (GIN) is present in 0.5–0.9% of renal biopsies and has been associated with anticonvulsants, antibiotics, NSAIDs, allopurinol, and diuretics (Table 84.2). Histologic features do not seem to distinguish the underlying cause of GIN. Treatment with a moderate dosage of prednisolone is associated with a good prognosis, irrespective of the underlying cause and the degree of interstitial fibrosis (Joss et al., 2007).

Drug classes

Different drug classes are associated with some particular clinical features of ATIN, as summarized in Table 84.3.

Non-steroidal anti-inflammatory drugs

NSAIDs, including cyclooxygenase 2 (COX-2) inhibitors, may precipitate AKI, particularly in vulnerable patients. NSAID use accounts for an estimated 15% of all cases of drug-induced AKI. A case–control study estimated a 3.2 relative risk (95% confidence interval (CI) 1.8–5.8) of AKI in otherwise healthy current users of NSAIDs. The NSAID-associated ATIN typically occurs after treatments > 1 year (in contrast to 12 days, on average, with beta-lactam antibiotics) and has a much lower incidence of fever, rash, and eosinophilia than other drug-induced ATIN (Pirani et al., 1987).

NSAID-associated ATIN exhibits a low grade of interstitial inflammation and it may often be accompanied by a nephrotic syndrome. Proteinuria, usually in the nephritic range, occurs in 70% of cases (Rossert, 2001). The onset of NSAID-induced nephritic syndrome is usually delayed, with a mean time to onset of 5.4 months after the start of NSAID therapy and ranging from 2 weeks to 18 months (Abraham and Keane, 1984; Clive and Stoff, 1984). NSAID-induced nephritic syndrome is usually reversible between 1 month and 1 year after discontinuation of NSAID therapy. During the recovery period, some 20 % of patients require dialysis. Steroids should be employed as in patients with idiopathic minimal change disease (Murray and Brater, 1993).

Changes in the glomeruli in these patients are minimal and resemble those of idiopathic minimal change disease, with marked epithelial-foot process fusion (Murray and Brater, 1993; Rotellar et al., 1989; Morgenstern et al., 1989). The mechanism of NSAID-induced nephrotic syndrome has not been fully characterized. It is thought to be the result of leukotriene release, from arachidonic acid via the lipooxygenase pathway, when the cyclooxygenase pathway is blocked. Leukotrienes increase glomerular and peritubular permeability, which may lead to the induction of TIN and proteinuria (Abraham and Keane, 1984; Clive and Stoff, 1984; Warren et al., 1989). Such patients should avoid subsequent administration of NSAIDs, as nephrotic syndrome relapse may occur with re-challenge (Mohammed and Stevens, 2000).

Radford et al. (1996), using the Mayo Clinic biopsy registry, reported that > 10% of biopsy-proven membranous nephropathy was attributable to NSAIDs, with a median duration of 43 weeks of drug ingestion. Nephrotic-range proteinuria was present for < 8 weeks, but reversed after discontinuation of the drug. Other rarer kidney injury mechanisms have also been reported with NSAIDs, including acute papillary necrosis (Atta and Whelton, 1997) and renal vasculitis (Leung et al., 1985). Adverse renal effects

Table 84.3 Clinical features of ATIN associated with specific drug classes

Drug class	Clinical features
Antibiotics	Common (e.g. 17% of methicillin-treated patients)
	Fever, rash, arthralgias, eosinophilia, eosinophiluria, and pyuria
	Cross-sensitivity between penicillin and cephalosporins
	Rifampicin-induced ATIN occurs with intermittent or discontinuous drug administration
	Associated allergic and hypersensitivity reactions and vasculitis on histology
NSAIDs	Common: 15% of all causes of AKI
	Oedema, congestive heart failure, hyponatraemia, hyperkalaemia, nephrotic syndrome may also occur
	Possibly associated renal lesions: papillary necrosis, minimal change disease, membranous nephropathy
Acid suppressants	Rash (rarely), inconsistent pyuria
Diuretics	Unknown incidence
	Rare rash, inconsistent pyuria
	Cross-reactivity between furosemide and sulphonamide antibiotics
	Vasculitis on histology

are generally reversible after discontinuation of NSAID treatment (Murray and Brater, 1993).

Cases of ATIN, membranous nephropathy, and minimal change disease following treatment with COX-2 inhibitors have also been reported (Rocha and Fernandez-Alonso, 2001; Alper et al., 2002; Henao et al., 2002; Markowitz et al., 2003; Brewster and Perazella, 2004). The rapid and complete resolution of these conditions following discontinuation of COX-2 inhibitors strongly supports their implication in the disease pathogenesis.

Proton pump inhibitors

It appears that PPIs have now become a leading cause of drug-induced ATIN, with an incidence of 8 cases per 10,000 patient-years (Simpson et al., 2006). ATIN develops, on average, 11 weeks after starting the PPI treatment (Geevasinga et al., 2006). Since 1992, when the first case of ATIN induced by omeprazole was reported (Ruffenach et al., 1992), all other agents in this class have been associated with ATIN (Torpey et al., 2004; Geevasinga et al., 2005; Simpson et al., 2006; Ricketson et al., 2009). In a study by Geevasinga et al. the outcome of patients with PPI-induced ATIN was good when the disease was early recognized; these patients rarely required renal replacement therapy and end-stage renal disease was not seen in any of them, although many developed mild-to-moderate CKD (Geevasinga et al., 2006). Accidental or unrecognized drug re-challenge after an initial episode of suspected PPI-induced ATIN is associated with a rapid onset of AKI, within a few days from exposure (Ruffenach et al., 1992; Christensen et al., 1993; Assouad et al., 1994; Gronich et al., 1994).

Antimicrobials

β-lactam antibiotics

β-lactam antibiotics (penicillins and cephalosporins) are frequently involved in the development of hypersensitivity syndrome (Baldwin et al., 1968; Border et al., 1974). Most patients who develop ATIN after treatment with a cephalosporin have a history of penicillin allergy (Toto, 1990; Alexopoulos, 1998; Rossert, 2001). The duration of exposure to the causative drug is relatively short, ranging from a few days to a few weeks. Fever, rash and/or eosinophilia are seen in > 75% of patients. Urinary abnormalities, like proteinuria, leucocyturia and haematuria, also occur in approximately 75% of cases. Although most patients with β-lactam-induced ATIN recover their renal function, irreversible CKD may sometimes develop (Baldwin et al., 1968; Border et al., 1974; Schellie and Groshong, 1999; Papachristou et al., 2006).

Other antibiotics

ATIN can also occur with other antibiotics, such as rifampicin, sulphonamides, and quinolones. Rifampicin-induced ATIN is associated with the production of anti-rifampicin antibodies and commonly manifests with oliguric AKI, proximal tubular injury, haemolytic anaemia, thrombocytopenia, and hepatitis. Approximately two-thirds of patients require renal replacement therapy (Campese et al., 1973; Toto, 1990; Alexopoulos, 1998; Rossert, 2001). ATIN induced by sulphonamide antibiotics may be associated with typical hypersensitivity reactions, such as fever, rash, and eosinophilia (Kleinknecht et al., 1983). HIV patients, transplant recipients, and those with pre-existing CKD are prone to develop sulphonamide-induced ATIN more than other individuals (Perazella, 2000, 2003). However, this may be due to the frequent use of sulphonamide antibiotics in these patients. Fluoroquinolones may also cause ATIN. In contrast to rifampicin and sulphonamides, hypersensitivity syndrome associated with fluoroquinolones is rare. Ciprofloxacin is the most common causative agent in this class, but cases of ATIN from norfloxacin, ofloxacin, and levofloxacin use have also been described (Toto, 1990; Alexopoulos, 1998; Rossert, 2001) .

Protease inhibitors

Protease inhibitors have become the mainstay of therapy for patients with AIDS. Renal complications, particularly crystalluria, were early recognized as adverse effects of these drugs. However, more recent reports indicate that ATIN (with foreign body-type giant cells) may also occur, particularly with indinavir (Sarcletti et al., 1998; Olyaei et al., 2000).

Diagnosis

A diagnosis of ATIN should be considered in any patient with clinical manifestations of a hypersensitivity reaction, unexplained AKI, and a history of recent exposure to a possibly offending drug (Rossert, 2001; Toto, 2001). Some clinical features (Table 84.3) and ancillary tests may be helpful in diagnosing drug-induced ATIN. Unfortunately, none of these tests has sufficient accuracy for a certain diagnosis, except renal biopsy. However, biopsy is indicated only when diagnosis is unclear or when the patient does not improve after discontinuation of the suspected medication.

Laboratory tests

Characteristic laboratory findings include an acute rise in plasma creatinine concentration, eosinophilia, leucocyturia with white cell casts and eosinophiluria. Eosinophiluria helps confirm the diagnosis of ATIN with an estimated sensitivity and specificity of 67% and 83%, respectively (Rossert, 2001); however, it can also be found in patients with rapidly progressive glomerulonephritis and with renal atheroembolism. Gross or microscopic haematuria and urinary red blood cell casts have also been described. However, occasional patients show bland sediment, with few cells or casts (Lo et al., 1993). Thus, a relatively normal urinalysis should not exclude the diagnosis of ATIN. Proteinuria is usually mild (< 1 g/day), but nephrotic-range proteinuria may occur in cases with associated minimal change disease or membranous nephropathy induced by NSAIDs or, sometimes, by ampicillin, rifampicin, interferon or ranitidine (Neugarten et al., 1983; Averbuch et al., 1984; Clive and Stoff, 1984; Gaughan et al., 1993; Praga and González, 2010).

Tubular function disorders have also been described, including salt-wasting syndrome, proximal tubular damage with type II renal tubular acidosis and Fanconi syndrome, and distal tubular damage, with type I renal tubular acidosis and sodium or potassium abnormalities. Involvement of collecting ducts in the medulla and papillae may be associated with polyuria (Choudhury and Ahmed, 2006).

Increased serum immunoglobulin E levels, suggesting an allergic response, have been reported in some patients with drug-induced ATIN (Linton et al., 1980), but this is an inconsistent finding.

Imaging studies

There are no imaging studies to accurately confirm or exclude ATIN. Renal ultrasonography and CT scanning may demonstrate

normal or enlarged kidneys, with increased cortical echogenicity or density. The role of gallium-67 scanning for the diagnosis of ATIN remains unclear; however, in patients who are poor candidates for renal biopsy, it may be useful in distinguishing ATIN from acute tubular necrosis (Graham et al., 1983; Linton et al., 1985).

Kidney biopsy

Kidney biopsy remains the gold standard for the diagnosis of drug-induced ATIN. The main pathological findings are interstitial inflammation and tubulitis (Fig. 84.1A). The hallmark of ATIN is the inflammatory infiltrate, consisting of T lymphocytes, monocytes, and a variable number of plasma cells and eosinophils (Fig. 84.1B), associated with oedema, within the renal interstitium, sparing the glomeruli and the blood vessels (Michel and Kelly, 1998; Rastegar and Kashgarian, 1998). Occasionally, granuloma formation with epithelioid giant cells may be seen (Fig. 84.1C). In an immunohistochemical study of interstitial infiltrates in cases of ATIN secondary to NSAIDs and β-lactam antibiotics, the mononuclear cell component was found to consist of 71.7% T cells (with equal numbers of CD4+ and CD8+ cells), 15.2% monocytes, and 7.4% B cells (D'Agati et al., 1989). Peritubular infiltration and occasional lymphocytic invasion beyond the TBM may occur with mild-to-severe tubular damage.

Many drugs can induce a granulomatous reaction. In a series of 46 patients with GIN, the most frequent aetiologies were drug-induced disease and sarcoidosis, representing 44.7% and 28.9% of cases, respectively (Bijol et al., 2006). In this study, drug-induced GIN was mainly caused by antibiotics and NSAIDs. The pathological findings in drug-induced GIN are indistinguishable from those seen in the setting of sarcoidosis or other forms of GIN (Bijol et al., 2006). Interestingly, a higher incidence of persistent renal impairment is found in cases with interstitial granulomas than in those without granulomas (Grunfeld et al., 1993). Immunofluorescence microscopy is usually negative, although rare cases with linear deposits of immunoglobulins and complement along the TBM, suggesting an antibody-mediated inflammatory response, have been described in patients with methicillin-induced ATIN (Border et al., 1974).

Outcomes

Recovery of renal function was observed in the great majority of cases, after discontinuation of the offending drug, with or without associated glucocorticoid therapy (Galpin et al., 1978; Schwarz et al., 2000; Rossert, 2001). The probability of recovery depends on the duration of AKI prior to diagnosis, and ideally this should not exceed two weeks. The recovery of the kidney function is often incomplete, with persistent elevation of serum creatinine in up to 40% of cases (Rossert, 2001; Baker and Pusey, 2004). Acute dialysis may be required (Handa, 1986; Koselj et al., 1993; Bhaumik et al., 1996), but only about 10% of patients remain dialysis-dependent on long-term (Baker and Pusey, 2004; Clarkson et al., 2004; Laberke and Bohle, 1980). Poor prognostic factors include prolonged AKI (> 3 weeks), ATIN associated with NSAID use, and certain histologic findings, such as interstitial granulomas (Grunfeld et al., 1993), diffuse versus patchy inflammation, interstitial fibrosis, and tubular atrophy (Laberke and Bohle, 1980; Bhaumik et al., 1996; Schwarz et al., 2000).

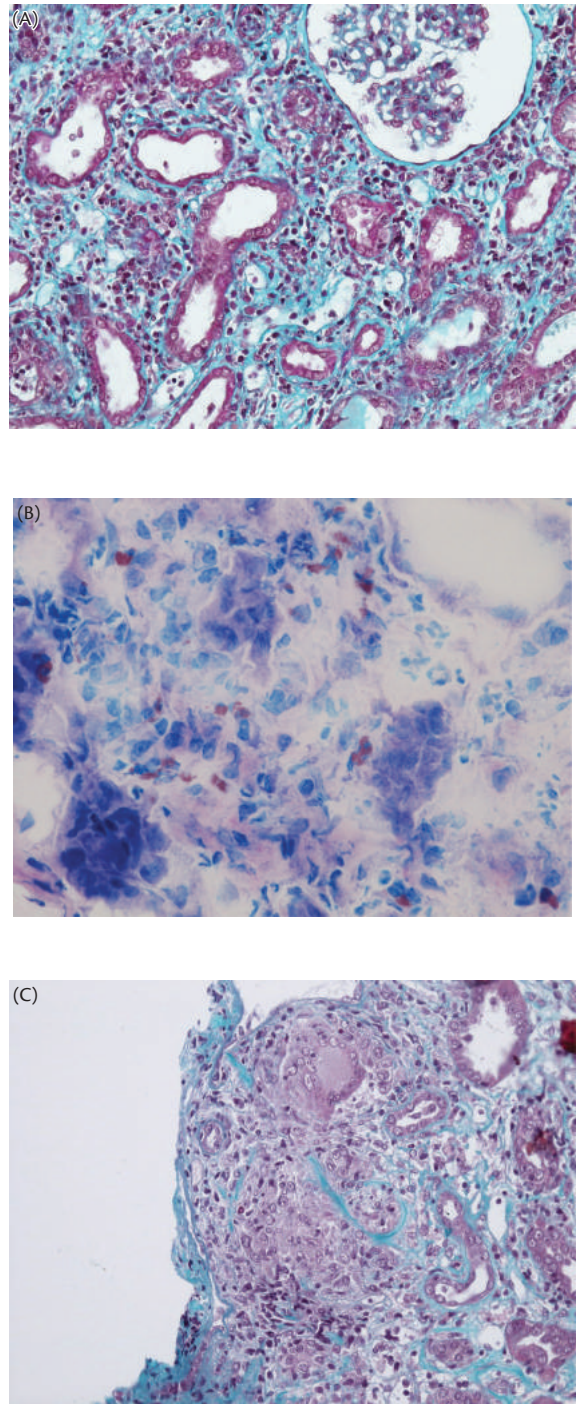

Fig. 84.1 Drug-induced ATIN with: (A) Prominent interstitial inflammation with lymphocytes, eosinophils, and focal plasma cells, associated with tubulitis (trichrome Masson; magnification ×100). (B) Eosinophils (magnification ×400). (C) Interstitial granuloma, composed of a well-circumscribed aggregate of epithelioid histiocytes and multinucleated giant cells (magnification ×200).

Treatment

The optimal therapy of drug-induced ATIN remains to be defined, since there are no randomized controlled trials. A proposed management algorithm is presented in Fig. 84.2 (adapted from Kodner and Kudrimoti, 2003).

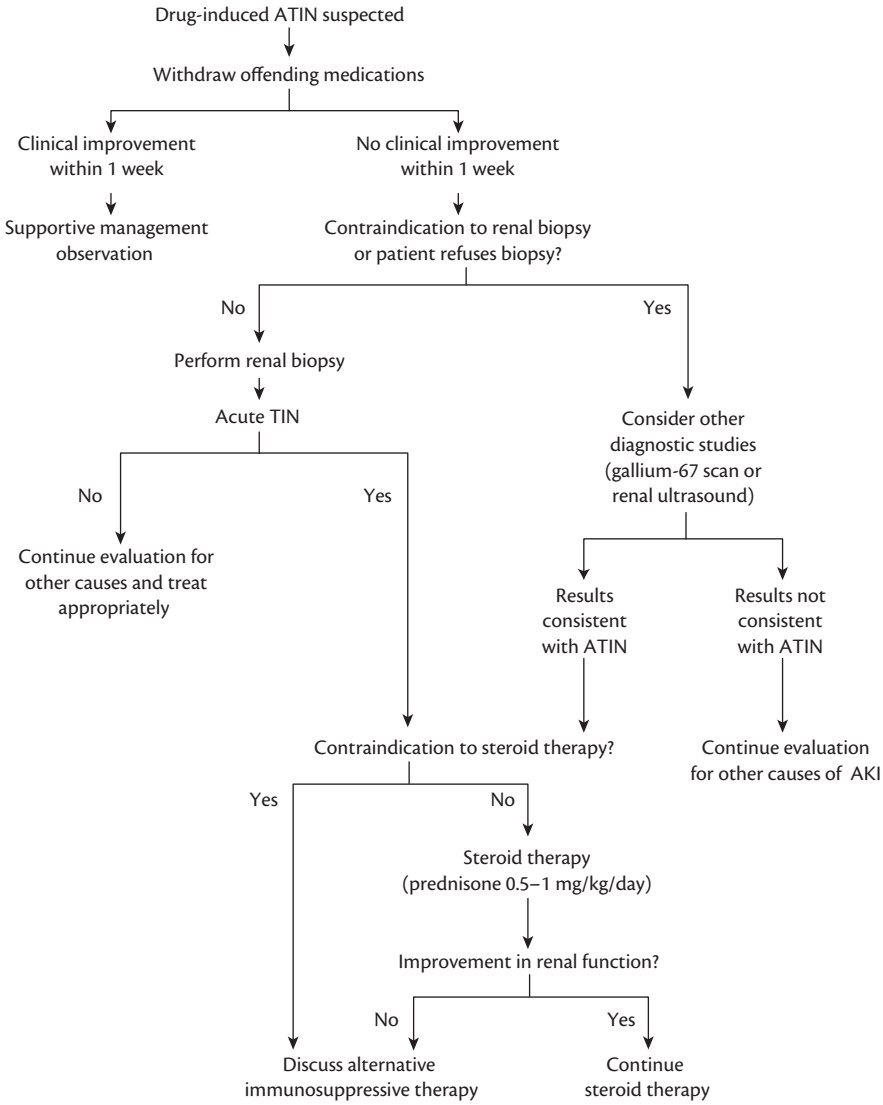

Fig. 84.2 Algorithm for the management of drug-induced ATIN.
Source data from Kodner and Kudrimoti (2003).

Supportive care

Discontinuation of the potentially causative drug is the mainstay of therapy and the first necessary step in the early management of suspected or biopsy-proven drug-induced ATIN (Michel and Kelly, 1998; Rossert, 2001). No other therapy is required if a patient's renal function shows improvement within 1 week following drug cessation (Buysen et al., 1990). However, a considerable proportion of patients (36%) may develop CKD (Baker and Pusey, 2004).

Glucocorticoid therapy

There are no randomized controlled trials of glucocorticoid therapy in patients with drug-induced ATIN and the available data is conflicting. Thus, the decision to initiate steroids should be guided by the patient's clinical course following withdrawal of the offending drug.

Several retrospective series demonstrated no benefit from glucocorticoid therapy (Koselj et al., 1993; Bhaumik et al., 1996; Schwarz et al., 2000; Clarkson et al., 2004). In one series, including 42 cases of biopsy-proven drug-induced ATIN (NSAIDs 44%, antibiotics 33%, and PPIs 7%), 26 patients were treated with steroids (intravenous methylprednisolone for 3 days followed by oral prednisone tapered over 3–6 weeks), whereas the remaining 16 were not; there was no difference in serum creatinine between the two groups at 1, 6, and 12 months (Clarkson et al., 2004).

Improvement in kidney function following glucocorticoid therapy has been suggested by several uncontrolled studies (Galpin et al., 1978; Handa, 1986; Buysen et al., 1990). A multicentre retrospective study involving 61 patients (Gonzalez et al., 2008) suggested a beneficial influence of corticosteroids on the outcome of drug-induced ATIN. An earlier start of therapy (day 13 vs day 34) was associated with a better recovery of renal function (Appel, 2008; González et al., 2008), a lower need for dialysis after 18 months (4% vs 44% of cases), and lower serum creatinine levels (2.1 mg/dL vs 3.7 mg/dL). Among treated patients, those who started steroids within 7 days from withdrawal of the offending drug were significantly more likely to recover renal

function than those who received steroids after this period (odds ratio 6.6, 95% CI 1.3–33.6).

Given the potential benefit and the relative safety of short-term steroid therapy, it seems reasonable to treat patients with corticosteroids if they do not show significant improvement in serum creatinine within 3–7 days after discontinuation of the offending agent. The optimal dose and duration of therapy are unclear; one suggested regimen consists of prednisone at a dose of 0.5–1 mg/kg per day (without exceeding 60 mg/day) for 1 month, beginning a gradual taper after the serum creatinine has returned to or near baseline, for a total therapy duration of 3 months (Clarkson et al., 2004). Most patients are likely to improve within the first 1 or 2 weeks (Clarkson et al., 2004). In patients with more severe AKI, therapy may be initiated with intravenous methylprednisolone (0.5–1 g/day for 3 consecutive days) (Clarkson et al., 2004).

Other therapies

There is limited experience with alternative agents in patients who are steroid-dependent, steroid-resistant (as with NSAID-induced ATIN), or cannot tolerate glucocorticoids. There are a few case reports and small series using mycophenolate mofetil (MMF) (Preddie et al 2006) and ciclosporin (Zuliani et al., 2005). The largest study (Preddie et al., 2006) included eight patients with biopsy-proven ATIN who had received glucocorticoids for at least 6 months and became steroid-dependent. MMF was then given for 13–34 months. All patients were subsequently able to discontinue corticosteroids and all but two patients showed significant improvement in serum creatinine.

Summary and recommendations

1. Antibiotics, NSAIDs, and PPIs are the most common drugs inducing ATIN.
2. Only 10% of patients present with the classical triad of rash, fever, and eosinophilia. Urinalysis usually reveals leucocyturia and haematuria; white cell casts may also be present. Eosinophiluria occurs in 80% of cases. Proteinuria is usually mild to moderate. Tubular function abnormalities may be seen.
3. The potentially inducing agent must be immediately discontinued. Most cases improve spontaneously thereafter, within 3–7 days. Indications for kidney biopsy include uncertainty regarding the diagnosis and lack of spontaneous recovery following cessation of the offending drug.
4. In cases with no improvement of renal function within a week after drug discontinuation, early initiation of corticosteroids (0.5–1 mg/kg per day for 1 month, followed by gradual taper for a total therapy duration of 3 months) will typically improve the course of the disease within 1–2 weeks.
5. In patients who are steroid-dependent, steroid-resistant, or cannot tolerate glucocorticoids, the optimal therapy approach is not known, but MMF, ciclosporin, or cyclophosphamide may be considered.

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CHAPTER 85

Other toxic acute tubulointerstitial nephritis

Benjamin J. Freda and Gregory L. Braden

Ethylene glycol

Ethylene glycol intoxication produces severe neurologic changes, increased osmolal and anion gap acidosis, from glycolic, glyoxylic, and oxalic acids, and may cause acute kidney injury (AKI) within 72 hours of ingestion. However, AKI from ethylene glycol often leads to chronic kidney disease (CKD) and sometimes to end-stage renal disease (ESRD) requiring long-term dialysis.

Autopsy studies of patients who died 22–44 hours after ethylene glycol ingestion, before acute peritoneal dialysis or haemodialysis were available, demonstrated significant calcium oxalate monohydrate (COM) deposition, occluding the lumens of proximal tubules, along with cytoplasmic deposition in the tubular cytoplasm, easily detectable by birefringence on polarized microscopy, but there was no tubular necrosis (Pons and Custer, 1946). In patients with delayed therapy or delayed presentation, proximal tubular degeneration and necrosis accompanied proximal tubule COM deposition. Serial renal biopsies in these patients revealed the disappearance of tubular COM crystals, but persistent COM crystals in the interstitium and gradual interstitial fibrosis. Some patients remained on dialysis permanently and others had variable stages of CKD after dialysis was discontinued. Patients with repeated exposure to low-dose ethylene glycol all had severe CKD, leading to long-term dialysis (DeSilva and Mueller, 2009).

There are several mechanisms whereby ethylene glycol induces renal tubular toxicity. The ethylene glycol metabolites, glycolaldehyde and glyoxylate, incubated *in vitro* with human proximal tubule HK-2 cells caused ATP depletion and phospholipid and enzyme destruction (Poldelski et al, 2001). Moreover, studies of cultured human proximal tubule cells have shown that COM crystals may kill these cells at concentrations in the range measured in human intoxications (McMartin, 2009). In addition, studies of ethylene glycol toxicity in animals correlate the extent of renal damage to the level of tubular COM crystal deposition. COM crystals can alter phospholipid membrane structure and function and induce reactive oxygen species and mitochondrial dysfunction (McMartin, 2009). Taken together, these studies support multiple pathways whereby ethylene glycol induces severe renal tubular damage leading to CKD and the need for chronic dialysis, particularly in patients with delayed presentation or delayed therapy.

Ethylene glycol intoxication usually presents with abdominal pain, severe nausea and vomiting, mental status changes and severe anion gap metabolic acidosis, usually associated with an osmolal gap > 10 mOsm/kg H_2O. More severe central nervous system complications include seizures, delirium, and coma. The urinalysis usually shows an excess of crystals, including calcium oxalate dihydrate (envelope-shaped) and/or monohydrate (resembling dog biscuits or spindles).

Urgent haemodialysis is indicated to remove both ethylene glycol and its toxic metabolites. In addition, fomepizole inhibits hepatic alcohol dehydrogenase and prevents formation of toxic metabolites from ethylene glycol. This agent should be administered intravenously (IV) as early as possible, at a dose of 15 mg/kg, with subsequent dosing every 12 hours, until dialysis has removed all excess ethylene glycol and the serum bicarbonate, anion gap, and the osmolal gap have returned to normal. During haemodialysis, a continuous infusion of fomepizole 1–2 mg/kg per hour should be administered, since it is removed by dialysis. If fomepizole is not available, ethanol can be administered IV to inhibit alcohol dehydrogenase, but this leads to temporary alcohol intoxication which could lead to further complications in these acutely ill patients. Where available, ethylene glycol blood levels can be used to guide therapy. Haemodialysis is usually continued for 2 hours after the serum bicarbonate and anion gap have returned to normal, to prevent rebound intoxication after dialysis is completed.

