CHAPTER

49 Immunoglobulin A Nephropathy and Henoch-Schönlein Purpura

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Immunoglobulin A nephropathy (IgAN), the most common primary glomerulonephritis in the world,[1–3] is characterized by IgA-containing immune deposits in the glomerular mesangium. Berger and Hinglais described the disease in 1968 as a new entity based on the observation of "intercapillary deposits of IgA-IgG" using immunofluorescence examination of renal biopsy specimens from patients presenting with recurrent hematuria.[4] Subsequently, it was established that the IgA deposits are exclusively of the IgA1 subclass.[5] The same immunohistologic features are found in renal biopsy specimens from patients with Henoch-Schönlein purpura (HSP) and nephritis (HSPN) who have systemic findings of an IgA-associated vasculitis affecting the skin, gut, and joints.[6–9] On the other hand, biopsies of clinically normal skin of some patients with IgAN have deposits of IgA in the walls of dermal capillaries.[10] This finding, coupled with the shared biochemical abnormalities of circulating IgA1, has led to the postulate that the two diseases, IgAN and HSPN, represent the opposite ends of a spectrum of a disease process.[9,11]

IMMUNOGLOBULIN A NEPHROPATHY

Diagnosis

The histopathologic diagnosis of IgAN is usually clear and straightforward, with little need to consider a differential diagnosis. The key is the immunohistochemical identification of IgA deposition in the glomerular mesangium.

Immunofluorescence

A definitive diagnosis of IgAN can be made only by examination of renal cortical tissue with immunofluorescence microscopy or immunoperoxidase techniques. IgA is the dominant or codominant immunoreactant and is present predominantly in the mesangium, even in apparently normal or minimally affected glomeruli. Complement component C3 is usually found in the same distribution and is commonly accompanied by IgG, IgM, or both, although often with less intense fluorescence. Confocal microscopy has shown that when immune deposits show an outer layer of C3 rather than IgA, renal biopsy specimens exhibit more severe damage.[12] C1q and C4 are found rarely; if present in substantial quantities, the possibility of lupus nephritis should be entertained.[13]

Capillary loop fluorescence for IgA is observed most frequently in patients with clinically active disease. Such biopsy specimens may also show fibrinogen in the mesangium and capillary walls and IgM in areas of glomerular sclerosis. Walls of small and medium-sized blood vessels may contain abundant granular C3.

Light Microscopy

The light microscopic hallmark of IgAN is expansion of mesangial area with proliferation of mesangial cells and increased extracellular matrix. In patients with mild disease, these changes may be quite focal and segmental. Some glomerular tufts may appear to be normal. Capillary loops usually are patent, with normal configuration of capillary walls. However, in more florid disease, mesangial proliferative activity results in the matrix extending peripherally and circumferentially in the capillary walls, resulting in a double-contouring or "tram-tracking" effect, usually with lumen narrowing. In active disease, there may be tuft necrosis associated with an exudate of fibrin and infiltration of neutrophils, some of which may show karyorrhexis. This feature is often associated with crescents in Bowman's space.

In long-standing disease, areas of segmental tuft collapse and sclerosis, sometimes with overlying hyalinosis, are seen that usually are associated with broad synechiae. In progressive disease, the end result is glomerular obsolescence and sclerosis. All of these lesions may be found in one biopsy specimen. Focal segmental glomerulosclerosis may arise by several mechanisms, including postinflammatory scarring, compensatory hemodynamic changes after loss of nephrons, and primary damage to podocytes.[14–16]

Proportional to the degree of glomerular damage, there may be tubulointerstitial disease. When active glomerular disease is present, there often is interstitial edema associated with mild to moderate infiltrate of mononuclear cells and scattered neutrophils. Secondary tubular damage also may be evident. Interstitial scarring and tubular atrophy

are features of advanced disease.[17] Hypertension-mediated damage may be seen patients with advanced disease. In an effort to standardize the description of the histologic features of the disease, an international consensus working group of nephrologists and nephropathologists has recently proposed a histologic classification scheme, the Oxford classification, based on light microscopic features.[18,19]

Electron Microscopy

Ultrastructural studies show varying degrees of expansion and proliferation of mesangial cells and extracellular matrix, and electron-dense deposits of differing sizes and amounts in the matrix. Deposits are particularly common in paramesangial areas. Corresponding to the segmental nature of the disease process, the distribution and amount of deposits may be quite patchy. Some mesangial sites may be distinctly free of deposits, yet others in the same glomerulus may be packed with them. These deposits are usually solid and homogeneous. Electron-dense deposits are occasionally found in the subepithelial and subendothelial areas of the glomerular basement membranes. Deposits in the latter location may be associated with focal necrotizing glomerular lesions on light microscopy.

Nephrotic syndrome with the pathologic features of minimal change disease has been noted in a few patients with IgAN.[20] In other patients, glomerular basement membranes are uniformly thin and this observation probably signifies the coexistence of two common conditions: IgAN and thin basement membrane nephropathy. However, one study of IgAN biopsies[21] described 40% with thin glomerular basement membranes, so perhaps mesangial IgA deposits interfere in some way with synthesis of normal glomerular basement membranes. The histologic features of IgAN are illustrated in Figure 49.1.

