CHAPTER

27 Urinary Tract Tuberculosis

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Over a century ago, Osler noted that tuberculosis is the net result of two pathologic processes: "In all tubercles two processes go on: the one—caseation—destructive and dangerous; and the other—sclerosis—conservative and healing. The ultimate result in a given case depends upon the capabilities of the body to restrict and limit the growth of the bacilli."[1]

Perhaps in no other form of tuberculosis are these processes so important in determining the impact of the tubercle bacillus on an organ system as in genitourinary tuberculosis. Progressive destruction and caseating necrosis of the kidney ultimately leading to "autonephrectomy" have long been recognized as possible catastrophic complications of renal tuberculosis. However, progressive ureteral and calyceal scarring seen during healing can result in severe obstructive uropathy and comparable loss of renal function. Therefore, medical and surgical management of genitourinary tuberculosis must focus on both aspects of the tuberculous process, with emphasis on the early diagnosis and prevention of both tissue damage and excessive scarring. Achieving these goals can be challenging because genitourinary tract tuberculosis can be a particularly occult process. This chapter outlines a practical approach to this problem, based on established epidemiologic, pathogenetic, and clinical principles.

ETIOLOGY

Robert Koch first identified the tubercle bacillus in 1882. His classic report defined staining procedures for the direct observation of bacilli in clinical specimens (including the use of aniline dyes for "acid-fastness"), culture techniques on solid medium for the in vitro passage of bacilli isolated from clinical or experimental lesions, and subsequent inoculation of guinea pigs with cultured material to confirm its etiologic role in tuberculosis.[2] Demonstrating an etiologic role for the tubercle bacillus in tuberculosis became the basis of "Koch's postulates," the standard criteria for etiologic research in infectious disease.

Mycobacterium tuberculosis, the human tubercle bacillus, is one of approximately 90 species of higher bacteria with unusual shared structural and tinctorial properties.[3,4] All mycobacteria, members of the genus Mycobacterium, have the ability to take up aniline dyes, such as those contained in carbolfuchsin, and to resist decolorization by washing in alcohol acidified with inorganic acid (e.g., 95% ethanol, 3% HCl). This unique property correlates with the extremely high lipid content of mycobacterial cell walls. Although all mycobacteria are obligate aerobes, they are found in nature in disparate settings: some species are soil and water saprophytes, whereas others are true pathogens of amphibians, reptiles, birds, and various mammals. M. bovis, the bovine tubercle bacillus, has virtually disappeared as a human pathogen in modern societies through tuberculin testing of cattle and pasteurization of dairy products. A variety of mycobacterial species can be pathogenic in humans (e.g., M. avium-intracellulare), whereas others have been characterized as human saprophytes (M. gastri, M. smegmatis). M. tuberculosis is distinguished from the many other "atypical" mycobacteria by its metabolic properties, rate of growth, pigment production, and virulence in experimental infection in guinea pigs, as well as by genomic features that facilitate direct speciation. M. tuberculosis characteristically appears as a small, slender, slightly curved rod 2 to 4 μm in length with a diameter of 0.3 to 0.6 μm. Bacilli can appear singly or in small clusters on clinical specimens. Unlike infected pulmonary secretions where the density of organisms commonly is high, the low density of bacilli in urine samples, as well as their possible confusion with saprophytic mycobacteria, makes urine acid-fast stains impractical for rapid diagnosis. Although M. tuberculosis can grow on simple synthetic media, typically in intertwining aggregates known as serpentine cords, its slow growth rate (15 to 20 hours doubling time) necessitates culture periods of up to 6 to 8 weeks for the appearance of visible colonies. Optimal growth requires high partial pressures of oxygen, as in air, although bacilli can remain viable but metabolically dormant under greatly reduced PO_2. This is particularly relevant for the progression of renal tuberculosis (see later).

The mycobacterial cell wall accounts not only for acid-fast staining, but for some of the important host–parasite

interactions as well. In addition to a peptidoglycan cell wall layer common to conventional bacteria, a second glycan layer encases the organism.[5,6] This arabinogalactan layer is covalently linked to the peptidoglycan layer and also contains esters of mycolic acids, which are very large fatty acids that are unique to mycobacteria. A number of complex glycolipids reside in the outermost layer—"cord factor" (trehalose dimycolate), phosphatides, and sulfatides—but are not covalently linked to the glycan layers.[6] Cord factor is responsible for growth in serpentine cords in vitro and is a virulence factor in vivo.[7] These cell wall moieties (lipoarabinomannan, trehalose dimycolate and its sulfated derivatives) have multiple effects on mycobacterial virulence: they inhibit phagosome maturation and fusion with lysosomes,[6,8] reduce cell surface expression of key host antigen presentation proteins and costimulatory molecules, thus diminishing the presentation of mycobacterial antigens by infected macrophages,[9] and even modulate macrophage survival and apoptosis.[10]

EPIDEMIOLOGY

Tuberculosis and HIV infection are each responsible for approximately 1.8 million deaths worldwide each year (which includes ~400,000 deaths due to dual infections, especially in resource-limited settings).[11] The World Health Organization (WHO) estimates that approximately one third of the world's population is latently infected with M. tuberculosis with approximately 9 million new cases occurring each year. Although more than 90% of cases occur in the developing world with significant overlap among symptomatic HIV infected individuals,[12] 10 to 15 million individuals in the United States are infected with M. tuberculosis, mostly with latent tuberculosis infection.[13,14]

The long-term secular decline in tuberculosis incidence that followed the development of successful antituberculous chemotherapy was disrupted in the 1980s by a decline in the support of tuberculosis control programs, as well as the interrelated challenges of the HIV epidemic, troubling social trends producing growing populations of homeless and incarcerated individuals, and the rising incidence of drug-resistant tuberculosis infections.[15–17] These processes often acted in synergy to produce epidemics of tuberculosis, frequently involving multiply drug-resistant strains, among vulnerable populations in hospitals, correctional facilities, residential care facilities, and homeless shelters.[18,19] The number of reported U.S. tuberculosis cases in 1992 (~26,000) roughly equaled those of 1982, erasing a decade of progress in tuberculosis control. An intensification of tuberculosis control measures, including greater emphasis on intensive initial empiric therapy, sensitivity testing of clinical isolates, and reliance on directly observed therapy, has helped to regain control of the tuberculosis epidemic, and by 2010 only 11,181 new cases were reported.[20]

Tuberculosis in the United States is primarily an urban disease with 75% of the new cases occurring in the 99 metropolitan areas that have populations of more than 500,000. Increasingly, in the United States tuberculosis is found among immigrants and minority groups. Approximately 80% of reported cases in 2010 occurred in Asian, Hispanic/Latino, and African American residents in roughly comparable numbers, whereas whites accounted for only 16% of cases. The nationwide incidence of tuberculosis was 3.6/100,000 overall, with marked variation by ethnicity and immigrant status: the incidence was highest among Asians and Pacific Islanders (22.5/100,000) and was lowest among non-Hispanic whites (0.9/100,000). In 2010 only 40% of cases occurred in native-born individuals, and in many states over 70% of cases occurred among foreign-born individuals. Dual infection with HIV was reported in approximately 10% of cases.[20] In Europe, similar patterns of increased tuberculosis have been seen among immigrants from high tuberculosis incidence countries.[21–23] In addition, relatively high rates of extrapulmonary tuberculosis and drug-resistant tuberculosis have been observed among these immigrant populations.[24,25]

Although the proportion of extrapulmonary disease has nearly tripled from 7.6% to 21% of reported cases of tuberculosis in the United States over the past 40 years, the relative incidence of genitourinary infections among all forms of extrapulmonary tuberculosis has gradually declined.[26] Regional lymph node infections remain the most commonly encountered form of extrapulmonary tuberculosis—genitourinary disease, once common,[27] has declined to 6.5% of extrapulmonary tuberculosis cases in the United States over the past 20 years or so, a frequency roughly comparable to that of tuberculous meningitis.[26] Similar low rates of genitourinary tuberculosis have been reported recently from both low incidence (France)[28] and high incidence countries (Nepal).[29] As outlined later and in Figure 27.1, extrapulmonary tuberculosis is the result of hematogenous spread from a pulmonary site of primary infection. Thus, genitourinary tuberculosis is observed in two clinical settings: commonly, as a late manifestation of earlier clinical or subclinical pulmonary infection and, rarely, as part of the multiorgan infection seen with disseminated (miliary) tuberculosis.

Statistics from the prechemotherapy era indicated that approximately 3% of unselected autopsy patients and 26% of those dying of tuberculosis had evidence of genitourinary tract tuberculosis at autopsy.[30] This high rate of genitourinary disease has declined with effective treatment of pulmonary tuberculosis. Currently, it is estimated that significant genitourinary disease will develop in approximately 4% to 8% of non–HIV-infected individuals with pulmonary tuberculosis if adequate therapy is not instituted.[31]

Traditionally, genitourinary tuberculosis has been a disease of young to middle-aged adults with a slight male predominance.[27,31–34] Although genitourinary tuberculosis has been reported in children,[35–37] it is quite uncommon, and seen today in the rare young child with concomitant miliary disease[37] or in school-age children with somewhat more indolent clinical features similar to those seen in adults.[36] Approximately one quarter of the patients with genitourinary tuberculosis have a history of diagnosed tuberculosis

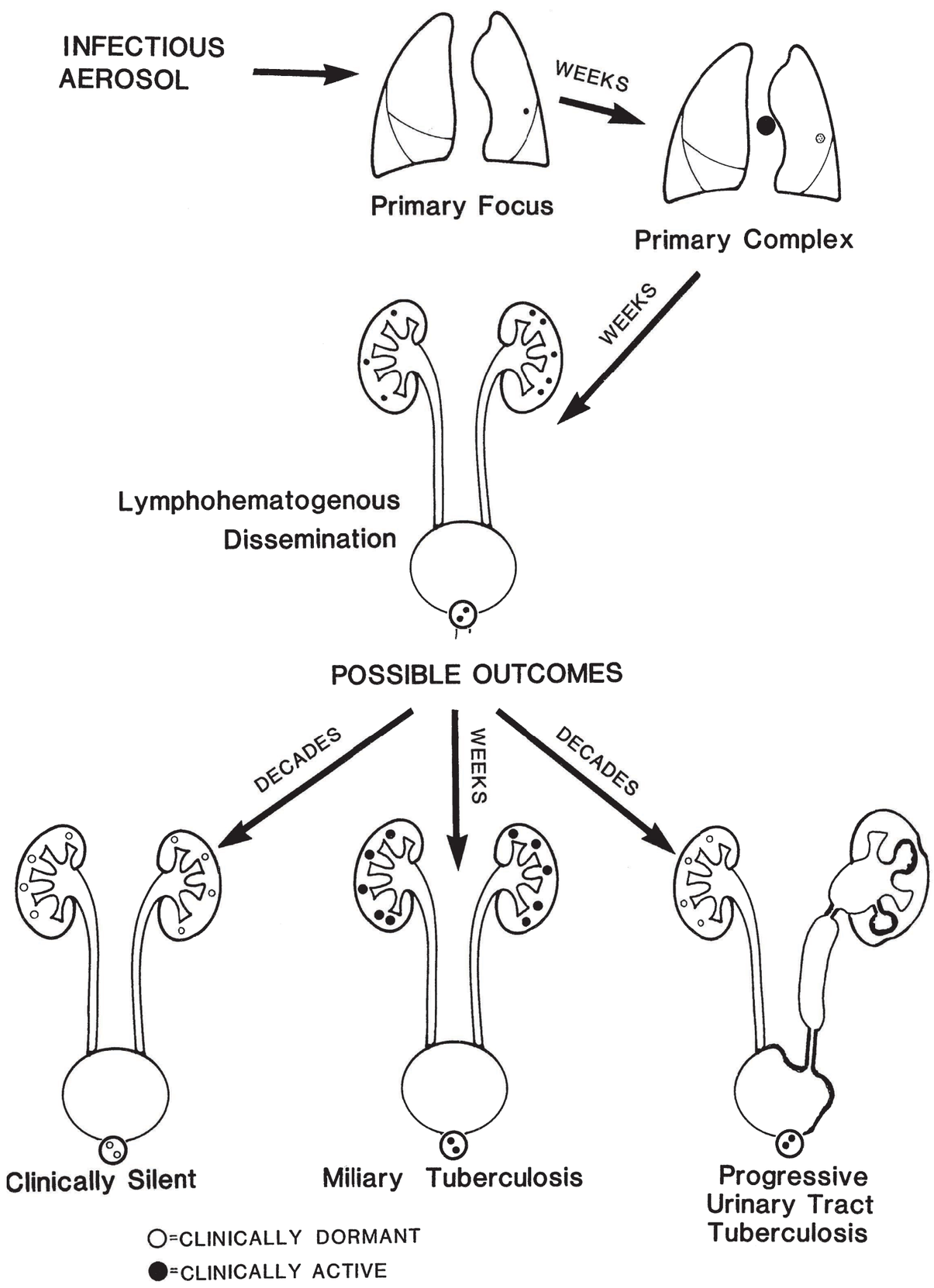


FIGURE 27.1 Schematic representation of the pathogenesis of urinary tract tuberculosis.