Chlorinated hydrocarbons

Carbon tetrachloride (CCl_4) has been used as an antihelminthic agent, as a solvent in dry cleaning or as an insecticide. However, due to severe hepatic and renal toxicity, its use has recently been limited to the synthesis of chlorofluorocarbon refrigerants. The two carbon chlorinated solvents, trichloroethylene and tetrachloroethylene are still used in dry cleaning, synthesis of fumigants, and as solvents in paints and varnishes.

When the latter agents are abused by sniffing paint thinners or cleaning solvents, both agents can cause acute tubular necrosis and hepatic necrosis, but neither cause CKD. In contrast, irreversible acute tubular necrosis from CCl_4 has been reported with numerous crystals in proximal tubular lumens, which stain as calcium by Von Kossa stain, associated with interstitial fibrosis (Morrin, et al., 1961). However, two series of 19 patients intoxicated with CCl_4, primarily by inhalation, described AKI in 50–100% of patients, often supported by peritoneal dialysis or haemodialysis, but none developed CKD (Ruprah et al., 1985). Although these and other solvents were thought to cause glomerulonephritis, better epidemiologic studies have found no association between solvents and glomerulonephritis (Harrington et al., 1989). The mechanism of

CCl_4 toxicity is likely due to its liver metabolism via cytochrome P450 2E1 to highly reactive free trichloromethyl radicals causing lipid peroxidation.

Toxicity from these agents is dominated by hepatic necrosis due to direct hepatocyte toxicity, leading to irreversible liver failure, hepatic encephalopathy, ascites, circulatory failure, and death. These patients most often die before liver transplantation can be considered.

Management of chlorinated hydrocarbon intoxication is largely supportive, as in any haemodynamically unstable patient. If the skin is contaminated, all clothing should be rapidly removed and all exposed skin should be washed with large volumes of water; however, soap should not be used, as it may enhance the skin absorption of chlorinated hydrocarbons. Gastric aspiration can be attempted to lessen the gastrointestinal absorption of the agent. Although there is no specific antidote, *N*-acetylcysteine may minimize hepatotoxicity and hyperbaric oxygen may be useful. Dialysis is ineffective in removing chlorinated hydrocarbons.

Paraquat

Paraquat is a commonly used herbicide, which causes human toxicity by the generation of reactive oxygen species. Even small amounts of ingested paraquat can be lethal and the case fatality rate is > 50% (Pond, 1990; Gawarammana and Buckley, 2011). Paraquat is rapidly absorbed and eliminated unchanged in the urine over 24 hours. Poisoning can be confirmed by measuring paraquat in plasma or urine. Clinical presentation depends on the amount ingested, but starts with nausea, vomiting, and a burning sensation in the mouth, throat, chest, and abdomen. Paraquat is concentrated in the lungs and oxidant damage ensues, with severe inflammation and fibrosis. Pulmonary oedema can develop within 24–48 hours and many patients develop acute respiratory distress syndrome. Severe impairment in gas exchange can occur in the absence of significant radiographic changes (Kim et al., 2009).

Renal dysfunction is common during the first week after ingestion and can occur as early as 24–48 hours in more severely poisoned patients. Proximal tubular dysfunction may occur, including glucosuria, tubular proteinuria, aminoaciduria, and impaired sodium, urate, and phosphorus handling. In one study, > 50% of 278 patients poisoned with paraquat developed AKI, with approximately 35% having RIFLE class 'Failure' (Kim et al., 2009). Most patients were non-oliguric. When the initial serum creatinine was ≥ 1.2 mg/dL, the survival rate was only 14%. AKI usually developed within the first 5 days after ingestion. The amount of paraquat ingested correlated with the severity of AKI; importantly, however, renal recovery was the rule in survivors. In addition, baseline serum uric acid is an independent predictor of mortality and AKI, possibly as a marker of the severity of oxidative damage (Kim et al., 2011).

Initial treatments include standard resuscitation measures, gastrointestinal decontamination and enhancing the renal elimination of paraquat. IV saline should be used to optimize intravascular volume and renal excretion of paraquat. In patients with airway stability, bentonite, Fuller's earth, and activated charcoal should be orally administered to enhance gastrointestinal adsorption and elimination (Gawarammana and Buckley, 2011). Gastric lavage should be avoided in most cases, because paraquat is caustic. Various antioxidant and anti-inflammatory agents have also been used (Gawarammana and Buckley, 2011). Although haemodialysis, haemofiltration, and haemoperfusion can remove paraquat, the clinical impact of these procedures is small, given the rapid accumulation of paraquat in lung tissue. In patients with severe poisoning, it is unlikely that extracorporeal removal will be beneficial, and palliative care is the most suitable approach. Haemodialysis, haemofiltration, or haemoperfusion can be considered in patients thought to have a chance to survive; however, it is unclear if one modality is preferred over the others or whether extracorporeal clearance improves clinical outcomes (Fienfeld, 2006).

Toxic mushrooms

Of the thousands of different species of mushrooms, < 100 are known to be toxic to humans. The clinical presentation of toxic mushroom exposure varies from mild gastrointestinal discomfort to organ failure and rarely, death (Berger and Guss, 2005). Depending on the type of ingested mushroom and predominant toxin, 14 clinical syndromes have been described. Early onset toxicity (< 6 hours after exposure) mainly involves the gastrointestinal tract and the central nervous system. Importantly, delayed toxicity can appear > 6–24 hours after exposure to certain mushrooms and include encephalopathy, liver and renal failure, as well as rhabdomyolysis (Diaz, 2005).

Multiple mushroom-derived toxins have been associated with the development of nephrotoxicity. The most common expression of nephrotoxicity is AKI. Depending on the timing of presentation and type of mushroom, AKI has been identified as early as 6 hours after exposure and as late as 1–2 weeks (West et al., 2009; Talmud et al., 2011).

Cortinarius

The genus *Cortinarius* contains around 2000 different species of mushrooms, several of which are poisonous to humans. Most poisonings have been reported with *Cortinarius orellanus* ('Fool's webcap') and the toxicity is attributed to the bipyridine compound, orellanine. This mushroom is found mostly in wooded areas throughout Europe. Orellanine is not destroyed by cooking and the toxicity arises mainly from the generation of toxic free radicals, resulting in damage to renal tubular cells (Mount et al., 2002). Gastrointestinal symptoms are followed by acute tubulopathy and variable progression to CKD.

In 90 cases of *Cortinarius* poisoning, the development of nephrotoxicity was delayed, with a median time to onset of 8.5 days (Danel et al., 2001). Thirty-five patients had renal biopsies 1–9 weeks after onset of AKI. Most cases showed TIN or tubular necrosis, with variable degrees of interstitial oedema and fibrosis (Danel et al., 2001). Many patients required acute dialysis (74%) and about 50% developed CKD, with 68% of these requiring either chronic dialysis or kidney transplantation.

Treatment of *Cortinarius* toxicity is mainly supportive. Various techniques aimed at toxin removal, including haemoperfusion and plasma exchange, have been tried without success. This may be a result of the short-lived presence (likely < 2–3 days) of the toxin in plasma. Thus, at the time of patient's presentation, it is possible that most of the toxin is already concentrated in renal tissue (Danel et al., 2001).

Amanita phalloides

Several species from the genus *Amanita* are associated with significant nephrotoxicity, especially *Amanita phalloides*, otherwise

known as 'Deathcap'. This mushroom is associated with the majority of fatal mushroom ingestions. Amatoxins are not denatured by heating and are readily absorbed from the gastrointestinal tract. They act as potent inhibitors of DNA transcription in tissues with a high rate of protein synthesis (Karlson-Stiber and Persson, 2003). These compounds are extremely hepatotoxic and ingestion of one mushroom may be fatal.

Patients present with acute diarrhoea and abdominal colic after 6–24 hours from ingestion. This can be followed by elevations in serum transaminase levels and in some patients, fulminant renal, liver and cardiac failure, within 2–4 days. Confirmation of amatoxin poisoning is difficult, because clinical assays are not readily available and bedside tests are cumbersome and non-specific (Beuhler et al., 2004). Efforts should be made to obtain a sample of the ingested mushroom for analysis and identification by an experienced mycologist. Post mortem renal biopsies showed severe acute tubular necrosis in proximal convoluted tubules with some interstitial oedema and mononuclear cell infiltration (Fineschi et al., 1996).

Beyond supportive care and gastrointestinal decontamination with repeated doses of activated charcoal, many unproven strategies have been used to enhance toxin elimination and removal, including plasmapheresis, charcoal haemoperfusion, thioctic acid, silibinin, intravenous penicillin, and *N*-acetylcysteine (Diaz, 2005). For patients with progressive liver failure, the Molecular Absorbent Regenerating System (MARS®) has been used as a bridge to liver transplantation. In survivors, hepatic and renal recovery may occur, with some patients developing immune-mediated chronic active hepatitis. One case has been reported with hepatic recovery, but with dialysis-dependent renal failure (Garrouste et al, 2009).

Amanita smithiana

Amanita smithiana can be found mainly in the western part of North America. Most patients present with nausea, vomiting and abdominal pain, within 5–6 hours of ingestion. This contrasts to most *Amanita phalloides* poisonings, where diarrhoea is the predominant gastrointestinal symptom, occurring commonly > 6 hours after ingestion (West et al., 2009). The renal failure in *Amanita smithiana* poisoning is also delayed, seen usually 3–5 days after ingestion. The main renal lesion is acute tubular necrosis. Treatment is supportive and most patients recover renal function, even when dialysis is required temporarily (West et al., 2009).

Other toxic mushrooms

Gyromitra spp. mushrooms can cause gastrointestinal symptoms with toxicity progressing to hepatic dysfunction, methaemoglobinaemia and haemolysis. Haem-induced AKI, rhabdomyolysis, and hepatorenal syndrome may also develop.

Tricholomas equestre mushrooms can be associated with AKI from rhabdomyolysis (Bedry et al., 2001).

Paxillus involutus ingestion can lead to an allergic immune-mediated haemolysis and resultant haem-induced AKI (Schmidt et al., 1971).

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CHAPTER 86

Chronic tubulointerstitial nephritis: overview

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Introduction

The term 'interstitial nephritis' was first used by Councilman in 1898 (Baker and Pusey, 2004) to describe renal lesions he observed in several patients who had died from scarlet fever and diphtheria. Those lesions included interstitial oedema and sterile cell infiltrate. Sixteen years later, Volhard and Fahr included interstitial nephritis in their classification of kidney diseases (Weening and Jennette, 2012).

The interstitium and the tubules—representing around 80% of the renal mass—are distinct but interrelated structural components of the kidneys, and damage to one of them is typically associated with damage to the other. Therefore, the term 'tubulointerstitial nephropathy' (TIN) is now preferred. TIN describes a group of renal diseases characterized by interstitial infiltration with inflammatory cells, interstitial oedema and/or fibrosis, as well as tubular atrophy. According to the clinical presentation, TIN is classified into *acute TIN* (ATIN)—with sudden onset and acute kidney injury (AKI)—and *chronic TIN* (CTIN)—with insidious onset and slow progression towards end-stage renal disease (ESRD). However, ATIN may sometimes become CTIN, when both acute and chronic lesions coexist at some point. TIN may further be classified as *primary* (with inflammation limited to the tubules and interstitium, without significant changes in the glomeruli and the vessels) and *secondary* (when tubulointerstitial lesions are associated with dominant glomerular or vascular disease). In this chapter, we will focus on the general features of primary CTIN.

Epidemiology

The prevalence of CTIN varies with geographical area, diagnostic criteria employed, and indications for renal biopsy. In an autopsy series reported in 1978, CTIN was found in 0.2% of cases (Zollinger and Mihatsch, 1978, pp. 407–10). In a study from 1975, among patients who underwent renal biopsy for chronic kidney disease (CKD) of unknown aetiology, the prevalence of CTIN was found to be 22% (Murray and Goldberg, 1975). In more recent renal biopsy registries, CTIN comprise between 1.5% of cases in Romania (Covic et al., 2006) and 4.4% in the Czech Republic (Rychlík et al., 2004). The prevalence of CTIN among ESRD patients on renal replacement therapy was reported to be 9.6% in the ERA-EDTA registry in 2003 (including nine European countries) (Stengel et al., 2003) and 7.2% in the US in 2010 (United States Renal Data System, 2010).

Aetiology

The aetiologic spectrum of CTIN is remarkably wide. The most common causes are shown in Table 86.1 (Eknoyan and Truong, 1999; Braden et al., 2005; Remuzzi et al., 2007). Among these, drugs are responsible for > 70% of cases, followed by infections—15.8% (Baker and Pusey, 2004).

Clinical manifestations

The onset of CTIN is insidious and the course is slowly progressive towards ESRD, typically over several years. Patients are often asymptomatic and the disease is diagnosed during routine laboratory check-ups, screening for CKD, or assessment of arterial hypertension. However, the blood pressure is usually normal until advanced stages of CTIN (López-Novoa et al., 2011).

The clinical presentation of CTIN is dependent of the aetiology and the severity of renal lesions. Thorough history taking may reveal drug intake (such as analgesics or NSAIDs), herbal therapy, or exposure to industrial chemicals. A history of haematological malignancies (such as multiple myeloma, leukaemia, or lymphoma) or solid tumours treated with chemotherapy is also significant. Some patients may have urological diseases like kidney stones and recurrent urinary tract infections, or a history of urologic surgery. Clinical signs suggestive of systemic diseases such as systemic lupus erythematosus, Sjögren syndrome, cryoglobulinaemia, sarcoidosis, or amyloidosis may be found on physical examination.

Tubular dysfunctions are common and their pattern and severity depend on the location and extension of tubular lesions, as well as on the aetiology. Agents that damage the proximal tubule—like heavy metals and immunoglobulin light chains deposition—may induce type 2 (proximal) renal tubular acidosis (RTA) or Fanconi syndrome, consisting of bicarbonaturia, hyperphosphaturia, glucosuria, aminoaciduria, uricosuria, and tubular proteinuria (Rastegar and Kashgarian, 1998; Eknoyan and Truong, 1999). Agents affecting the loop of Henle and the collecting duct—like analgesics, hypercalciuria/hypercalcaemia, urate nephropathy, and sickle cell disease—may cause a decrease of sodium or water reabsorption ability, the latter resulting in nephrogenic diabetes insipidus. Distal tubular damage can be induced by light chain deposition disease, chronic pyelonephritis or vesicoureteric reflux, and typically presents with type 1 (distal) RTA, associated with hypokalaemia, renal stone formation, and nephrocalcinosis (Eknoyan and Truong,

Table 86.1 Aetiology of CTIN

Drugs (see Chapter 87)	Analgesics: see Chapter 87
	NSAIDs: aspirin, COX-2 inhibitors (see Chapter 87)
	Antiviral agents (nucleoside inhibitors): cidofovir, tenofovir, adefovir
	Calcineurin inhibitors: ciclosporin, tacrolimus
	Antineoplastic agents: cisplatin, ifosfamide, nitrosourea, methotrexate
	Lithium
Infectious diseases	Acute bacterial pyelonephritis (Chapter 177), leptospirosis (Chapter 191), haemorrhagic fever with renal syndrome (Chapter 188), HIV/AIDS (Chapter 187), tuberculosis (Chapter 196)
Immune-mediated diseases (Chapter 93)	Sarcoidosis, Sjögren's syndrome, systemic lupus erythematosus, cryoglobulinaemia
Heavy metals (Chapter 88)	Lead, cadmium, mercury
Metabolic disorders	Hyperuricaemia/hyperuricosuria, hypercalcaemia/hypercalciuria, hyperoxaluria, hypokalaemia, methylmalonic acidaemia
Haematologic disorders	Multiple myeloma (Chapter 153), light-chain deposition disease (Chapter 155), amyloidosis (Chapter 152), sickle-cell disease (Chapter 167)
Genetic disorders	Autosomal dominant interstitial kidney disease including medullary cystic kidney disease (Chapter 318), cystinosis (Chapter 339), Dent disease, adenine-phosphoribosyl-transferase deficiency, autosomal dominant hypoparathyroidism, karyomegalic interstitial nephropathy, mitochondrial mutations (Chapter 340), autosomal dominant polycystic kidney disease (Chapter 306)
Urinary tract obstruction (Chapter 356)	Tumours, stones, bladder outlet obstruction, vesicoureteric reflux (Chapter 355)
Miscellaneous	Balkan endemic nephropathy (Chapter 90), Chinese herbs nephropathy (aristolochic acid; Chapter 89), radiation nephropathy (Chapter 91)
Idiopathic	

AIDS = acquired immunodeficiency syndrome; COX = cyclooxygenase; HIV = human immunodeficiency virus; NSAIDs = non-steroidal anti-inflammatory drugs; SLE = systemic lupus erythematosus.

1999; Braden, 2005). In most cases of CTIN, variable combinations of the three tubular syndromes are seen.

Low-molecular-weight proteinuria (usually < 1.5 g/day and not > 2.5 g/day) is characteristic, as well as leucocyturia, white blood cell casts, and haematuria (Rastegar and Kashgarian, 1998). During the course of the disease, the glomerular filtration rate (GFR) progressively decreases. Renal imaging (ultrasound, intravenous pyelogram, computed tomography, or magnetic resonance) may reveal urinary tract obstruction, vesicoureteric reflux, kidney stones, or parenchymal calcifications, as causes of CTIN. In advanced stages, the kidneys appear shrunken and may have irregular outlines. Additionally, a kidney biopsy is often needed for the diagnosis of CTIN and its aetiology.

Pathology

In patients with CTIN, the size of the kidneys usually decreases with the progression of the disease. The renal surface may be scarred, as in analgesic nephropathy and chronic pyelonephritis, or finely granular, as in Balkan endemic nephropathy. Papillary necrosis, sclerosis or calcification may be associated with analgesic nephropathy or chronic pyelonephritis.

On light microscopy, tubular atrophy, interstitial fibrosis, and a variable degree of interstitial cell infiltrate are the hallmarks of CTIN. Tubular changes are usually patchy, with areas of atrophic tubules alternating with dilated tubules with compensatory hypertrophy. The atrophic tubules have variably thickened and lamellated tubular basement membrane (TBM), simplified and flattened epithelia, and sometimes the lumen is filled with an eosinophilic periodic acid–Schiff (PAS) stain-positive material (Nadasdy and Sedmak, 2007). The interstitial fibrosis may be focal or diffuse and the extracellular matrix may contain various types of collagen, derived from interstitial fibroblasts and from tubular epithelial cells (Tang et al., 1994). A variable interstitial infiltrate may be seen, consisting of activated T lymphocytes, macrophages, and, more rarely, B lymphocytes, plasma cells, and eosinophils (Eknoyan and Truong, 1999). In sarcoidosis, certain forms of vasculitis, and infections with mycobacteria, fungi, and parasites, interstitial granulomas may develop (Joss et al., 2007).

Glomerular changes are often associated. Periglomerular fibrosis, thickening of the Bowman's capsule, focal segmental glomerulosclerosis, or ischaemic glomerular lesions can be found. Vascular changes are also present in patients with hypertension.

Immunofluorescence or immunohistochemistry can add useful information. Immunoglobulin and complement granular deposits may be seen along the TBM in some immune complex-mediated CTIN. Electron microscopy has limited diagnostic value; it shows the lamellated structure of the TBM and, possibly, the presence of granular aggregates at this level (Nadasdy and Sedmak, 2007).

Pathogenesis

In CTIN, various triggering factors activate tubulointerstitial inflammation and repair mechanisms, followed by fibrosis and progressive renal parenchyma destruction (López-Novoa et al., 2011). Major causes fall into genetic, immune/autoimmune, infective, and toxic categories (see Table 86.1).

Genetics including Autosomal Dominant Interstitial Kidney Disease

Some genetic causes are mentioned in Table 86.1. Genetic discoveries have emphasised how different genes may lead to similar or overlapping phenotypes and given rise to the concept of Autosomal Dominant Interstitial Kidney Disease (ADIKD) (see Chapter 318), which may be caused by mutations in a number of genes including *UMOD*, *REN1*, *HNF1B*, and *MUC1*. Some of these mutations add particular clinical features (e.g. typically gout, diabetes with *UMOD*, *HNF1B*), but others are characterized only by a clinically rather featureless CTIN.

Antigens

No nephritogenic antigens are known for human interstitial nephritis, not even the target of the rare condition of anti-tubular

basement membrane (anti-TBM) disease, in which an interstitial nephritis is accompanied by antibody fixation to the TBM, but not the GBM (Yoshioka et al., 2002; Remuzzi et al., 2008).

Tubular injury may lead to expression of nephritogenic antigens, either derived from tubular cells and TBM or from exogenous antigens processed by tubular cells (Remuzzi et al., 2008).

Exogenous and endogenous antigens processed by tubular epithelial cells may also trigger inflammatory reactions. Tubular cells may act as antigen-presenting cells in response to proinflammatory cytokines—including interferon (IFN)-gamma, interleukin (IL)-1, and tumour necrosis factor alpha (TNF-α)—may enhance the antigen-presenting capacity of tubular cells by increasing the expression of MHC class II molecules and of intercellular adhesion molecule (ICAM)-1 (Rubin-Kelley and Jevnikar, 1991).

Furthermore, tubular cells may have co-stimulatory effects on the interstitial T lymphocytes, by expressing CD40, ICAM-1, and vascular cell adhesion molecule (VCAM)-1 (Remuzzi et al., 2008).

Exposure of tubular epithelial cells to immune, chemical or biomechanical triggering factors leads to activation of NF-κB and downstream release of proinflammatory chemokines, cytokines and growth factors, such as plasminogen activator inhibitor (PAI)-1, IL-1, IL-6, monocyte chemoattractant protein-1 (MCP-1)/chemokine ligand 2 (CCL2), CCL5 (RANTES), and TNF-α (Tashiro et al., 2003; Gong et al., 2004).

Urinary tract obstruction

In obstructive uropathies, increased intratubular pressure and stretch activate tubular epithelial cells. As a consequence, transforming growth factor beta 1 (TGF-β1) is upregulated and induces epithelial-to-mesenchymal transition and tubulointerstitial fibrosis via tubular SMAD3 signalling. Other reactions to stretch have also been demonstrated *in vitro*, including activation of mitogen-activated protein kinases (MAPKs), with subsequent generation of arachidonic acid metabolites, caspase activation, and apoptosis. In addition, activation of epidermal growth factor receptor (EGFR) stimulates the production of inducible nitric oxide synthase (iNOS) via nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription (STAT)-3 (Broadbelt et al., 2009; Rohatgi and Flores, 2010).

Cell-mediated immunity

In experimental models, the initiation of the interstitial inflammatory process may vary, depending on the triggering agent and on the model design. Rag-2 null mice lack mature B and T lymphocytes and are protected from fibrosis induced by ureteric obstruction. Transfer of CD4+ T cells in these animals stimulates fibrogenesis (Tapmeier et al., 2010). Renal fibrosis after ischaemia-reperfusion injury also depends on persistent infiltration of activated and effector-memory T lymphocytes (Ascon et al., 2009). Most frequently, the CD4+, CD8+, and CD3+ cells are the effector lymphocytes infiltrating the tubulointerstitial compartment involved in renal fibrogenesis. For example, CD8+ cells are considered the predominant effector cells in anti-TBM disease, in Heymann nephritis, and in the murine doxorubicin nephrosis (Remuzzi et al., 2008; Zeisberg and Neilson, 2010).

In infection-induced CTIN, experimental unilateral renal artery stenosis, protein overload models, or reduction of renal mass, macrophages are initially the dominant infiltrating cells (Remuzzi et al., 2008). For example, in the protein overload model of kidney disease, macrophage infiltration is an early process, whereas helper and cytotoxic T cells become involved only about 2 weeks later. The helper T cells tend to decrease in number after 3 weeks, and cytotoxic T cells after 7 weeks. It seems that T-cell depletion using anti-T-cell monoclonal antibodies does not affect the macrophage infiltration (Eddy, 1989). In this model, it seems that macrophage infiltration is dependent on signalling molecules expressed by tubular cells, like MCP-1, VCAM-1, and ICAM-1. A strong correlation between the degree of macrophage infiltration and the extension of fibrosis has been demonstrated in CTIN. Furthermore, macrophage depletion was shown to prevent fibrogenesis in mice (Duffield et al., 2005; Nishida and Hamaoka, 2008).

Macrophages are versatile cells, which are able to modulate the expression of their surface receptor proteins and secreted cytokines in dependence of local stimuli and can fulfil various functions. Macrophages have been classified into M1 and M2. The M1 macrophages are attracted and activated by IFN-γ (synthesized mainly by T-helper (Th)-1 cells) and by lipopolysaccharides via toll-like receptor (TLR)-4 and are involved in fibrogenesis. Following their activation, these macrophages will stimulate iNOS activity and enhance their phagocytic capacity. Interleukin IL-l-α/β induces the release of IL-8 and CCL2, which further stimulate neutrophil and macrophage recruitment. The M2 macrophages are activated by interleukins IL-4, IL-13 and IL-10. The activation by IL-4 results in increased expression of scavenger receptor proteins (such as the mannose receptor, CD36) on the M2 cell. These cells have less phagocytic capacities, but higher macropinocytosis abilities, and their function seems to be the clearance of debris when the inflammatory process extinguishes (Ricardo et al., 2008).

Mast cells and dendritic cells have also been found in interstitial infiltrates of patients with CTIN. Dendritic cells are antigen-presenting cells, playing an essential part in antigen processing after tubulointerstitial injury. During proteasomal processing of proteins, they may create new antigenic targets. Mast cells are involved in lung and liver fibrosis and in the synthesis of proinflammatory cytokines and chemokines; however, mast cell-deficient mice were shown to develop severe renal interstitial fibrosis, associated with high levels of TGF-β (Zeisberg and Neilson, 2010). The roles of mast and dendritic cells in CTIN are still unclear.

Fibrosis

Interstitial fibrosis encompasses excess deposition of extracellular matrix components (collagen types I, III, V, VII, and XV, and fibronectin), components of the TBM (collagen IV and laminin), and *de novo* synthesized proteins (such as tenascin, fibronectin isoforms, and laminin chains), in parallel with a reduction of the renal parenchyma (López-Novoa et al., 2011).

Upregulation of several cytokines, chemokines, and growth factors during the inflammatory response is the driving force for the recruitment and activation of fibroblasts. Several Th-2 cytokines (IL-4, IL-5, IL-13, and IL-2) play a very important role in this process, with IL-13 being considered the dominant effector (Blease et al., 2001). These Th-2 cytokines cooperate with TGF-β to induce fibrosis. On the other hand, Th-1-associated cytokines, IFN-γ and IL-12, as well as IL-10 (also known as human cytokine synthesis inhibitory factor) are fibrosis inhibitors (Wynn, 2008). TGF-β inhibits the expression of metalloproteases (MMPs) and

stimulates PAI-1, an MMP inhibitor (Roberts et al., 1992). A number of other molecules in the renal interstitium, including TGF-α, EGF, platelet-derived growth factor (PDGF), TNF-α, IL-1, IL-6, oncostatin M, endotoxin, and thrombin may enhance the expression of tissue inhibitor of metalloprotease (TIMP)-1 (Eddy, 2000). Overexpression of MMP-2 induces fibrosis (Cheng et al., 2006), by degradation of TBM and promotion of epithelial-mesenchymal transition. Aberrant matrix synthesis by collagen remodelling cannot explain alone the reduction of kidney size in patients with CTIN. Most probably, the collapse of the kidney parenchyma also contributes to this process (Hewitson, 2009).