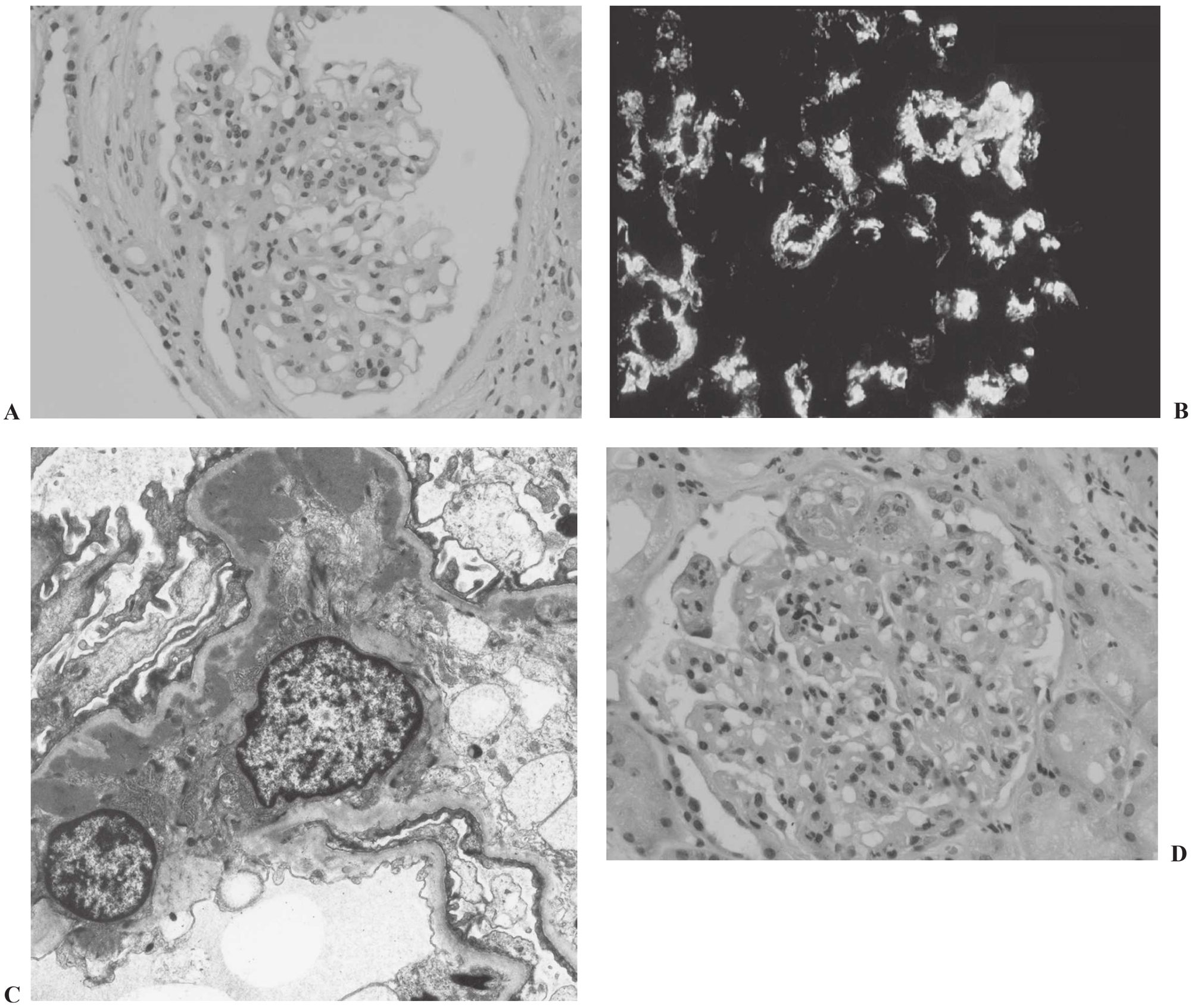

FIGURE 49.1 **A:** Glomerulus showing mesangial hypercellularity and increased mesangial matrix. (Hematoxylin and eosin stain, magnification, ×200.) **B:** Glomerulus, with brightly fluorescing mesangial deposits of IgA. (Fluorescinated antihuman IgA, magnification ×200.) **C:** Electron micrograph of glomerular mesangium showing multiple mesangial electron-dense deposits typical of IgA nephropathy. (Magnification ×3,000.) **D:** Glomerulus showing an acute lesion with segmental fibrinoid change and karyorhectic debris. (Hematoxylin and eosin, magnification ×200.) (*continued*)