(usually of the lung). In an additional 25% to 50% of patients, changes compatible with old pulmonary tuberculosis can be found on chest X-ray films made at the time of diagnosis of genitourinary tract disease.[27,31–33]

Thus, in the non–HIV-infected individual a considerable interval exists between the onset of pulmonary infection and the diagnosis of active genitourinary tuberculosis. Considering patients with early clinical manifestations of primary tuberculous infection (i.e., erythema nodosum, pleurisy, or hilar adenopathy), the time lapse is most commonly 16 to 25 years; intervals exceeding 40 years have been well documented. If one looks at patients with reactivation pulmonary tuberculosis, the time lapse is usually about 4 to 8 years, but still may be as long as several decades.[31,32,38]

There are several epidemiologic implications of these observations. Decreasing the incidence of genitourinary tuberculosis requires the identification and treatment of persons with pulmonary infection prior to the development of extrapulmonary disease. Second, long after the incidence of pulmonary tuberculosis falls, the incidence of genitourinary disease will remain relatively stable, because a reservoir of patients with silent genitourinary tract infection will persist for decades after the incidence of new pulmonary infection falls.[24–26] Thus, the rise in tuberculosis cases that occurred in the late 1980s and early 1990s virtually guarantees an increase in extrapulmonary infections such as genitourinary disease in the next few decades, unless extensive case finding and effective treatment of these individuals are achieved. This task will be rendered particularly difficult because the burden of disease has fallen heavily on those with poorer access to skilled medical care—foreign born, the homeless, the incarcerated, migrant farm workers, and inner city ethnic minority groups.[16,17,20,39] Finally, it is clear that the age of the population with genitourinary tract tuberculosis, and other forms of extrapulmonary tuberculosis, reflects the average age at presentation of active pulmonary tuberculosis—significantly younger among immigrants, urban ethnic minority populations, and the disadvantaged, and over the age of 50 among other groups.[25]

In assessing epidemiologic factors that might predispose to tuberculosis, it is important to emphasize that fewer than 10% of persons with latent tuberculosis infection (reflecting a positive tuberculin skin test or in vitro interferon-γ release assay) ever become ill from this infection.[40] Of this group,

approximately 3% to 5% have manifestations of genitourinary tract disease.[27] In addition to exposure to tuberculosis in high incidence countries, public health factors including crowding, homelessness, poverty, drug addiction, and incarceration, all amplified by the AIDS epidemic,[12] play a significant role in the spread of tuberculosis.

A minimum estimate of clinical tuberculosis in HIV-infected patients is approximately 15% worldwide[11] and 8.6% in the United States,[20] with a somewhat higher incidence (13.8%) in adults 25 to 44 years of age.[41] The annual rate of tuberculosis among tuberculin skin test positive HIV-infected individuals in the United States has been reported to be 35 to 162 cases per 1,000 person years, although in Africa the risk of clinical tuberculosis may be as high as 5% to 10% annually.[42] These variations reflect differences in the prevalence of tuberculosis and immunodeficiency in different population groups. Thus, the rate of tuberculous disease among HIV-infected, tuberculin positive individuals in the United States is roughly 10 times higher than that among comparable HIV-infected, tuberculin negative individuals,[43] and is approximately 80 to 370 times that of the general American population.[44] The continued refinement and availability of antiretroviral therapy combined with antituberculous therapy has altered the natural history of tuberculosis in HIV-infected individuals and, when combined with vigorous public health efforts to identify and monitor treatment, the prognosis of both HIV and tuberculosis in dual-infected patients has improved dramatically.[12,45–47] Dual therapy is often challenging due to drug interactions: for example, rifabutin is required instead of rifampin if a protease inhibitor is used. Fluconazole metabolism is increased in the presence of rifampin[48] and other agents, thus complicating care in these patients. Despite the need for care in constructing the therapeutic regimen, early diagnosis and appropriate therapy of both infections are critical to the patient's survival.[41,44,46,47]

Two epidemiologic patterns of mycobacterial infection are observed in HIV-infected individuals. Individuals from population groups with a low rate of endemic tuberculosis, such as gay men and those with posttransfusion HIV disease, primarily have difficulties with disseminated M. avium-intracellulare infection. In contrast, HIV-infected individuals who either belong to or interact with populations bearing a high rate of endemic tuberculosis (those in developing countries, immigrants from these countries, the homeless, intravenous drug users, prisoners, and, in the United States and other developed countries, the inner city poor) are primarily afflicted with disseminated M. tuberculosis.[44,45] Careful molecular epidemiologic studies have demonstrated that in HIV-infected individuals, outbreaks of tuberculosis resulted in either progressive primary disease or reinfection of individuals whose immunity had been attenuated by the effects of progressive HIV disease.[49,50]

In HIV-infected individuals tuberculosis is often the AIDS-defining illness, not infrequently occurring early in the course of HIV infection. In contrast to other AIDS-related opportunistic infections, the $CD4^+$ count is not a reliable indicator of tuberculosis risk among HIV-infected persons.[44] Extrapulmonary disease, often in conjunction with pulmonary disease, is common,[44] and the time course for the development of disseminated disease may be greatly abbreviated in these individuals. In this setting, genitourinary disease is less commonly seen as an isolated phenomenon, but rather as part of disseminated infection. The incidence of HIV infection among patients with extrapulmonary tuberculosis was significantly elevated in the initial phases of the HIV epidemic,[51] but at present the rate of extrapulmonary tuberculosis in dually infected individuals is comparable to that seen in HIV-uninfected patients.[26] Serial New York City data confirmed aggressive dual therapy led to a reduced rate of extrapulmonary tuberculosis in dually infected individuals.[45]

The coexistence of tuberculosis with HIV infection has already had major public health consequences on the control of tuberculosis. Because HIV infection both increases the burden of infectious tubercle bacilli and obscures the symptoms (owing to the impaired inflammatory response of these immunosuppressed individuals), these people are highly efficient transmitters of tuberculosis. The expected consequence of this is the potential for a marked increase in the occurrence of secondary cases, and even epidemics, in contacts of these individuals, particularly in medical settings, crowded living conditions, prisons, and shelters for the homeless. Those populations most at risk for both HIV infection and tuberculosis, and the coexistence of these two infections, are the same populations with the highest incidence of drug-resistant tuberculosis. The result of this concordance of events is that the tuberculosis that can be amplified by the HIV epidemic includes a high potential for drug-resistant disease, particularly in the former states of the Soviet Union and more generally in resource-limited settings, and can complicate both the management of individual patients and the public health strategies that must be taken to protect the community.[11]

One additional epidemiologic consideration is the possibility that urine from patients with urinary tract tuberculosis could transmit tuberculosis to household members. Vasquez and Lattimer[52] reported a doubling of the incidence of tuberculin positivity among children of parents with active urinary tract tuberculosis without active pulmonary disease. Other observers have been unable to confirm this finding. Our policy has been not to isolate persons with isolated urinary tract tuberculosis but to consider their urine potentially infectious and to maintain contact precautions when handling it.

PATHOGENESIS OF TUBERCULOSIS

Systemic Aspects

The host–pathogen interaction in tuberculosis involving a slowly proliferating pathogen that resists host microbicidal mechanisms stands in stark contrast to conventional bacterial disease, where despite the pathogen's rapid proliferation, the host's resources (complement fixation, opsonization, phagocytosis, and ready lysis within phagocytic cells)

are formidable. The pathogenesis of tuberculosis reflects the balance of intrinsic mycobacterial virulence and the host immunologic response. The classic response in tuberculosis, the formation of granulomas, is ordinarily protective for the host by limiting the proliferation and spread of M. tuberculosis, but may be pathogenic as well, because it may lead directly to tissue injury in the form of caseation.[53–55] Thus, the clinical manifestations of tuberculosis represent not only the consequences of mycobacterial proliferation but also host reparative and destructive responses. In the absence of immunosuppression, the lifetime risk of symptomatic M. tuberculosis infection among latently infected individuals is only ~10%. Similarly, the risk of developing extrapulmonary disease, such as genitourinary tuberculosis, is rather low. An increased understanding of the molecular mechanisms responsible for host defense against mycobacterial infections has led to a growing appreciation that human susceptibility to mycobacterial infection may be attributable in significant measure to host genetic factors, as well as to the intrinsic virulence of M. tuberculosis isolates.[56–58]

Tubercle bacilli are inhaled as small particle aerosols and gain direct access to the alveoli.[53] Presently, ingestion of M. tuberculosis with primary localization of disease in the intestinal tract or oropharynx is rare. The small aerosol inoculum multiplies slowly and is phagocytosed by polymorphonuclear leukocytes, pulmonary macrophages, and dendritic cells. Mycobacteria interact with respiratory epithelium,[59] alveolar surfactant proteins,[60] and both the classic[61] and alternate complement systems,[62] but interactions with macrophage Toll-like receptors (TLRs 2, 4, and 9)[63–65] play a critical role in initiating the host immune response. TLRs are pattern-recognition proteins, expressed on macrophages and dendritic cells, which serve as innate immune receptors.[66] Each TLR binds one or more of a variety of microbial products (endotoxin [lipopolysaccharide], bacterial DNA, flagellin, mycobacterial lipoarabinomannan, etc.) and transduce inflammatory signals culminating in the activation of NF-κB and transcription of tumor necrosis factor α (TNF-α) and interferon-γ.[67] Following opsonization by C3, M. tuberculosis binds to phagocytic cell surface complement receptors and is phagocytosed.[62] Mycobacteria suppress the intracellular calcium flux that normally accompanies phagocytosis and inhibits macrophage activation and phagolysosome maturation.[68,69] M. tuberculosis can also directly adhere to, infect, and translocate across alveolar epithelial cells and endothelial cells,[70–72] facilitating access to lung interstitium and the pulmonary microcirculation, enhancing early dissemination to extrapulmonary foci.

The host response to mycobacterial infection has been called the IL-12–interferon-γ axis.[56,58] Macrophage activation via TLR signaling and other early events is associated with secretion of TNF-α and IL-12 and the related cytokines IL-18 and IL-23[65,73] as well as by activation of NO synthase 2, leading to the synthesis of reactive nitrogen intermediates.[65] The cytokines program resting T lymphocytes toward an inflammatory Th1 response. Activated Th1 lymphocytes secrete as their dominant cytokines interferon-γ as well as TNF-α, and this in turn activates macrophages and enhances their mycobactericidal activity. TNF-α also triggers apoptosis of infected macrophages, which may inhibit mycobacterial replication (see later). The use of TNF-α antagonists (e.g., etanercept, infliximab, and adalimumab) as disease-modifying agents in the treatment of rheumatoid arthritis and other inflammatory diseases confirms a central role for TNF-α in the host response against mycobacterial infection. These therapies have been associated with rapidly progressive tuberculosis, impaired granulomatous reactions in tissue biopsies, and a high rate of extrapulmonary disease.[74]

In the initial stages of primary infection, resting macrophages have a limited ability to lyse mycobacteria, and the bacillary titer rises despite entrapment within macrophage and granulocyte phagosomes and lysophagosomes. Some bacilli can even escape from these organelles and replicate freely within the cytoplasmic compartment.[75] Macrophage-mediated killing of intracellular M. tuberculosis requires the L-arginine-dependent generation of reactive nitrogen intermediates, such as nitric oxide, and this capability is greatly enhanced following macrophage activation by interferon-γ and TNF.[65,76] Thus, infected macrophages program T cells toward a Th1 response which in turn augments macrophage-mediated mycobacterial killing. Foamy macrophages are characteristically seen in caseating granulomata and offer a protected locus of mycobacterial persistence; the disruption of these macrophages helps to recycle M. tuberculosis to the extracellular milieu.[77] T cell-infected macrophage interactions are more complex because several cytolytic T cell effector populations are generated which can lyse infected macrophages.[78,79] In addition to the expansion of conventional peptide-specific $CD4^+$ and $CD8^+$ $\alpha\beta$ T-cell receptor-expressing populations,[79] T cells with a double negative phenotype (CD4-, CD8-) expressing $\gamma\delta$ T-cell receptors recognize mycobacterial phospholipid antigens presented by MHC-like molecules (e.g., CD-1) and lyse infected macrophages via Fas–FasL interaction.[80] These phospholipid antigens are also recognized by $CD8^+$ $\alpha\beta$ T-cell receptor-expressing cytotoxic T lymphocytes, triggering perforin-mediated cytotoxicity, and by natural killer (NK) T cells, which possess NK markers as well as $\alpha\beta$ T-cell receptors.[81] In at least some instances, immune lysis of infected macrophages appears beneficial to the host. Perforin-mediated lysis of infected macrophages reduces M. tuberculosis viability by 50% in vitro,[81] and may be important in vivo in reducing the number of infecting tubercle bacilli. The cytotoxic granules that contain perforin also contain granulysin, a lipid-binding protein that has potent mycobactericidal activity in the presence of perforin.[82] In contrast, Fas-mediated lysis of macrophages does not affect mycobacterial viability, but may be important in reducing antigen presentation and dampening the immune response. The immune lysis of heavily infected macrophages may facilitate the phagocytosis of released mycobacteria by additional activated macrophages. These newly recruited cells have a lower bacillary

burden and may be more effective at killing their intracellular bacilli, or serve as target cells for cytotoxic T lymphocytes.

In addition to their direct cytotoxic activities, the activated lymphocytes secrete a variety of cytokines, including interferon-γ, migration inhibitory factor (MIF), granulocyte-macrophage colony-stimulating factor, TNF-α, IL-12, and inhibitory cytokines such as interleukin-4 (IL-4)[83] and IL-10.[84,85] IL-4 production undermines the host Th1 response, and triggers tissue fibrosis,[86] a characteristic finding in chronic tuberculosis. In HIV-infected individuals coinfected with M. tuberculosis, immunosuppressive cytokines (e.g., IL-10) produced by macrophages/monocytes diminish the T-lymphocyte response in vitro, suggesting that Th2-like activity contributes to uncontrolled, systemic spread in these patients.[87] Macrophages are recruited to infiltrate the area of mycobacterial growth to form granulomas and mature into epithelioid cells by the macrophages' elaboration of TNF[88]; this process requires NK T cells.[89] In spite of macrophage activation, the killing of intracellular mycobacteria by human macrophages is often incomplete.[69]

The outcome of early tuberculous disease covers a spectrum from granuloma formation with efficient containment and healing to slowly progressive disease at the site of the primary pulmonary infection, or to clinically significant systemic spread of disease. Mycobacterial dissemination is actually the rule rather than the exception (Fig. 27.1). Although most bacilli are contained within macrophages initially, their continued proliferation disrupts the macrophages and the bacilli return to the extracellular environment. Most are engulfed again, but some bind to respiratory epithelial cells and ultimately translocate to the microcirculation[71,72] or are carried in the lymphatic drainage and produce regional lymphadenitis. Alternatively, some viable mycobacteria may reach regional lymph nodes while entrapped within dendritic cells or migratory macrophages. Progressive infection within the lymph node contaminates efferent lymph, and when sequential lymph node barriers fail, thoracic duct lymph delivers mycobacteria to the venous blood, seeding the pulmonary bed as well as extrapulmonary sites, such as the skeletal system, lymph nodes, and, most frequently, the kidneys.