Myofibroblasts (activated fibroblasts) synthesize extracellular matrix components and also remodel the matrix to increase its density via β-1-integrins (Kelynack et al., 1999). Interstitial myofibroblasts may have the origin in the perivascular area or may result from local cell proliferation, circulating mesenchymal cells, tubular epithelial cells (by epithelial-to-mesenchymal transition) or endothelial cells (by endothelial-to-mesenchymal transition). In a unilateral ureteral obstruction model of CTIN, around 38% of interstitial fibroblasts originated from epithelial-to-mesenchymal transition, 9% from circulating precursors, and 53% from local proliferation (Hewitson, 2009). The differentiation and proliferation of myofibroblasts, as well as collagen synthesis, is stimulated by TGF-β-1 and PDGF, which are released by tubular and interstitial cells and by infiltrating inflammatory cells (Boor et al., 2010).

Ischaemia

An important role in the development of interstitial fibrosis is played by chronic ischaemia. Elevated synthesis of angiotensin II and decreased production of nitric oxide may contribute to ischaemia, by inducing vasoconstriction (Nangaku, 2006). In the early stages of CTIN, the renal vasculature also seems to be damaged by apoptosis. The developing interstitial fibrosis, the endothelial-to-mesenchymal transition (with loss of endothelial cells), as well as the downregulation of vascular endothelial growth factor (VEGF), all contribute to the rarefaction of peritubular microvessels and ensuing interstitial hypoxia. With the expansion of the interstitial matrix, the diffusion distance of oxygen from the peritubular vessels to the tubular epithelia increases, thus further impairing the oxygen supply (Remuzzi et al., 2008). In its turn, hypoxia contributes to the progression of tubulointerstitial fibrosis by further stimulating the epithelial-to-mesenchymal transition and promoting matrix components synthesis by fibroblasts (Higgins et al., 2007). On the other hand, the endogenous hepatocyte growth factor (HGF) can decrease TGF-β1 expression and prevent epithelial-to-mesenchymal transition (Mizuno et al., 2001).

Therapy

Therapeutic intervention in CTIN has the following objectives and methods:

1. Stopping the action of triggering agents—for example, early discontinuation of nephrotoxic drugs and exposure to nephrotoxins, treating pyelonephritis with antibiotics, or surgical removal of urinary tract obstructions
2. Specific treatment of underlying systemic autoimmune, haematological, and metabolic diseases
3. Reducing the progression of interstitial inflammation and fibrosis.

Angiotensin II exerts profibrotic effects in the heart, liver, and kidney, by directly inducing NADPH oxidase activity and synthesis of reactive oxygen species, by increasing the expression of TGF-β1, and by triggering fibroblast proliferation and activation. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have been shown to reduce cardiac, hepatic, and renal fibrogenesis and to slow down the progression of CKD, though not specifically in ATIN (Wynn, 2008). Other interventions, such as blood pressure control, reduction of proteinuria, and control of blood glucose and lipids are recommended (Hewitson, 2009).

Regression of established fibrosis by stimulating collagen degradation is a possible therapeutic approach for CTIN. Pirfenidone, a pyridone compound, may reduce fibrosis by inhibiting fibroblast growth factor (FGF), EGF, PDGF, and TGF-β1. In 2011, the European Commission approved the use of pirfenidone in Europe for idiopathic pulmonary fibrosis. In some experimental studies of kidney disease (anti-Thy-1 glomerulonephritis and the ureteral obstruction model), pirfenidone has produced interesting results (Shimizu et al., 1997, 1998). More recent clinical studies tend to confirm its efficacy in patients with focal segmental glomerulosclerosis (Cho et al., 2007) and diabetic nephropathy (Sharma et al., 2011).

Encouraging results have also been obtained in experimental models with relaxin, a naturally occurring hormone (Hewitson et al., 2010). It seems that relaxin signalling, by inhibiting SMAD2 phosphorylation, can interfere with TGF-β1-mediated renal myofibroblast differentiation and collagen production (Mookerjee et al., 2009).

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CHAPTER 87

Drug-induced chronic tubulointerstitial nephritis

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Introduction

Several drugs can cause chronic tubulointerstitial nephritis (CTIN), including analgesics, lithium, antineoplastic chemotherapeutic agents (cisplatin, nitrosoureas), and immunosuppressive drugs (ciclosporin, tacrolimus).

Many of the drugs that cause acute tubulointerstitial nephritis (ATIN) may also induce CTIN. Patients who develop the acute form of drug-induced TIN generally recover fully (Fig. 87.1). A few, however, do not recover and progress to CTIN; such is the case of cisplatin toxicity. On the other hand, drugs like analgesics, lithium, and nitrosourea, typically induce CTIN only after prolonged exposure (several months or years); in such cases, the renal disease has an insidious onset and a slow course.

There are several ways in which injury to the tubulointerstitium can occur, and these can involve either immune-mediated or non-immune-mediated (direct toxicity) mechanisms. The diagnosis largely depends on the history of exposure to such nephrotoxic drugs. The recognition of a potential association between a patient's renal disease and the previous administration of certain drugs is crucial, because, unlike in other forms of renal disease, the progression of these nephropathies can be prevented and even reversed, by simply avoiding additional exposure.

The functional abnormalities depend on the site of the nephron that is mainly involved, which in its turn depends on the offending drug; for example, proximal tubular dysfunction is associated with cidofovir toxicity, distal tubular dysfunction (with salt wasting, acidosis, and hyperkalaemia) is commonly seen in lithium nephropathy, whereas medullary injury with impaired urine concentrating ability is characteristic of analgesic nephropathy. Renal biopsy can confirm the diagnosis.

Although renal biopsy is indispensable for assessing the severity of pathologic lesions in drug-induced CTIN, it is not acceptable in some cases and cannot be performed serially because of its invasive nature. In those cases, urinary monocyte chemotactic peptide-1 (MCP-1) levels correlated with and were predictive of the severity of acute lesions in drug-induced TIN, whereas neutrophil gelatinase-associated lipocalin (NGAL) and α1-microglobulin levels showed the highest correlation coefficient with tubular atrophy (Wu et al., 2010).

The lack of effective therapies for advanced CTIN, in general, highlights the importance of making an early diagnosis, when the progression of the disease can effectively be stopped or even reversed, essentially by avoiding any further exposure of the patient to the offending drug.

Analgesic nephropathy

In the 1970s and 1980s, analgesic nephropathy was the cause of end-stage renal disease (ESRD) in up to 20% of patients on dialysis in some countries (including Australia and Belgium), but it has now become a relatively rare condition, following market withdrawal of phenacetin in most countries (Table 87.1). Although initially thought to be exclusively associated with phenacetin-containing combinations, analgesic nephropathy can also be caused by other drugs, including acetaminophen, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) (De Broe and Elseviers, 2009).

For half a century, a large number of epidemiologic studies have linked prolonged and excessive consumption of analgesic mixtures to a renal disease characterized by papillary necrosis and CTIN (Sandler et al., 1989; Perneger et al., 1994; Elseviers and De Broe, 1995, Elseviers et al., 1995). The incidence varies greatly from study to study, depending primarily on the region or country where the investigation was performed. In Europe, the percentage of analgesic nephropathy among patients with ESRD undergoing long-term dialysis varies widely, from only 0.1% in Ireland, Norway, Poland, and Hungary to 18.1% in Switzerland (Elseviers and De Broe, 1993). According to the Analgesic Nephropathy Network of Europe study, the average European incidence of analgesic nephropathy among patients who were started on renal replacement therapy in 1991 to 1992 was 6.4% (Elseviers et al., 1995). In Australia and Canada, 11% and 2.5% incidence rates have been reported, respectively (Gault and Wilson, 1978; Kincaid-Smith, 1990). In the United States, 1.7–10% of the ESRD cases are thought to be the result of analgesic nephropathy in various regions (Gonwa et al., 1981; Perneger et al., 1994).These large geographic differences may be explained by differences in local habits, psychosocial factors, availability of these drugs, and probably also the frequency of correct diagnosis and reporting.

Analgesic nephropathy occurs in about 4 out of 100,000 people with long-term consumption of large amounts of analgesics, most often combinations of acetaminophen (paracetamol), phenacetin, aspirin, and NSAIDs. The nephrotoxicity of phenacetin is likely to be due to its major metabolite, paracetamol. Aspirin achieves higher medullary and cortical concentrations than paracetamol (Elseviers et al., 1995). The risk of developing renal disease is dependent on

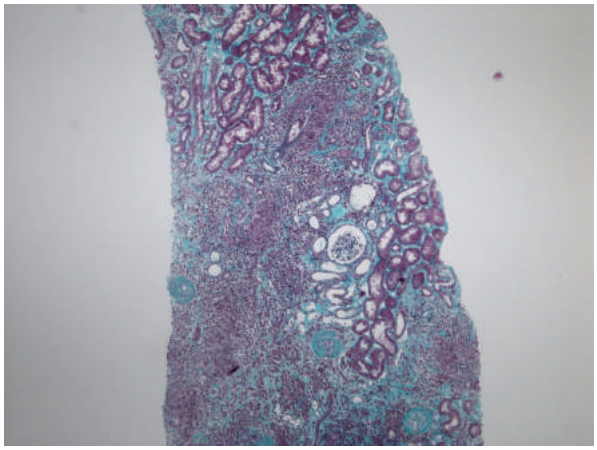

Fig. 87.1 Drug-induced TIN with marked chronicity. The tubules appear shrunken and atrophic, and are separated by extensive interstitial fibrosis. (TM; magnification ×400.)

the frequency and duration of analgesic abuse. In epidemiologic studies, patients with analgesic nephropathy used analgesics virtually every day for several years, so that the cumulative amount of individual analgesic intake was > 1–3 kg. A total dose of at least 1 kg of phenacetin (i.e. 1 g/day for 3 years) is necessary to cause analgesic nephropathy (Elseviers et al., 1995). This usually occurs as a result of self-medication, for some type of chronic pain. The prospective controlled longitudinal epidemiological studies reported by Dubach et al. (1975, 1978) clearly demonstrated a significant association between analgesic consumption and renal disease. Nevertheless, in only a small number of analgesic abusers does nephropathy develop, and progression of chronic kidney disease (CKD) may be stopped with discontinuation of analgesics. Nowadays, the decrease in availability of phenacetin-containing and other analgesic mixtures has led to a marked reduction in the number of new cases of analgesic nephropathy.

The clinical manifestations associated with analgesic abuse are well recognized and have been reviewed extensively (Nanra, 1993). Analgesic nephropathy is most common in women (85% of cases) in the fourth and fifth decades of life, who have a history of low back pain, migraine headaches, or other chronic musculoskeletal pain. Analgesic nephropathy may show a familial clustering and the increased prevalence of human leucocyte antigen (HLA)-B12 in patients with this disease suggests a possible role for some genetic factor(s) (Nanra, 1993).

Table 87.1 Clinical findings in analgesic nephropathy

Finding	Frequency
Headache	35–100%
Pyuria	50–100%
Anaemia	60–90%
Hypertension	15–70%
Gastrointestinal symptoms	40–60%
Urinary tract infection	30–60%

From Murray and Goldberg (1978).

Analgesic nephropathy is often asymptomatic. The clinical manifestations are non-specific and may include slowly progressive CKD, sterile pyuria, mild proteinuria, and haematuria (Table 87.1). Virtually all patients with analgesic nephropathy have a urine concentrating defect, and 25% also have an acidifying defect; however, frank renal tubular acidosis is seen in only 10% of cases, when the glomerular filtration rate (GFR) is significantly reduced. These tubular function abnormalities may be associated with clinical manifestations and complications like nocturia, muscle cramps, renal stones, medullary nephrocalcinosis, and renal osteodystrophy. Clinical gout occurs in 4.5% of patients with normal renal function and in 26.5% of those with low GFR. Urinary tract infections are a late complication, which occurs in 30–60%, and may be recurrent (Murray and Goldberg, 1978). Haematuria is found in up to 35% of patients (Nanra, 1980) and may be related to urinary tract infections, stones, malignant hypertension, associated glomerular disease, or uroepithelial tumours. In some patients, episodes of papillary necrosis may occur, manifested with gross haematuria and flank pain, occasionally accompanied by obstruction and infection (Griffin et al., 1995). Glomerular disease may be associated with CTIN in approximately 60% of patients with proteinuria > 3.5–5.0 g per day.

Fifteen to 70% of patients develop hypertension, sometimes secondary to renal artery stenosis. Malignant hypertension has been observed in 6.9% of cases. Urinary tract obstruction is a serious complication and may be due to a fragment of necrotic or calcified papilla, a stone, a transitional cell pelvic or ureteral tumour, or a postinflammatory ureteral stricture. Concomitant urinary tract infection may lead to septicaemia or pyonephrosis, potentially fatal complications (Nanra, 1993).

The diagnosis of analgesic nephropathy should not be solely based on renal biopsy. Renal imaging techniques, such as sonography and particularly computed tomography, are the best methods for diagnosis in the appropriate clinical context (Elseviers et al., 1995). The Analgesic Nephropathy Network of Europe study showed that shrinkage of renal mass, bumpy renal contours and the presence of papillary calcifications are the most useful criteria in diagnosing analgesic nephropathy, with a sensitivity of 96%, 57%, and 85%, respectively, and a specificity of 37%, 92%, and 93%, respectively. The combination of these three criteria resulted in a sensitivity of 85% and a specificity of 93% (Elseviers et al., 1995; De Broe and Elseviers, 1998). Radiocontrast examinations may be helpful in the diagnosis of papillary necrosis.

The pathological renal changes in analgesic nephropathy have been well documented. The primary lesion is renal papillary necrosis; the CTIN lesions are secondary, resulting from obstruction. Renal papillary necrosis extending into the medulla may involve several papillae (Nanra, 1993; Griffin et al., 1995). Gross appearance and early light microscopic findings are most distinctive of this entity. The kidneys are small and shrunken, with irregular contours and papillary calcifications. On histology, the capillaries beneath the urothelium in the renal pelvis exhibit basement membrane thickening and calcification. This vascular injury leads to papillary ischaemia and eventual necrosis. Necrotic tissue may slough off or become calcified. There is compensatory hypertrophy of the columns of Bertin, while the suprapapillary cortex undergoes atrophy.

Non-renal manifestations of the analgesic syndrome include gastrointestinal manifestations (peptic ulcer in 40%), haematological

abnormalities (anaemia in 60–90%, which may be haemolytic, splenomegaly in 10%), headache (80%), psychiatric disorders (90%), cardiovascular complications, premature ageing, skin hyperpigmentation, and gonadal and pregnancy-related manifestations.

Malignancy may occur after 20 years of analgesic abuse, on average, in about 10% of patients. However, it can sometimes occur even long after cessation of analgesic consumption (Bengtsson et al., 1978). The major analgesic-associated tumour is transitional cell carcinoma of the uroepithelium; however, hypernephroma, sarcoma, and chorioepithelioma have also been reported (Bengtsson et al., 1978). The tumour tends to be multifocal and, in 5% of cases, bilateral simultaneous renal pelvic carcinomas have been described (Bengtsson et al., 1978). In one study in patients with analgesic-associated tumours, the mean intake of phenacetin was 9.1 kg, the mean drug exposure time was 17 years, and the mean induction time was 21 years (Bengtsson et al., 1978).

The diagnosis of analgesic nephropathy obviously relies on the history of heavy analgesic abuse. Computed tomography may reveal reduced renal size, 'bumpy' renal contours, as well as bilateral microcalcifications at the papillary tips and ring shadows, typical of papillary necrosis. These findings are usually lacking or less prominent in other forms of CTIN (Mackinnon et al., 2003; Pintér et al., 2004).

The exact pathogenesis of the toxicity of analgesic compounds and the primary target of the toxic reactions are unknown. Inhibition of prostaglandin synthesis and immunologic reactions are unlikely causes (Mihatsch and Zollinger, 1993). It is possible that metabolites of phenacetin, aspirin, or paracetamol, under the influence of cytochrome P450 mono-oxygenase, bind covalently to cellular proteins and cause toxic damage (Nanra, 1993).

Long-term follow-up studies have shown that the main complications of long-term analgesic abuse are progression to ESRD, accelerated atherosclerosis, and increased incidence of uroepithelial carcinomas. In a study of 323 consecutive patients with analgesic nephropathy followed for up to 66 months, the renal function improved in 17%, remained stable in 50%, and worsened in 23% of cases; 12% presented with ESRD and either died or required initiation of dialysis within 6 months (Nanra, 1980). Nanra (1980) found that patients with analgesic nephropathy and ESRD, treated either with dialysis or with renal transplantation had worse outcomes in comparison with patients with glomerulonephritis, experiencing a significantly higher mortality rate over a 6-year period (50.8% vs 15.8%).

There is no specific therapy for analgesic nephropathy. Treatment is supportive and includes discontinuation of analgesic use and abundant fluid intake. The decline in GFR can be expected to progress if drug consumption is continued. On the other hand, the renal function can stabilize or even improve in many patients if analgesic abuse is stopped in time (De Broe and Elseviers, 1998).

Lithium nephropathy

Lithium is commonly used in the treatment of bipolar disorder. It may induce acute kidney injury, as well as CKD. Possible renal complications of lithium treatment are shown in Box 87.1. The major risk factors for lithium nephrotoxicity appear to be the duration of drug exposure and the cumulative dose (Presne et al., 2003); other risk factors include episodes of acute intoxication, older age, comorbidity (such as hypertension, diabetes mellitus, hyperparathyroidism, and hyperuricaemia), and concomitant use of other antipsychotic medications.

Box 87.1 Lithium nephrotoxicity

- Nephrogenic diabetes insipidus and impairment of urinary concentration
- Incomplete distal renal tubular acidosis
- Chronic tubulointerstitial nephropathy
- Hypercalcaemia
- Distal tubular microcysts
- Acute kidney injury
- Glomerulonephritis.

The first suggestion that progressive impairment of GFR may occur in lithium-treated patients came from Hestbech et al. (1977). Long-term lithium use is associated with CKD in 15–20% of patients, who develop a slow decline in GFR (Boton et al., 1987; Bendz et al., 1994; Presne et al., 2003) of about 3 mL/min per year and an average course to ESRD of 20 years (Presne et al., 2003). The degree of interstitial fibrosis on renal biopsy may be directly related to the duration of therapy and the cumulative dose of lithium (Presne et al., 2003). Among patients with affective disorders, Walker et al. (1982) found that those treated with lithium had higher serum creatinine and β2-microglobulin and lower ^{51}Cr-EDTA clearance, compared to those not treated with lithium. However, they failed to show any difference in renal histology between the two groups, except for microcyst formation in the lithium-treated patients. In rats, prolonged lithium administration at high doses was associated with an increase in the size of the tubules and of the kidneys (Kling et al., 1984), but no evidence of nephron loss or progressive interstitial lesions. Rabbits treated with lithium chloride (50–250 mmol/kg of food, over 12 months) developed significant interstitial fibrosis, tubular atrophy, glomerular sclerosis, and cystic tubular lesions. Microcysts have been demonstrated on magnetic resonance imaging and ultrasonographic studies (Farres et al., 2003) and located histologically in the distal and collecting tubules.

Nephrogenic diabetes insipidus (with polyuria, polydipsia, and impaired renal concentrating capacity) is the most usual renal complication of maintenance lithium therapy (Walker, 1993). This disorder results from downregulation of aquaporin-2 water channels in the collecting duct (Christensen et al., 2004) and occurs in up to 50% of patients receiving lithium therapy (Boton et al., 1987). Impaired concentrating ability is usually reversible after lithium discontinuation, although it may persist for as long as 12–18 months (Rabin et al., 1979). CTIN may develop in a small subset of patients who have had frequent episodes of acute lithium toxicity, with high serum drug levels (Hestbech et al., 1977; Bucht et al., 1980), and it is probably the result of repeated tubulointerstitial injury and repair. Cases of lithium-induced nephrotic syndrome have rarely been reported (Tam et al., 1996; Markowitz et al., 2000; Presne et al., 2003). A study from the Columbia University showed that 25% of patients who underwent kidney biopsy and were diagnosed with lithium nephropathy also had nephrotic syndrome (Markowitz et al., 2000); these patients had a histologic pattern of focal segmental glomerulosclerosis. The nephrotic syndrome could be the

result of lithium interaction with anionic sites on the glomerular basement membrane (Tam et al., 1996).

Lithium nephropathy appears to be a slowly progressive disease, unless lithium administration is stopped early enough. Progression to ESRD may occur even after lithium discontinuation in patients with an initial serum creatinine > 2.5 mg/dL (221 μmol/L). Additionally, systemic and intraglomerular hypertension may induce secondary glomerulosclerosis (Hansen et al., 1979; Markowitz et al., 2000), thus contributing to the progression of CKD. One study showed that the prevalence of lithium nephropathy is 0.2% in ESRD patients on maintenance dialysis (Presne et al., 2003). The authors calculated that the duration of lithium intake until ESRD was 19.8 years and the estimated cumulative lithium dose was 5231 g per patient.

Annual monitoring of serum sodium, creatinine, and GFR is recommended in patients receiving lithium therapy. Polyuria and polydipsia usually resolve rapidly following drug withdrawal. However, since lithium is so clearly beneficial in most treated psychiatric patients, polyuria is often considered an acceptable side effect and does not prompt the discontinuation of therapy. On the other hand, it is more difficult to decide appropriate management in a patient who has been on lithium for many years and in whom there is evidence of progressive glomerular and tubular dysfunction. Close monitoring of serum lithium is essential, because nephrotoxicity is usually dose-dependent; maintaining levels between 0.4 and 0.8 mmol/L is recommended. Since renal handling of lithium resembles that of sodium, the elevation of its serum levels usually occurs in states of volume depletion, renal insufficiency, and concomitant therapy with diuretics and/or NSAIDs.

Amiloride may be used in the treatment of lithium-associated polyuria, since it prevents lithium entry into the distal tubule. Caffeic acid phenethyl ester (CAPE), a known component of honeybee propolis, can be protective against oxidative stress in ischaemia-reperfusion and toxic renal injuries; used in experimental rat models, CAPE was shown to prevent lithium-induced tubular damage (Oktem et al., 2005). *N*-acetylcysteine, a drug that is effective in preventing radiocontrast-induced nephropathy, was also capable to reduce lithium-induced tubular injury in Sprague–Dawley rats (Efrati et al., 2005).

Calcineurin inhibitor-induced nephropathy

Although indispensable in the management of solid organ transplantation, calcineurin inhibitors ciclosporin and tacrolimus can cause acute and chronic nephrotoxicity. The mechanism appears to be largely dependent on the potent vasoconstrictive effects of these drugs. CTIN induced by ciclosporin or tacrolimus is common among patients receiving kidney, heart, liver, and pancreas transplants. In renal transplant recipients, ciclosporin- and tacrolimus-induced CTIN is similar to chronic allograft nephropathy. Most of these patients have a slow course, with mild impairment of renal function remaining stable for a long time. On the other hand, up to 10% of heart transplant recipients develop rapidly progressive renal insufficiency and eventually require dialysis. This condition is rare in bone marrow transplant recipients, because such patients receive these immunosuppressive drugs for a short time and generally at lower doses.

Patients treated with calcineurin inhibitors are at high risk of developing renal injury (Burdmann et al., 2003), manifested either as acute azotaemia, which is largely reversible after dose reduction, or as chronic progressive renal disease, usually irreversible (Kopp and Klotman, 1990; de Mattos et al., 2000, Naesens et al., 2009). Chronic nephrotoxicity typically occurs after 6–12 months of therapy. A similar pattern of renal injury is seen with the use of both ciclosporin and tacrolimus, suggesting a drug class effect. However, tacrolimus has less renal toxicity at lower doses, without compromising overall outcomes (Ekberg et al., 2007; Shihab et al., 2008).

The pathologic features of calcineurin inhibitors-induced chronic nephropathy include vascular changes (arteriolopathy), associated with patchy (striped) interstitial fibrosis, tubular atrophy, and glomerular sclerosis (Burdmann et al., 2003). Ciclosporin arteriolopathy is characterized by thickening of the arteriolar wall, infarction of myocytes, protein deposits in the vessel wall, and hyalinosis. Such vascular changes compromise the blood supply to the tubulointerstitium, possibly setting the stage for the development of CTIN. Ciclosporin is directly toxic to the tubular epithelium, where it induces epithelial vacuolization and swelling of mitochondria, and it also promotes the expression of mRNA for type I collagen, which may contribute to renal fibrosis. Although the pathogenesis of such lesions is clearly multifactorial, a dominant factor is ciclosporin-induced vasoconstriction, an effect that is directed largely to the afferent arteriole and one that reduces the GFR and renal blood flow. Tubular blood supply is compromised as postglomerular blood flow is reduced, thereby incurring tubular ischaemia.

The factors responsible for chronic calcineurin inhibitor nephrotoxicity are not well understood. The development of interstitial fibrosis is associated with increased expression of osteopontin, a potent macrophage chemoattractant secreted by the tubular epithelial cells (Pichler et al., 1995), chemokines, a class of cytokines that are strong chemoattractants for a variety of haematopoietic cells (Benigni et al., 1999), and transforming growth factor-beta (TGF-β), a powerful stimulator of extracellular matrix production (Shihab et al., 1997; Islam et al., 2001). TGF-β appears to be induced in part by decreased secretion of nitric oxide (Shihab et al., 2000), as well as by increased local concentrations of angiotensin II, possibly explaining some of the beneficial effects observed with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (Burdmann et al., 1995; Shihab et al., 1997).

Ciclosporin is a substrate for the transmembrane pump P-glycoprotein. There is some experimental evidence that decreased expression of this pump may contribute to increased ciclosporin levels, leading to nephrotoxicity (Del Moral et al., 1998; Koziolek et al., 2001), as in several polymorphisms of its gene (Hauser et al., 2005). This suggests that underlying genetic factors that increase ciclosporin concentrations in the kidney may play a role in chronic nephrotoxicity. Short-term studies suggest that low doses of ciclosporin may not lead to renal dysfunction (Deray et al., 1992; Ekberg et al., 2007), as shown in the CAESAR study (Ekberg et al., 2007). The replacement of ciclosporin with non-nephrotoxic immunosuppressive agents may improve renal dysfunction in patients with ciclosporin-induced nephrotoxicity.

Several metabolic abnormalities are recognized as complications of calcineurin inhibitors nephrotoxicity, including hyperkalaemic (type IV) renal tubular acidosis, renal magnesium wasting, and hyperuricaemia by decreased urate clearance, which can be severe enough to provoke gout attacks and tophi. Both ciclosporin and tacrolimus frequently cause hypertension. Sometimes, thrombotic

microangiopathy may also occur, as a result of the vasoconstrictive, salt-retaining, and nephrotoxic effects of these drugs, and can further contribute to the renal disease.

Many agents have been tried aiming to reduce the nephrotoxic effects of calcineurin inhibitors, including fish oil, calcium channel blockers, thromboxane synthesis inhibitors, and pentoxifylline; however, none of these has proved to be clearly effective. Animal and human studies suggest that concurrent administration of calcium channel blockers may be protective against ciclosporin nephrotoxicity, probably by counteracting the renal vasoconstriction (Palmer et al., 1991); on the other hand, some calcium-channel blockers (such as verapamil, diltiazem, and nicardipine) may cause elevations in plasma ciclosporin concentrations. ACEIs seem to be less effective and carry the risk of hyperkalaemia in patients who may have ciclosporin-induced type IV renal tubular acidosis.