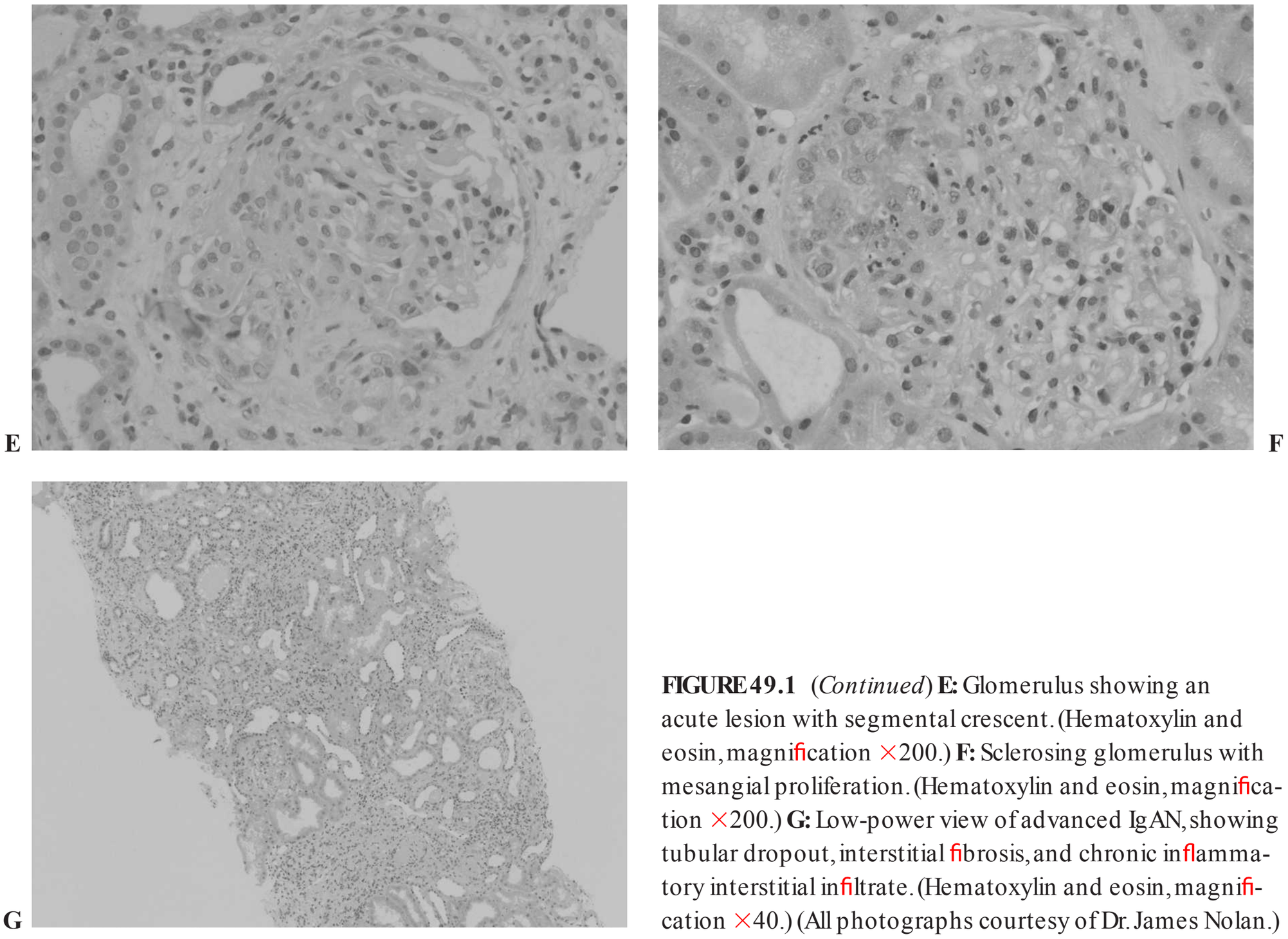

FIGURE 49.1 (*Continued*) **E:** Glomerulus showing an acute lesion with segmental crescent. (Hematoxylin and eosin, magnification ×200.) **F:** Sclerosing glomerulus with mesangial proliferation. (Hematoxylin and eosin, magnification ×200.) **G:** Low-power view of advanced IgAN, showing tubular dropout, interstitial fibrosis, and chronic inflammatory interstitial infiltrate. (Hematoxylin and eosin, magnification ×40.) (All photographs courtesy of Dr. James Nolan.)

Pathogenesis

Kidney as Innocent Bystander

IgAN recurs frequently in renal allografts.[22–26] Moreover, in isolated instances in which a kidney was transplanted from a donor with subclinical IgAN into a patient with non-IgA-nephropathy renal disease, the immune deposits cleared from the affected kidney within several weeks.[27] These clinical observations suggest that the cause of IgAN is extrarenal and there is considerable evidence indicating that the mesangial deposits originate from circulating IgA-containing immune complexes. It is well established that patients with IgAN frequently have elevated circulating levels of IgA and IgA-containing immune complexes.[28–30] Idiotypic determinants are shared between the circulating complexes and the mesangial deposits[31]; however, a disease-specific idiotype has not been identified.[32] Circulating immune complexes in patients with IgAN contain IgA1,[28,33,34] the only IgA subclass in the mesangial immunodeposits.

Analysis of the glycosylation of IgA1 in patients with IgAN has yielded novel insights into the mechanisms underlying immune complex formation and mesangial deposition.[30,34–40] Specifically, galactose deficiency in IgA1 O-glycans appears to be a key pathogenetic factor.[36] Circulating complexes in patients with IgAN contain IgA1 with galactose-deficient hinge-region O-linked glycans.[30,34,37,41] Notably, galactose-deficient IgA1 is the predominant glycosylation variant of IgA1 in the mesangial deposits, as determined by analyses of IgA1 eluted from glomeruli of nephrectomized kidneys or biopsy specimens from patients with IgAN.[42,43] A relationship between galactose deficiency and nephritis also has been underscored by two other observations: (1) galactose-deficient IgA1[44] and IgA-IgG circulating complexes[45] are found in sera of patients with HSPN but not in sera of patients with HSP and (2) patients with IgA1 myeloma have high circulating levels of IgA1, but only those with aberrantly glycosylated IgA1 develop immune-complex glomerulonephritis.[46,47]

Immunobiochemistry of IgA1: Galactose-deficient IgA1

IgA1 and IgA2 represent two structurally and functionally distinct subclasses of IgA in humans.[48] IgA1 contains a unique hinge-region segment between the first and second constant-region domains of the heavy chains (Fig. 49.2A), with a high content of proline, serine, and threonine, that is the site of attachment of O-glycans. Up to six of the nine possible sites are occupied in each hinge region. These IgA1 O-glycans consist of N-acetylgalactosamine with a β1,3-linked galactose that may be sialylated.[49–54] Sialic acid can be attached to N-acetylgalactosamine also