Thus, limited hematogenous dissemination due to low grade bacillemia can occur early in the process of granuloma formation when the number of mycobacteria is small, and most organisms are found intracellularly within the macrophages comprising the granuloma. Small granulomas rapidly form at the metastatic foci because mycobacterial immunity is evolving or is already established at the time of dissemination. Although the bacilli may remain viable, the granulomas may remain clinically silent for decades.

Granuloma formation may itself contribute to the pathogenesis of severe tuberculosis.[53] Granulomas are active lesions with continued ingress of immune T lymphocytes and monocytes.[54,90] Shortly after microscopic granulomas become well established, polymorphonuclear leukocytes and monocytes enter the lesion.[91] The resultant phagocytosis is accompanied by exocytosis of lysosomal contents with local tissue destruction. This leads to a characteristic local necrotic process, known as caseation. Macrophage disruption returns the mycobacteria to the extracellular environment, where their proliferation accelerates.[53] Communication of the caseating granuloma with the bronchial tree restores favorable metabolic conditions, and mycobacterial titers can increase by several logarithms. This highly infected material can spread endobronchially to produce additional foci of pulmonary tuberculosis or excavate into a pulmonary vessel, leading to intense bacillemia. Such severe hematogenous dissemination commonly is responsible for miliary tuberculosis rather than limited extrapulmonary disease. In miliary tuberculosis, the systemic features of illness overshadow the asymptomatic renal involvement.

Pathogenesis of Renal Tuberculosis

Local factors play a significant role in the evolution of clinically significant renal tuberculosis. The small silent renal granulomas resulting from silent hematogenous dissemination are typically found bilaterally in the renal cortex and arise from capillaries within and adjacent to glomeruli (Fig. 27.2).[92] A glomerular location is not surprising in view of their high rate of perfusion (increased likelihood of bacillus delivery during sparse bacillemia) and their favorable oxygen tension. Such cortical granulomas usually remain dormant for decades. In some patients, however, bacillary

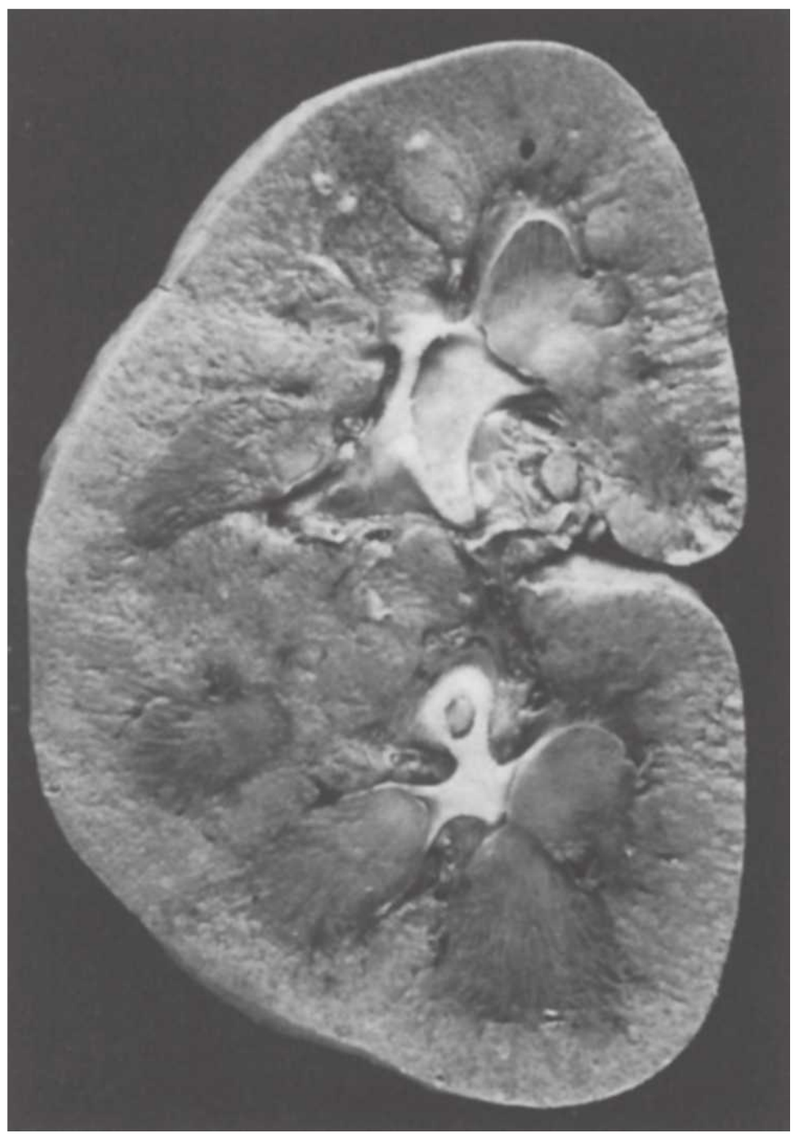


FIGURE 27.2 Early renal tuberculosis. Three small granulomas are visible in the cortex. The adjacent papillary tip is involved as well. (From Kollins SA, Hartman GW, Carr DT, et al. Roentgenographic findings in urinary tract tuberculosis. *Am J Roengentol Radium Ther Nucl Med.* 1971;121:487, with permission.)

proliferation within the glomerular capillary leads to capillary rupture and delivery of organisms into the proximal tubule. Clinically important renal tuberculosis, therefore, is usually initially localized to the medulla. This is likely caused by entrapment of mycobacteria and infected macrophage debris within the loop of Henle[92] and the known impairment of phagocyte function associated with the hypertonic environment found in the medulla.[93,94]

Analogous to progressive pulmonary disease, granulomas may enlarge in the medulla, leading to caseation and papillary necrosis. Such intraparenchymal granulomas may persist as mass lesions but commonly cavitate into the calyceal system. Despite bilateral hematogenous seeding of the kidneys, clinically significant disease is usually unilateral.[92] Communication of the caseating granuloma with the collecting system usually is responsible for the spread of bacilli to the renal pelvis, ureters, bladder, and accessory genital organs and is analogous to the endobronchial spread of infection seen in cavitary lung disease.[30] Lymphatic spread to contiguous structures also occurs in addition to epithelial infection by a luminal mechanism,[95] and direct hematogenous seeding of pelvic genital organs with clinical sparing of the kidney can occur occasionally.[30] In addition to the direct parenchymal destruction associated with advanced renal lesions, the fibrosis that accompanies the granulomatous process within the collecting system, such as infundibular strictures and renal pelvic kinking, adds an obstructive mechanism that may contribute significantly to progressive renal dysfunction.

PATHOLOGY

The caseating granuloma is the classic microscopic finding in essentially all forms of tuberculosis (Figs. 27.3 and 27.4). Medlar[92] characterized the early pathologic findings in renal tuberculosis by meticulously examining microscopic sections of kidneys from patients who died of pulmonary tuberculosis. Bilateral microscopic renal involvement is the rule, although the extent of involvement usually is asymmetric. Granulomas vary greatly in size, from lesions contained within a single glomerulus to large caseous abscesses, as well as in the apparent density of acid-fast bacilli.

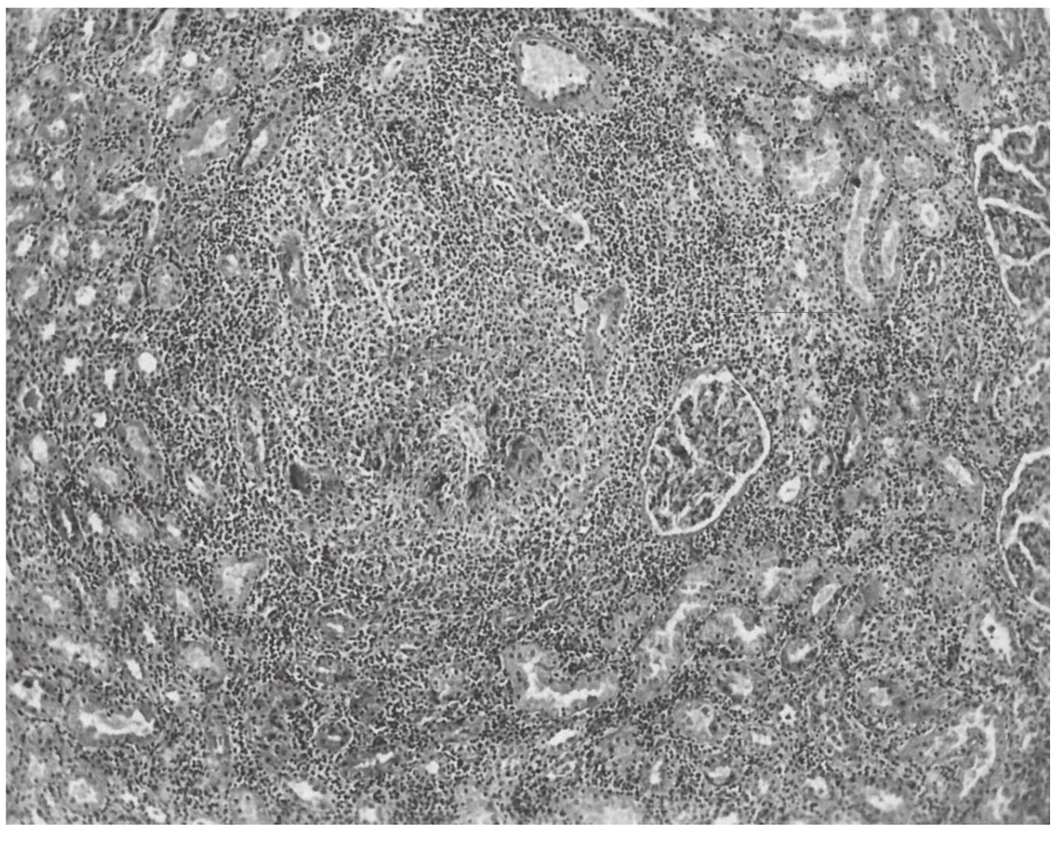


FIGURE 27.3 A caseating granuloma in the renal cortex. In addition to the necrotizing granuloma in the center of the field, a diffuse interstitial infiltrate of lymphocytes is seen. Some tubules are preserved (H&E, magnification ×79).

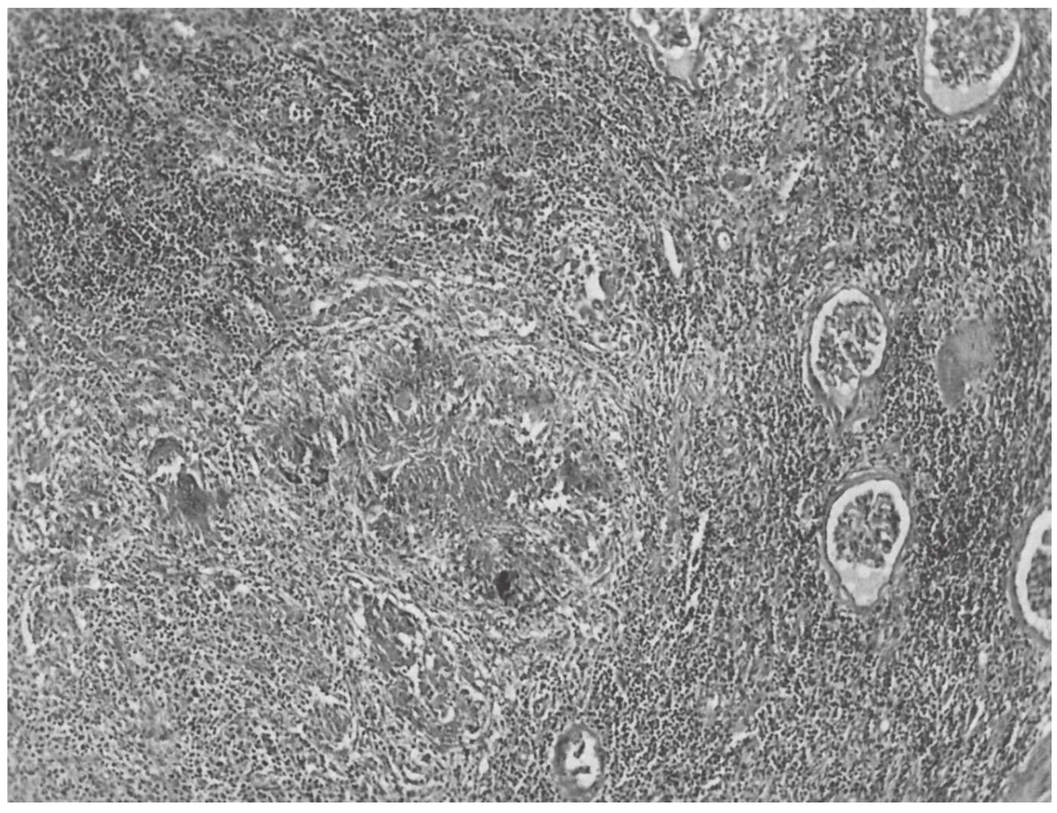


FIGURE 27.4 Renal cortical tissue showing destruction of tubules and a diffuse lymphocytic infiltrate with focal caseating granulomas. The glomeruli are spared (H&E, magnification ×79).