The best way of minimizing calcineurin inhibitors nephrotoxicity is to reduce the doses and target trough levels of these drugs. Completely stopping their administration or switching to other immunosuppressive agents (like rapamycin), especially in patients with more advanced renal disease, should also be considered.

Aminosalicylates

The association between the use of 5-aminosalicylic acid (5-ASA) and the development of CTIN in patients with inflammatory bowel disease (IBD) gained recognition in the 1990s, after the publication of several case reports. The adverse effects of 5-aminosalicylates are similar and include the common occurrence of fever and rash in > 10% of patients. Hypersensitivity responses have been described in multiple organ systems, most commonly the kidney (Moss and Peppercorn, 2007). Aminosalicylate-associated nephrotoxicity most frequently takes the form of an indolent, slowly progressive CTIN (Corrigan et al., 2000; Arend and Springate 2004).

The disease is more prevalent in males, with a male/female ratio of 5.3/1. The age of reported cases ranged from 14 to 45 years. There is no relationship between the duration of 5-ASA treatment and the risk of renal disease (Riley et al., 1992; Ransford and Langman, 2002). In contrast with analgesic nephropathy, where renal lesions were only observed after several years of drug abuse, CTIN associated with 5-ASA may occur during the first year of treatment in 50% of cases (World et al., 1996; Corrigan and Stevens, 2000; Cunliffe, 2002). The incidence of TIN among patients taking 5-aminosalicylates is between 1 in 200 to 1 in 500 patients (World et al. 1996; Arend and Springate, 2004; Gisbert et al., 2007), although some studies suggest a much lower rate of occurrence. Elseviers et al. prospectively evaluated 1529 patients with IBD, followed up to 1 year, in 27 European centres. Although renal impairment occurred in 2.2% of patients, there was no relation with 5-ASA use. In fact, a possible association with 5-ASA had an estimated prevalence of 1.3–3.3 cases per 1000 patients (Elseviers et al., 2004). The incidence of nephrotoxicity in IBD patients taking 5-ASA therapy seems to be < 0.5%, as shown by pooled data from 2671 patients receiving this treatment for a total of 3070 years of follow-up, and in whom serum creatinine or creatinine clearance were measured regularly (Gisbert et al., 2007). Based on data from the UK General Practice Research Database (Van Staa et al., 2004), mesalazine and sulfasalazine had comparable risks of nephrotoxicity in adult patients with IBD (0.17 vs 0.29 cases per 100 person-years, respectively).

It has been demonstrated that high pharmacological doses of 5-ASA induced necroses of proximal convoluted tubules and papillary necroses, similarly to salicylates—not surprisingly, as the molecular structure of 5-ASA is very close to that of salicylic acid, phenacetin, and acetaminophen (Bilyard et al., 1990; Schreiber et al., 1997).

Drug withdrawal leads to restoration of renal function in 60% of cases, if the diagnosis is made within 10 months from initiation of treatment (Gisbert et al., 2007), and renal outcome depends on the degree of renal damage at diagnosis (Gisbert et al., 2007).

Serial monitoring of serum creatinine and urinalysis is recommended for all patients on 5-aminosalicylate therapy: before initiation of treatment, each month for the first 3 months of treatment, quarterly for the remainder of the first year, and annually (World et al. 1996; Corrigan et al., 2000) or bi-annually thereafter (Arend and Springate, 2004).

Antineoplastic agents

Cisplatin is an agent used in the treatment of various solid tumours. The kidney is its major route of excretion. The drug and its metabolites are highly concentrated in the renal cortex, thereby predisposing to nephrotoxicity. Acute toxicity is usually reversible and may in part be derived from the vasoconstrictive effects of cisplatin. Hypomagnesaemia is one of the most serious side effects of the drug and could be life-threatening; it develops in over 70% of patients and persists for months in 50% of these, even after the drug is stopped. Toxicity is mitigated or prevented by adequate hydration, diuresis, and slow intravenous infusion of the drug.

Nitrosoureas, carmustine (BCNU), lomustine (CCNU), and semustine (methyl-CCNU) are used in the treatment of malignant melanoma, brain tumours, and lymphomas. Dose-dependent nephrotoxicity may be insidious and occurs months after cessation of therapy. ESRD can occur in up to 50% patients after receiving 1.2–1.5 g/m^2 of semustine.

Others

Cidofovir, a monophosphate nucleotide analogue of deoxycytidine, has been employed almost exclusively to treat cytomegalovirus retinitis in patients with the acquired immunodeficiency syndrome (AIDS) and is also being increasingly used as a therapeutic option against other viral infections. The most important adverse effect of cidofovir is dose-dependent nephrotoxicity. Approximately 50% of patients receiving cidofovir in clinical trials developed proteinuria, an increase in serum creatinine by at least 0.4 mg/dL or a decrease in GFR below 55 mL/min (Gilead Sciences, Inc., 1996). Renal dysfunction is usually reversible after discontinuation of the drug. However, a few cases of ESRD associated with the use of cidofovir in HIV-positive individuals have been reported (Vandercam et al., 1999; Meier et al., 2002). Topical or intralesional use of cidofovir may also be rarely associated with renal dysfunction (Bienvenu et al., 2002; Naiman et al., 2004).

Propriothiouracil has been widely used to treat hyperthyroidism since the 1940s. Major side effects are agranulocytosis, hepatitis, vasculitis, and lupus-like syndrome, whereas kidney impairment is uncommon. Only a few cases of CTIN have been reported, with diffuse interstitial collagen accumulation (Nakahama et al., 1999).

Conclusion

Drug-induced CTIN is probably an underestimated cause of CKD. At the same time, it is often preventable and easily treatable, if diagnosed early. Physicians should be familiar with the wide range of medications potentially harmful to the kidneys, and be aware of the damage they may induce. The incidence of drug nephrotoxicity is only expected to rise, in parallel with the worldwide ageing population. This is due to frequent comorbidities, polypharmacy, and age-related structural renal changes. The diagnosis of drug-induced CTIN requires vigilance and knowledge of drug pharmacokinetics and pharmacodynamics; it is a multidisciplinary task, involving clinicians, pharmacists, and clinical chemists.

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CHAPTER 88

Heavy metal-induced tubulointerstitial nephritis

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Introduction

Humans are exposed to various potentially toxic agents in their living and occupational environments. Some of these agents are metals, which may enter the human body through oral, inhalation, or transdermal routes, and may exert effects on all organ systems (Soderland et al., 2010). Several well-known, as well as lesser-known associations exist between exposure to heavy metals and chronic kidney disease (CKD). Extremely high environmental and occupational exposure to metals is rarely seen nowadays. Nevertheless, exposure to substantially lower levels is still regarded as an important cause of acute kidney injury (AKI) and CKD, particularly in the developing world. During the last years, there has been an increasing interest in the potential synergistic toxic effect of low exposure to multiple metals (Hambach et al., 2013).

Due to its important blood flow, large endothelial surface, high metabolic activity through multiple enzyme systems, the high concentration of filtered chemicals in tubular fluid and in tubular cells, and the biotransformation of chemicals and protein unbinding, the kidney is highly vulnerable to the effects of toxic agents. Exposure to heavy metals may occur at the workplace, but industrial contamination of ground water, as well as inhalation of polluted air, and consumption of drugs or contaminated food are also recognized as important sources of heavy metals intoxication, which may induce CKD also in individuals without occupational exposure (Soderland et al., 2010). In this chapter, the renal effects of heavy metals, including lead, cadmium, arsenic, chromium, mercury, and uranium, are discussed in general, with a special focus on tubulointerstitial nephritis (TIN).

Lead

The toxic effects of lead have been known for more than 2000 years, and the first reported case of nephrotoxicity associated with lead dates back to the nineteenth century. Environmental exposure may occur via lead paint and lead pipes, which may still be present in older houses, contamination of food during processing, indoor firing ranges, cigarette smoke, and contaminated air and soil near lead-processing industries. Occupational exposure occurs during battery manufacturing, welding, and use of lead solder. At present, exposure to extremely high concentrations of lead is less common than it once was, due to improved industrial management and the fact that this metal is no longer added to fuel and paint. Nevertheless, increased exposure to lead is still a public health problem in some developing countries in Africa, Asia, and Latin America, due to contaminated water and soil resulting from poor industrial preventive measures (Sabath and Robles-Osorio, 2012).

Lead nephropathy typically occurs when the blood lead concentration exceeds 400 micrograms/L. The disease presents with minimal proteinuria, a bland urinary sediment, hyperuricaemia, and often hypertension. The kidneys have a granular surface and reduced size. Renal biopsies show tubular atrophy and interstitial fibrosis, without cellular infiltration. In the proximal tubules, acid-fast nuclear inclusion bodies, consisting of a lead-binding protein complex, can be detected (Moore et al., 1973; Goyer, 1989; Evans and Elinder, 2011).

Renal effects, however, may also be seen at much lower levels. A study, in which 4813 individuals with or without high blood pressure were included, having mean blood lead levels of 42 micrograms/L and 33 micrograms/L, respectively, revealed that the prevalence of elevated serum creatinine was 11.5% and 1.8%, whilst it was seen in 10.0% and 1.1% of the subjects with CKD, respectively. These data made the authors conclude that low-level exposure to lead is associated with CKD, particularly in patients with hypertension (Muntner et al., 2003). Results from follow-up studies carried out in Taiwan by Lin et al. indicated that individuals with chronic nephritis and a glomerular filtration rate (GFR) < 60 mL/minute and low-to-moderate exposure to lead (urinary lead excretion 80–600 micrograms/24 hours post ethylenediaminetetraacetic acid (EDTA) administration) experienced faster deterioration of renal function (Lin et al., 2003). In an experimental study, Roncal et al. showed that low-lead exposure accelerates CKD in 5/6th nephrectomized rats, primarily by raising blood pressure and accelerating microvascular and tubulointerstitial injury (Roncal et al., 2007). The pathophysiological mechanism(s) underlying lead-induced CKD is not yet fully understood and various hypotheses have been put forward, including the induction of oxidative stress, generation of free radicals, and interference with calcium-dependent enzymatic reactions, which in turn may result in high blood pressure, inflammation, apoptosis, and, ultimately, development of chronic renal lesions (Sabath and Robles-Osorio, 2012) (Fig. 88.1).

Diagnosing chronic lead nephropathy is difficult, given the unreliability of non-invasive tests. It relies mainly on a history of exposure to lead, in patients with significant and otherwise unexplained renal abnormalities. The EDTA mobilization test,

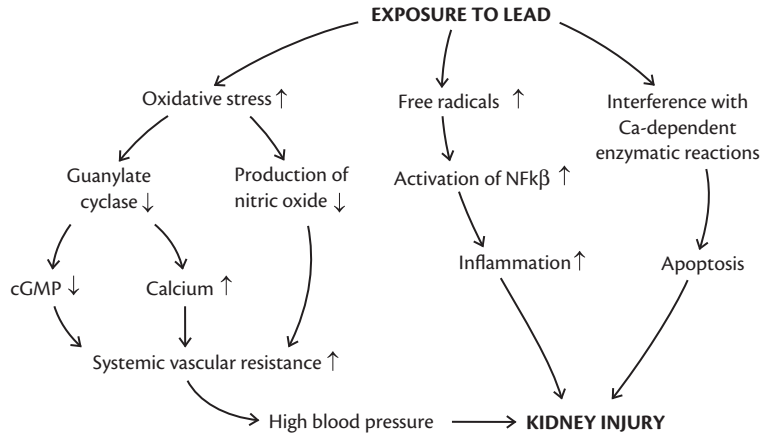

Fig. 88.1 Pathophysiological mechanisms of lead-induced kidney injury.
Adapted from Sabath and Robles-Osorio (2012).

which consists of measuring whole-blood or 24-hour urine lead levels over 1–4 days after parenteral administration of 1–3 g of calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$), may be helpful to assess the body lead burden (Wedeen, 2008). Alternatively, X-ray fluorescence may be used to detect increased bone lead concentrations, reflecting cumulative lead exposure.

Although lead-induced AKI can sometimes be reversed by increasing the rate of lead excretion through chelation therapy, there is no evidence that such therapy reverses established TIN (Wedeen, 2008).

Cadmium

Environmental sources of cadmium include combustion of fuels, industrial and household waste, tobacco smoke, sewage, contaminated sea food, vegetables and cereals, and (Indian) medicinal herbs (Hellström et al., 2001; Dey et al., 2009; Soderland et al., 2010). Cadmium is a by-product of mining and is used industrially in steel plating and manufacturing of plastics and nickel-cadmium batteries.

Low serum metallothionein levels, iron deficiency, older age, female gender, and residence in the proximity of industrial cadmium sources have all been reported to hold an increased risk for cadmium toxicity (Berglund et al., 1994; Staessen et al., 1994).

During the 1950s, Japanese doctors began to recognize an association between environmental exposure to cadmium and an increased incidence of renal tubular dysfunction, CKD, and a type of osteomalacia known as 'itai-itai' (Emmerson, 1970). Studies carried out later on in occupationally exposed workers also revealed an association between cadmium and an increased risk of developing kidney disease and osteomalacia (Adams et al., 1969). After the publication of several studies by Bernard and colleagues (Lauwerys et al., 1993), the scientific community became aware that even low-level cadmium exposure was associated with nephrotoxic effects and that up to 7% of the exposed population developed CKD.

In many studies, the nephrotoxic effects of cadmium have been assessed by measurements of kidney biomarkers, such as β_2-microglobulin (β2M), *N*-acetyl-β-D-glucosaminidase (NAG), kidney injury molecule-1 (KIM-1), intestinal alkaline phosphatase (IAP), and retinol binding protein (RBP) (Nishijo et al., 2006; Prozialeck et al., 2007; Hambach et al., 2013). The results of these studies again suggested that cadmium toxicity can occur at much lower levels of exposure than those recognized by the World Health Organization. Moreover, it has recently been shown that nephrotoxicity from low-level cadmium exposure is aggravated by co-exposure to lead (Hambach et al., 2013). However, it is still a matter of debate whether increased urinary excretion of such biomarkers can predict later development of CKD; prospective studies over several years are required to clarify this issue. In this respect, it is worth mentioning that Nishijo et al., in a 15-year follow-up study in inhabitants of the cadmium-polluted Kakehashi river basin area in Japan, showed an increased mortality risk in those with urinary β2M levels as high as 10,000 micrograms/g creatinine (Nishijo et al., 2006). The histopathological renal examination revealed that the glomeruli were relatively well preserved in number and size, but the tubules were markedly damaged, with luminal obstruction. The mechanism responsible for the decrease in GFR due to cadmium nephrotoxicity is still uncertain; some authors suggested that cadmium exerts a direct effect on the glomeruli, whilst others postulated that cadmium-induced tubular damage can lead to TIN, which in turn results in an alteration of GFR (Takebayashi, 1980; Nordberg et al., 2008).

The mechanisms of cadmium nephrotoxicity have been summarized in an elegant review by Sabath and Robles-Osorio (2012). Cadmium circulates in blood as cadmium-metallothionein-1 (MT-1) complex, which is filtered by the glomeruli and entirely reabsorbed in the S1 segment of the proximal tubular cells, by megalin- and cubulin-mediated endocytosis (Klassen et al., 2004). Within these cells, the cadmium-MT-1 complex is stored and broken down by lysosomes, after which free cadmium is released and transported to the cytoplasm by divalent metal transporter-1 (DMT-1) (Nordberg et al., 2008; Cucu et al., 2011) (Fig. 88.2). The activation of protein kinase C increases the expression of DMT-1, thereby increasing cadmium-induced tubular toxicity (Olivi et al., 2001). Free cadmium accumulates in mitochondria, resulting in mitochondrial dysfunction and formation of free radicals, which in turn activate caspase enzymes and apoptosis. Free cadmium

may also bind to protein sulfhydryl groups and thus affect the structure and function of these proteins. The accumulation of free cadmium in tubular cells induces the expression of DMT-1 mRNA, haem oxygenase-1 (HO-1) mRNA, and pro-apoptotic genes—all involved in renal toxicity; however, no such effects are seen when cells are exposed to the cadmium-MT-1 complex (Cucu et al., 2011).

Determination of cadmium concentration in blood reflects acute exposure, whilst urinary excretion of cadmium is used to assess the body cadmium burden and to evaluate chronic exposure. An isolated increase in urinary β2M is an important evidence of early proximal tubular dysfunction.

Several studies have reported that the presence of diabetes, increased levels of tissue anti-MT-1 antibodies, and/or concomitant exposure to organic arsenic hold an increased risk for cadmium-induced renal dysfunction, even with cadmium exposure levels as low as those occurring in the general population in many countries. Although further studies are needed to confirm these findings, it has been postulated that for individuals with such associated risk factors there may not exist a threshold for cadmium renal toxicity (Hambach et al., 2013).

There is no specific treatment for cadmium-induced renal disease, other than supportive care and change of residence area, to avoid further cadmium exposure.

Mercury

Mercury intoxication can result from consumption of water, fish, or cereals contaminated by ethyl mercury, used as a pesticide. Dental amalgam fillings have also been reported as sources of mercury. Additionally, accidental exposure to mercury has been described from breakage of mercury-containing thermometers and use of metallic mercury or mercury-containing ointments, creams, and drugs. Occupational exposure may occur in dental, chloralkali, and recycling industries, as well as in battery manufacturing (Fowler et al., 2008; Soderland et al., 2010).

The first well-documented outbreak of acute methyl mercury (MeHg) poisoning occurred in Minamata, Japan, in 1953 and was due to the consumption of fish contaminated by waste drain from a chemical factory. The clinical picture of this poisoning, described in 1956 under the name of 'Minamata disease', was dominated by neurological symptoms, but low-molecular-weight proteinuria was also reported (Ekinoa et al., 2007).

The kidney is the main excretion route and target organ for mercury accumulation. With regard to its renal handling, mercury shares common pathways, to a certain extent, with lead and cadmium (Barbier et al., 2005) (Fig. 88.3). It is filtered by the glomeruli and reabsorbed by the proximal convoluted tubules. Acute mercury poisoning may result in acute tubular necrosis, particularly involving the proximal tubules. Increased exposure to mercury can cause tubular damage, characterized by low-molecular-weight proteinuria and possible further development of chronic TIN (Li et al., 2010; Soderland et al., 2010). In addition to tubulointerstitial lesions, a typical nephrotic syndrome may also occur. Some patients developed severe tubular damage, with excessive urinary losses of sodium, and a nephrotic syndrome, with only trivial morphological glomerular damage (i.e. minimal change disease), following prolonged treatment of psoriasis with mercurial diuretics or mercury-containing ointments. Nephrotic syndrome has also been reported after long-term exposure to mercury-containing paint additives, antirheumatoid medication, skin-lightening cream, hair-dyeing agents, and mercury vapour. Examination of renal biopsies in such cases revealed a typical membranous nephropathy, with minimal or no tubular injury (see Chapter 82) (Becker et al., 1962; Fowler et al., 2008; Li et al., 2010). Renal lesions may depend on the type of mercury compounds involved (organic versus inorganic), as well as on the valence of the metal.

Biological monitoring of mercury concentrations is useful for assessing both the exposure level and the health risks (Elinder et al., 1994), but it may be complicated by the fact that both organic and inorganic mercury compounds are produced in the body and can be found in blood and urine. Urinary mercury is thought to correlate best with the amount of mercury within the kidneys (Zalups, 2000) and it is mainly associated with exposure to metallic mercury vapour or inorganic mercury compounds. In individuals who are not occupationally exposed, the urinary mercury concentrations seldom exceed 10 micrograms/L. There is now general consensus that if mercury-to-creatinine ratio in 24-hour urine is > 50 micrograms/g, nephrotoxicity is highly probable and comprises cytotoxic lesions of the proximal tubule (e.g. enzymuria and increase in tubular antigens) and functional changes (e.g. proteinuria, increase in serum β2M) (Roels et al., 1999). It is still a matter of debate whether combined measurements of mercury levels and biomarkers like leucine aminopeptidase (LAP) or NAG may yield a better prediction of renal disease (Mason et al., 2001).

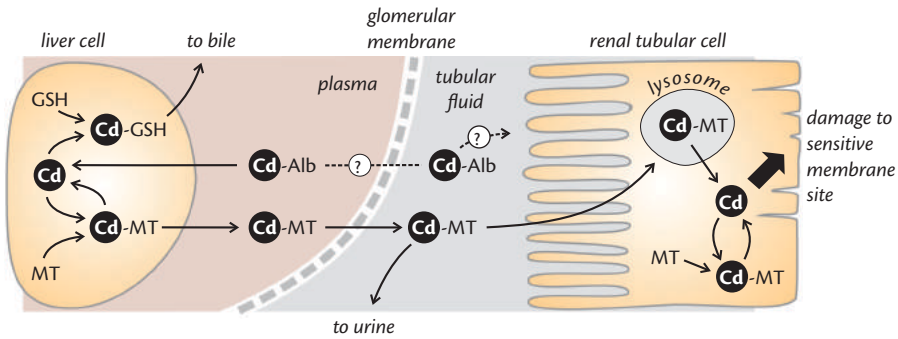

Fig. 88.2 Pathways of cadmium uptake and interaction with target sites in the kidney.
Adapted from Nordberg et al. (2008).

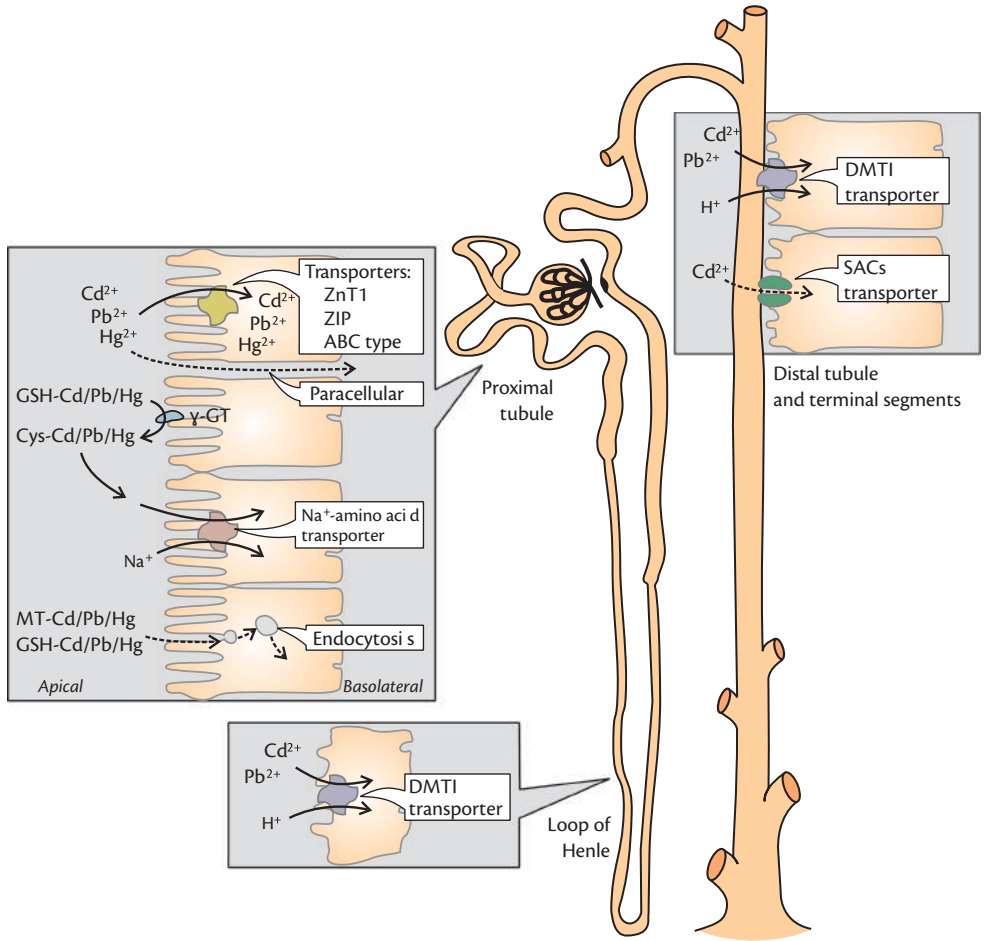

Fig. 88.3 Mechanisms involved in the uptake of cadmium (Cd), lead (Pb), and mercury (Hg) along the nephron.
Adapted from Barbier et al. (2005).

Treatments currently available for mercury poisoning involve the use of thiol-based chelating agents, such as British anti-Lewisite (BAL or dimercaprol), penicillamine, 2,3-dimercaptopropane-1-sulphonate (DMPS), and 2,3-dimercaptosuccinic acid (DMSA) (Sällsten et al., 1994; Fowler et al., 2008). Clinical studies have shown that chelation therapy successfully lowers the mercury body burden and increases urinary mercury excretion. Complete reversal of mercury-induced nephrotic syndrome has been reported in adults, as well as in infants, after dimercaprol treatment and withdrawal of the source of exposure (Wilson et al., 1952; Williams and Bridge, 1958).

Uranium

Uranium is the heaviest of all naturally occurring elements. Its biological effects were described in literature as early as the 1820s (Soderland et al., 2010). Human beings are constantly exposed to a certain amount of uranium, because it is widely present in its natural form in food, air, soil, and water. The repercussions of this exposure on human physiology and pathophysiology are not yet fully understood (Vicente-Vicente et al., 2010). Natural exposure, overexposure, and intoxication can occur by ingestion, inhalation, or skin contact. Uranium accumulates mainly in the bones (66%), kidneys (8%), and liver (16%). The metal is excreted in the urine. It is rapidly eliminated from the blood, whilst removal from organ depots occurs slowly (La Touche et al., 1987; International Commission for Radiation Protection, 1996).

Animal studies, as well as studies in occupationally exposed workers, have shown that the major health hazard of uranium is chemical kidney toxicity, rather than radiation (Zamora et al., 2009). In animal studies, renal effects have been reported after acute uranium intoxication, but it is not clear if these effects are able to trigger chronic renal lesions and if such lesions progress irreversibly and independently of the presence of the metal. The findings of Bijlsma et al., who studied urinary uranium excretion and kidney function in professional assistance workers several years after their acute exposure to uranium following the air disaster in Amsterdam, suggest that this would not be the case (Bijlsma et al., 2008).

Chronic ingestion of uranium from drinking water has been associated with glucosuria, microalbuminuria, β_2-microglobinuria, phosphaturia and hypercalciuria (Zamora et al., 1998). Studies in occupationally exposed populations have also reported aminoaciduria and low-molecular-weight proteinuria. A non-significant trend towards higher serum creatinine levels has been observed in an epidemiological study in individuals residing in close proximity to a uranium processing plant in Ohio (Pinney et al., 2003). In a 20-year follow-up study of a Gulf War depleted uranium (DU) cohort, renal biomarkers showed minimal DU-related effects on proximal tubular

function and cytotoxicity, but a significant increase in some urinary biomarkers was observed when urine concentrations of multiple metals, including uranium, were examined together (McDiarmid et al., 2013). Histopathological data in humans are scarce; however, studies in rats showed that chronic DU contamination, in addition to functional disturbances, can also induce structural renal damage, including interstitial fibrosis (Zhu et al., 2008). Possible mechanisms of uranium toxicity have been suggested by Vicente-Vicente et al. in an excellent review (2010) (Fig. 88.4).