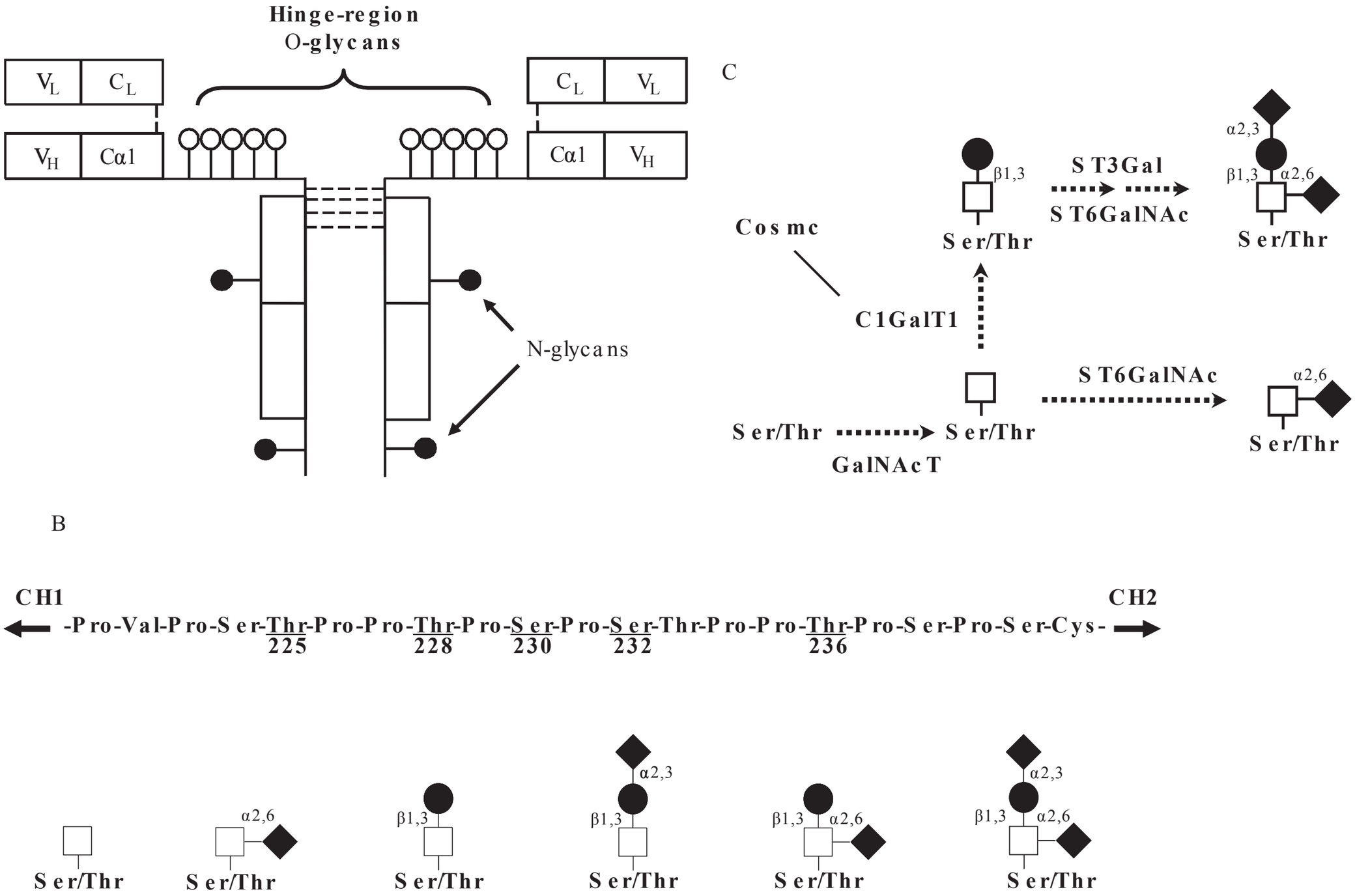

FIGURE 49.2 Structure and glycosylation of human IgA1. **A:** Monomer of IgA1 has two *N*-glycans and three to six *O*-glycans per heavy chain. **B:** Hinge-region amino acid sequence with common sites of *O*-glycan attachment and *O*-glycan variants of circulatory IgA1. The first two structures on the left side are galactose-deficient *O*-glycans. **C:** *O*-glycosylation of IgA1 is initiated by attachment of *N*-acetylgalactosamine to serine or threonine by UDP-*N*-acetylgalactosamine:polypeptide *N*-acetylgalactosaminyltransferases (GalNAc-Ts). The sites to be *O*-glycosylated and their order are determined by the specific set of GalNAc-Ts expressed in a particular cell type. *N*-acetylgalactosamine is then modified by addition of β1-3-linked galactose in a reaction catalyzed by UDP-galactose: *N*-acetylgalactosamine-α-Ser/Thr β,3-galactosyltransferase 1 (C1GalT1). Formation of active C1GalT1 depends on a specific chaperone, Cosmc. The *N*-acetylgalactosamine-galactose disaccharide can be further modified by attaching sialic acid to the galactose and/or *N*-acetylgalactosamine residues.