Most renal granulomas originate as vascular lesions in the cortex. Although glomerular lesions predominate, with foci within the capillary tuft, granulomas may develop within capillaries in relation to the convoluted or collecting tubules. Lesions within the collecting system per se are usually at the nadir of the loop of Henle or in the pyramidal collecting tubule, always draining a vascular granuloma (Fig. 27.2), and presumably developing in response to ulceration and discharge of these lesions into the collecting system. Focal sparing of tubules, glomeruli, or both within the granulomas is characteristic of renal tuberculosis (Figs. 27.3 and 27.4).

Clinically significant caseation progresses from the medullary collecting system lesions.[96] The enlarging medullary abscess extends to the papilla and commonly produces papillary necrosis. It may replace the medullary pyramid and persist as a parenchymal cavity, or tuberculoma, or discharge into the draining calyx. Several pyramids may be involved individually with a variable extent of destruction or may coalesce to destroy the bulk of the renal parenchyma (Fig. 27.5). Infection of the calyces, pelvis, and ureter is followed by stricture formation, so that caliectasis[97] and tuberculous pyonephrosis ("caseocavernous renal tuberculosis") are common in advanced disease. The end-stage kidney is nonfunctional ("autonephrectomy") and destroyed by the combined necrotizing and obstructive processes. Calcification in advanced lesions is common and may be focal or generalized, which produces a "putty" or "cement" kidney.

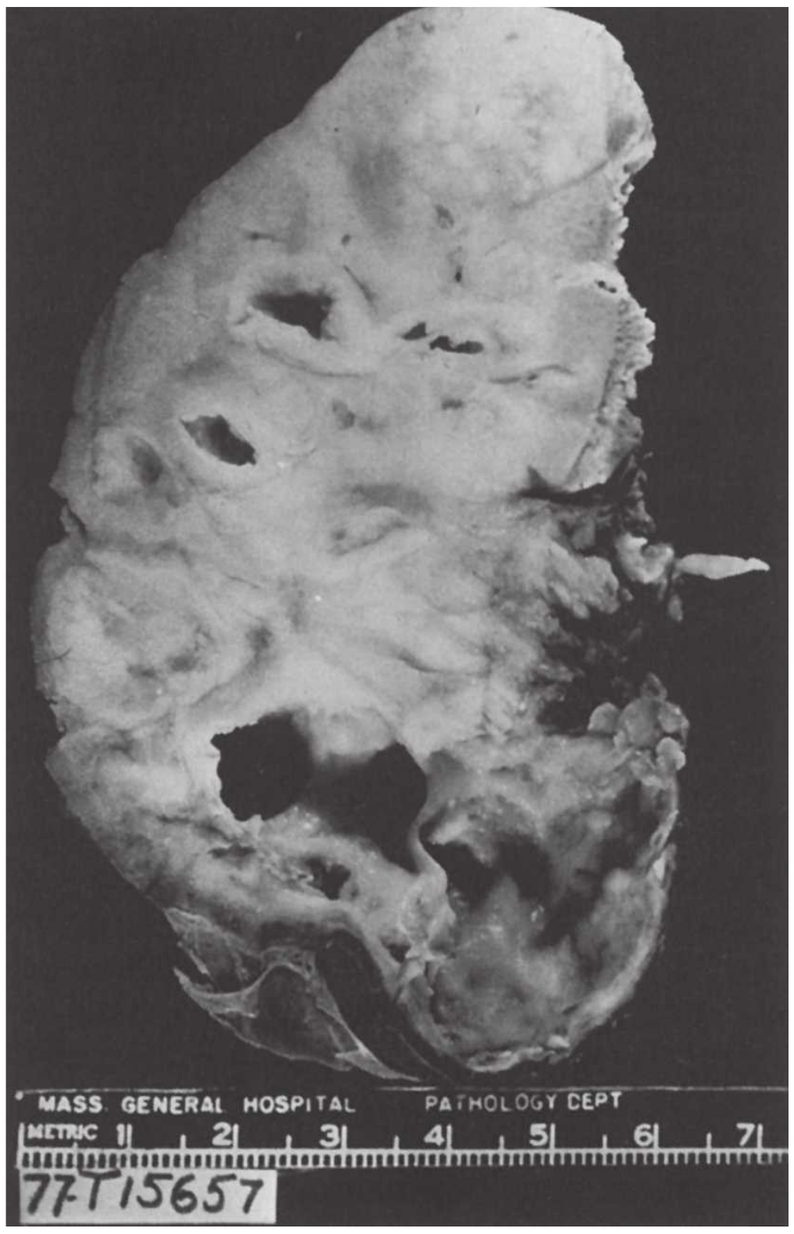


FIGURE 27.5 Renal tuberculosis with replacement of most of the parenchyma by caseous necrosis. There is cavitation of pyramids.

CLINICAL FEATURES

Urinary tract tuberculosis is notorious for its insidious mode of presentation, with approximately 20% of cases diagnosed unexpectedly at operation or autopsy. As many as 20% to 56% of patients with active urinary tract tuberculosis detected on the basis of an abnormal urinalysis or culture deny either constitutional symptoms of tuberculosis or symptoms referable to the urinary tract.[31–34,98,99] One measure of the frequently occult nature of urinary tract tuberculosis comes from Lattimer's classic report[99] wherein 18 of 25 physicians with renal tuberculosis were diagnosed only after developing far-advanced cavitary disease. If physicians with ready access to medical care have renal tuberculosis overlooked, then the problem is only compounded in the highest risk populations—inner city minority groups, immigrants from the developing countries of the world (particularly those undergoing social disruption), and the indigent elderly—all of whom have relatively poor access to medical care.

Roughly 75% or more of patients with urinary tract tuberculosis present with symptoms suggesting urinary tract inflammation. Such symptoms resemble those of conventional bacterial urinary tract infection—dysuria, urgency, frequency, mild or moderately severe back or flank pain, hematuria, nocturia, and pyuria. Renal colic, owing to the passage of clots or stones, may be observed in as many as 10% of patients.[31,32] Severe pain localized to the kidneys is uncommon but has been reported.[100] Epididymal thickening reflecting tuberculous epididymitis should heighten suspicion of upper tract tuberculosis. Noteworthy for their infrequency are the constitutional symptoms usually associated with tuberculosis—fever, weight loss, night sweats, and anorexia. Fewer than 20% of non-HIV infected patients with tuberculosis restricted to the urinary tract have constitutional symptoms, and the presence of such constitutional symptoms should suggest the presence of active tuberculosis in other organs as well.[31–33,98]

As noted previously, the extent of renal dysfunction secondary to tuberculous infection can be quite variable, from small focal areas of infection and scarring unassociated with any functional impairment to gross parenchymatous destruction and complete loss of function. As in any other form of tubulointerstitial nephritis (see Chapter 35), patients with renal tuberculosis may be subject to dehydration because of a concentrating defect, a tendency to lose salt, or both.[101] However, any patient with these findings should be evaluated for possible concomitant tuberculous adrenal disease (Addison disease), particularly when constitutional symptoms are present.[102,103]

Early diagnosis and therapy offers the best hope of limiting renal function loss resulting from parenchymatous infection and destruction. It is also important to identify patients experiencing renal functional loss due to hydronephrosis secondary to obstruction induced by the tuberculous process. Here the second element of the pathologic process induced by tuberculosis, sclerosis, exerts its effects. Strictures, usually either at the ureteropelvic junction or at the lower end of the ureter, can result in hydronephrosis and loss of renal function. Obstruction and hydronephrosis can develop during therapy because such sclerotic strictures are frequently part of the healing process. The clinician must be alert to this possibility, because correction of such obstruction is the best way to preserve renal function in patients with tuberculosis.[31,32,97,104–109]

There are three other major complications of renal tuberculosis: hypertension, superinfection with conventional bacteria, and nephrolithiasis. In 1940, Nesbit and Ratliff[110] reported that hypertension could be cured by the removal of a tuberculous kidney, an observation subsequently confirmed by other authors.[111–114] Subsequent data suggest that this is an uncommon event. First, hypertension may not be more common in patients with renal tuberculosis (<5% of those with tuberculous kidney infection are hypertensive) than in the general population. Second, surgical cure of hypertension in these patients appears to be the exception rather than the rule.[31,32,111] Renal vein renin sampling may be useful in predicting the outcome of surgery for patients with hypertension and renal tuberculosis.[115] Reversible renovascular hypertension due to direct involvement of the renal artery by tuberculous vasculitis has been rarely observed.[116]

Both nephrolithiasis and bacterial superinfection of a urinary tract rendered anatomically abnormal by the tuberculous process are not uncommon. Nephrolithiasis has been

reported in 7% to 18% of patients with renal tuberculosis, and superinfection has been reported in 12% to 50% of patients with urinary tract tuberculosis.[32]

The delivery of large numbers of M. tuberculosis into the urine of patients with renal tuberculosis is the major cause of tuberculous infection of the ureters and bladder. In both loci, scarring and contractures are the major results of tuberculous infection, again the not-so-benign effects of "healing." The result is a small, contracted bladder with greatly thickened walls. There are three functional consequences of this process: a small bladder capacity, incomplete emptying and thus a predisposition to secondary bacterial infection, and, most serious of all, vesicoureteral reflux.[117,118]

The incidence of genital infection in association with urinary tract tuberculosis is very different in the two sexes. In men, such dual involvement is relatively common. Indeed, genital disease may lead to the recognition of extensive urinary tract infection as noted previously. Epididymitis, with or without orchitis, presenting as a scrotal mass or discomfort, is the most common manifestation of male genital tuberculosis. The majority of such patients are free of constitutional complaints.[98,99,119] The importance of this form of tuberculosis is underlined by the report of Ferrie and Rundle[119] that 75% of their patients with tuberculous epididymoorchitis already had evidence on pyelogram of tuberculosis involving the bladder, ureters, kidneys, or all of these organs at the time they presented with their epididymal disease. Epididymitis can present decades after apparently adequate therapy for renal tuberculosis.[120]

Tuberculous prostatitis, an uncommon locus of genitourinary disease, may present with a mass lesion (mimicking prostatic carcinoma), pain, or both, rather than systemic symptoms in most patients and is frequently associated with urinary tract disease (Fig. 27.6). The prostate, like the epididymis and testes, can be infected either by means of the hematogenous route or more directly from infected urine.[121]

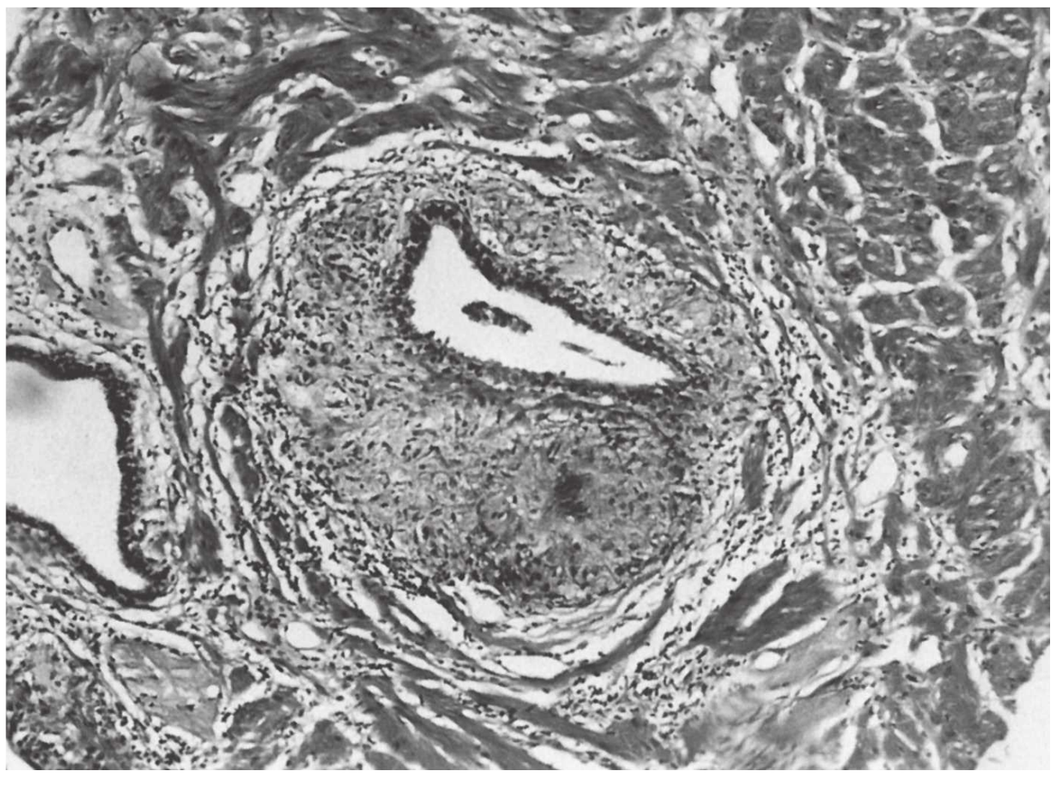


FIGURE 27.6 Prostatic tissue with epithelioid granulomatous reaction surrounding a duct (H&E, magnification ×125).

Viable organisms frequently persist in the prostate long after other parts of the genitourinary system have been sterilized.[31,121] Persistent prostatic infection is presumably related to the same difficulty in delivering effective antimicrobial therapy to the prostate that is responsible for persistent conventional bacterial prostatitis.