To date, the best method of diagnosing uranium exposure is the detection of the metal in urine. There are no specific biomarkers for uranium-related nephrotoxicity, but general markers of kidney injury may be useful in cases suspected to have been exposed to this metal (Vicente-Vicente et al., 2010).

Cessation of exposure is the first line of therapy. Once uranium has been taken up by target organs, therapy with chelating agents, like EDTA or diethylenetriaminepentaacetic acid (DTPA), should be initiated. Although these agents can remove the metal from critical tissues and prevent it from binding to target cells, there is no evidence that this can help the recovery of renal damage.

Arsenic

Arsenic is one of the most widespread environmental pollutants and millions of people (mostly in Asia and Latin America) suffer from exposure to the element, since it is a common contaminant of drinking water. Other sources of arsenic are seafood, pesticides (causing food contamination), and products for wood preservation. A less common source is medication, such as arsenic trioxide, used in the treatment of acute promyelocytic leukaemia, and certain drugs used for sleeping sickness and leishmaniasis (Mahmudur-Rahman et al., 2009; Sabath and Robles-Osorio, 2012). Although renal involvement in arsenic poisoning has been reported, it remains an underdiagnosed cause of kidney disease.

High concentrations of arsenic in the drinking water have been associated with an increased mortality from CKD (Meliker et al., 2007; Smith et al., 2012). Few reports in the literature deal with the effects of arsenic on renal function in the general population. Hsueh et al. studied 125 individuals with a GFR < 60 mL/minute and 229 subjects with normal renal function and found a weak but significant association between urinary arsenic levels and decreased renal function ($r^2 = 0.04$, $P < 0.001$) (Hsueh et al., 2009). Arsenic levels in serum and blood cells correlate with the worsening of kidney disease and with the development and progression of CKD. These effects have been attributed to arsenic-induced oxidative stress (Zhang et al., 1995; Sasaki et al., 2007). Huang et al. evaluated urinary biomarkers, the possible role of oxidative stress, and the effect of co-exposure to environmental low-levels of arsenic and cadmium in 290 adults from the general population. They found NAG, malondialdehyde (MDA), and 8-hydroxydeoxyguanosine (8-OHdG) to positively correlate with both arsenic and cadmium exposure. Interestingly, the effects of concomitant exposure to both metals on these biomarkers were more pronounced than those of exposure to only one of them. Based on these findings, it was suggested that chronic exposure to low levels of arsenic and/or cadmium may produce tubular damage in the human kidney through oxidative stress (Huang et al., 2009).

Little is known about the histopathology of arsenic-induced renal injury in humans. A case of TIN associated with elevated urinary arsenic concentration was reported by Prasad and Rossi (1995). In a patient with no history of diabetes, hypertension, heart disease or hepatitis and no family history of CKD, increased urinary arsenic levels (91.0 micrograms/L) were found, together with normal cadmium and mercury concentrations. Light microscopy of the renal biopsy showed normal glomeruli, extensive interstitial fibrosis, with tubular atrophy and a focus of cellular infiltrate, mainly consisting of lymphocytes. These findings were interpreted as chronic TIN. Following changes in the patient's diet, which was based on 'organically grown health food', and cessation of intake of over-the-counter vitamins, the arsenic content in the urine dropped to 6.5 micrograms/L, concomitantly with a decrease in serum creatinine from 2.0 mg/dL to 1.7 mg/dL.

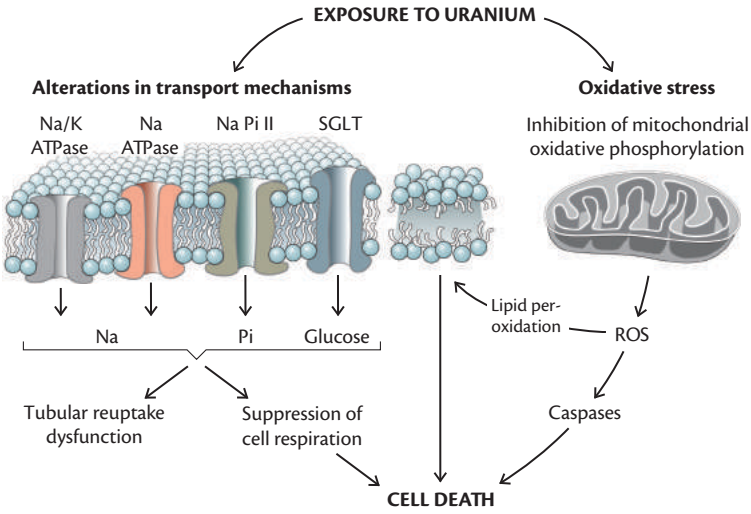

Fig. 88.4 Possible mechanisms involved in uranium nephrotoxicity.
Adapted from Vicente-Vicente et al. (2010).

Data on the pathophysiological mechanisms of arsenic nephrotoxicity are scarce. The multidrug resistance-associated protein 2 (MRP-2) transporter, together with aquaporins, favours the entry of arsenic in proximal tubular cells. Once taken up by these cells, arsenic seems to induce its toxic effects through glutathione depletion, which in turn increases oxidative stress by induction of free radicals. This hypothesis is supported by the reduction of arsenic toxicity by administration of selenium, a well-known antioxidant agent (Messarah et al., 2012).

Chromium

Whilst the role of chromium has been intensively studied in oncology (Seidler et al., 2013), its potential renal toxicity has been largely overlooked. Exposure to chromium can occur mainly by intake of contaminated food, inhalation of polluted air, or skin contact during chromium handling at the workplace. Other sources of chromium exposure may consist in drinking contaminated well water and residing in the proximity of uncontrolled hazardous waste sites or industrial plants that use or process chromium.

Nephrotoxic effects of chromium have been demonstrated in animal studies (Hojo and Satomi, 1991). Chromates and chromic acid used in the treatment of certain skin diseases have been reported to cause fatal cases of acute nephritis. Necropsies of such cases revealed acute tubular necrosis, without glomerular lesions (Petersen et al., 1994). Other studies reported renal function impairment in subjects with a high urinary chromium concentration (Hsueh et al., 2009). Petersen et al. (1994) described the case of a 48-year-old man, who developed chronic TIN after long-term occupational exposure to chromium. His renal biopsy showed totally or partially sclerotic glomeruli, focal interstitial fibrosis, with scattered lymphocytes, and tubular atrophy, but no tubular necrosis (Petersen et al., 1994).

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CHAPTER 89

Aristolochic acid nephropathy caused by ingestion of herbal medicinal products

M. Refik Gökmen and Graham M. Lord

Introduction and epidemiology

The association between aristolochic acid (AA) ingestion and progressive renal interstitial fibrosis first came to light in the context of an outbreak of severe renal failure in more than 100 patients in Belgium starting in the early 1990s. The initial report described nine women who presented either requiring dialysis or with rapidly progressive renal impairment, all of whom had taken a slimming regimen prescribed by the same clinic (Vanherweghem et al., 1993). This regimen had been modified in June 1990 to include extracts of two Chinese herbs, labelled as *Stephania tetrandra* and *Magnolia officinalis*. Although these products were banned by the Belgian authorities in 1992, it soon emerged that these plant species were not in fact the true culprits. Subsequent investigations showed that *S. tetrandra* in this regimen had in fact been replaced with *Aristolochia fangchi*, and phytochemical analysis further showed the presence of AA, rather than the expected tetrandrine (Vanhaelen et al., 1994). More recently, the detection of AA-DNA adducts in renal tissue from patients with 'Chinese herbal nephropathy' has provided more definitive confirmation of AA involvement in affected patients (Schmeiser et al., 1996; Nortier et al., 2000). Together with data demonstrating the characteristic pattern of nephrotoxicity caused by AA administration in experimental animals, these observations have led to the replacement of the term 'Chinese herbal nephropathy' with the more accurate 'aristolochic acid nephropathy' (Debelle et al., 2008).

Since the first description of the Belgian cohort, other cases and case series have been reported in a number of European countries, as well as the United States, Japan, Korea, China, Taiwan, and Hong Kong (Debelle et al., 2008; Gökmen et al., 2013). These reports attest that AA-containing remedies have been (and continue to be) used for a variety of indications, including eczema, acne, liver disease, arthritis, and chronic pain. However, the number of people affected by aristolochic acid nephropathy (AAN) worldwide remains unclear. Investigators from China have reported that thousands of cases have been identified among patients previously labelled as having chronic tubulointerstitial nephritis (CTIN) of unknown origin, and describe 300 cases identified between 1997 and 2006 in one centre in Beijing (Yang et al., 2011). In addition, *Aristolochia* species are known to be used for a wide variety of indications in many regions of the world where AAN has not yet been described, including Africa, South America, and the Indian subcontinent (Vanherweghem, 1997; Heinrich et al., 2009).

Risk factors

It is estimated that 1500–2000 people were exposed to AA as part of the slimming regimen in the Belgian outbreak; of these approximately 100 are known to have developed renal disease (Vanherweghem, 1998). The only risk factor for the development and progression of renal disease which has so far been defined with any certainty is the cumulative dose of AA. In the Belgian cohort, where patients received a number of pharmaceutical products including fenfluramine and acetazolamide alongside herbal products, the ingested dose of *A. fangchi* emerged in multiple regression analysis as the only significant drug predicting the rate of progression of CKD (Martinez et al., 2002). Although theoretical reasons why co-administration of fenfluramine or acetazolamide might potentiate AA nephrotoxicity have been suggested (Martinez et al., 2002), the worldwide prevalence of AAN outside the Belgian outbreak suggests that AA alone is sufficient to cause the disease. In a Chinese cohort, among 280 patients with chronic AAN, the median cumulative intake of aristolochic acid I (AAI), the main component of the plant extract AA was found to be 1.01 g (Yang et al., 2011), although reported exposures as small as 0.025 g were seen in those affected. A retrospective review of 199,843 persons in the Taiwanese National Health Insurance reimbursement database observed that reported ingestion of > 60 g of Fangchi or of > 30 g of Mu-Tong was associated with an increased risk of CKD (Lai et al., 2009). However, in light of the variations in the concentration of AA in different herbal preparations, there is unlikely to be a 'safe dose' of these products.

All the published AAN case series, including those from China and Taiwan, note a marked female preponderance among affected individuals. The available epidemiological data do not allow assessment of whether female gender represents a genuine risk factor, or whether this reflects the known increased use of Chinese herbal products by women. Finally, genetic studies in Balkan endemic nephropathy (BEN) may provide new insights into the genetic factors conferring risk to those exposed to AA (Stefanovic et al., 2006).

Association with Balkan endemic nephropathy

BEN is a CTIN found in farming villages close to tributaries of the Danube river in Bosnia, Bulgaria, Croatia, Romania, and Serbia (see Chapter 90). First described in the 1950s (Tanchev et al., 1956; Danilovic, 1958), BEN is notable for showing a familial, but not inherited, pattern of distribution, and a strong association with urothelial malignancy (Stefanovic et al., 2006). In the early stages of the disease, BEN is characterized by tubular dysfunction, whereas marked tubular atrophy and hypocellular interstitial fibrosis is seen in more advanced disease.

The role of environmental exposure to AA in the aetiology of BEN is now well documented. The striking pathological similarity between the first described cases of AAN and BEN was noted in the original report of the Belgian outbreak. Indeed, environmental exposure to AA had first been suggested as a cause of BEN in 1969, when Ivić found contamination of wheat flour by the seeds of *Aristolochia clematitis*, a weed that is common in wheat fields in endemic areas (Ivić, 1969; Hranjec et al., 2005). More recently, definitive proof of AA exposure in patients with BEN has come from the use of the ^{32}P-postlabelling technique to detect AA-specific DNA adducts in renal cortical and urothelial malignant tissue (Arlt et al., 2002; Grollman et al., 2007; Arlt et al., 2007, Jelaković et al., 2012). Furthermore, 78% of the examined tumours were found to have A:T→T:A transversion mutations in the *TP53* gene, which is a hallmark mutation in AA-induced carcinogenesis and rarely seen in urothelial malignancies unrelated to AA (Arlt et al., 2001). With BEN pathologically indistinguishable from AAN caused by ingestion of Chinese herbal products, definitive evidence of AA exposure in affected individuals, and evidence of AA as an environmental toxin in endemic areas, it is highly likely that BEN represents a form of AAN.

Clinical features and investigations

Clinical features and basic investigations

Most patients with AAN present with renal insufficiency, anaemia, a urine sediment with a few red and white blood cells, and mild proteinuria (typically, < 1.5 g/24 hours). In keeping with the known toxic effects of AA on proximal tubular cells, proteinuria tends to consist of low-molecular-weight proteins that are usually filtered at the glomerulus, but reabsorbed by proximal tubular cells (Kabanda et al., 1995). Small numbers of patients presenting with acute kidney injury or with a Fanconi syndrome of tubular dysfunction have also been reported (Tanaka et al., 2000; Yang et al., 2000; Krumme et al., 2001). Both in Chinese herb-associated AAN and BEN, the degree of anaemia seen has been noted to be more severe than expected with the decrease in glomerular filtration rate (GFR), perhaps as a result of early destruction of erythropoietin-producing peritubular cells (Reginster et al., 1997). Renal ultrasonography reveals shrunken kidneys, which can be asymmetrical and irregular in cortical outline.

No serum or urinary biomarkers have so far been demonstrated to have clinical utility in the diagnosis of AAN. Recent studies have reported that a number of urinary proteins, including beta-2-microglobulin and alpha-1-microglobulin, are elevated in patients with AAN, compared with either those with glomerulonephritis and hypertensive nephrosclerosis (Stefanovic et al., 2011), or those with diabetic nephropathy, acute kidney injury and healthy controls (Pešić et al., 2011). Although this is promising, it is not yet clear whether these findings simply represent non-specific tubular damage. Further studies are required to determine and evaluate novel non-invasive biomarkers for AAN.

Renal histology

Given the non-specific clinical features, pathological examination of renal biopsy tissue is usually essential for a diagnosis of AAN. The characteristic findings are extensive interstitial fibrosis and tubular atrophy, typically with more marked fibrosis of the outer renal cortex (Fig. 89.1). Infiltration of the interstitium by inflammatory cells is seen in some patients (Pozdzik et al., 2010), although the degree of inflammation is typically less than in other fibrotic interstitial diseases. While the glomeruli are relatively preserved, global glomerular obsolescence and ischaemic changes are common in more advanced disease. Vascular involvement typically consists of fibrous hyperplasia of arteriolar walls. Urothelial atypia is observed almost universally (Fig. 89.2); in 40–46% of patients there is also multifocal transitional cell carcinoma *in situ* (Nortier et al., 2003).

DNA adduct analysis

Exposure to AA leads to the formation of covalent AA-DNA adducts, which persist as a specific long-term biomarker of AA exposure. Where possible, identification of AA-DNA adducts using the ^{32}P-postlabelling technique can form an important part of establishing the diagnosis of AAN (Lord et al., 2001; Arlt et al., 2004). In most cases, this requires the extraction of DNA from a fresh (unfixed) biopsy core of renal tissue; alternatively a presumptive diagnosis of AAN can be confirmed following the identification of adducts in nephrectomy specimens.

Natural history

The majority of patients diagnosed with AAN show a relentless course towards end-stage renal disease (ESRD). In a follow-up study of the original Belgian cohort, the 2-year actuarial survival rate without ESRD was only 17%, compared with 74% in a control group with other CTIN (Reginster et al., 1997). The experience in other centres has been similar, with the median rate of change in eGFR being −3.5 mL/min/year in the largest Chinese case series (Yang et al., 2000). Those with a relatively preserved GFR at presentation (< 2 mg/dL or 176 μmol/L) appear to have a reduced risk of progression to stage 5 CKD (Reginster et al., 1997), although, as

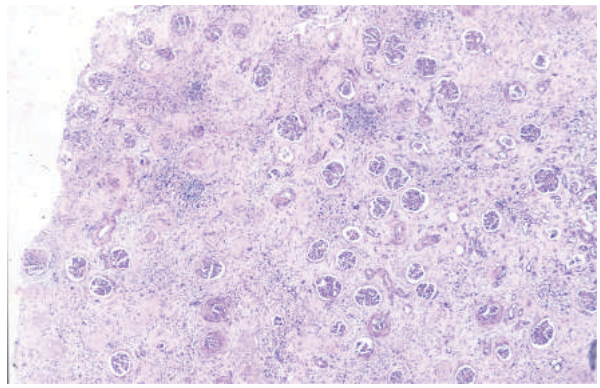

Fig. 89.1 Low-power view of renal cortex from a patient with AAN, showing extensive hypocellular interstitial fibrosis associated with marked tubular atrophy.

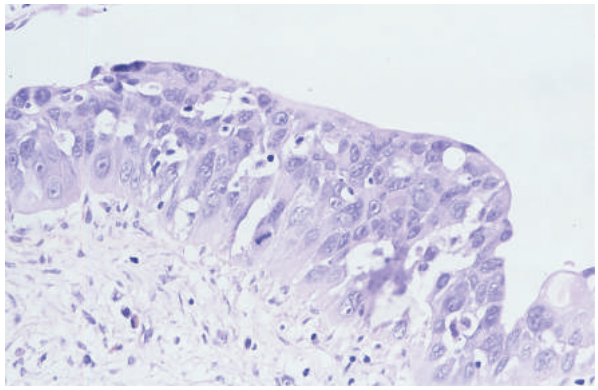

Fig. 89.2 High-power view of ureteric epithelium showing cellular atypia and dysplasia.
Pathological images provided by Professor T. H. Cook, Imperial College London.

noted above, the single best predictor of the degree of renal insufficiency and the rate of decline of residual renal function has been found to be the cumulative dose of AA ingested.

Association with urothelial malignancy

A key feature of the natural history of AAN, irrespective of the mode of exposure, is the risk of urothelial malignancy. Although almost all documented cases of urothelial malignancy have been in AAN patients requiring renal replacement therapy, extensive urothelial cell atypia is a common finding in biopsy specimens from patients with less severe renal impairment (Nortier et al., 2000). A number of observational studies have helped in quantifying the risk of malignancy in individuals exposed to AA, with a reported prevalence of high-grade carcinoma *in situ* or invasive lesions in 40–46% of AAN patients who have kidneys and ureters removed prophylactically. The majority of tumours arise in the upper urinary tract, although an increased incidence of late-onset bladder tumours has also been reported (Lemy et al., 2008).

Aetiology and pathogenesis

Experimental studies have shown that the main targets of AA nephrotoxicity are the tubular and interstitial compartments, with an early phase of acute tubular necrosis preceding the development of tubular atrophy and interstitial fibrosis (Okada et al., 2003; Sato et al., 2004; Lebeau et al., 2005). Tubular cells undergo apoptosis after exposure to AA (Gao et al., 2000; Hsin et al., 2006), while both epithelial-to-mesenchymal transition of tubular cells and activation of resident tissue fibroblasts are likely to contribute to the extensive interstitial fibrosis seen in AAN (Pozdzik et al., 2008). In common with other fibrotic processes, transforming growth factor (TGF)-β and its downstream signalling pathways have been implicated in AA-induced fibrosis (Pozdzik et al., 2008; Zhou et al., 2010).

The mechanisms of AA-induced carcinogenesis are well characterized, although it is unclear whether the nephrotoxic and carcinogenic effects of AA are related; there has been at least one report of AA-associated urothelial malignancy in the absence of severe renal impairment (Nortier et al., 2003). AA is genotoxic and mutagenic after metabolic activation (Schmeiser et al., 2009). A number of enzymes are involved in the activation of AA, with NAD(P)H:quinone oxidoreductase (NQO1) being the most important (Stiborova et al., 2008). The key mutagenic moiety resulting from this process is an electrophilic cyclic *N*-acylnitrenium ion that reacts preferentially with purine bases in DNA, forming covalent DNA adducts. These adducts can be detected by ^{32}P-postlabelling analysis and serve as a long-lasting biomarker of AA exposure (Fernando et al., 1993; Nortier et al., 2000; Jelaković et al., 2012). The majority of oncogenic mutations associated with AA exposure are A:T→T:A transversion mutations arising from the incorporation of an adenine residue opposite the adduct during DNA replication (Broschard et al., 1994; Attaluri et al., 2010). A:T→T:A transversions mutations are commonly identified in the oncogene *TP53* in areas of urothelial atypia and in urothelial malignancies (Lord et al., 2004) both in patients with herbal product-related AAN and in BEN (Grollman et al., 2007).

The total cumulative dose of AA has emerged as the key risk factor for the development of renal disease and malignancy following AA exposure. Few other risk factors have been identified; the female preponderance of reported cases worldwide is deemed likely to be the result of increased uptake of AA-containing medicinal products among females. A number of studies have also reported polymorphisms in genes encoding AA-activating enzymes such as NQO1 and cytochrome P450 enzymes as being associated with increased cancer risk in AAN and BEN patients, although some of these associations have not been confirmed in subsequent reports(Stefanovic et al., 2006; Atanasova et al., 2005; Toncheva et al., 2004).

Treatment and outcome

Prevention

Given the severe consequences of AA ingestion, prevention of exposure to AA is a key public health priority. In the European Union, the 2004 Traditional Herbal Products Directive has, since 1 May 2011, required that all traditional herbal medicines must be registered and approved; no products containing AA have been approved (European Union, 2004). In the United States, the Food and Drug Administration issued an alert in 2001 warning consumers and the herbal medicine industry of the dangers of AA (Food and Drug Administration, 2001), and import alerts are in force allowing the seizure of any product containing AA. In the Far East, the medicinal use of most AA-containing plant species has been banned in Hong Kong, Taiwan, and mainland China, although certain AA-containing products are still permitted in China under the supervision of Chinese medicine practitioners (World Health Organization, 2004; Poon, 2007). Despite these regulatory measures, there is still cause for concern. Products containing AA are still available over the Internet (Gold and Slone, 2003), and some practitioners continue to dispute the evidence that AA causes serious harm. Tighter local regulation of practitioners and outlets of alternative and herbal medicine is required, as well as a robust international system of surveillance to identify products containing AA (Gökmen and Lord, 2012).

Disease-specific management

AAN is notable for the rapid progression to ESRD, despite cessation of AA-containing products. Although there are no randomized trials in humans, there is currently no evidence that renin–angiotensin system blockade with ACE-inhibitors or angiotensin receptor blockers can improve renal function or delay progression. A study in a rat model of AAN showed no difference in outcome with sodium restriction or with treatment with enalapril,

or enalapril and candesartan combined (Debelle et al., 2004). There is, however, some evidence that steroid treatment can modify the course of the disease. A non-randomized study of steroid therapy in the original Belgian cohort of AAN patients showed a significant slowing in the progression of CKD in 12 treated patients compared with well-matched historical controls from the Belgian registry (Vanherweghem et al., 1996). Based on the available evidence, a therapeutic trial of steroids may be warranted in patients with a diagnosis of AAN and an estimated GFR of > 20 mL/min.

Aside from steroid therapy for appropriately selected patients, the priorities in the management of AAN are similar to those in other causes of CKD: careful blood pressure control, cardiovascular risk reduction, management of metabolic complications, and timely preparation for renal replacement therapy.

Dialysis and transplantation

As with most patients with end-stage kidney disease, transplantation is the treatment of choice for AAN patients requiring renal replacement therapy. Patients should be evaluated for pre-emptive living donor transplantation with combined bilateral nephro-ureterectomy. The disease has not been found to recur following transplantation (Reginster et al., 1997), although, if bilateral nephro-ureterectomy is not performed at or before transplantation, the risk of malignancy in the native urinary tract after transplantation has been reported to be as high as 52.9% over a median follow-up period of 57 months (Yuan et al., 2009). If transplantation is delayed, or is not possible on medical grounds, haemodialysis is preferred to peritoneal dialysis, given the extensive surgical intervention that patients with AAN are likely to require.

Urological management

Given the substantial risk of malignancy, many nephrologists would advise that all patients with a confirmed diagnosis of AAN be offered bilateral nephro-ureterectomy at the point of needing renal replacement therapy. As noted above, this would best be performed in the context of planned living donor renal transplantation. In patients with AAN who do not yet require renal replacement therapy, ongoing surveillance with computed tomography imaging and ureteroscopy is warranted. The role of cystectomy is unclear, as the incidence of bladder tumours has been found to be lower than that of upper tract malignancy. Patients and clinicians will need to consider the relative merits of regular urine cytology, cystoscopy, non-invasive imaging and prophylactic radical cystectomy on an individual basis. However, many individuals may choose to undergo cystectomy if AA-DNA adducts are detected in bladder specimens. It is hoped that non-invasive biomarkers may be identified that will better guide these difficult management decisions.

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CHAPTER 90

Balkan endemic nephropathy

Milan Radović and Adalbert Schiller

Epidemiology

During World War II, clinical observations of a slowly progressive form of chronic kidney disease (CKD) with familial clustering led to the initial descriptions of Balkan endemic nephropathy (BEN). After 1950, independently from each other, authors from three Balkan countries (Danilovic in Yugoslavia, Foarta, Tonea, Bruckner, Lazarescu, and Zosin in Romania, and Dimitrov, Tanchev, and Ivanov in Bulgaria) reported high death rates from uraemia in certain small geographical areas. The first cases were detected in the Kolubara region in Serbia (Danilović et al., 1957), Mehedinti and Caras-Severin counties in Romania (Bruckner et al., 1979), and the Vratsa region in Bulgaria (Puchlev et al., 1979). Soon after, BEN was also reported in Croatia (Pichler et al., 1959; Čeović et al., 1979), Bijeljina-Posavina, in Bosnia and Herzegovina, and Kosovska Vitina, Pomoravlje, and West Morava, in Serbia (Danilović, 1979).

BEN affects both genders evenly. Most patients are farmers. The peak incidence of BEN onset was initially described to be in the third and fourth decades of life; however, this has recently shifted towards older ages (Bukvić et al., 2009). In endemic areas, the incidence of BEN ranges from 55 to 85 new cases per 100,000 inhabitants and per year (Janković et al., 2011), whereas the prevalence is 0.5–4% (Stefanović and Cosyns, 2005). In the same areas, the incidence of end-stage renal disease (ESRD) due to BEN varies between 5.4 and 12.8 patients per million-population; however, a decreasing trend has been noticed during the past few decades (Čukuranović et al., 2007). Approximately 11% of all patients treated with haemodialysis in countries with endemic regions had BEN as a cause of ESRD (Djukanović et al., 2002); this prevalence has remained relatively stable during the last 10 years (Čukuranović et al., 2007; Janković et al., 2011).

Clinical manifestations

BEN is a disease with an insidious onset and slow, progressive course. When associated with urothelial cancers, haematuria, pain, and urinary tract obstruction may occur.

The diagnosis of BEN is based on a patient's medical history, physical examination, laboratory tests, kidney imaging, and additional investigations. The diagnostic criteria were established by Danilović in 1979 and updated by Djukanovic et al. in 2007, as follows:

1. Farmers residing in endemic areas
2. Family history of BEN
3. Mild proteinuria (< 500 mg/day)
4. Low urinary specific gravity (< 1.010), or low urinary osmolality (< 850 mOsm/kg in patients < 20 years old to < 600 mOsm/kg in those > 60 years old)
5. Anaemia (haemoglobin < 13.0 g/dL in men and post-menopausal women and < 12.0 g/dL in pre-menopausal women)
6. Azotaemia (defined as serum creatinine > 125 μmol/L or serum urea > 8.0 mmol/L)
7. Symmetrically small kidneys, with smooth outlines

The presence of the first three criteria and at least one of the remaining four raises the suspicion of BEN, whereas definite BEN requires five criteria (of which the first two are mandatory). However, these criteria enable only the detection of advanced BEN cases and offer little support for the differential diagnosis with other CKDs. More recently, other investigations, such as urinary alfa-1-microglobulin and microalbuminuria, have been proposed as additional diagnostic criteria for BEN, but they still need validation (Radović and Djukanović, 2004; Djukanović et al., 2007, 2008; Imamović et al., 2008; Gluhovschi et al., 2011; Pešić et al., 2011).