by an α2,6 linkage. The carbohydrate composition of the O-linked glycans in the hinge region of normal human serum IgA1 is variable (Fig. 49.2B). The prevailing glycans include galactose-N-acetylgalactosamine disaccharide and its mono- and di-sialylated forms.[30,51,54–58] Galactose-deficient variants with terminal N-acetylgalactosamine or sialylated N-acetylgalactosamine are rarely found in the O-glycans of normal serum IgA1.[51]

The first step in the O-glycosylation of the IgA1 hinge region, with selection of the sites to be modified and the control of the sequence in this process, is accomplished by one of the few enzymes of the UDP-N-acetylgalactosamine:polypeptide N-acetylgalactosaminyltransferase family. In the second step, N-acetylgalactosamine is then modified by addition of β1-3-linked galactose, as detailed in Figure 49.2C. Lastly, one or both sugars can be further modified by the addition of sialic acid.[59]

In patients with IgAN, the basis of the aberrant O-glycosylation of IgA1 has been determined by using immortalized IgA1-secreting cell lines generated from circulating mononuclear cells. The galactose deficiency develops due to changes in expression and activity of key enzymes involved in O-glycosylation in the IgA1-producing cells (Fig. 49.2C).[60] These changes in expression corresponded to decreased enzymatic activity of galactosyltransferase and elevated activity of sialyltransferase. Moreover, studies by other investigators identified mucosal, but not systemic, immune responses as the integral part of the aberrant O-glycosylation of IgA1.[61,62] However, mechanisms involved in these pathways and their regulation remain to be elucidated.

Aggregates of IgA1 and Immune Complexes with Antibody Specific for Galactose-deficient IgA1

Normal circulatory IgA has a relatively short half-life (~5 days) due to its rapid catabolism by hepatocytes.[63] Hepatocytes express the asialoglycoprotein receptor[52,64] that binds glycoproteins through terminal galactose or N-acetylgalactosamine residues.[52,64,65] Because the structural prerequisite for binding is a terminal galactose or N-acetylgalactosamine, the absence or enzymatic removal of the otherwise terminal sialic acid is essential for effective binding.

Galactose-deficient IgA1 is retained in the circulation for prolonged intervals.[66] Galactose deficiency in itself should not hinder disposal of IgA1 molecules because the asialoglycoprotein receptor recognizes terminal N-acetylgalactosamine as well as galactose.[65] However, if the N-acetylgalactosamine is linked to sialic acid or is occupied by an antibody, it cannot be recognized by the receptor.[41,67] Because galactose-deficient IgA1 is present primarily within immune complexes, it is plausible to speculate that this IgA1 does not effectively reach the hepatic asialoglycoprotein receptor. The larger size of the complexes, compared to that of uncomplexed IgA1, precludes binding to this receptor because the relatively small endothelial fenestrae block entry into the space of Disse. It is thus quite possible that immune complexes containing aberrantly glycosylated IgA1 are not efficiently cleared from the circulation and eventually deposit in the mesangium after passing through larger fenestrae in the glomerular capillaries.[69–72] In animals, high-molecular-mass immune complexes induce more severe glomerular lesions than do small complexes.[68]

Mesangial Deposition of IgA1 and Inducement of Mesangial Injury

Immune complexes containing aberrantly glycosylated IgA1 can activate human mesangial cells in vitro, resulting in a proliferative response and overproduction of extracellular matrix components and cytokines/chemokines.[37,41,73–75] Multiple studies have pointed to activation through an IgA-specific receptor(s) on mesangial cells. However, none of the known IgA receptors (CD89, asialoglycoprotein receptor, and polymeric immunoglobulin receptor) are expressed on human mesangial cells.[37,41,76] Among the candidate receptors that may mediate binding of IgA1 and IgA1 complexes are CD71 (transferrin receptor)[73,77,78] and the Fcα/μ receptor.[79] CD71 appears to be the major IgA1 receptor on proliferating human mesangial cells.[73,78,80] Notably, expression of CD71 is enhanced in the mesangia of IgAN patients and it colocalizes with IgA1 deposits.[81] Engagement of CD71 by IgA1 induces cellular proliferation and cytokine production (e.g., interleukin [IL]-6, tumor growth factor [TGF]-β).[80] This induction of cellular proliferation and cytokine production by IgA1 is inhibited completely by anti-CD71 antibody.[80] It is not clear, however, whether CD71 is the only receptor or if any other receptor(s) plays a role in the activation of mesangial cells.

Although the signaling pathways and detailed mechanisms of the activation of mesangial cells by IgA1-containing immune complexes remain to be elucidated, it is generally agreed that mesangial cells represent the primary target in IgAN. There are two hypotheses for mechanisms leading to activation of mesangial cells by IgA1 in IgAN (Fig. 49.3). Both theories propose multiple hits and involvement of aberrantly glycosylated IgA1 and antiglycan antibodies. The first assumes formation of immune complexes in the circulation and their subsequent mesangial deposition and activation of mesangial cells (Fig. 49.3, solid lines).[34,37,60,82] The other theory proposes that some of the aberrantly glycosylated IgA1 molecules are in the mesangium as lanthanic deposits, and later bound by newly generated antiglycan antibodies to form immune complexes in situ (Fig. 49.3, broken lines).[83]