Urethral and penile tuberculosis are both quite uncommon but may present with strictures, fistulous tracts, and ulcerating or papulonecrotic skin lesions. Both these forms of tuberculous infection may reflect seeding from infected urine, spread from a contiguous lower genitourinary source such as the prostate, or from direct hematogenous seeding.[104,121] Primary penile tuberculosis has been reported to occur owing to the direct inoculation of M. tuberculosis into a wound following ritual circumcision, after the use of contaminated surgical instruments, sexual contact with women with tuberculosis of the female genital tract, or from contaminated clothing.[104,122,123]

In contrast, tuberculosis of the female reproductive tract is quite distinct from urinary tract tuberculosis. The incidence of renal disease in women with genital tuberculosis is less than 5%, which is little different from that found in patients with pulmonary or skeletal tuberculosis.[124] The explanation for this difference between men and women is clear: Whereas involvement of the male genital tract usually occurs from direct extension or from infected urine, the female genital tract is almost always infected hematogenously, with seeding of the fallopian tubes and then secondary extension from this site. Thus, the major manifestations of female genital tuberculosis—infertility, secondary amenorrhea, vaginal bleeding, and pelvic pain—are quite separate from the manifestations of urinary tract tuberculosis.[31,32 124,125]

Given its insidious nature, routine laboratory studies are quite important in raising the possibility of genitourinary tuberculosis (see later). By far the most useful screening test is urinalysis. As emphasized by Simon and associates,[31] virtually the only time when a urinalysis is normal and a urine culture is positive for M. tuberculosis is in the patient with miliary dissemination, in whom the urinary tract seeding is a recent and perhaps insignificant event. In contrast, essentially every patient with established urinary tract tuberculosis has an abnormal urinalysis with pyuria, hematuria, or both. The old clinical teaching that the asymptomatic patient with pyuria, particularly with an acid urine and a urine culture that fails to reveal conventional bacterial pathogens, must be considered as having tuberculosis until proved otherwise remains true today.[31–33,98,99] Although there are other causes of "sterile pyuria," such as Chlamydia trachomatis or invasive fungal infection, tuberculosis must be excluded in patients with these findings. An abnormal urinalysis should be followed by the placement of an intermediate-strength tuberculin test (5 TU). Virtually every patient with urinary tract tuberculosis who is not receiving systemic steroids, anti-TNF-α therapy, or who has not been rendered anergic by such debilitating conditions as advanced malignancy or HIV infection has a positive tuberculin test. In contrast, fewer

than 20% of patients with urinary tract tuberculosis have abnormalities on tests that measure systemic illness (i.e., anemia, changes in white blood cell count, low serum albumin, etc.).[31,32] Similarly, azotemia at presentation is quite infrequent, because severe bilateral obstructive uropathy is uncommon. Approximately two thirds of patients with urinary tract tuberculosis have evidence of old or current tuberculosis on chest roentgenography.[14,31,32]

ATYPICAL MYCOBACTERIAL INFECTION

Genitourinary infection caused by atypical mycobacterial organisms is quite rare. A Taiwan university hospital recently reported a series of such patients[126]: surprisingly, underlying metabolic disease including chronic renal disease and diabetes mellitus was frequent whereas the incidence of HIV infection or steroid use was quite low. Patients presented with typical refractory lower tract urinary symptoms but had a high rate of systemic symptoms, including fever, and came to medical attention soon after the onset of symptoms, in contrast to patients with M. tuberculosis, who had a low rate of systemic complaints and often presented with persistent symptoms. A variety of nontuberculous mycobacteria was recovered by urine culture. M. avium-intracellulare accounted for 33% and the rapidly growing M. abscessus and M. fortuitum as well as M. gordonae caused another 40% of cases. Destructive and obstructive urinary tract disease, as seen with M. tuberculosis, was common.

In addition, a few cases of prostatic or epididymal infection, or both, owing to M. kansasii have been reported.[127,128] Disseminated disease due to this organism has also been reported in immunocompromised patients, with hematogenous seeding associated with a granulomatous reaction in the kidney and isolation of M. kansasii in the urine.[129] This form of genitourinary infection was more prominent in the early years of the HIV epidemic and currently in resource-limited settings with high rates of advanced HIV-associated immunosuppression.[130]

Diagnosis

The isolation of M. tuberculosis by urine culture is the definitive diagnostic test in renal tuberculosis. Early morning urine specimens are preferred over 24-hour urine samples,[14] because mycobacterial viability falls with prolonged exposure to acid urine.[131] In order to detect the low rate of bacilluria, three to five specimens should be submitted. Samples are routinely decontaminated by limited exposure to acid or alkaline solutions and then concentrated by centrifugation. Neither direct nor amplified nucleic acid hybridization probes are licensed for rapid diagnosis of urinary M. tuberculosis given their borderline sensitivity (~70%) compared to traditional culture,[132] although newer real-time polymerase chain reaction (PCR) methodology may prove as sensitive and specific as culture for the identification of urinary M. tuberculosis.[133]

Cultures are established on standard solid mycobacterial media, either egg-based (Löwenstein-Jensen) or agar-based (Middlebrook 7H10). These media also contain aniline dyes, such as malachite green, to inhibit the growth of bacterial contaminants. The transparent agar medium facilitates early visualization of microcolonies by approximately 1 week. Newer automated liquid based (Middlebrook 7H12) radiometric or colorimetric culture techniques have yields comparable to culture on solid media, with considerably more rapid recovery times.[134]

Microbiologic identification is based on colonial morphology, growth rate and optima (37°C, carbon dioxide-enriched atmosphere), absence of pigment production, accumulation of niacin, reduction of nitrate, and absence of significant catalase activity.[14] Commercial oligonucleotide reagents are available for the rapid speciation of primary isolates by nucleic acid hybridization techniques.

Other rapid diagnostic techniques have been developed but are not licensed yet for routine clinical use. These include high performance liquid chromatography to identify the spectrum of mycolic acids in the bacterial cell (which is useful after 7 to 10 days of culture), enzyme-linked immunosorbent assay (ELISA) techniques to detect mycobacterial protein antigens, and the detection of tuberculostearic acid by gas chromatography and mass spectroscopy.

In retrospective analyses of patients with renal tuberculosis, urine cultures were reported to be positive in ~70% to 90% of cases.[27,31–33] In patients with negative cultures despite optimal processing of multiple samples, the diagnosis is often reached by the recovery of M. tuberculosis from other sites (e.g., sputum or surgical specimens) in the setting of abnormal urinalyses and imaging, together with a positive tuberculin reaction. Some culture-negative patients have enclosed intraparenchymal granulomas which have not yet drained into the collecting system. When tissue specimens are submitted for mycobacterial culture, they are best macerated using sterile sand with a mortar and pestle, because automated homogenization methods may heat samples excessively and kill any mycobacteria present.[131]

Successful mycobacterial isolation provides an opportunity to perform drug susceptibility testing in addition to confirming the diagnosis of genitourinary tuberculosis. Drug susceptibility testing is strongly recommended on initial isolates from all patients, but is critically important in evaluating patients who previously received chemotherapy and in patients epidemiologically linked to known cases of drug-resistant tuberculosis.[14]

Radiology

Radiologic evaluation has long played a central role in the diagnosis and long-term management of patients with renal tuberculosis.[135,136] There is excellent correlation between the pathology of renal tuberculosis and the corresponding abnormalities seen by excretory urography.[137] Even plain films of the abdomen are valuable, as genitourinary

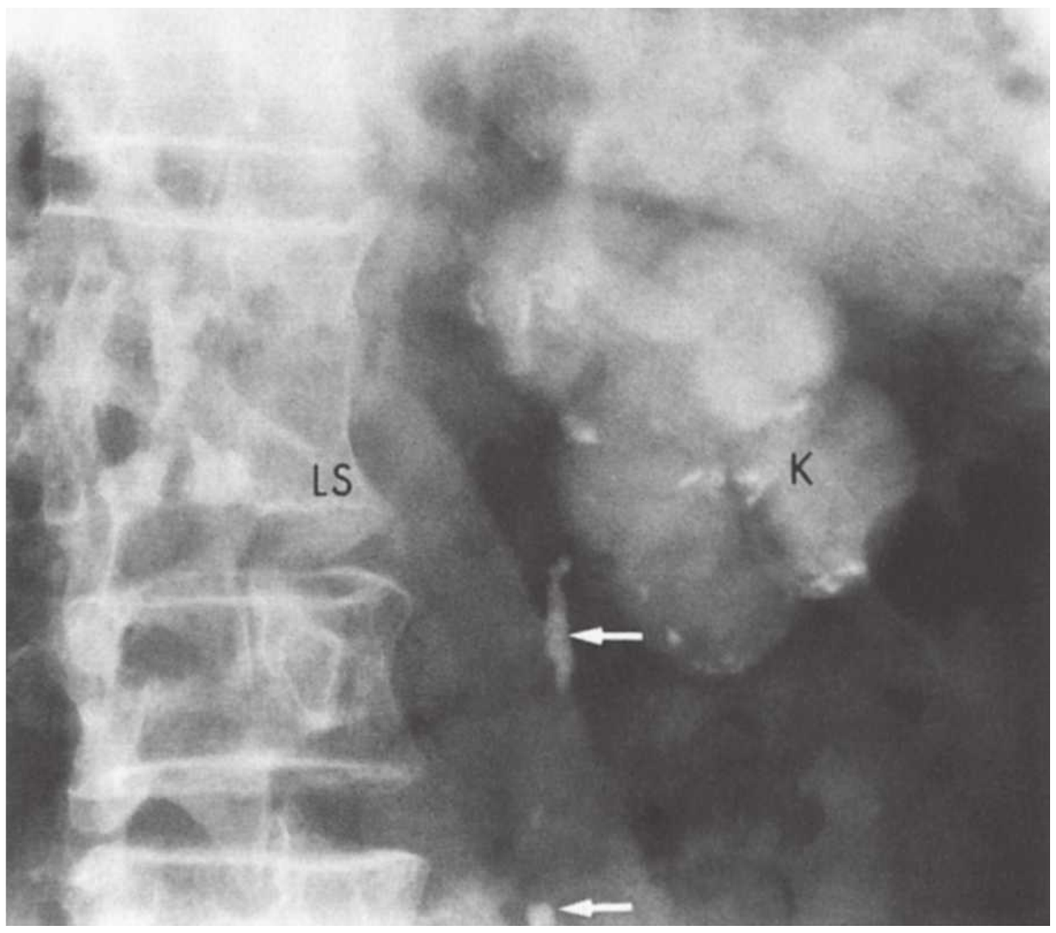


FIGURE 27.7 Plain film of the abdomen shows a left autonephrectomy with calcification of the kidney parenchyma and the left ureter (*arrows*). There is tuberculous involvement of the lumbar spine, resulting in fusion of the intervertebral disc space. *K,* kidney parenchyma; *LS,* lumbar spine.

calcifications (present in up to 50%)[138] as well as other extrapulmonary foci of mycobacterial disease (vertebral, mesenteric lymph node, adrenal glands) may be present (approximately 10%) (Figs. 27.7 and 27.8).[138] Chest radiographs show evidence of tuberculosis in 50% to 75% of patients with active renal disease.[31,32,139] In the remainder, the primary pulmonary granuloma, responsible for hematogenous spread, heals and may no longer be detectable by radiograph, but the metastatic renal granulomas progress to cause local destruction.

Excretory urography including nephrotomography traditionally has been the standard diagnostic imaging technique. In recent years, computed tomography (CT) with contrast, particularly helical CT, has provided increased delineation of renal parenchymal abnormalities, although contrast administration (with risks of allergy and nephrotoxicity) is still required, and the total radiation dose exceeds that of traditional excretory urography. Cross-sectional imaging including CT, magnetic resonance imaging (MRI), and sonography, provide a framework for assessing the renal parenchyma, adrenals, bladder, and genital organs that complements excretory urography.[140,141]

The earliest stage of renal involvement, the cortical granuloma (Fig. 27.2), is associated with positive urine mycobacterial cultures but negative excretory urograms. The spread of infection to the medulla and the evolution of cavitary disease in the papillae represent the earliest changes detectable radiologically (Fig. 27.9). Papillary granulomas caseate and rupture into the collecting system. The resulting small communicating cavities may be single or multiple but

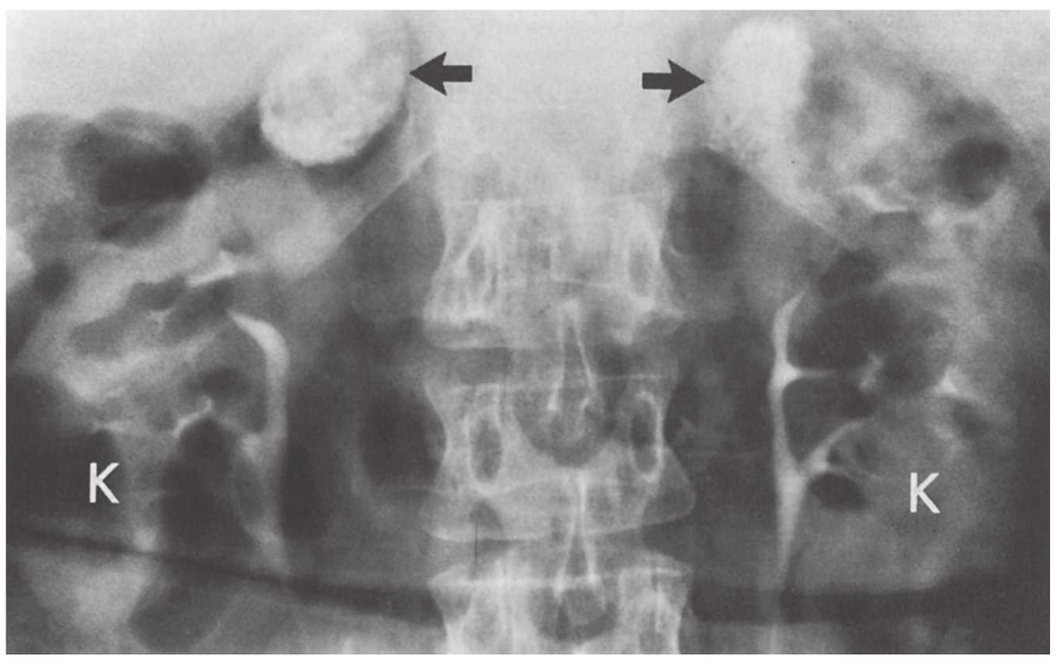


FIGURE 27.8 Tuberculous calcification of both adrenal glands (*arrows*). Intravenous urogram demonstrates the normal kidneys. *K,* normal kidneys.