Typically, BEN patients are farmers in their fifth or sixth decade of life, with a positive family history of CKD, residing in villages where other inhabitants also have CKD. Physical examination is often unremarkable. Patients may be pale, or with a grey or yellowish skin colour (xanthodermia). Mild hypertension can be found.

Laboratory examination of urine sediment is typically negative. If haematuria is found, the patient should be promptly investigated for urothelial cancer or glomerular disease. Urine specific gravity is low. Urinalysis reveals mild (usually < 500 mg/day) tubular proteinuria. Decreased glomerular filtration rate (GFR) is a common finding. Additionally, normochromic normocytic anaemia is often present.

Renal imaging exams (ultrasound, intravenous pyelogram, computed tomography, and magnetic resonance) reveal markedly reduced kidney size, with a smooth outline. Ultrasound is the most cost-effective and reliable method for diagnostic screening (Ležaić et al., 2008; Hanjangsit et al., 2010). Radiology studies are also performed in search for upper urothelial cancers.

Kidney biopsy is usually not indicated in BEN patients, for the following reasons: (a) diagnostic criteria are not based on histology, (b) the kidneys have reduced size and cortical thickness, and (c) biopsy findings do not influence the therapy options. However, the lack of pathological studies is one of the most important reasons why the pathophysiology of BEN is still unclear.

The differential diagnosis of BEN should particularly consider Chinese herbs nephropathy, as well as other toxic chronic tubulointerstitial nephritis (CTIN), such as analgesic nephropathy,

where kidneys have bumpy contours and papillary calcifications and medical history reveals analgesic abuse (Elseviers et al., 1995).

Aetiology and pathogenesis

The aetiology of BEN has remained unclear for the last 50 years. However, some of its features (its limited geographical distribution and its association with urothelial cancers) suggest that both genetic and environmental factors are probably involved.

Genetic

BEN does not show a typical Mendelian inheritance pattern. Nevertheless, offspring of BEN patients are at high risk of developing CKD and they were sometimes found to have reduced kidney size and cortex thickness, elevated blood pressure (Dimitrov et al., 2006, 2007), as well as high CRP levels, suggesting an early inflammatory state, which is inversely related to the renal cortex width (Karmaus et al., 2009). Reduced GFR and tubular proteinuria have also been detected in family members of BEN (especially female) patients (Stefanović et al., 2002; Arsenović et al., 2005; Dimitrov et al., 2006).

Several genetic factors have been implicated in the aetiopathogenesis of BEN, including abnormalities in chromosome 3q25–3q26, transforming growth factor beta (*TGF-β*) gene, genetic heterogeneity of xenobiotic-metabolizing enzymes or immune system genetic defects. The predisposition for urothelial cancers of BEN patients could be due to germline mutations in tumour suppressor genes or acquired somatic mutations in oncogenes (Toncheva et al., 1998, 2002). Since the angiotensin receptor gene is located on the 3q chromosome (Goodfriend et al., 1996; Heiber et al., 1996), the potential role of angiotensin-converting enzyme (ACE) gene polymorphism in the development of interstitial fibrosis in BEN has been suggested (Huskić et al., 1996), but not yet confirmed (Krcunović et al., 2010). Genetic deficiencies of enzymes such as lecithin-cholesterol acyltransferase (LCAT), erythrocyte delta-aminolevulinate dehydratase (ALA-D), and cytochrome P450 2D6 have also been suggested to play a role in BEN (Djordjevic et al., 1991; Nikolov et al., 1991; Pavlovic et al., 1991). More recently, cytochrome P450 3A5*1 (CYP3A5*1) (Atanasova et al., 2005) and glutathione-S-transferase M1 (GSTM1) wild-type (Andonova et al., 2004) allele carriers were found to be associated with a higher risk of BEN.

Aristolochic acid

The occurrence of BEN in immigrants to (Čeović et al., 1985) and in emigrants from endemic regions (Nikolić et al., 2006) strongly suggests the role of environmental factors in the aetiology of this disease. Many such factors have been suspected so far, but aristolochic acid currently appears to be the most convincing one. The relation between aristolochic acid and BEN was first described by Ivić in 1969 and was later supported by the detection of *Aristolochia clematitis* in wheat, wheat flour, and bread consumed by inhabitants of endemic regions. The incorporation of aristolochic acid into the genome of patients with BEN and urothelial cancers was confirmed a few years ago (Grollman and Jelaković, 2007; Grollman et al., 2007).

Aristolochic acid nephropathy is discussed in detail in Chapter 89. It is a genotoxic mutagen, forming DNA adducts after metabolic activation. Aristolochic acid DNA and aristolactam-DNA adducts in renal cortex and AT-TA *p53* mutations were found in patients with both BEN and urothelial cancers (Arlt et al., 2007; Slade et al., 2009; Jelaković et al., 2012).

Aristolochic acid is able to promote both renal interstitial fibrosis and urothelial carcinogenesis. The role of aristolochic acid in BEN is also suggested by similarities in the clinical course and histological features between BEN and aristolochic acid (Chinese herbs) nephropathy. However, there may be a genetic predisposition for a particular aristolochic acid metabolic processing and an individual susceptibility for BEN (Vanherweghem et al., 1993; Cosyns et al., 1994; Depierreux et al., 1994; Cosyns et al., 2001; Arlt et al., 2002; de Jonge and Vanrenterghem, 2008), to explain the high incidence in the region.

Other toxins

Poisoning of the drinking water with water-soluble carcinogenic hydrocarbons from Pliocene-epoch lignites (Orem et al., 2004) was another explored hypothesis. Almost all endemic areas in the Balkans are lying over Pliocene lignites. These lignites contain water-soluble organic compounds, including polar polycyclic aromatic hydrocarbons and aromatic amines, which are known to be carcinogenic. This hypothesis has not yet been confirmed, despite some preliminary findings (Schiller et al., 2008).

The role of environmental trace elements, like cadmium, lead, silica, manganese, copper, and selenium, has also been suggested (Diven et al., 1979; Stefanović et al., 2006), but still remains unclear.

Ochratoxin A (OTA), a product of *Penicillium* or *Aspergillus* strains, which may contaminate foods, is a nephrotoxic, teratogenic, immunotoxic, and carcinogenic mycotoxin. OTA may cause tissue injury via oxidative DNA damage and lethal or sublethal cellular cytotoxicity (Kamp et al., 2005). It has also been shown to have a dose-dependent oncogenetic effect *in vitro* (Arlt et al., 2001; Cosyns et al., 2001; Mally et al., 2007; Slade et al., 2009). OTA-induced DNA adducts have been shown in animal models. It has been suggested that CYP3A5*1 allele carriers can convert more efficiently OTA into genotoxic metabolites (Pfohl-Leszkowicz, 2009). This mycotoxin has been considered as a possible aetiologic factor for BEN; however, a direct relation between OTA contamination and BEN has not been demonstrated. Furthermore, the clinical course of BEN is typically much slower than the one seen in OTA-induced nephropathy (Cosyns et al., 2001; Hassen et al., 2004).

Infection

A viral aetiology for BEN was a topic of research during the 1970s and 1980s. Coronavirus-like particles were found in the blood and kidney biopsies of BEN patients (Apostolov and Spasić, 1975; Georgescu et al., 1978; Uzelac-Keserović et al., 2000). Other studies suggested a role for adenoviruses (Georgescu et al., 1978) and papovaviruses (Stoian et al., 1983). In Bulgarian BEN patients, elevated urinary levels of neopterin—a marker of activated T-helper-1 immune response, viral infections, and malignancies—have been identified (Toncheva et al., 2003). The viral hypothesis of BEN aetiology still awaits confirmation.

Metabolomics

Recently, proton nuclear magnetic resonance (^{1}H NMR) spectroscopic analysis has been used for metabolomic studies of the urine of BEN patients from Romania and Bulgaria. Principal component analysis clustered healthy controls from both countries together. Bulgarian BEN patients clustered separately from Bulgarian controls, whereas Romanian patients not only clustered away from controls, but also clustered separately from the Bulgarian patients.

Moreover, the urinary metabolomics of two individuals among Romanian controls clustered within the Romanian BEN group. One of these had been suspected of incipient BEN at the time of selection as a 'healthy' control. At least two conclusions emerged from this pilot study: (1) metabolomic urinalysis could predict BEN before the development of clinical signs, and (2) considering the separate clustering of BEN patients from Romania and Bulgaria, a different aetiology in different geographic areas is likely (Mantle et al., 2011).

Models

There is no specific or validated experimental model for BEN. However, aristolochic acid-, OTA-, and ciclosporin-induced experimental nephropathies can mimic some of the BEN features (Ferluga et al., 1991; Pichler et al., 1995).

Pathology

The kidneys of BEN patients are smoothly outlined and symmetrically shrunken. In advanced stages, a kidney's weight may be reduced to as little as 30 g. In up to 35% of cases, urothelial carcinoma of the renal pelvis or ureter can be found, and in 13% of cases, it is bilateral (Djokić et al., 1999).

The histopathology of BEN is characterized by diffuse fibrosis of the cortical interstitium, tubular atrophy, and absence of cellular interstitial infiltration, which classifies BEN among non-inflammatory CTIN. The study by Ferluga and colleagues, including the largest number of kidney biopsies in BEN patients (50 cases), found interstitial fibrosis in 98% and tubular atrophy in 96% (Ferluga et al., 1991; Trnačević et al., 1991).

BEN kidneys show striped cortical, hypocellular interstitial fibrosis, interstitial oedema, and tubular atrophy. These changes, scattered in the early stages, become diffuse in the later stages, when hypocellular interstitial fibrosis is prevailing. Fibrosis surrounds the proximal tubules, whose epithelia become flattened and atrophic. The structure of the glomeruli is normal in the early phase of the disease, but later may have an ischaemic appearance (Hall et al., 1978; Dojčinov et al., 1979; Sindjić et al., 1979; Ferluga et al., 1991). Blood vessels may show afferent artery hyalinosis and, occasionally, peritubular capillary wall thickening (Sindjić et al., 1979) (Fig. 90.1). In some cases, rare foci of segmental sclerosis or intracapillary lesions mimicking thrombotic microangiopathy were seen. The medulla is usually preserved. There is a striking histologic resemblance of BEN with chronic ciclosporin nephropathy (Ferluga et al., 1991).

Immunofluorescent microscopy findings are non-specific. Scanty, granular segmental immunoglobulin M (IgM) or C3 deposits may occasionally be present in the glomeruli. Rarely, the tubular basement membrane may show granular C3 deposits. Arterial walls may also contain C3 and, rarely, IgM deposits. On immunohistochemistry staining, overexpression of laminin in the interstitial capillaries and in the tubules, as well as a co-expression of vimentin and cytokeratin in the tubular epithelial cells, has been described (Savić et al., 2002).

Electron microscopy shows increased interstitial bundles of collagen fibres and elongated, stellate fibroblast-like cells. The intercellular junctions of tubular cells are widened. The tubular basement membrane is thickened and it splits up the peritubular capillary basement membrane. Peritubular endothelial cell swelling is present. The glomeruli are preserved, with occasional mild thickening of the glomerular basement membrane (Hvala et al., 2005).

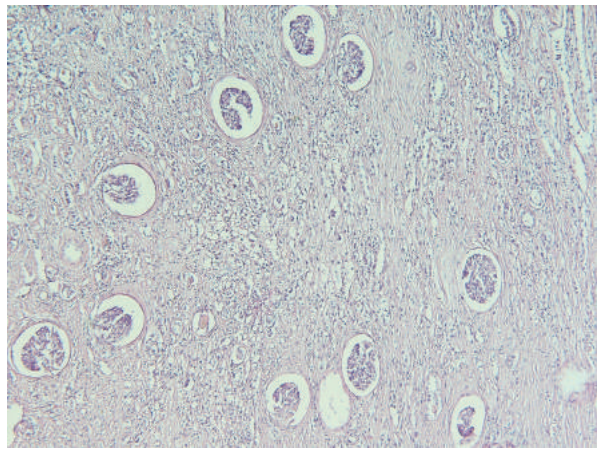

Fig. 90.1 Balkan endemic nephropathy (optical microscopy, haematoxylin-eosin): striped cortical, diffuse hypocellular interstitial fibrosis, tubular atrophy with interstitial oedema. Fibrosis surrounds the proximal tubules, whose epithelia are flattened and atrophic. The structure of the glomeruli shows an ischaemic appearance. Afferent artery hyalinosis and peritubular capillary wall thickening is seen.

Courtesy of Prof. Dr Jasmina Marković—Lipkovski, Institute of Pathology, University of Belgrade, School of Medicine, Belgrade, Serbia.

Treatment and outcome

Since the aetiology is unknown, there is no specific treatment and no prevention strategies for BEN.

Avoidance of exposure to aristolochic acid is difficult (Schiller et al., 2008). Even in such a scenario, an embedded genetic imprint may reside within the kidneys and contribute to the occurrence of tubulointerstitial nephritis in emigrants from endemic regions.

The treatment of BEN is non-specific and similar to other CKD cases of unknown aetiology, including blood pressure control, preferably by using ACE inhibitors or angiotensin receptor blockers, treatment of dyslipidaemia, anaemia, and CKD-related mineral and bone disorder. Patients with ESRD caused by BEN can be treated by either dialysis or kidney transplantation. Careful evaluation for urothelial cancers is mandatory. Since BEN is characterized by acellular urine sediment, the finding of haematuria in a BEN patient is an indication for thorough diagnostic imaging workup (Djokić et al., 2001, 2006).

Upper urothelial cancers in renal transplant recipients occur 50 times more frequently in patients with BEN than in those without BEN (Bašić-Jukić et al., 2007; Zivcić-Kosić et al., 2007).

The life expectancy of BEN patients is similar to that of the general population. BEN specific mortality is 0.65 per 100,000 inhabitants; however, when urothelial cancers also develop, the mortality raises significantly to 4.7–9.0 per 100,000 inhabitants (Bukvić et al. 2000; Miletić-Medved et al., 2005).

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CHAPTER 91

Radiation nephropathy

Lisa M. Phipps and David C. H. Harris

Introduction

Radiation nephropathy is defined as renal injury caused by ionizing radiation. This insult can occur when a patient receives total body irradiation (TBI) as part of the conditioning prior to bone marrow transplantation or local field irradiation for malignancy; damage results from inclusion of the kidney in the field of radiotherapy. It has also been described in patients receiving targeted radionuclide therapy with small molecules radiolabelled with high doses of beta-emitting radionuclides (Stoffel et al., 2001; Breitz, 2004).

Radiation nephropathy is difficult to define and diagnose, as many patients undergoing radiation therapy are also receiving potentially nephrotoxic antineoplastic, antibacterial, antifungal, and antiviral agents, and may also be affected by tumour lysis syndrome. Radiation nephropathy may also result from radiation accidents.

Epidemiology

Patients may develop symptoms and evidence of abnormal renal function from as early as 6 months to as long as 19 years after irradiation treatment (Thompson et al., 1971). The extent of damage is both volume- and dose-related (Cheng et al., 2008). Radiation nephropathy results in a progressive loss of renal function. Previous or concurrent antineoplastic chemotherapy may potentiate the effect of radiation on the kidney (Cohen et al., 1995).

The kidneys are inherently radiosensitive organs and are thus major dose-limiting structures in abdominal radiotherapy fields (Yang et al., 2010). There remains debate about the primary site of injury. The endothelium of both glomerular and peritubular capillaries appears to have the highest proliferative activity and thus is postulated to be the most susceptible to radiation damage (Nadasdy et al., 1994). However, renal tubular epithelial cells seem to be more radiosensitive than epithelial cells from other tissues (Krochak and Baker, 1986). The exact threshold of radiation beyond which radiation nephropathy occurs is yet to be determined. Fractionation decreases the risk. In rodent models, a single dose of irradiation that resulted in radiation nephropathy did not cause the disease when fractionated into multiple, separated doses (Stewart et al., 1994). However, once damage has occurred, the pathological findings are the same, regardless of how the radiation was delivered (Lawton et al., 1991). The growing kidney appears to be more sensitive to irradiation than the adult kidney (Mitus et al., 1969).

Doses of 10 Gy or more involving the abdomen are associated with a > 5% decrease in the size of the primarily irradiated kidney within 1 year of exposure (Yang et al., 2010). The tolerance dose associated with a 5% risk of renal dysfunction at 5 years after single, whole-kidney irradiation was reported to be 23 Gy, and that associated with a 50% risk at 5 years was found to be 28 Gy (Keane et al., 1976). The tolerance dose after TBI is 14 Gy in adults (Tarbell et al., 1988). It is recommended that renal shielding be implemented for doses above this range (Henk et al., 1967).

It is generally accepted that the kidney has some capacity to repair sublethal radiation injury during fractionated irradiation (Dewit et al., 1990). This has been demonstrated experimentally in Wistar rats (Yildiz et al., 2000). Previous renal irradiation results in a loss of re-irradiation tolerance. This was demonstrated in renal-irradiated mice administered a range of second (single) doses after either a 2- or 26-week period. Doses required to give a 50% incidence of damage (RD50) were significantly lower than those causing RD50 following initial treatment alone (1.4 Gy compared to 3.3 Gy) (Stewart et al., 1994).

With regards to environmental radiation, such as atomic bomb or nuclear power plant explosions, the doses that people close to the event are exposed to will likely result in death from bone marrow or gastrointestinal failure before renal impairment would have time to develop (Cohen, 2000). Long-term, low-dose environmental exposure (levels of radiation above background levels, yet below that which could induce acute effects, usually associated with cell death) may result in chronic radiation nephropathy. Evidence of histopathological changes consistent with radiation nephropathy (glomerular and tubular degeneration, desquamation, regeneration, and nuclear pyknosis) has been detected in Ukrainian patients living in areas radiocontaminated by the Chernobyl nuclear reactor accident (Romanenko et al., 2001). An increased incidence of pre-eclampsia and renal impairment in pregnant women has also been associated with environmental radiation exposure. A five-fold increase in pre-eclampsia was demonstrated in women from Belarus in the 4 years after the Chernobyl reactor accident (Petrova et al., 1997) although other factors could explain this.

Clinical features

The clinical presentation of radiation nephropathy falls into four broad categories, based on clinical features and timing of onset (Krochak and Baker, 1986) (Table 91.1).

Acute radiation nephropathy

This presents with an abrupt onset of renal dysfunction, 6–12 months after exposure. The reason that nephropathy does not manifest until at least 6 months after radiotherapy is due in part to mitotic rate of renal tubule cells, as radiation-induced cell

Table 91.1 Clinical syndromes associated with radiation nephropathy

Syndrome	Onset	Clinical features
Acute radiation nephritis	6–12 months	Abrupt onset, raised serum creatinine, anaemia, hypertension, proteinuria, microscopic haematuria
Chronic radiation nephritis	1–19 years	Insidious onset, features of chronic renal failure
Hypertension	From 18 months	May be benign or malignant, with retinopathy, congestive heart failure, and encephalopathy
Asymptomatic proteinuria	From 18 months	Intermittent proteinuria, normal serum creatinine

death is expressed at the time of the next mitosis (Soranson and Denekamp, 1986).

Patients may present with symptoms of advanced renal failure, with lethargy, oedema, headaches, and shortness of breath. Hypertension is an almost universal finding. This is thought to be due in part to the systemic effect of radiation, resulting in increased peripheral resistance, which induces an increase in systemic blood pressure. Volume expansion and renovascular disease may also play a role. Renal artery stenosis as a complication of abdominal irradiation has been well described (Dean and Abels, 1945; Staab et al., 1976; Gerlock et al., 1977; McGill et al., 1979).

Patients have increased serum creatinine, proteinuria, and microscopic haematuria. There may be an associated significant anaemia, contributing to the patient's symptomatology (Luxton and Kunkler, 1964). The anaemia is usually hypochromic microcytic and can be due in part to haemolysis, although a positive response to erythropoietin therapy in patients with radiation nephropathy suggests that erythropoietin deficiency plays a substantial role (Cohen, 2000).

Haemolytic anaemia is due to thrombotic microangiopathy (TMA) (Breitz, 2004). The presentation of TMA may range from mild and subclinical, with fragmented cells on blood smear and low platelet count, to a fulminant presentation with thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome. How much TMA is attributable specifically to radiation exposure is difficult to ascertain, as affected patients are often exposed to other agents known to cause this syndrome (e.g. chemotherapy, immunosuppressants).

The prognosis of acute radiation nephropathy has been linked to the severity of the hypertension (Krochak and Baker, 1986). Patients who survive the acute phase are left with varying degrees of chronic renal impairment. The renal dysfunction is not always progressive.

Chronic radiation nephropathy

This may occur as a sequela of acute radiation nephropathy, or present more indolently. Cases have been reported to present as late as 19 years after exposure to radiotherapy. Patients present with features of chronic renal impairment. Imaging reveals small atrophic kidneys. Chronic radiation nephropathy has also been described in patients exposed to long-term, low-dose environmental radiation (Romanenko et al., 2001).

Benign or malignant hypertension

Hypertension is a prominent feature of both acute and chronic radiation nephropathy, but may occur in isolation (Cohen, 2000). Benign hypertension can occur from 18 months to years after exposure. Benign hypertension may develop into malignant hypertension (see Chapter 216) over many years. Malignant hypertension occurs within the same time frame as benign hypertension. Patients may present with symptoms of retinopathy, congestive heart failure, pleural and pericardial effusions, encephalopathy, and seizures (Luxton, 1961; Tarbell et al., 1988). Renal impairment is not usually a prominent feature.

Asymptomatic proteinuria

Proteinuria may occur in the absence of abnormal renal function. It may be intermittent. It has not been demonstrated to progress to renal impairment (Krochak and Baker, 1986; Breitz, 2004).

Investigations

Serum biochemistry

Serum urea and creatinine are raised consistent with the fall in GFR. There is a tendency towards hyperkalaemia, due to suppression of the renin–aldosterone axis (Cohen, 2000). Lactic dehydrogenase may be raised if haemolysis is present.

Haematology

The degree of anaemia is disproportionately worse than would usually be expected for the degree of renal impairment. Blood film may reveal evidence of haemolysis. Thrombocytopenia may be noted, in the presence of underlying TMA.

Urine

Urinalysis may reveal proteinuria, microscopic haematuria, and occasional pyuria. Proteinuria is generally non-nephrotic, up to 2 g/day (Cohen, 2000). Urinary excretion of β_2 microglobulin may be increased, reflecting underlying tubular cell damage (Dewit et al., 1990).

Nuclear medicine scans

Technetium-labelled diethylene triamine pentaacetic acid (Tc-DTPA) can detect a fall in GFR as early as 6 months post irradiation in affected individuals, even in the presence of a normal serum creatinine (Dewit et al., 1990). Dimercaptosuccinic acid (DMSA) scintigraphy can demonstrate a decline in tubular function from as early as 6 months after exposure (Dewit et al., 1990).

Renal biopsy

There are limited biopsy studies of humans early in the disease process. As a result, the majority of specimens show changes of end-stage kidney damage, in which the initial injury can no longer be recognized (Fajardo et al., 1976). There are morphological similarities between radiation nephropathy and haemolytic-uraemic syndrome (see Chapter 174). There are no pathognomic changes, and diagnosis is suspected based on clinical features, consistent history, and the following pathological findings:

Glomeruli

There may be aneurysmal dilatation of capillary loops, obliteration of tufts, and segmental or total glomerulosclerosis (Guinan et al.,

1988; Borg et al., 2002). There is arteriolar intimal thickening and endothelial cell dropout. There may be evidence of obstruction of the glomerular capillaries by platelets and fibrin (Fajardo et al., 1976). Mesangial hyperplasia is a prominent feature (Tarbell et al., 1988). There is often amorphous material separating glomerular endothelium from the glomerular basement membrane (Figs 91.1 and 91.2). On electron microscopy this material appears to be basement membrane-like material deposited on the endothelial aspect of the basement membrane.

Tubules and interstitium: atrophic tubules with hyaline casts are prominent, as is interstitial fibrosis (Kapur et al., 1977; Lawton et al., 1991).

Vessels: segmental arteries may display endothelial proliferation, with evidence of complete occlusion. Smaller arteries and arterioles demonstrate evidence of fibrinoid necrosis.

The electron microscopy changes consist of folded thickened glomerular basement membranes, with areas of attenuation. Endothelial and mesangial cells reveal hypertrophic changes, with an increase both in cell size and cytoplasmic organelles. The nuclei are lobulated and show margination of chromatin. These changes are thought to be a direct effect of radiation damage, as they are not seen in biopsies of patients with malignant hypertension (Kapur et al., 1977). (See Fig. 91.1.)

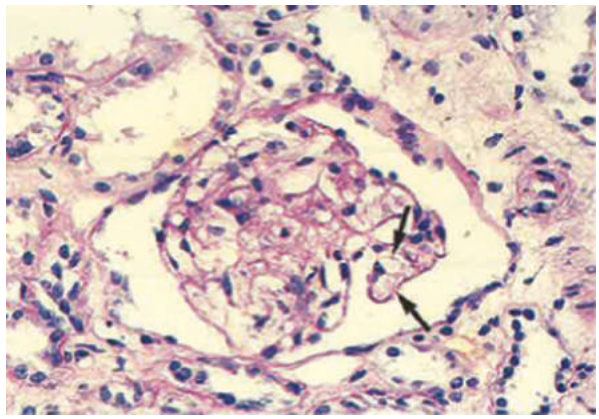

Fig. 91.1 Glomerulus from a patient with radiation nephropathy, showing mesangiolysis, mesangial expansion, thickening, and splitting (arrows) of glomerular capillary wall.

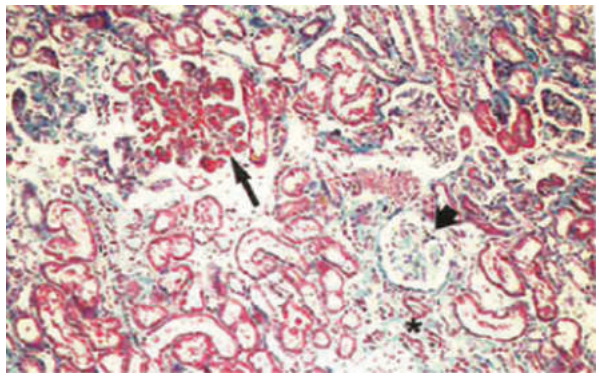

Fig. 91.2 Low power view from a patient with radiation nephropathy demonstrating glomerular thrombosis (arrow) and sclerosis (arrowhead) with tubular degeneration and fibrosis (asterisk).

Pathophysiology and pathology

Glomerular damage

Glomerular endothelial injury was visible at 3 weeks post irradiation in a porcine model (Robbins et al., 1993). Endothelial disruption and leucocyte adherence is followed by subendothelial expansion (Jaenke et al., 1977). There is a concurrent increase in platelet adhesion (Verheij et al., 1994) and subsequent vascular and glomerular microthrombi. Glomerular scarring ensues. Similar changes occur in the peritubular capillaries (Fig. 91.1). Experimental models have demonstrated significant increases in glomerular von Willebrand factor along with decreased levels of ADPase (a potent inhibitor of platelet adhesion) after irradiation, with an associated increase in deposition of fibrinogen, thought to contribute to microthrombi formation (Stewart et al., 2001).