Mesangial cells activated by immune complexes containing galactose-deficient IgA1 proliferate and overproduce extracellular matrix proteins, cytokines, and chemokines.[37,39,73,74,78,84–87] These processes, when unchecked for substantial periods of time, may lead to expansion of the glomerular mesangium and, ultimately, glomerular fibrosis with loss of glomerular filtration function. Furthermore, humoral factors (e.g., tumor necrosis factor [TNF]-α and TGF-β)[38,86,88,89] are released from mesangial cells activated by IgA1-containing immune complexes and alter podocyte gene expression and may thus increase glomerular permeability (Fig. 49.3). This mesangio-podocyte communication may be a mechanism to explain the occurrence of proteinuria and segmental glomerular sclerosis and tubulointerstitial injury in IgAN.[14,86] Moreover, pathogenicity of IgA1 immune complexes may be enhanced in the presence of systemic signs of oxidative stress, and it has been hypothesized that oxidative stress may affect expression and progression of the disease.[90]

Genetic Influences

Genetic factors are known to play an important role in susceptibility to IgAN, as indicated by worldwide reports of extended multiplex pedigrees.[91–98] Familial IgAN has offered a convenient tool for genetic studies and provided insight into the mechanism of inheritance. In some families, segregation of IgAN has been consistent with an autosomal-dominant transmission with incomplete penetrance. The incomplete penetrance, consistent with a complex-disease model, may reflect a requirement for additional genetic or environmental factors for clinical manifestation of the disease.

Gene mapping studies of diseases with complex determination are difficult and, thus far, no single mutation has been conclusively demonstrated to cause IgAN. Several genome-wide studies of familial IgAN have linked various loci with disease, including chromosomes 6q22-23 (named IGAN1), 4q26-31, 3p24-23, and 2q36.[95,99,100] In contrast to the linkage studies, association studies involve a collection of sporadic cases and a group of unrelated controls. These studies can be performed for specific preselected genes (candidate-gene association studies) or on a genome-wide