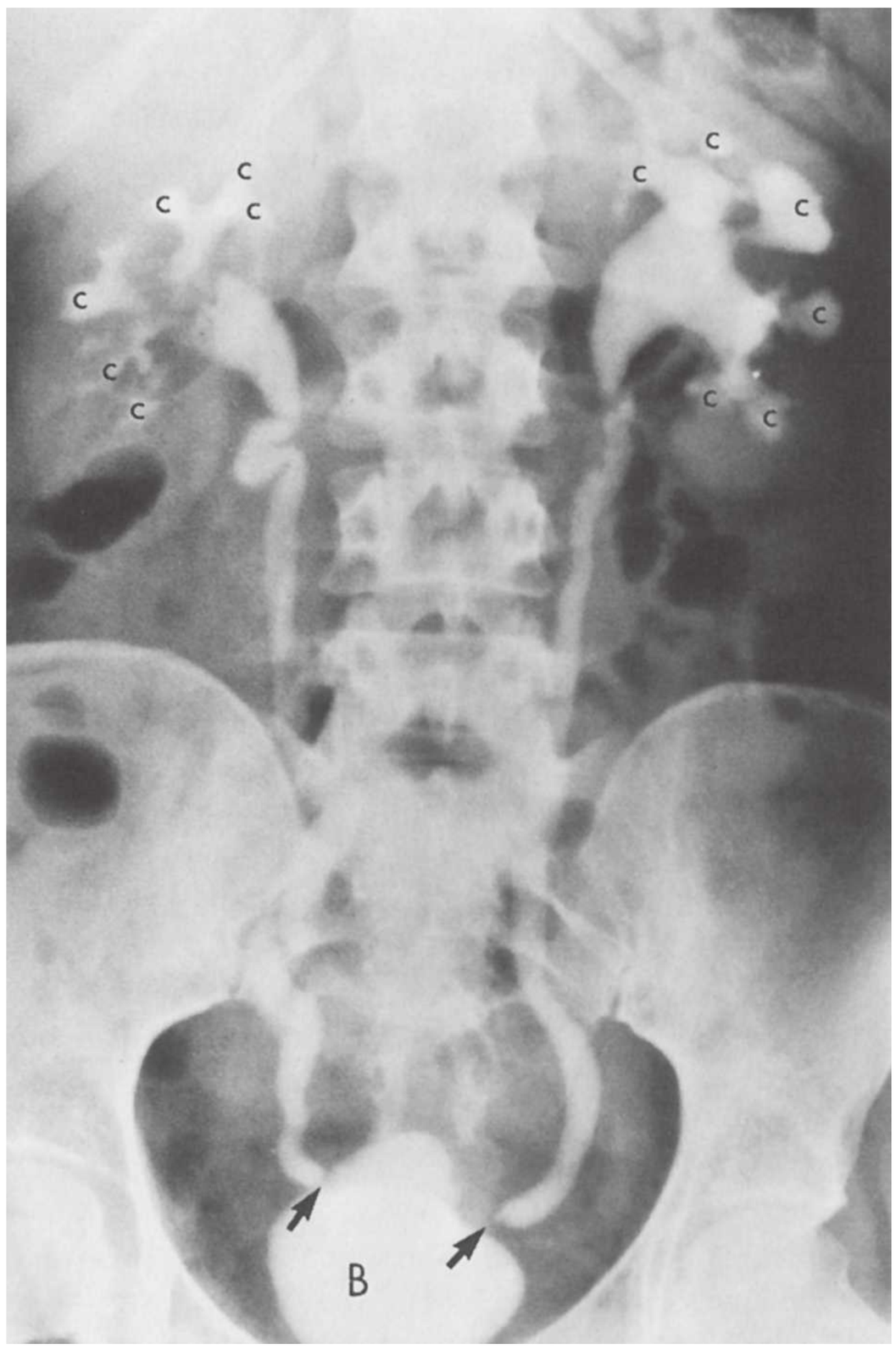


FIGURE 27.9 Intravenous urogram in a patient with active urinary tuberculosis, demonstrating papillary necrosis diffusely involving all the calyces in both kidneys. There is a small irregular bladder and narrowing of both distal ureters (*arrows*). *B,* bladder; *C,* calyces.

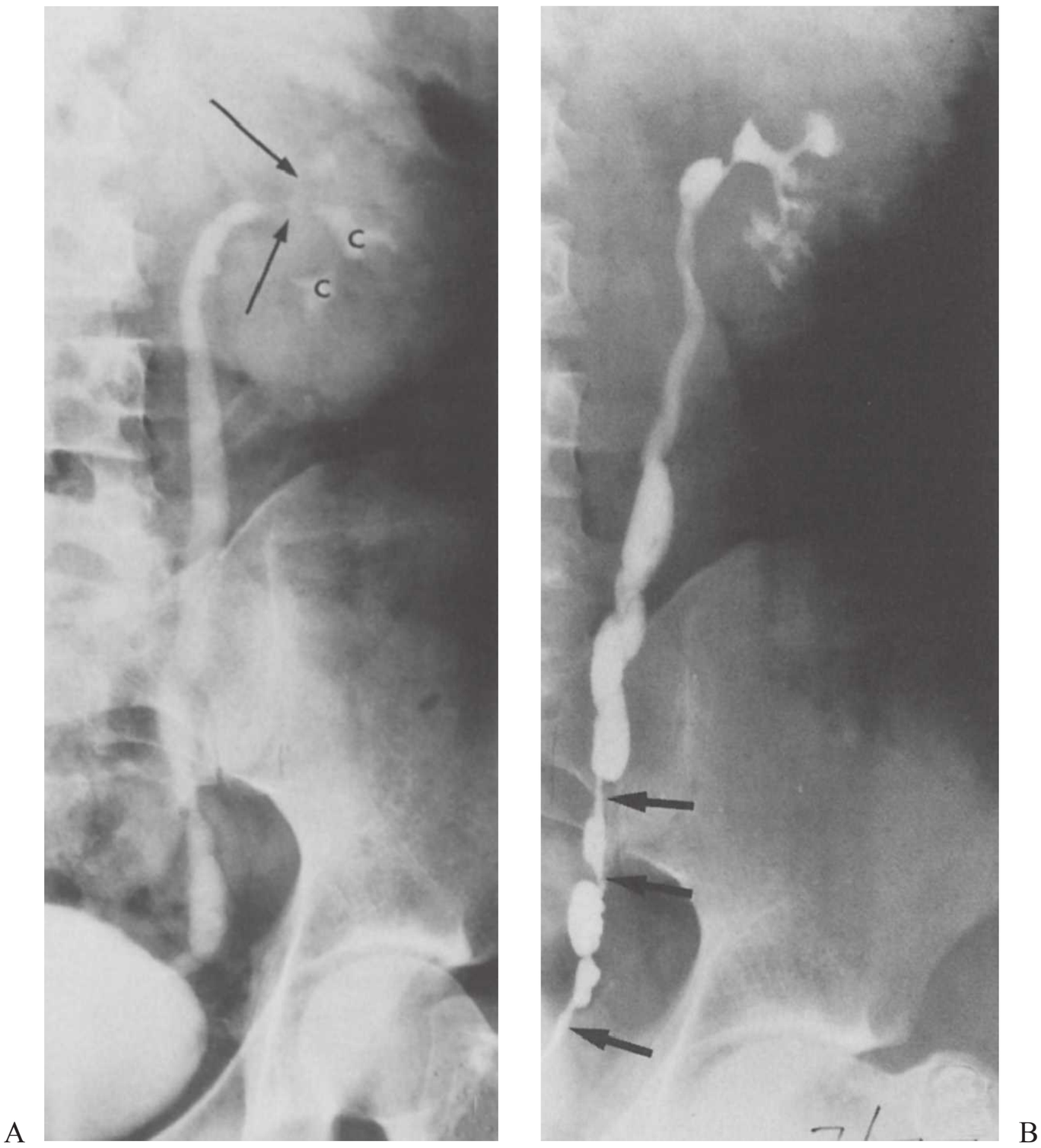
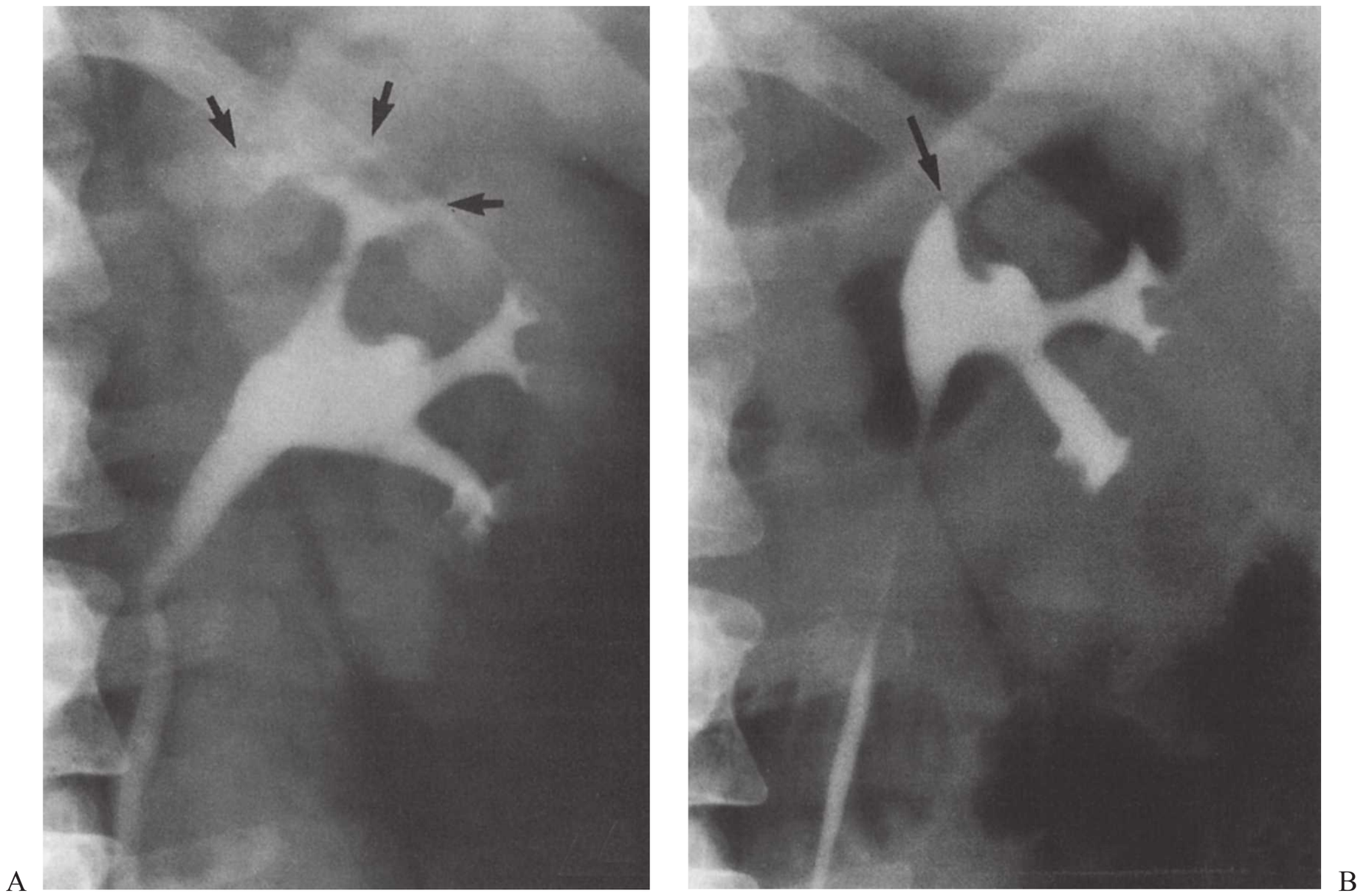


FIGURE 27.10 **A:** Intravenous urogram shows tuberculous narrowing of the left renal pelvis and upper pole infundibulum (*arrows*) and papillary necrosis of the lower pole calyces. The left ureter is moderately dilated and irregular in contour. **B:** Left retrograde pyelogram 6 months later, documenting fibrotic narrowing of the distal ureter (*arrows*) during antituberculous therapy. Tuberculous ureteritis commonly heals by cicatrization and may lead to severe obstruction of the collecting system. *C*, calyces.

are usually unilateral and may mimic papillary necrosis of other etiologies. With time, they enlarge in an irregular fashion, with shaggy margins, and may progress to involve the entire medullary pyramid. A consequence of papillary cavitation is spread of infection to the uroepithelium and submucosa of the draining calyx. The resulting fibrotic reaction leads to stenosis and even complete stricture of the calyceal infundibulum. Thus a medullary cavity may be excluded from the collecting system and an abscess, or localized tuberculous pyonephrosis, ensues. These lesions may be difficult to distinguish from a truly noncommunicating caseous parenchymal cavity. Advanced medullary disease may lead to renal cortical scarring as well. Amorphous calcification is frequently seen (Fig. 27.7) and may progress to outline the entire granuloma. Both the parenchymal tuberculous granuloma and the noncommunicating pyonephrosis may be confused with primary mass lesions; CT,[140,141] ultrasonography,[141,142] and, in selected cases, magnetic resonance[141,143] or even positron emission tomography (PET)-CT[144] may be helpful by confirming the nonneoplastic, cystic, and avascular properties of the mass.