The initial endothelial disruption results in filtrate extruding from the capillaries, with protein and other high-molecular-weight blood components escaping into the extravascular space. This protein gradually becomes insoluble, resulting in impaired diffusion of oxygen and other essential metabolites (Breitz, 2004).

Tubular damage

Tubular epithelial cells appear to be more radiosensitive than epithelial cells from other tissues (Emery et al., 1970). Radiobiological data reveal that tubular epithelial cells have limited capacity to repair lethal and sublethal damage (Deschavanne et al., 1980), particularly if exposed to unfractionated radiation. The tubular compartment may be further damaged indirectly by ischaemia secondary to radiation injury of the renal microvasculature (Krochak and Baker, 1986). Constriction of the tubular lumen at the origin of the proximal tubule (the glomerulotubular neck) has been demonstrated in porcine and rat radiation nephropathy (Cohen et al., 2000).

Hypertension

In large field or total body irradiation, increases in peripheral resistance may also induce a compensatory increase in systemic blood pressure (Krochak and Baker, 1986). In experimental rats hypertension occurred after TBI, irrespective of renal shielding, however the degree of hypertension was less in the renal-shielded group (Wachholz and Casarett, 1970).

Treatment and outcome

Renal protection in the form of blocking or shielding devices to decrease the dose of irradiation to the kidneys has been shown to decrease the incidence of radiation nephropathy. Partial renal shielding during TBI has been demonstrated to reduce the incidence of radiation nephropathy from 29% with no shielding to 14% with 15% renal shielding, and to 0% with 30% renal shielding (Lawton et al., 1992). The Wilms Tumour Study group from the United Kingdom recommends renal shielding during radiotherapy after unilateral nephrectomy for Wilms tumour (Taylor, 1997).

As with all renal diseases, hypertension needs to be controlled. In experimental models, the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists (ARBs) appears to have additional benefits above those of other classes of antihypertensive agents (Cohen, 2000). The mechanistic basis for the increased efficacy of these agents is uncertain but may include their anti-inflammatory, antifibrogenic, and antimitogenic activity

(Molteni et al., 2001; Cohen et al., 2002; Suzuki et al., 2003). It has been hypothesized that they act to limit the consequences of endothelial cell damage (Moulder et al., 1998b; Molteni et al., 2001) by prevention of radiation-induced proliferation (Moulder et al., 2002a). The initiation of ACEI or ARB therapy before the clinical onset of experimental radiation nephropathy has been demonstrated to provide additional benefits in slowing the progression of the renal disease (Cohen et al., 1996). Whether a similar benefit of early therapy occurs in human subjects is yet to be determined.

Aspirin may have a preventative effect by inhibiting the increased platelet adhesion (Sinzinger and Firbas, 1985). There is experimental evidence for a beneficial effect of dexamethasone in rats (Geraci et al., 1992); however, such a benefit has not been demonstrated in humans (Baldwin and Hagstrom, 1962).

Despite evidence of protection in other radiation-induced injuries (such as that of leucocytes) there has been no demonstrated benefit from the use of antioxidants such as vitamin A (Balabanli et al., 2006) and retinoic acid (Moulder et al., 1998a, 2002b) in the treatment of radiation nephropathy (Cohen et al., 2009).

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CHAPTER 92

Urate nephropathy

Duk-Hee Kang and Mehmet Kanbay

Introduction

Gout is recorded from ancient times, but hyperuricaemia seems to be increasing in incidence now. Its association with nephropathy dates back to lead poisoning (Chapter 88), but it is now clear that there are genetic (and very likely other) explanations for this coincidence (Chapter 316), it is not simply that urate levels or crystals are necessarily nephrotoxic.

Renal damage induced by hyperuricaemia

In urate oxidase knockout mice, uric acid rapidly increases in serum, and precipitates in the renal tubules, resulting in acute kidney injury (AKI) (Wu et al., 1994). This experimental model may share some features with the human tumour lysis syndrome; however, it may not be appropriate for understanding the renal effects of protracted milder hyperuricaemia.

Recent data have shown that moderate and persistent uric acid elevations may also be detrimental to the kidney. A rat model of hyperuricaemia, using uricase inhibitor oxonic acid, enabled studies of renal damage associated with this condition. These hyperuricaemic rats showed preglomerular arterial disease, renal inflammation, and hypertension, via activation of the renin–angiotensin system (Kang et al., 2002; Mazzali et al., 2002; Nakagawa et al., 2003). It has been speculated that the resulting thickening and macrophage infiltration of the afferent arteriole walls may induce postglomerular ischaemia. The reduction in vascular lumen could also provide a stimulus for the increase in renin expression, which contributes to the development of severe arterial hypertension (Mazzali et al., 2001, 2003; Kang et al., 2002). Furthermore, there is evidence that the arteriolopathy also leads to ineffective autoregulation and increased transmission of systemic pressures to the glomerulus (Sanchez-Lozada et al., 2002, 2005), which can worsen the renal damage. In addition, uric acid turned out to be pro-oxidative under certain circumstances (Bagnati et al., 1999).

Several epidemiological studies have found that serum uric acid is an independent risk factor for the development and progression of chronic kidney disease (CKD). In one study, hyperuricaemia was associated with a 10.8-fold higher risk in women and a 3.8-fold higher risk in men for the development of CKD, compared to subjects with normal uric acid levels (Iseki et al., 2004). This increased risk was independent of age, body mass index, systolic blood pressure, smoking, and proteinuria. An elevated serum uric acid was also associated with a significantly increased risk of CKD in a study on > 49,000 male individuals (Tomita et al., 2000).

Urate (gout) nephropathy

Gout is a disorder of purine metabolism, characterized by hyperuricaemia and urate crystal deposition within and around the joints (Richette and Bardin, 2010). The most important single risk factor for developing gout is the raised serum uric acid level.

The recognition of increased comorbidity burden in patients with gout rendered it as a systemic disorder rather than simply a musculoskeletal disease. Older studies reported that 25% of gout patients had proteinuria, 50% had renal insufficiency, and 10% to 25% developed end-stage renal disease (Brochner-Mortensen, 1958; Talbott and Terplan, 1960). More recently, in a large retrospective cohort study, Primatesta et al. (2011) found that, out of 177,637 gout patients, more than half (58.1%) had one or more comorbidities, including hypertension (36.1%), dyslipidaemia (27.0%), diabetes (15.1%), and ischaemic heart disease (10.2%), as the most common ones. The prevalence of CKD in this population was 3.2%. However, in other studies, the prevalence of CKD among patients with gout was much higher: 39% (Fuldeore et al., 2011) and 30% (Wu et al., 2012). These discrepant findings may be due to differences in patient selection criteria and in the definitions of CKD.

In autopsy studies, renal histologic abnormalities have been described in as many as 75–99% of patients with gout. Gout nephropathy (also known as chronic uric acid nephropathy or urate nephropathy) is a form of CKD induced by the deposition of monosodium urate crystals in the distal collecting ducts and the medullary interstitium, associated with a secondary inflammatory reaction. Other histologic findings include arteriolosclerosis, glomerulosclerosis, and tubulointerstitial fibrosis. Urate crystal deposition has previously been considered as the mediator of renal injury (Greenbaum et al., 1961); however, these deposits were found to be focal rather than diffuse (Linnane et al., 1981). The diagnosis of gout nephropathy may often be problematic, as histologic findings may be indistinguishable from benign nephrosclerosis or from age-associated renal changes.

In patients with gout, the renal blood flow was found to be disproportionately low in comparison with the glomerular filtration rate (Berger et al., 1975; Yu et al., 1979; Yu and Berger, 1982). The fractional excretion of uric acid is usually < 10%. Proteinuria occurs in a minority of cases, and it is usually mild to moderate. The urinary sediment also shows minor or no changes. On the other hand, hypertension is very common, occurring in 50–60% of patients, and its prevalence increases as the renal function gets worse. Serum creatinine is usually normal or only mildly increased (Berger and Yu, 1975; Yu and Berger, 1982; Yu et al., 1979). An excessively high serum uric acid in relation to serum creatinine

(e.g. > 9 mg/dL vs < 1.5 mg/dL, > 10 mg/dL vs 1.5–2.0 mg/dL, or > 12 mg/dL vs > 2.0 mg/dL) may evoke the diagnosis of gout nephropathy.

Urate (gout) nephropathy seems to be related to other factors than hyperuricaemia alone. This is suggested by the focal nature of renal uric acid crystal deposition, the inconsistent response to uric acid-lowering therapy, and the common association of gout with other risk factors for CKD.

Management of urate nephropathy

Some studies suggested that reduction of serum uric acid could improve gout nephropathy (Briney et al., 1975; Patial and Sehgal, 1992), whereas others did not confirm such benefits (Rosenfeld, 1974). However, it seems reasonable to try to lower serum uric acid in subjects with hyperuricaemia, especially when it is markedly elevated (> 10 mg/dL). The consumption of uric acid-raising foods should be reduced, including those with high purine content, fructose, and alcohol drinks.

In patients with CKD, uricosuric agents are known to be ineffective (Perez-Ruiz et al., 1998). On the other hand, xanthine oxidase inhibitor allopurinol is a potent uric acid-lowering agent. However, severe hypersensitivity reactions to allopurinol have been reported, including Stevens–Johnson syndrome, with fever, liver dysfunction, and AKI (Anderson and Adams, 2002). Most individuals with allopurinol hypersensitivity were found to be human leucocyte antigen (HLA)-B58 positive; therefore, screening for HLA-B58 may be considered before allopurinol prescription, in order to avoid such potentially life-threatening events (Jung et al., 2011). Furthermore, high doses of allopurinol may cause xanthine or allopurinol crystal intratubular deposition, leading to a worsening of the renal disease.

An alternative to allopurinol is febuxostat, a non-purine-analogue inhibitor of xanthine oxidase. Dose adjustment of this drug is not required in patients with impaired renal function and no cases of hypersensitivity syndrome have been reported with its use (Becker et al., 2005).

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CHAPTER 93

Immune-mediated tubulointerstitial nephritis

Liviu Segall and Adrian Covic

Introduction

Immune-mediated tubulointerstitial nephropathies (TINs) are generally encountered in the context of systemic or extrarenal autoimmune diseases, such as sarcoidosis, Sjögren's syndrome, systemic lupus erythematosus, inflammatory bowel disease, TINU syndrome, and IgG4-related disease. The pathogenesis of these TINs is complex and more or less unclear; it usually involves leukocyte activation, autoantibodies, immune complex deposition, complement activation, and release of inflammatory cytokines and growth factors. Immune-mediated glomerulonephritis or other complications, such as renal stone disease, may sometimes be associated with TIN and contribute to renal damage. Tubulointerstitial inflammation most commonly has a chronic pattern, although acute forms of TIN may also occur. Furthermore, inflammation may be granulomatous (as in sarcoidosis or Crohn's disease) or non-granulomatous. Immunofluorescence staining can sometimes reveal immune complex deposits or anti-tubular basement membrane (TBM) autoantibodies. Systemic immunosuppressive therapies are almost always required to prevent progression to irreversible interstitial fibrosis, tubular atrophy, and end-stage renal disease.

Sarcoidosis

Sarcoidosis is a systemic disorder of unknown aetiology that usually occurs in young people, 20–40 years old, and is characterized by the presence of non-caseating granulomas in various organs, particularly the respiratory tract (Nunes et al., 2007). It has a slight female predominance (1.5:1) (James et al., 1984; Baughman et al., 2001) and it affects African Americans 3–20 times more often than white people (Iannuzzi et al., 2007). It is additionally discussed in Chapter 156.

The pathogenesis of sarcoidosis is unclear, but it is postulated that exposure to unknown environmental factors triggers an inflammatory response involving macrophages and CD4+ helper T-cell activation, which participate in the formation of granulomas (Newman et al., 1997). A critical role in the development of granulomas is played by cytokines like interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α), interleukin 12 (IL-12), and interleukin 18 (IL-18) (Roach et al., 2002; Baughman et al., 2005; Semenzato et al., 2005). Infectious agents such as *Propionibacterium acnae* (Ishige et al., 1999) and a genetically determined abnormal response to inhaled antigens (Valentonyte et al., 2005) have been suggested, among other factors, as possible contributors to the origin of sarcoidosis.

Many patients with sarcoidosis are initially asymptomatic and diagnosis is evoked by incidental findings of bilateral hilar lymphadenopathy on chest radiographs—a typical feature of this disease. Other patients present with complaints such as persistent dry cough, fatigue, weight loss, fever, night sweats, eye redness, enlarged peripheral lymph nodes, or erythema nodosum (ATS/ERS/WASOG Committee, 1999; Nunes et al., 2007). At onset, 84% of patients have intrathoracic disease and up to 30% show extrapulmonary involvement (Rizzato, 2001); the latter may include skin, liver, spleen, eyes, lymph nodes, central nervous system, salivary glands, mucosae, joints, heart, bone marrow, muscles, and kidneys (Baughman et al., 2003; Nunes et al., 2007). Moreover, sarcoidosis often induces disturbances of calcium metabolism: hyperproduction of vitamin D by activated macrophages in granulomatous lesions causes increased absorption of dietary calcium, which may subsequently lead to hypercalcaemia, hypercalciuria, and renal stone formation (Muther et al., 1981; Singer and Adams, 1986).

The evolution and severity of the disease are highly variable. Spontaneous remission occurs in most patients within a few years; however, in some cases there may be a more chronic and unfavourable course. Pulmonary fibrosis is the most common severe complication (ATS/ERS/WASOG Committee, 1999). Death may result from lung, heart, and central nervous system involvement (Reich, 2002).

The diagnosis of sarcoidosis is based on suggestive clinical and radiographic findings, presence of non-caseating granulomas on biopsies, and exclusion of all other granulomatous disorders, such as mycobacterial, spirochaetal, fungal, and parasitic infections (Nunes et al., 2007; Rao and Sabanegh, 2009). Hypercalciuria (more commonly seen than hypercalcaemia) and elevated serum levels of angiotensin-converting enzyme (ACE) further support the diagnosis; the latter abnormality results from production of ACE by active epithelioid cells within granulomas, but it is not specific for sarcoidosis (Johns and Michele, 1999).

The therapy of sarcoidosis mainly depends on its clinical severity: 30–70% of patients with mild disease never need to be treated. On the other hand, those with cardiac, neurological, renal, or ocular involvement not responding to topical agents or with malignant hypercalcaemia always require systemic anti-inflammatory and/or immunosuppressive drugs. Corticosteroids are the mainstay of therapy, as they impede granuloma formation and are generally efficient against most active clinical manifestations; however, frequent relapses may occur, especially if steroids are stopped too early (Nunes et al., 2007). Antimalarial drugs are indicated in

mild isolated skin involvement (Baughman, 2002). Azathioprine is a useful steroid-sparing agent, as well as methotrexate, which is beneficial in both pulmonary and extrapulmonary disease, particularly cutaneous, ophthalmic, neurologic, and musculoskeletal (Baughman, 2002). Cyclophosphamide has sometimes been used, with good results, in severe steroid-resistant sarcoidosis. More recently, the TNF-α inhibitor infliximab was also shown to be effective in a double-blind study in patients with severe lung disease (Baughman et al., 2006), as well as in some small series and case reports with refractory lupus pernio, uveitis, or central nervous system involvement (Yee and Pochapin, 2001; Baughman and Lower, 2001; Mallbris et al., 2003; Pettersen et al., 2002).

Renal involvement in sarcoidosis (Table 93.1) is generally considered to be rare, but it is probably underestimated (Mahevas et al., 2009). In a series of > 800 patients with sarcoidosis (James 1984), the incidence of clinical kidney disease was reported to be 1%. On the other hand, in small series of biopsy reports, some degree of morphological renal involvement has been described in as many as 50% of cases (Bergner et al., 2003). In practice, renal manifestations can be seen in association with other localizations of sarcoidosis or as the initial and/or sole presentation of the disease (Berliner et al., 2006).

Table 93.1 Renal involvement in sarcoidosis (Berliner et al. 2006)

Hypercalcaemia	Affects 10–20% of patients, can cause acute kidney injury or chronic kidney disease secondary to nephrocalcinosis
Hypercalciuria	Most common renal manifestation, affecting up to 50% of patients, caused by glomerular filtration of excess blood calcium and suppression by calcitriol of parathyroid hormone activity in the nephron; risk factor for nephrolithiasis
Granulomatous interstitial nephritis	The classic renal lesion of sarcoidosis with non-caseating granulomatous inflammation; although found in a substantial number of kidneys at autopsy in patients with sarcoidosis, only represents a very small proportion of clinically relevant renal failure
Glomerular disease	Rare; many different associated lesions, with membranous nephropathy perhaps the most common
Renal tubular dysfunction	Common; may include proximal or distal renal tubular acidosis, Fanconi syndrome, mild urinary concentrating defects or frank diabetes insipidus, and metabolic alkalosis
Renovascular disease	Rare; associated with severe hypertension; may be caused by renal artery stenosis from granulomatous angiitis or renal artery encasement by an external inflammatory mass
Obstructive uropathy	Rare; genitourinary tract structures may be obstructed by external lymphoid masses or direct sarcoid involvement in genitourinary tissues, causing obstructive uropathy

Most often, the renal involvement is secondary to the vitamin D and calcium metabolism abnormalities associated with sarcoidosis. Nephrolithiasis has been reported in up to 14% of patients (Muther et al., 1981; Singer and Adams, 1986), whereas nephrocalcinosis is thought to be the main cause of end-stage renal disease (Muther et al., 1981; Casella and Allon, 1993). Obstructive uropathy may also occur, as a result of retroperitoneal granulomas, retroperitoneal fibrosis, renal stones, or ureteral involvement (Gil et al., 2010). Sarcoidosis-related glomerular diseases are rare and their mechanisms are unclear (Göbel et al., 2001); cases of membranous nephropathy (Toda et al., 1999), diffuse proliferative or crescentic glomerulonephritis (Van Uum et al., 1997), and focal segmental glomerulosclerosis (Casella and Allon, 1993) have been described so far.

Sarcoid tubulointerstitial nephritis (TIN) is a less common cause of renal impairment. Autopsies of patients with sarcoidosis found TIN in 7–23% of cases, but many of these were asymptomatic (Longcope and Freiman, 1952; Berliner et al., 2006).

The two largest series of patients with sarcoid TIN published so far included 94 (Berliner et al., 2006) and 47 cases (Mahevas et al., 2009), respectively. These studies have shown that, in contrast with the female predominance of pulmonary sarcoidosis, the sex ratio in patients with TIN is approximately 1.76:1 in favour of males. The most common urinary abnormality is moderate proteinuria, usually < 1.0 g/day. Microscopic haematuria and sterile pyuria are found each in 20–30% of cases, while glycosuria and hypercalciuria are less frequent. At presentation, most patients have severe renal dysfunction, with a mean serum creatinine of 4.8 mg/dL (Berliner et al., 2006) and an estimated glomerular filtration rate (GFR) of 20 mL/min per 1.73 m^2 (Mahevas et al., 2009). The large majority also have extrarenal localizations of sarcoidosis, although chest radiographs are often normal. Serum ACE is typically increased; however, due to its low specificity and lack of correlation with kidney disease severity, it is not useful as a diagnostic tool, but mainly as a marker of disease activity and response to therapy (Berliner et al., 2006).

On renal biopsy, the interstitial inflammatory infiltrate is confined mainly to the renal cortex (Longcope and Freiman, 1952) and has a granulomatous pattern in about 80% of cases; yet, no granulomas are found in the remainder 20% (Mahevas et al., 2009). Sarcoid granulomas are non-caseating and consist of macrophages, CD4+ T lymphocytes, and multinucleated giant cells (Utas et al., 1999; Göbel et al., 2001). Gallium-67 radiotracer scanning has been used to help diagnosis or to monitor disease activity, especially in patients with pulmonary sarcoidosis; however, the sensitivity and specificity of this test for the renal disease are unknown and its value as a diagnostic tool is questionable (Pagniez and Delvallez, 1989; Berliner et al., 2006).

Corticosteroids are very efficient for the treatment of renal sarcoidosis (Hannedouche et al., 1990; Brause et al., 2002; Robson et al., 2003; Rajakariar et al., 2006) and are capable to induce remission even in patients with advanced kidney disease (Simonsen and Thysell, 1985). However, renal function recovery is often incomplete, particularly in cases with chronic and irreversible lesions (Hannedouche et al., 1990; O'Riordan et al., 2001; Brause et al., 2002). Serial renal biopsies in treated patients may show disappearance of granulomas, but no changes or even worsening of interstitial fibrosis (Farge et al., 1986; Hannedouche et al., 1990).

The appropriate intensity and duration of therapy is unclear; however, it appears that prolonged administration is required to

prevent progression to end-stage renal disease. Most protocols suggest an induction dose for prednisolone of 0.5–1 mg/kg per day, given for at least 6–12 months, with subsequent tapering to the minimal effective maintenance dose (Newman et al., 1997; O'Riordan et al., 2001; Brause et al., 2002; Berliner et al., 2006). If steroids are tapered or withdrawn too rapidly, relapse and progression of sarcoidosis can occur (Singer and Evans 1986; Robson et al., 2003; Joss et al., 2007; Mayer et al., 2008). Fortunately, relapses usually respond to increased steroid doses (Hannedouche et al., 1990; Mills et al., 1994). In the aforementioned study by Mahevas et al., all 47 patients were initially treated with prednisone, for a median duration of 18 months, and 10 of them also received intravenous pulse methylprednisolone. The mean estimated GFR (eGFR) gradually increased from 20 to 44 (after one month), to 47 (after 1 year), and to 49 mL/min per 1.73 m^2 (after a median follow-up of 24 months). Renal function long-term improvement was directly correlated with the response obtained at 1 month and inversely related to the initial histologic fibrosis score. Relapses occurred in 17 patients and these were purely renal (N = 3), purely extrarenal (N = 10), or both (N = 4) (Mahevas et al., 2009).

Various steroid-sparing drugs have been tried in steroid-dependant, intolerant, or refractory cases, but experience with such agents is very limited (Thumfart et al., 2005). In a 13-year-old boy with sarcoid TIN (initially treated with steroids, but having developed steroid toxicity), therapy with infliximab led to partial recovery of renal function and disappearance of renal granulomas on biopsy (Thumfart et al., 2005). Mycophenolate mofetil (Moudgil et al., 2006) and mizoribine (Ito et al., 2009) were also shown to successfully maintain remission in two isolated cases of paediatric patients with TIN.

Patients with sarcoidosis have received transplanted hearts, lungs, livers, and kidneys without an apparent increase in morbidity compared with other transplant recipients (Padilla et al., 1997). However, little is known about the incidence rate and outcomes of sarcoidosis recurrence in renal allografts. In a series of 18 patients (Aouizerate et al., 2010), after a median follow-up of 42 months, the patient and graft survival rates were 94% and the mean GFR was 60 mL/min per 1.73 m^2; recurrence of sarcoidosis was seen in five patients (27%), with extrarenal involvement in two and renal involvement in three cases.

Systemic lupus erythematosus

Lupus nephritis is discussed more broadly in Chapter 161 and following chapters.

Systemic lupus erythematosus (SLE) is characterized by abnormalities of immune regulation and loss of self-tolerance, triggering systemic autoimmune reactions. These reactions include the activation of autoreactive B cells that produce antibodies against nuclear and other antigens. Circulating immune complexes are deposited at multiple sites, including the kidneys, where they induce complement activation and a massive cascade of inflammatory events (Benigni et al., 2007). Immune complex deposition and inflammation occur in both the glomeruli and the tubulointerstitium and, if left untreated, they may result in scarring and irreversible chronic kidney disease (Lahita 2004).

Glomerulonephritis (GN) is the most prominent and best studied feature of lupus nephritis (LN). Moreover, the current approach to the treatment of LN is largely guided by the International Society of Nephrology/Renal Pathology Society classification of the GN (Weening et al., 2004). Lupus nephritis, including its pathogenesis, clinical manifestations, diagnosis, and therapy, is described in detail elsewhere in this book; therefore, we shall focus in the following only on some particularities of the tubulointerstitial component.

Tubulointerstitial involvement is very common in patients with LN (Hsieh et al., 2011), although its clinical manifestations are hardly remarkable. The urinary signs of tubulointerstitial damage, like haematuria and pyuria, are non-specific and difficult to distinguish from those of GN. Isolated tubular proteinuria is exceptional and renal tubular dysfunctions, such as impaired urine concentrating ability and renal tubular acidosis (RTA), are rarely clinically significant (Balow, 2005).

However, the presence and severity of tubulointerstitial damage on renal biopsy is recognized as a risk factor for progression to end-stage renal disease (Schwartz et al., 1982; Esdaile et al., 1989; Nath, 1992; Hsieh et al., 2011), while, in contrast, the NIH activity index, which primarily assesses glomerular inflammation, does not have a similar prognostic value (Austin et al., 1983; Esdaile et al., 1989; Neumann et al., 1995). Furthermore, the presence of tubulointerstitial scarring is more predictive of subsequent renal failure than glomerular scarring (Schwartz et al., 1982; Esdaile et al., 1989; Hsieh et al., 2011). Unlike GN, the severity of TIN does not correlate with titres of serum anti-double-stranded DNA (anti-dsDNA) antibodies (Hsieh et al., 2011) and, occasionally, TIN can occur independently of GN (Singh et al., 1996; Mori et al., 2005; Moyano et al., 2009). These data indicate that, in LN, the pathogenic mechanisms of TIN may be somewhat different from those involved in the GN (Chang et al., 2011).

Immune complexes are found in the tubular basement membrane (TBM) in about 50% of patients with LN, more frequently in those with endothelial rather than mesangial GN pattern (Stewart Cameron, 1999). Tubulitis (active infiltration and invasion of tubules by mainly lymphocytes and monocytes) is often seen in active disease, whereas in more chronic disease, the interstitium is invaded by a variable amount of collagen (Molino et al., 2009). The tubulointerstitial infiltrate is often organized into well-circumscribed T:B cell aggregates or into germinal centres containing follicular dendritic cells, both of these formations being strongly associated with the TBM immune complexes (Chang et al., 2011). Proximal tubular epithelial cells seem to play an active role in tubulointerstitial damage, by releasing proinflammatory cytokines when exposed to anti-dsDNA antibodies (Yung et al., 2005). Interestingly, titres of autoantibodies against monomeric C-reactive protein correlate positively with interstitial inflammation, tubular atrophy, and interstitial fibrosis, suggesting a possible role for these antibodies in the pathogenesis of TIN (Tan et al., 2008). Cases have been reported in which tubulointerstitial inflammation was linked to immune complex deposition in the capillary walls of the interstitium (Hayakawa et al., 2006) or to CD8+ cytotoxic T cells (Omokawa et al., 2008).

Immunoglobulin G4-related disease

Immunoglobulin G4-related disease (IgG4-RD), also known as IgG4-related multiorgan lymphoproliferative syndrome (IgG4-MOLPS), is a systemic disorder characterized by increased levels of serum IgG4 and infiltrates of IgG4-producing plasma cells, together with fibrosis, involving multiple organs (Zhang and Smyrk, 2010; Kim et al., 2011; Masaki et al., 2011).