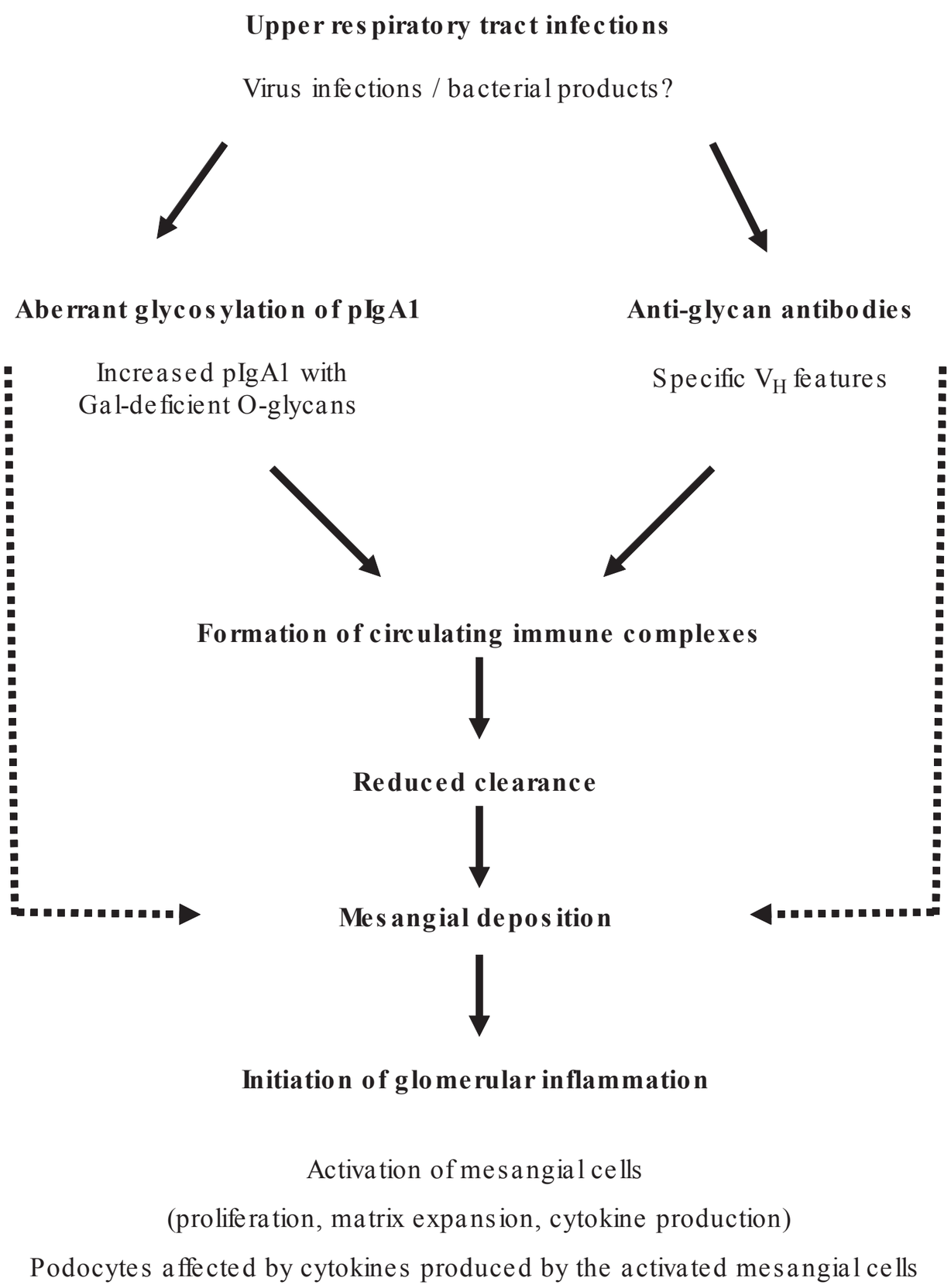

FIGURE 49.3 Mechanisms involved in IgAN pathogenesis. There are two hypotheses for mechanisms leading to the activation of mesangial cells by IgA1 in IgAN. Both theories propose multiple hits and involvement of aberrantly glycosylated IgA1 and antiglycan antibodies. The first assumes formation of immune complexes in the circulation and their subsequent mesangial deposition (*solid lines*).[34,82] Galactose-deficient IgA1 produced by a population of IgA1-secereting cells[60] is recognized by antiglycan antibodies with specific characteristics of variable region of the heavy chain[82] and, consequently, immune complexes are formed from autoantigen (galactose-deficient IgA1) and autoantibody (glycan-specific antibody). It further assumes that some of the circulating complexes are pathogenic—that is, able to deposit in the mesangium and activate the resident mesangial cells.[37] The other theory proposes that some of the aberrantly glycosylated IgA1 molecules are in the mesangium as lanthanic deposits, and later bound by newly generated antiglycan antibodies to form immune complexes in situ (*broken lines*).[83]

scale to provide an unbiased examination of the genome, with the ability to detect and correct for population stratification. Replication of findings in independent cohorts is necessary for validation of both approaches.[101]

A single, unreplicated genome-wide association study (GWAS) in a small European cohort (533 cases) has reported association of IgAN with a human leukocyte antigen (HLA) locus.[102] A recent replicated GWAS of a cohort of 3,144 IgAN cases of Chinese and European ancestry identified five loci.[103] These loci explained up to a tenfold variation in interindividual risk and cumulatively accounted for 4% to 7% of the disease variance and included three independent loci in the major histocompatibility complex, a common deletion of CFHR1 and CFHR3 at chromosome 1q32 (complement factor H-related genes) and chromosome 22q12. The risk allele frequencies also strongly paralleled the prevalence of IgAN in the different populations. Furthermore, many of the IgAN-protective alleles imparted increased risk for other autoimmune or infectious diseases, suggesting complex selective pressures on allele frequencies.[103] It is likely that studies with larger cohorts, and thus higher power, will define additional genetically influenced components in the pathogenesis of IgAN.

Recent studies of the glycosylation abnormalities of IgA1 offered prospects for a phenotypic biomarker for IgAN.[104–109] A new quantitative lectin-binding assay enabled investigation of the inheritance of galactose-deficient IgA1 in familial and sporadic forms of IgAN.[110] A high serum galactose-deficient IgA1 level was present in most index cases, as well as many of their first-degree relatives, whereas levels in spouses were indistinguishable from those in controls, eliminating an environmental effect. Segregation analysis of galactose-deficient IgA1 suggested inheritance of a major dominant gene with an additional polygenic component. The inheritance of galactose-deficient IgA1 has been confirmed in Chinese patients with familial and sporadic adult IgAN[39,111] and in pediatric patients with IgAN and HSPN.[94] Thus, aberrant IgA1 glycosylation is a common inherited defect that provides a unifying link in the pathogenesis of HSPN and familial and sporadic IgAN in many populations worldwide. GWAS studies using this new phenotype will likely provide information about the genetic and biochemical pathways leading to production of galactose-deficient IgA1 by IgA1-secreting cells.[60] Furthermore, elevated circulatory levels of galactose-deficient IgA1 are antecedent to disease. However,

as most family members with elevated levels are asymptomatic, IgA1 glycosylation abnormalities are not sufficient to produce IgAN and additional cofactors, such as antiglycan antibodies,[82] are required to trigger formation of pathogenic immune complexes (Fig. 49.3).

Clinical Disease

Incidence and Prevalence

The reported incidence and prevalence of IgAN varies widely, and depends, to some degree, on variations in criteria for renal biopsy in different countries. Studies from Europe have estimated the incidence at 15 to 40 new cases per million population per year. The incidence is higher in Japan and Korea,[112,113] where screening for urinary abnormalities is routinely performed in school-aged children. Prevalence rates, expressed as a percentage of renal biopsy diagnoses, are reported to be 20% to 40% in Asia, Australia, Finland, and southern Europe. In the United States, the rate may be as low as 2% but in a large nephropathology referral practice IgAN accounted for 14% of nontransplant renal biopsies in adults aged 20 to 39 years.[114] Although local enthusiasm for detecting asymptomatic urinary abnormalities and then biopsying those individuals undoubtedly contributes greatly to these variations, there also appear to be important differences in susceptibility across different ethnic groups.[1–3,98] For example, IgAN is less common in central Africa and New Zealand Polynesians than in Caucasians of European origin. In African Americans, the prevalence is equal to that of European Americans in some regions of the United States.[115] Subclinical disease without urinary abnormalities is more common. In Japan, a study of renal allografts revealed mesangial IgA deposits in 16% of 510 kidneys at engraftment, of which 21% had mesangial proliferation.[116] In Singapore and Germany, IgA mesangial deposits were found in 2% and 4.8% of cases in two series of unselected autopsy examinations, respectively.[117,118]

Uncertainties about true incidence and different approaches to individuals with asymptomatic urinary abnormalities also affect estimations of prognosis. Patients with milder disease will exhibit a more benign clinical course and some will even enter clinical remission. However, most patients will have persistent urinary abnormalities (microscopic hematuria ± proteinuria), and 20% to 40% of untreated patients will progress to end-stage renal failure.[98,119] As a result, IgAN is a significant component in the national budgets for end-stage renal failure replacement therapy in many countries. For some patients, the interval to renal demise will be relatively short (months to several years) because of more aggressive disease and/or late presentation, whereas for others the interval may be decades.