The discharge of caseous material infects the renal pelvis, ureter, and bladder as well. Renal pelvic involvement is manifested by obstructive changes involving portions of the kidney due to stenosis or kinking of the pelvis or the entire organ due to ureteropelvic junction stenosis (Figs. 27.10 and 27.11). Thus poor visualization by excretory urography may be segmental or involve the entire kidney. Ureteral disease initially presents as mucosal irregularity, together with diffuse dilatation or narrowing due to inflammation or edema (Figs. 27.9 and 27.10).[145] There may be a single focus or multiple areas of ureteral involvement. In addition to an irregular border, the combination of multiple strictures and accompanying segmental dilation leads to a beaded or corkscrew configuration (Fig. 27.10). Unlike nonspecific strictures, tuberculous lesions may extend for several centimeters and are usually present together with ipsilateral renal disease. In some instances, intramural fibrosis leads to a rigid "pipestem" ureter. Calcification and even calculi may be present as well. Ureterovesical junction involvement may produce a stricture responsible for ureteral obstruction or a patulous, rigidly dilated orifice associated with vesicoureteral reflux.

Bladder involvement similarly begins with focal mucosal irregularity and progresses to produce a small, contracted trabeculated bladder with intramural thickening (Figs. 27.9 and 27.12). Occasionally, calcification of the bladder wall may occur.



A B

FIGURE 27.11 Intravenous urograms 14 years apart. **A:** Early change of renal tuberculosis with papillary necrosis of the upper pole calyces (*arrows*). **B:** Fourteen years later, there has been complete stenosis of the left upper pole infundibulum (*arrow*) as the tuberculous process heals by scarring.

The excretory urogram has long been the radiologic standard for evaluating patients with renal tuberculosis because of its capacity to record focal calyceal abnormalities, including cavitation, scarring, and obstruction, and to survey the collecting system in equal detail simultaneously. Sonography cannot record erosive calyceal abnormalities or distinguish advanced caseous disease from focal pyonephrosis. Sonography may, however, play a role in monitoring the possible development of hydronephrosis.[141,142] CT studies, particularly when intravenous contrast reagents are administered, have become the procedure of choice for diagnosing and assessing renal tuberculosis (Fig. 27.13). Thus, in early or focal disease, obstruction of a single major calyx or a group of minor calyces may be observed; tuberculous involvement of the renal pelvis may be visualized as either dilatation owing to ureteropelvic junction obstruction or diffuse pelvic contraction. With advanced disease, small, atrophic kidneys, often with one or more low density areas, are observed.[140] Calcifications of the genitourinary system and extrarenal intra-abdominal disease can likewise be observed at the same time.[140,141,146] Sonographic and CT studies are particularly useful in patients with advanced disease when there is nonvisualization of the affected kidney by excretory urography. Angiography has been used in the past for the rare patient when isolated focal disease caused by obstruction or cavitation has mimicked a primary renal mass,[147] but MRI has largely supplanted the need for arteriography.[141,143] The obliterative arteritis that accompanies progressive caseation is responsible for the avascular appearance of the granulomatous mass with pruning and obliteration of the interlobar arteries.[147] As noted above, tuberculous arteritis of the main renal artery is exceedingly rare.[116]

Clinical Management

The advent of effective chemotherapy has revolutionized the clinical management of urinary tract tuberculosis, although the recent increase in drug-resistant infection, amplified by the AIDS epidemic, threatens this success. Whereas in the prechemotherapeutic era extirpative surgery was the only hope of controlling infection, today medical cure is the rule. There is a continuing need for surgical intervention, but now it is primarily for the correction of anatomic abnormalities caused by scarring rather than for the removal of infected tissues. The two goals, then, in the management of urinary tract tuberculosis are the conservation of tissue and function (both with medical treatment and surgical relief of obstruction resulting from tuberculous scarring) and antimycobacterial cure.

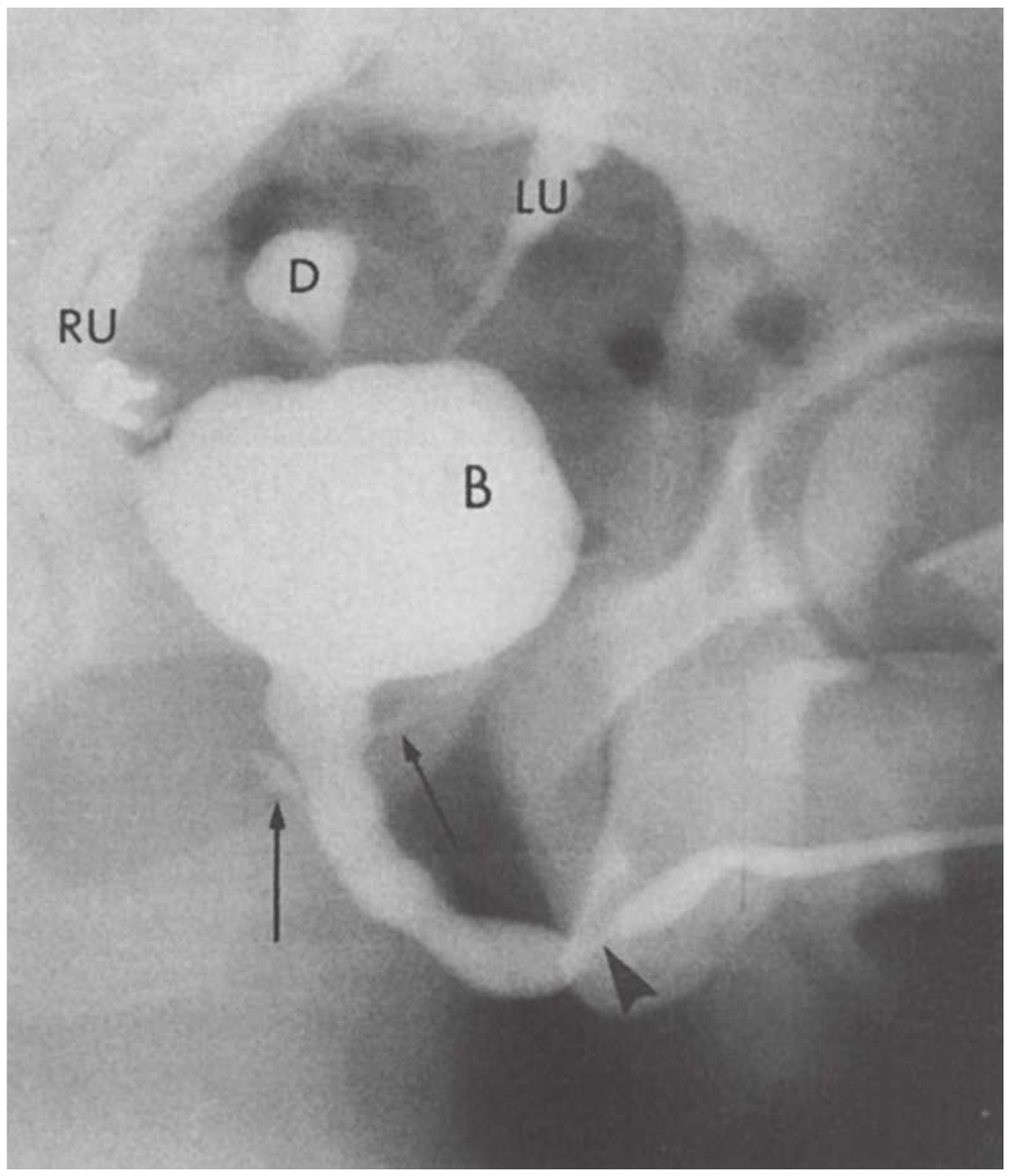


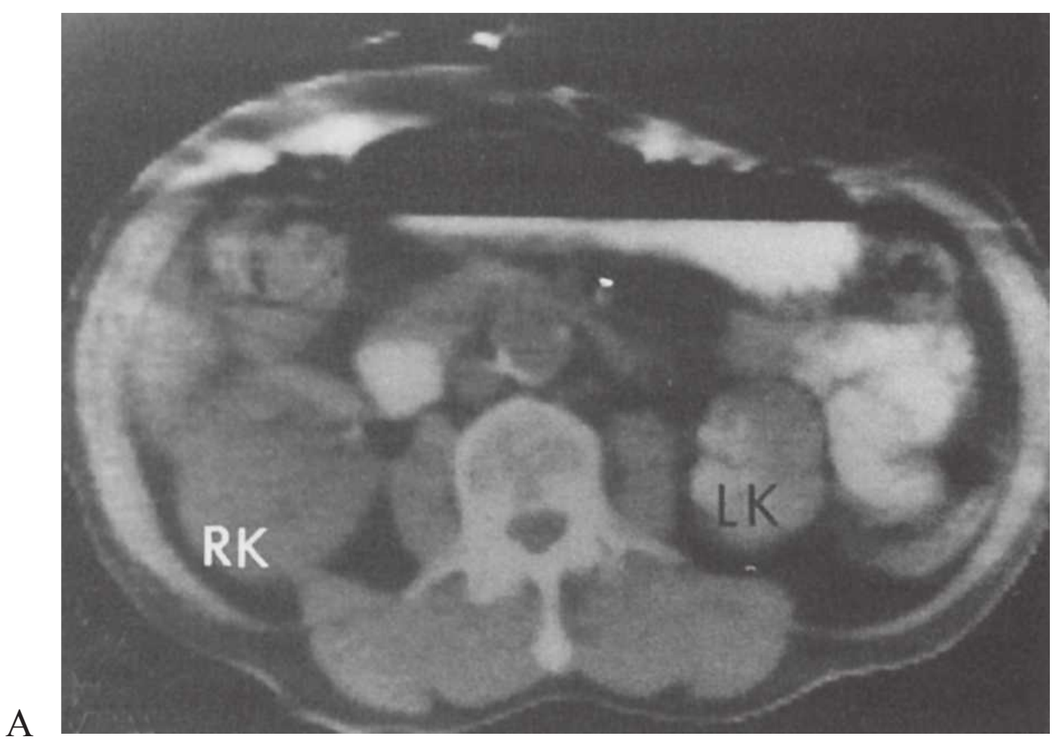
FIGURE 27.12 Voiding cystourethrogram in a young man with left renal tuberculosis, showing reflux into duplicated ureters of a normal right kidney and into an abnormal single left ureter, with a concomitant distal stenosis. The bladder is markedly reduced in volume and there is a diverticulum at the dome. There is reflux of contrast into the prostatic gland (*arrows*) secondary to tuberculous prostatitis. There is a stricture of the midbulbous urethra (*arrowhead*), which is an unusual site for tuberculous involvement. *B,* bladder; *D,* diverticulum; *LU,* left ureter; *RU,* duplicated ureters.

CHEMOTHERAPY OF URINARY TRACT TUBERCULOSIS

The chemotherapeutic approach to tuberculosis is based on the following general principles (Table 27.1).[15,148,149]

1. Mycobacterium tuberculosis may persist in a viable form while multiplying slowly or even intermittently. It is believed that there are three populations of organisms that must be considered when treating patients with active tuberculous infection.[150] The largest number, and fortunately the most easily treated, are those that are extracellular, as within a cavity, where the pH is either neutral or alkaline. Because this group of organisms is actively multiplying, this is the population most easily treated with two or more bactericidal drugs. Also, because it is quantitatively the largest population, drug resistance is most apt to emerge within this population if an inappropriate therapeutic program is employed. A much smaller population of slowly or intermittently multiplying organisms is found at an acid pH within macrophages. Finally, there are a variable number of organisms exhibiting slow or intermittent multiplication at a neutral pH within closed caseous lesions.