The disease was initially described in the pancreas, as an unusual form of chronic pancreatitis. It was originally called 'primary inflammatory sclerosis of the pancreas' (Sarles et al., 1961), but various other names were later coined, such as 'lymphoplasmacytic sclerosing pancreatitis', 'chronic sclerosing pancreatitis', 'non-alcoholic duct-destructive chronic pancreatitis', and 'inflammatory pseudotumour' (Kawaguchi et al., 1991; Sood et al., 1995; Ectors et al., 1997; Wreesmann et al., 2001). The concept of 'autoimmune pancreatitis' (AIP) was suggested in 1995 by Yoshida et al., who reported a patient with chronic pancreatitis, hyperglobulinaemia, circulating autoantibodies, and corticosteroid sensitivity (Yoshida et al., 1995). Subsequent studies confirmed the autoimmune nature of the disease and, in 2001, Hamano et al., discovered its association with elevated serum levels of IgG4 (Hamano et al., 2001). The idea of a systemic IgG4-related disease emerged in 2003, when Kamisawa et al., described widespread IgG4+ plasma cell infiltrates in patients with AIP (Kamisawa et al., 2003). Indeed, in the following years, it was found that almost every organ can be involved in this disease, including kidneys, liver, gallbladder, gastrointestinal tract, salivary and lacrimal glands, lungs, orbits, breasts, retroperitoneum, aorta, lymph nodes, skin, pituitary gland, and prostate (Kitagawa et al., 2005; Uehara et al., 2005; Zen et al., 2005; Deshpande et al., 2006; Shrestha et al., 2009; Cheuk and Chan, 2010). Although reported worldwide, IgG4-RD has been studied mostly in Japan, where it appears to have a relatively high incidence, possibly due to better diagnosis (Masaki et al., 2011). The diagnostic criteria for IgG4-RD have been recently defined by the group of Umehara et al. (Masaki et al., 2011), as shown in Table 93.2.

Renal involvement in IgG4-RD mainly consists of a TIN with typical plasma cell infiltration and TBM immune complex deposition (Watson et al., 2006; Cornell et al., 2007; Saeki et al., 2010). Glomerular disease may also be present, most commonly as membranous nephropathy (Watson et al., 2006; Saeki et al., 2009; Hill et al., 2009; Raissian et al., 2011) or, sometimes, as membranoproliferative (Morimoto et al., 2009) or crescentic GN (Katano et al., 2007).

In the largest published series of patients with IgG4-related kidney disease (n = 35) (Raissian et al., 2011), the average age at the time of diagnosis was 65 years (range 20–81) and 86% were men. Most patients (83%) also had extrarenal involvement. High serum IgG, IgG4 or total gamma globulin levels were found in 88% of cases, while 56% had hypocomplementaemia, with low C3 and/or C4 concentrations, and 33% had peripheral blood eosinophilia. Urinalysis revealed proteinuria > 1.0 g/day in eight and haematuria in six of 27 patients. The mean serum creatinine at presentation was 3.6 mg/dL (range, 0.9–9). Renal imaging showed abnormalities in 78% of cases, consisting of small low-attenuation lesions (usually bilateral and multiple), tumour masses or markedly enlarged kidneys. All 35 renal biopsies showed diffuse or multifocal interstitial infiltrates, consisting of plasma cells, mononuclear cells, and eosinophils. Focal mild mononuclear cell tubulitis was seen in most cases. In 30 cases, moderate-to-severe interstitial fibrosis and tubular atrophy was found, whereas five cases showed an acute TIN pattern, with minimal fibrosis. The glomeruli appeared normal or only with a mild mesangial matrix expansion. Immunohistochemistry showed moderate or marked increase in IgG4+ plasma cells in all specimens, and TBM IgG4-containing immune complex deposits in 83%.

The diagnosis of IgG4-related TIN should be considered especially in elderly male patients, presenting with unexplained urinary abnormalities and/or decreased eGFR, hypergammaglobulinaemia, and a history of other inflammatory organ involvement (Kim et al., 2011; Raissian et al., 2011). Radiologic methods such as galium-67 scintigraphy (Saeki et al., 2007), contrast-enhanced computed tomographic (CT) imaging (Takahashi et al., 2007; Kim et al., 2011), and ^{18}FDG-positron emission tomography scan (Nakajo et al., 2007; Lee et al., 2009) are helpful to detect renal and other organ lesions; however, the use of contrast media should be avoided in cases with impaired renal function. Raissian et al. recently proposed a set of criteria for the diagnosis of IgG4-related TIN (Raissian et al., 2011) (Table 93.3)

The differential diagnosis of IgG4-related TIN should take into consideration the so-called idiopathic hypocomplementaemic TIN with extensive tubulointerstitial deposits, an extremely rare disorder, with only 12 cases described so far (Kambham et al., 2001; Vaseemuddin et al., 2007; Gupta et al., 2010); however, it is currently believed that this entity might in fact be nothing else but unrecognized IgG4-TIN (Raissian et al., 2011). Other diseases that need to be excluded are Sjögren syndrome and lupus nephritis, which may have clinical similarities but usually no IgG4+ plasma

Table 93.2 Diagnostic criteria for IgG4-RD (Masaki et al. 2011)

1. Elevated serum IgG4 (> 135 mg/dL) AND
2. Histopathological features including lymphocyte and IgG4+ plasma cell infiltration (IgG4+ plasma cells/IgG+ plasma cells > 40%) with typical tissue fibrosis or sclerosis.

Note:

- It is necessary to distinguish IgG4-RD from other disorders, including sarcoidosis, Castleman disease, Wegener granulomatosis, lymphoma, and cancer
- Patients fulfilling only one of the above criteria are classified as 'suspected IgG4-RD'
- Patient fulfilling both (1) and (2) and having other distinct disorders (designated as 'XX'), are classified as having 'XX disease with suspected association with IgG4-RD'
- Patients diagnosed with IgG4-RD, but refractory to glucocorticoid treatment, should be re-diagnosed

Suspicious IgG4-RD:

1. Presence of only one can be enough for the suspicious IgG4-RD lesion:
   a. Symmetrical swelling of one of the lacrimal, parotid, or submandibular glands
   b. Autoimmune pancreatitis
   c. Inflammatory pseudotumour
   d. Retroperitoneal fibrosis
   e. Histopathological findings are similar to lymphoplasmacytosis or suspected Castleman disease
2. Presence of at least two would be sufficient for suspected IgG4-RD:
   (a) unilateral swelling of one of the lacrimal, parotid, or submandibular glands, (b) orbital tumorous lesion, (c) autoimmune hepatitis, (d) sclerosing cholangitis, (e) prostatitis, (f) patchy meningitis, (g) interstitial pneumonitis, (h) interstitial nephritis, (i) mediastinal fibrosis, (j) thyroiditis or hypothyroidism, (k) hypophysitis, (l) inflammatory aneurysm
3. Common findings in patients with IgG4-RD:
   (a) polyclonal hyper-IgG-gammopathy, (b) elevation of serum IgE or eosinophilia, (c) hypocomplementaemia or presence of immune complex in serum, (d) tumorous lesion or lymphadenopathy with strong accumulation in ^{67}Ga-scan or ^{18}FDG-PET-scan

Table 93.3 Diagnostic criteria for IgG4-related TIN (Raissian et al. 2011)

Histology	Plasma cell–rich tubulointerstitial nephritis with > 10 IgG4 + plasma cells/high power field in the most concentrated field (*mandatory criterion*)
	Tubular basement membrane immune complex deposits by immunofluorescence, immunohistochemistry, and/or electron microscopy (*supportive criterion, present in > 80% of cases*)
Imaging	Small peripheral low-attenuation cortical nodules, round or wedge-shaped lesions, or diffuse patchy involvement
	Diffuse marked enlargement of kidneys
Serology	Elevated serum IgG4 or total IgG level
Other organ involvement	Includes autoimmune pancreatitis, sclerosing cholangitis, inflammatory masses in any organ, sialadenitis, inflammatory aortic aneurysm, lung involvement, retroperitoneal fibrosis
The diagnosis of IgG4-TIN requires the histologic feature of plasma cell–rich TIN with increased IgG4+ plasma cells and at least one other feature from the categories of 'imaging', 'serology', or 'other organ involvement'	

cell interstitial infiltrates; furthermore, in SLE, GN is almost always the dominant feature (Raissian et al., 2011).

IgG4-RD is typically very sensitive to corticosteroids, which is the standard treatment for this disease. The initial response is spectacular, and even fibrotic lesions may show some improvement with this therapy (Masaki et al., 2011). On the other hand, spontaneous remissions, without any treatment, have also been described. As there are no randomized controlled studies comparing steroids to placebo, it is difficult to decide when or which patients should be treated. However, functional impairment of the pancreas, kidneys, lungs or liver can significantly reduce a patient's quality of life and survival duration; therefore, it seems reasonable to initiate steroids in those cases where any of these organs is involved, in order to prevent irreversible damage (Masaki et al., 2011).

Unfortunately, there is yet no consensus regarding the starting dose, the duration of the initial therapy, the tapering schedule, or the maintenance doses of steroids. A clinical prospective study has recently been started by a Japanese group, aiming to establish the optimal treatment strategy for IgG4-RD (Masaki et al., 2011). In this study, glucocorticoid treatment consists in oral prednisolone at an initial dose of 0.6 mg/kg per day, divided into three doses, with tapering by 10% every 2 weeks. A maintenance dose of 10 mg per day is continued for at least 3 months, and a further daily dose of prednisolone is left at the discretion of the attending physician; the final maintenance dose is to be decided in dependence of symptoms and clinical data in each case. The authors have noticed that most patients require 5–10 mg per day of prednisolone as a maintenance dose to prevent relapses, which may occur at a rate of 30–40% after steroid discontinuation (Masaki et al., 2011). Typically, response to treatment can be confirmed within several days. Superficial organs, such as the lacrimal, parotid, and submandibular glands, and lymph nodes, can be monitored by physical examination, but deep organs, like the pancreas or the kidneys, require imaging examination (CT) after 2 weeks of treatment; if the response is insufficient, a differential diagnosis work-up should be redone, to exclude other diseases, such as cancer, lymphoma, Castleman disease, or sarcoidosis (Masaki et al., 2011).

The response to treatment of the IgG4-related TIN has not been well studied but available data suggest favourable outcomes. In the series of Raissian et al., 21 patients were treated with prednisone and two patients additionally received mycophenolate mofetil. After a mean follow-up of 14.5 months, 17 of 19 patients with renal insufficiency showed a decrease in serum creatinine (from 3.5 mg/dL to 1.7 mg/dL), whereas only two patients failed to improve and developed end-stage renal disease. Interestingly, there was no correlation between the renal biopsy findings and the response to therapy, and even patients with extensive interstitial fibrosis responded to steroid treatment. In two cases there was a relapse upon steroid taper. Two patients treated with prednisone had normal renal function at baseline and remained stable on follow-up. In contrast, the five patients who received no treatment showed increasing or persistently elevated serum creatinine (Raissian et al., 2011).

As well as for other organ involvement in IgG4-RD, low-dose steroid maintenance therapy is most likely necessary to prevent relapses of TIN, although there is no consensus upon the recommended duration and dose. Long-term careful observation is required in all patients, regardless of maintenance therapy (Saeki et al., 2007; Aoki et al., 2009). There is little evidence concerning the treatment for relapsed and refractory cases; another course of steroids is usually effective, but other options may also be considered, including azathioprine (Chari, 2007), cyclophosphamide, methotrexate, mizoribine (Nanke et al., 2010), rituximab (Topazian et al., 2008; Khosroshahi et al., 2010), and bortezomib (Khan et al., 2010).

Sjögren syndrome

Primary Sjögren syndrome (pSS) is an autoimmune disorder involving the lacrimal and salivary glands. Its clinical presentation consists of keratoconjunctivitis and xerostomia (sicca syndrome), and its characteristic pathological feature is a lymphocytic infiltrate around the epithelial ducts of these glands. Extraglandular manifestations are seen in about 25% of patients and may include interstitial lung disease, cutaneous vasculitis, peripheral neuropathy, and lymphoma. Secondary Sjögren syndrome occurs in relation with other systemic autoimmune diseases, such as rheumatoid arthritis, systemic sclerosis, and SLE (Aasarød et al., 2000; Maripuri et al., 2009). Sjogren syndrome and related conditions are further considered in Chapter 166.

Kidney involvement has been reported in 4–67% of patients with pSS—this wide variation being probably explained by the different classification criteria used in the studies and the selection of patients (Pokorny et al., 1989; Eriksson et al., 1995; Goules et al., 2000; Bossini et al., 2001; Lin et al., 2010). TIN is the most common underlying renal pathological lesion (Enestrom et al., 1995), typically consisting of a plasmacytoid lymphocytic infiltrate (Maripuri et al., 2009). GN is generally less frequent, tends to develop late in the course of the disease (Skopouli et al., 2000), and may consist in focal segmental glomerulosclerosis, membranous nephropathy, or mesangial proliferative nephritis (Ren et al., 2008; Lin et al., 2010). In some of the largest published series of patients with pSS and biopsy-proven renal involvement, Maripuri et al. found TIN in 71% (chronic TIN in 46% and acute TIN in 25%) and GN in 29% of cases (Maripuri et al., 2009), Ren et al. described TIN in 85% and GN in 15% of cases (Ren et al., 2008), whereas Lin et al.

reported pure TIN in approximately 34%, pure GN in 37%, and combined TIN and GN in 29% of cases (Lin et al., 2010). TIN can manifest with distal (type I) RTA and less often with Fanconi syndrome (Kassan and Talal, 1987; Siamopoulos et al., 1992; Kobayashi et al., 2006). Hyposthenuria (Kassan et al., 1987) and hypokalaemia (Aasarød et al., 2000; Toy and Jasin 2008) may also occur. Distal tubular acidosis is generally asymptomatic but it increases the risk of stone disease and nephrocalcinosis (Moutsopoulos et al., 1991). Among 573 patients with pSS, Lin et al. found 192 patients (33.5%) with renal involvement, of which 126 (65.6%) had proteinuria (0.5 g/day, on average), 96 (50%) had RTA (type I in 91.7% of these), 45 (23.4%) had kidney stones and/or nephrocalcinosis, and 41 (21.3%) had renal insufficiency (Lin et al., 2010).

Patients with pSS and extraglandular manifestations are usually treated with systemic corticosteroids and, sometimes, other immunosuppressive drugs. However, there is limited evidence on the outcomes of organ involvement with such therapies, since available controlled and prospective studies were small and specifically designed to evaluate the sicca syndrome (Ramos-Casals et al., 2010). In the case series of Maripuri et al., 20 patients with pSS and biopsy-proven renal disease were treated with steroids (with a median initial dose of 40 mg/day and a median duration of 30 weeks); eight patients remained on maintenance corticotherapy for > 1 year, with a median dose of 5 mg/day. Two patients with severe TIN on biopsy received cyclophosphamide and one patient received rituximab, in addition to steroids. In 16 patients that were followed for more than 12 months, there was a significant improvement in eGFR and proteinuria. None of the patients progressed to end-stage renal disease, after a median follow-up of 38 months (range 3–192). The treatment was well tolerated, with no severe adverse effects attributable to immunosuppressive therapy. In conclusion, the authors suggested that all patients with pSS and renal involvement should receive a course of corticosteroids as first-line treatment (Maripuri et al., 2009). Rituximab might be an option for steroid-refractory cases, as it has shown good results in a controlled trial in patients with pSS and vasculitis (Ramos-Casals et al., 2010); however, the precise role of this drug remains to be defined by future research.

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory disease characterized by mucosal ulcerations of the digestive tract. It includes two main disorders: Crohn disease and ulcerative colitis. IBD results from a genetic predisposition to abnormal interactions between intestinal epithelial cells and luminal bacteria (Riis et al., 2007). Crohn disease generally involves the ileum and the colon, but it can affect any part of the intestine, often in a discrete manner, whereas ulcerative colitis involves the rectum and, sometimes, other parts of the colon, in a continuous pattern. Crohn disease can be associated with intestinal granulomas, strictures, and fistulas, but these are not characteristic of ulcerative colitis (Abraham and Cho 2009). Extraintestinal manifestations are common in IBD and may occur in up to 47% of patients (Danese et al., 2005), involving the skin, the eyes, the joints, the biliary tract, and the kidneys (Rothfuss et al., 2006).

Renal and urinary tract manifestations are seen in 4–23% of patients with IBD (Pardi et al., 1998) and often have a significant impact on the quality of life, morbidity, and mortality of these patients (Rothfuss et al., 2006). Malabsorption, bacterial overgrowth, and short bowel syndrome after resection may complicate with enteric hyperoxaluria; this, in turn, may lead to calcium oxalate stone formation, obstructive uropathy, chronic pyelonephritis, and fistulization of the urinary tract, which are probably the most common reno-urinary manifestations of IBD (Banner, 1987; Oikonomou et al., 2011). Proximal tubular dysfunction may often be detected in this setting (Kreisel et al., 1996; Fraser et al., 2001; Herrlinger et al., 2001; Mahmud et al., 2002), sometimes associated with proximal RTA and osteomalacia (Victorino et al., 1986; Pardi et al., 1998). IgA nephropathy and renal amyloidosis have also been described in IBD (Pardi et al., 1998; Filiopoulos et al., 2010).

Tubulointerstitial nephritis may occur in patients with IBD mainly as a result of treatment with 5-aminosalicylic acid (Mahmud et al., 2002; Rothfuss et al., 2006; Jose et al., 2009); however, cases of TIN have also been described independently of drug intake and these are thought to have an autoimmune pathogenesis (Kreisel et al., 1996; Mahmud et al., 1996; Fraser et al., 2001; Herrlinger et al., 2001; Izzedine et al., 2002; Poulou et al., 2006; Marcus et al., 2008; Oikonomou et al., 2011). Autoimmune TIN has been reported in only a few patients with Crohn disease (both children and adults); its occurrence was associated with exacerbation of the bowel disease. Renal biopsies showed a predominant lymphocytic infiltrate with characteristic non-necrotizing granulomas (Archimandritis and Weetch, 1993; Izzedine et al., 2002; Tovbin et al., 2000; Marcus et al., 2008). Response to treatment seems to be rather poor, with both steroids and infliximab (Marcus et al., 2008); all published cases progressed to end-stage renal disease, 30% of them in < 3 years (Oikonomou et al., 2011). One reported patient who underwent renal transplantation experienced deterioration in graft function during a post-transplantation relapse of Crohn disease (Archimandritis and Weetch, 1993). In ulcerative colitis, autoimmune TIN is also very rare; renal biopsy shows intense interstitial mononuclear infiltration with occasional eosinophils, fibrosis and tubular atrophy (Khosroshahi and Shoja, 2006). Hypokalaemia (due to chronic diarrhoea) may also play a role in inducing or aggravating TIN (Oikonomou et al., 2011).

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune cholestatic chronic liver disease, characterized by non-suppurative destruction of interlobular bile ducts, associated with high levels of serum IgM and the presence of circulating anti-mitochondrial antibodies. About 70% of patients with PBC have extrahepatic organ involvement, including the kidneys (Talwalkar and Lindor 2003).

The main feature of PBC-associated renal disease is distal RTA, which is found in one-third of patients, but usually with no clinical significance (Parés et al., 1981; Komatsuda et al., 2010). Only nine patients with TIN and PBC have been reported so far (Macdougall et al., 1987; Kamouchi et al., 1991; Kodama et al., 1996; Lino et al., 2005; Terrier et al., 2008), recently reviewed by Komatsuda et al. (2010). All of those patients were females, with a median age of 56 years (range 36–68). Eight of them had reduced eGFR, five had distal RTA, and five had Fanconi syndrome. The clinical manifestations of tubular involvement were hypokalaemia, bone pains and fractures, and urinary abnormalities, including mild proteinuria, glycosuria, and high urinary levels of β_2-microglobulin and *N*-acetyl-β-D-glucosaminidase. Renal biopsies showed severe

interstitial lymphocytic infiltration, tubulitis, and mild-to-moderate tubular atrophy and fibrosis. On the other hand, only mild or no glomerular or vascular abnormalities were found. In some cases, immunofluorescence revealed glomerular deposits of IgM in the mesangium and/or along the capillary walls. All nine patients were treated with steroids, with good results in seven patients and no effect in two patients (Komatsuda et al., 2010).

Tubulointerstitial nephritis and uveitis syndrome

Tubulointerstitial nephritis and uveitis syndrome (TINU) is a rare disease, of unknown origin, associating ocular and renal inflammation. It usually occurs in young females (Mackensen and Billing, 2009). Since its first description in 1975 (Dobrin et al., 1975), some 200 cases have been published to date.

The pathogenesis of TINU is unclear but it is thought to be immune mediated. Renal tubular and ciliary body epithelia possibly share similar antigens that may account for a cross-reactivity (Izzedine 2008). Abed et al. reported the presence of autoantibodies against a common tubular and uveal antigen in the serum of a TINU paediatric patient (Abed et al., 2008), while Shimazaki et al. published a TINU case in which serum antibodies against a 125-kDa renal and retinal protein were detected (Shimazaki et al., 2008). However, immunofluorescence studies of renal biopsies from patients with TINU could very rarely identify anti-TBM antibody deposition (Morino et al., 1983; Wakaki et al., 2001). On the other hand, TINU has occasionally been described in association with other autoimmune diseases, such as thyroiditis and rheumatoid arthritis, and in some patients with TINU serum antinuclear antibodies, rheumatoid factor, and anticardiolipin antibodies have been found (Mandeville et al., 2001). A recent report of a patient with recurrence of TINU after renal transplantation (Onyekpe et al., 2011) also suggests a role for circulating autoantibodies in the pathogenesis of this disease.

Genetic factors are also thought to be involved, since strong associations with human leucocyte antigen (HLA) haplotypes HLA-DRB1*01 and HLA-DQA1*01 (Levinson et al., 2003; Mackensen et al., 2008), as well as sporadic cases of monozygotic twins (Gianviti et al., 1994; Howarth et al., 2004) and familial clustering (Tanaka et al., 2001b; Dusek et al., 2008) have been reported. Furthermore, a role for recent infections with Epstein–Barr virus, herpes zoster virus, or *Chlamydia trachomatis* (Stupp et al., 1990; Cigni et al., 2003; Mandeville et al., 2001) and exposure to antibiotics or non-steroidal anti-inflammatory drugs (Mandeville et al., 2001) has also been suggested, without conclusive evidence. An interesting finding by Kase et al. was a significant increase in serum levels of Krebs von den Lunge-6 (KL-6) protein (a human glycoprotein secreted by type II pulmonary alveolar cells) in 17 patients with TINU syndrome, as compared to controls. Renal distal tubules also stained strongly with anti-KL-6 antibody, suggesting that high KL-6 levels may reflect the renal lesion of this disease (Kase et al., 2006).

The clinical onset of TINU is often with non-specific symptoms, such as malaise, fatigue, and fever, especially in children. The most common symptoms and laboratory findings are shown in Table 93.4. Ocular symptoms may precede (in 20% of cases) or follow the systemic ones (in 65%), by up to 14 months. (Mandeville et al., 2001; Izzedine 2008). Patients complain of eye redness, pain, photophobia, and blurred vision. The eye involvement consists of uveitis, which is typically non-granulomatous, bilateral, and limited to the anterior segment in about 80% of cases (Mandeville et al., 2001; Mackensen et al., 2007).

Table 93.4 The most common symptoms and laboratory findings in TINU (Mackensen and Billing 2009)

General symptoms	**%**
Fever	53
Weight loss	47
Fatigue	44
Anorexia	28
Weakness	28
Abdominal or flank pain	28
Arthralgias	17
Polyuria, nocturia	8
Ocular symptoms	
Eye pain or redness	77
Blurred vision	20
Photophobia	14
Laboratory abnormalities	
Blood:	
Anaemia	96
High creatinine	90
High ESR	89
High IgG levels	83
Urine:	
Proteinuria	86
High β_2-microglobulin	92
Pyuria	55
Haematuria	42

The renal signs may include pyuria (sometimes, with eosinophiluria), haematuria, and moderate proteinuria. Manifestations of proximal and/or distal tubular dysfunction, such as Fanconi syndrome and distal RTA, are also common (Igarashi et al., 1992; Yao et al., 2011). Renal ultrasound often shows enlarged kidneys with increased echogenicity, but these findings are non-specific (Michel and Kelly, 1998; Kodner and Kudrimoti 2003). Gallium scanning may be more sensitive, but also more invasive and equally non-specific (Mackensen and Billing 2009). The kidney biopsy remains the key diagnostic tool for TIN. Usually, light microscopy reveals a mixed inflammatory infiltrate with mononuclear cells including lymphocytes, plasma cells, and macrophages and, sometimes, also with eosinophils and neutrophils. Non-caseating granulomas have been found in 13% of cases (Dobrin et al., 1975; Mandeville et al., 2001; Herlitz et al., 2007). Immunofluorescence is generally negative, although tubular and glomerular immunoglobulin staining is occasionally observed (Mandeville et al., 2001).

Bone marrow, lymph node, and hepatic granulomas have also been described in some patients (Dobrin et al., 1975; Mandeville et al., 2001; Herlitz et al., 2007).

The differential diagnosis of TINU implies the exclusion of other possible causes of associated eye and kidney disease, such as sarcoidosis, Sjögren syndrome, SLE, Wegener's granulomatosis, Behçet disease, and infections (Mackensen et al., 2007). Other organ involvement (lungs, joints, skin), serology (ANA, ANCA), and biopsy findings are usually decisive.

The prognosis of TINU is favourable in the majority of patients. In several studies, ocular complications have occurred in 21% to 45% of cases, depending on follow-up duration, and consisted mainly of posterior synechiae and, more rarely, of optic disc oedema, cystoid macular oedema, and cataract (Mandeville et al., 2001; Goda et al., 2005; Mackensen et al., 2007). Concerning the kidney disease, the necessity of dialysis, for either acute or chronic renal failure, has rarely been reported (Mandeville et al., 2001); however, no long-term follow-up of nephritis patients has yet been published.

Although uveitis has sometimes been treated with topical steroids, TINU syndrome should be regarded as a systemic disorder and, therefore, as an indication for systemic anti-inflammatory and/or immunosuppressive therapy. Patients with nephritis left untreated may develop end-stage renal disease (Suzuki et al., 2004). However, no clinical trials have been undertaken to test the necessity or the type of treatment for TINU, and the only existing evidence comes from a few reported case series (Mandeville et al., 2001).

Systemic corticosteroids are used in most patients. The response is generally good for both the ocular and the renal disease (Takemura et al., 1999). However, the uveitis recurrence rate may be as high as 50% (Mandeville et al., 2001; Goda et al., 2005) to 100% (Takemura et al., 1999); therefore, its prevention is thought to require a relatively long-term treatment—possibly up to 12 months, (Mackensen et al., 2007). Doses of prednisone about 1 mg/kg per day for 2–3 weeks with subsequent taper are usually administered when renal impairment is severe or prolonged (Takemura et al., 1999). Usually, the renal function quickly returns to normal (Vohra et al., 1999), although increased urinary β_2-microglobulin levels may last for several months (Kobayashi et al., 2000). Even patients who require renal replacement therapy can hope to improve and discontinue dialysis (van Leusen and Assmann, 1988; Mandeville et al., 2001). Nevertheless, a number of patients fail to respond to steroids and show persistent acute inflammatory changes on renal biopsies even after 6–9 months of treatment (Tanaka et al., 2001a; Yanagihara et al., 2009). In cases with such prolonged or with relapsing course, mycophenolate mofetil or ciclosporin seem to be effective (Hinkle and Foster, 2008).

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