   Curative therapy requires eradication of all three populations of organisms. Because of pH constraints, differing abilities to penetrate at different sites, and inherent effects on the tubercle bacillus, each of the available antituberculous drugs is more or less effective for these different populations of M. tuberculosis. Rifampin and related agents (rifabutin and rifapentine) are the only drugs that are bactericidal for all three populations of M. tuberculosis. Isoniazid (INH) is bactericidal both for the actively growing organisms in cavities and for those slowly multiplying within macrophages. Streptomycin and the other injectable aminoglycosides are bactericidal only for the actively replicating extracellular organisms. Pyrazinamide is bactericidal only



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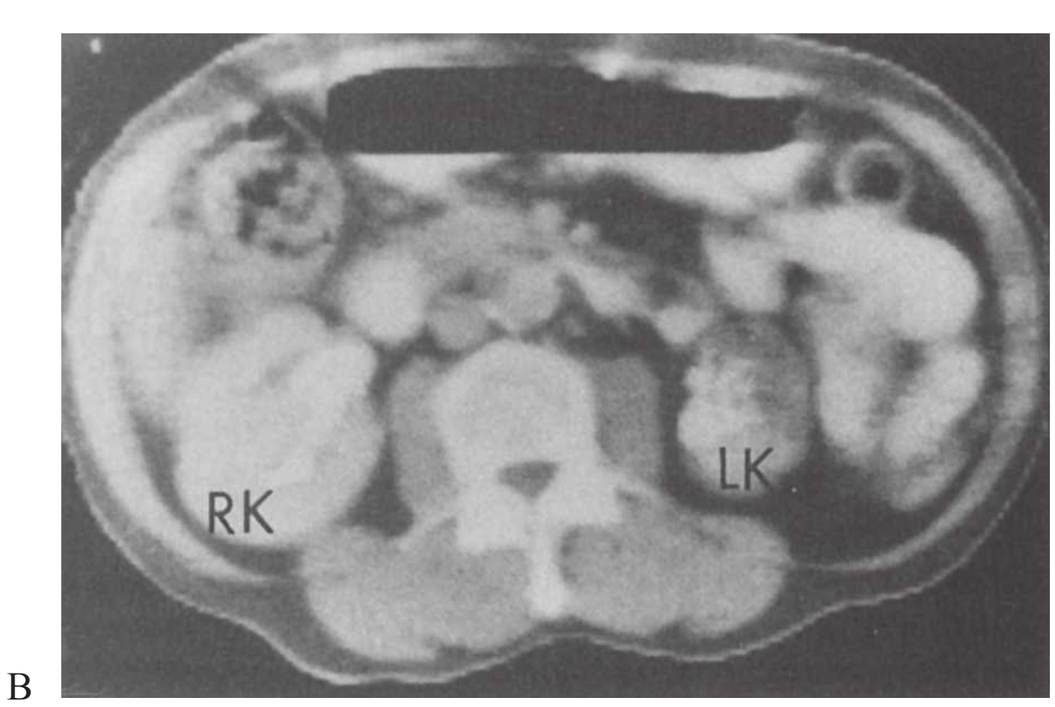
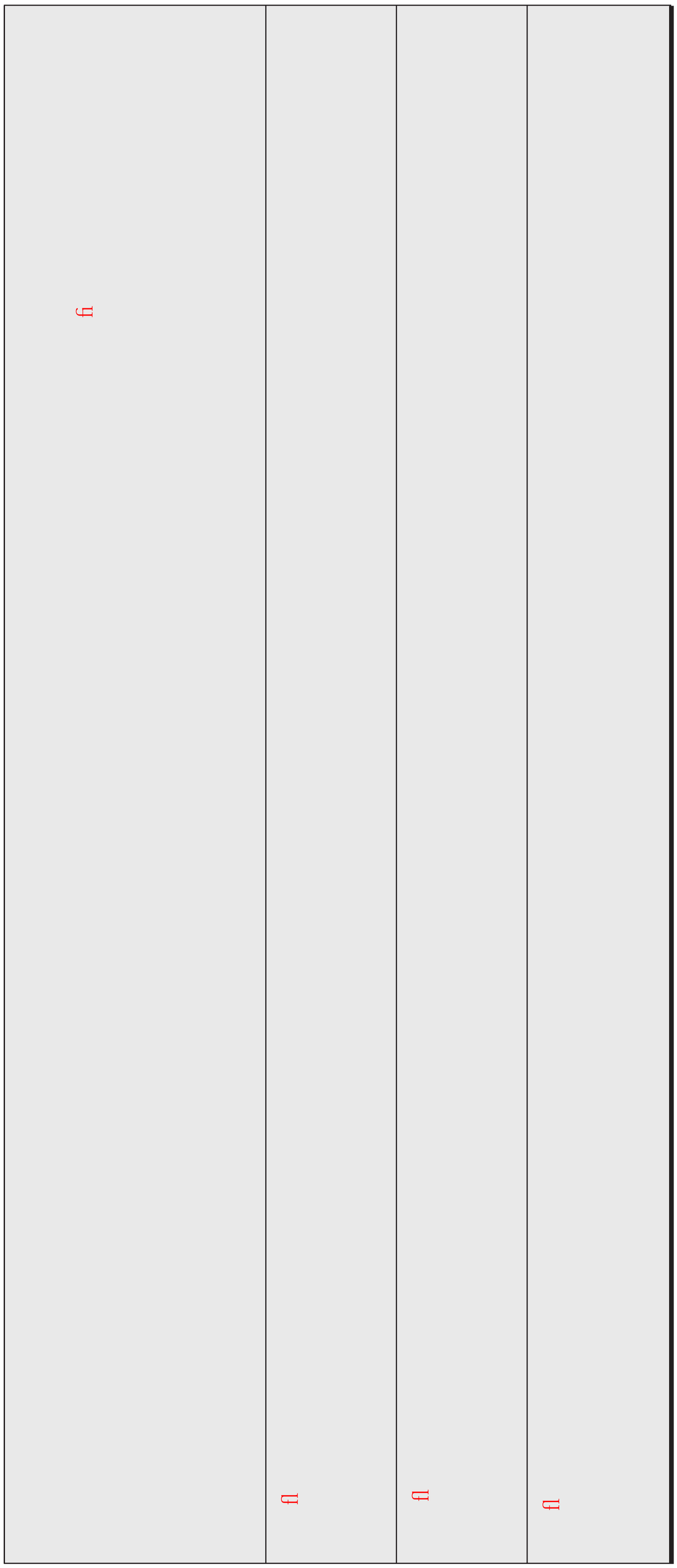


B

FIGURE 27.13 Computed tomography scans **(A)** before and **(B)** after the intravenous administration of contrast. There is a calcified nonfunctioning left kidney characteristic of a tuberculous autonephrectomy in a patient with old pulmonary tuberculosis. The right kidney is normal. *LK,* left kidney; *RK,* right kidney.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for intracellular organisms. All other drugs currently licensed for the treatment of tuberculosis are bacteriostatic. The fluoroquinolones— levofloxacin, moxifloxacin, and gatifloxacin —are bactericidal for M. tuberculosis in vitro (minimum bactericidal concentration of 2 μg/mL, in the setting of peak blood levels >4 μg/mL) and achieve excellent concentrations intracellularly. They are utilized in the treatment of patients who are intolerant of first line agents, or infected with isolates resistant to one or more first line antituberculous agents.[149] The primary role of bacteriostatic antituberculous drugs is to inhibit the development of mutants resistant to simultaneously administered bactericidal agents.

2. The spontaneous development of drug-resistant mutants of M. tuberculosis occurs at a rate of approximately 1×10^{-6}. The probability that a single organism would be resistant to two drugs simultaneously approximates the product of the probabilities of resistance to each drug alone ($1 \times 10^{-6} \times 1 \times 10^{-6} = 1 \times 10^{-12}$). Therefore, a major determinant of the number of drugs necessary to treat tuberculous infection is the number of organisms harbored by the individual. In the case of urinary tract tuberculosis without active infection at other sites, an organism burden of approximately 1×10^{7} is likely. Therefore, a minimum of two drugs to which the patient's isolate is susceptible is required for therapy. Use of only one effective drug, given the rate of mutation to drug resistance and the number of organisms present, would lead to not only clinical failure but also the selection of resistant organisms.
3. The epidemiology of drug-resistant tuberculosis is rather complex and reflects variations in resistance rates among different patient groups based on tuberculosis treatment history, ethnicity, and socioeconomic determinants. The rate of isoniazid monoresistance in the United States was largely unchanged between 1993 (4.1%) and 2005 (4.2%). INH resistance rates were elevated among both U.S. and foreign born Asian/Pacific Islanders, foreign born blacks, and U.S. born Hispanics. Resistance tracked with a history of tuberculosis, failure to complete timely antituberculous therapy, and a history of incarceration.[151] Interestingly, HIV serostatus did not confer an increased risk of INH resistance. Multidrug resistance (MDR-Tbc, INH + rifampin resistance) was identified in 1.3% of isolates in 2010, with rates of 1% in previously untreated patients and ~5% in previously treated individuals. Nearly all MDR-Tb isolates (89.4%) occurred in foreign born individuals.[20]
4. Because of the persistence of drug-resistant tuberculosis in the United States in recent years and the substantial rate of drug resistance in resource-limited settings, drug susceptibility testing should be performed routinely on all patient isolates, rather than just on isolates from high-risk patient groups. Because the most common cause of the development of de novo drug resistance is failure of compliance by the patient, directly observed therapy ("DOT") in which public health workers directly administer the therapy to the patient is often central to successful therapy. Particularly in urban areas, this strategy of enforced antituberculous therapy compliance has proved to be quite successful in blocking the spread of tuberculosis, particularly drug-resistant tuberculosis.[15,149]

The standard of care for urinary tract tuberculosis due to drug-sensitive organisms in a compliant patient is a 6-month regimen, with four-drug initial therapy (INH, rifampin, pyrazinamide, and ethambutol) for 2 months, followed by a 4-month course of INH and rifampin for 4 months[15,149]; ethambutol therapy may be discontinued when sensitivity data becomes available and confirms drug susceptibility. Patients not tolerating pyrazinamide should receive a 7 month continuation phase regimen of INH and rifampin (plus one or more of the other drugs listed until susceptibility testing results are known). More prolonged courses of therapy are indicated for any patient slow to respond to one of the standard regimens, those with miliary or central nervous system disease, those with significant immunosuppression (e.g., AIDS, organ transplant recipients, etc.), and children with multiple sites of involvement (including the skeleton).[148,149] Prolonged therapy for prostatic tuberculosis and advanced renal parenchymal disease is often recommended as well.[152]

HIV-associated tuberculosis is managed similarly to that observed in the HIV-negative population (although our preference is to prolong therapy for an additional 3 to 6 months in those with AIDS), with the following modifications to increase the probability of success: directly observed therapy for all patients with HIV-related tuberculosis; the substitution of rifabutin for rifampin in individuals receiving anti-HIV protease inhibitors because of the risk of drug interactions that affect the efficacy of treatment of both the HIV and the tuberculosis; and monitoring the responses to antituberculosis treatment to individualize the appropriate duration of antituberculosis therapy.[149] HIV-infected individuals initiating antituberculosis therapy soon after starting antiretroviral therapy may experience fever, lymphadenopathy, and exacerbation of symptoms which is now recognized as the immune reconstitution inflammatory syndrome.[149,153] This is seen primarily with advanced immunodeficiency (i.e., low CD4 counts) and can be treated by brief courses of systemic steroid therapy.[149,153]

The management of drug-resistant disease is determined by the results of in vitro susceptibility testing. Three agents including at least one of the front-line bactericidal agents (INH, rifampin, and pyrazinamide) to which the isolate is susceptible, are prescribed. INH resistant isolates may be treated with rifampin, pyrazinamide, and ethambutol, with fluoroquinolone therapy added if there is extensive disease. Rifampin monoresistant isolates are recognized primarily in HIV-infected individuals and require prolonged courses of therapy because rifampin is the cornerstone of highly active

short course antituberculosis regimens: treatment with INH, pyrazinamide, and ethambutol is recommended, with added fluoroquinolone therapy for extensive disease. Dual INH/rifampin resistance requires prolonged multidrug therapy including a fluoroquinolone and an injectable aminoglycoside in addition to two second line agents. The American Thoracic Society guidelines[149] outline treatment requirements for drug-resistant tuberculosis; expert infectious disease consultation should be sought for detailed clinical guidance.

Two types of genitourinary tract tuberculosis are particularly difficult to treat—"the autonephrectomized" kidney destroyed by tuberculosis and now presenting as a nonfunctioning, avascular, calcified, caseous mass, and prostatic tuberculosis. In both these circumstances, delivery of antituberculous therapy to the site of infection is fraught with difficulty. Indeed, as observed in the following, some authorities believe that all end-stage tuberculous kidneys should be removed surgically, and Dutt and Stead[152] noted that tuberculous abscesses must be surgically drained in any patient undergoing short-course therapy. As far as prostatic tuberculosis is concerned, we have observed patients who had been rendered culture negative with 2 years of therapy for urinary tract tuberculosis who, a few years later at the time of an incidental prostatectomy, were shown to harbor living M. tuberculosis at this sequestered site.

SURGICAL MANAGEMENT OF URINARY TRACT TUBERCULOSIS

In the prechemotherapy era, surgical ablation of infected foci was the only therapy available for renal tuberculosis. Without surgery, the 5-year survival rate for patients with renal tuberculosis was 15% to 42%, but with surgery, 10-year survival rates approached 50%.[154] With modern chemotherapy, urinary tract tuberculosis should be routinely curable, but surgical intervention is still required at times.[106–109] Surgical intervention is required for the relief of strictures, particularly ureteral strictures, which can result from the scarring process and may develop in nearly half of patients with renal tuberculosis.[106] Thus, ureteral stenting, sometimes preceded by balloon dilatation, ureteral reimplantations, and, in some cases, relief of intrarenal obstruction to urine flow are important aspects of the modern function-conserving approach to urinary tract tuberculosis.[106–109] Obstruction present at the time of diagnosis is usually addressed several weeks after initiating intensive antituberculous therapy, although percutaneous nephrostomy and stent placement to relieve severe obstruction can be performed acutely. The administration of corticosteroids together with antituberculosis chemotherapy to reduce the risk of progressive ureteral scarring and subsequent surgical intervention has long been discussed[31] but this practice remains unproven. Because ureteral strictures can develop on therapy, the possible need for surgical intervention continues long after cultures for M. tuberculosis turn negative, and close follow-up with periodic radiologic assessment is mandatory (see the previous discussion). Less commonly, patients whose bladders have been badly scarred by the tuberculosis process have such poor bladder function that bladder augmentation or even urinary diversion may be necessary to deal with unbearable urinary frequency, inadequate emptying, or both.[155,156]

Nephrectomy for the nonfunctioning end-stage tuberculous kidney,[152] once considered controversial, has gradually come to be recommended more routinely.[147,149,150] Nephrectomy is indicated for persistent microbiologic failure despite adequate chemotherapy, refractory pain, bacterial superinfection, severe symptomatic stone disease, or definite secondary hypertension. In patients with elevated surgical risk by virtue of age, underlying illness, etc., conservative management may be considered, but more generally nephrectomy is offered in this situation.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the great help of Dr. Isabel Yoder of the Department of Radiology and the late Dr. Robert McCluskey of the Department of Pathology of Massachusetts General Hospital for providing illustrations and for their wisdom in the preparation of this chapter.

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