Clinical Presentations

The variability of presentations and subsequent course is a feature of IgAN, and a list of the wide range of initial manifestations is shown in Table 49.1. There is an approximately 2–3:1 male preponderance.

49.1 Patterns of Clinical Presentation of IgAN

Common
- Synpharyngitic macroscopic hematuria ± loin pain
- Microscopic hematuria, usually with proteinuria
- Hypertension
- Chronic renal failure
- Henoch-Schönlein purpura

Uncommon
- Malignant hypertension
- Acute nephritic syndrome
- Acute renal failure
- Nephrotic syndrome

Macroscopic Hematuria. The most distinctive and, at least to the patient, dramatic presentation of IgAN is episodic macroscopic hematuria. This feature is the principal mode of presentation in children and young adults in the Western hemisphere.[120] There is a highly characteristic close temporal relationship between its onset and an upper respiratory tract infection, especially pharyngitis or tonsillitis, whereby visible hematuria occurs within 2 days of the sore throat. This timing led to the commonly used term "synpharyngitic hematuria," and differs from the 2- to 3-week gap between infection and macroscopic hematuria in postinfectious glomerulonephritis. Less frequently, macroscopic hematuria accompanies infections of other mucosal surfaces (e.g., gastroenteritis and urinary tract infections). This hematuria may be associated with systemic symptoms such as fever, malaise, fatigue, diffuse muscle aches, and abdominal or loin pain. It is usually short-lived, lasting less than a week, and its disappearance concurs with resolution of systemic symptoms. Occasionally there is associated transient acute renal impairment.

Differentiation from other causes of macroscopic hematuria (i.e., urinary tract infection or urolithiasis) is important because frequent and unnecessary radiographic and urologic investigations may ensue if the true cause is not recognized. Of utmost importance is the microscopic examination of the centrifuged urinary sediment, which displays dysmorphic red blood cells (altered in size and shape compared to normal red cells, indicating a glomerular origin[121]), plus granular and red-cell casts. Under these circumstances, renal biopsy is the appropriate first diagnostic procedure. Microscopic hematuria ± proteinuria usually persists between episodes of macroscopic hematuria. For reasons not yet clear, macroscopic hematuria due to IgAN rarely occurs after age 40, and such an event should raise suspicion for urinary tract malignancy or stones.

Asymptomatic Microscopic Hematuria and Proteinuria. At least one third of diagnoses of IgAN are made after investigating incidentally discovered microscopic hematuria, usually accompanied by proteinuria. This scenario can occur at any age, and is typical for older patients. Local attitudes to screening and evaluating asymptomatic urinary abnormalities dictate the frequency of such presentations. A common source of such referrals is medical examinations performed for work or insurance purposes.

Proteinuria and Nephrotic Syndrome. Proteinuria in the absence of hematuria is distinctly uncommon in IgAN. Nephrotic-range proteinuria is unusual, but can occur in the presence of either very active acute disease or advanced disease with considerable scarring. Occasionally, IgAN and minimal change disease occur together, and may simply be a chance association of two relatively common disorders. It is important to recognize this possibility because the nephrotic syndrome should be treated as for minimal change disease in isolation, with expectation of a similar response.[20]

Hypertension. IgAN is a major cause of hypertension in young adults. The widespread use of blood pressure screening programs may initially identify these patients. The dramatic presentation of malignant hypertension is also well recognized for IgAN, and renal biopsy findings often indicate severe and long-standing glomerular disease.

Acute Renal Failure. Acute renal failure is a rare presenting feature for IgAN. It may occur during episodes of macroscopic hematuria, possibly as a result of tubular obstruction/injury by red blood cells that resolves without specific therapy apart from occasional resort to temporary dialysis.[122] Alternatively, rapidly progressive renal dysfunction may be due to acute necrotizing, crescentic glomerular injury. It is important to document this severe manifestation of the disease by biopsy, as it is the strongest indication for aggressive therapy.

Chronic Kidney Disease. The proportion of patients with IgAN with chronic, established renal failure at presentation is uncertain because many who come to medical care late in their clinical course do not undergo the requisite renal biopsy. Undoubtedly some patients with end-stage renal failure with small kidneys had unrecognized IgAN for years. A reliable noninvasive marker for IgAN would clearly be helpful for the diagnosis of these patients. A presumptive, retrospective diagnosis can be made for renal transplant recipients for whom an allograft biopsy indicates IgAN.

Differential Diagnosis

Although clinical suspicion based on presenting features (e.g., synpharyngitic hematuria) will often lead to the correct diagnosis of IgAN, a renal biopsy is necessary for confirmation. No other investigation has been proven to reliably distinguish IgAN from other renal diseases. This fact is frustrating because it means that an invasive procedure is required for diagnosis, an approach often judged unnecessary in a person with isolated microscopic hematuria. Although microscopic hematuria and modest proteinuria are common in patients with membranoproliferative glomerulonephritis, Alport syndrome (hereditary nephritis), and thin basement membrane nephropathy, macroscopic hematuria is rare. Serum complement levels are typically reduced in patients with membranoproliferative glomerulonephritis. A family history of renal disease (without father-to-son transmission) often with concomitant hearing loss is typical of the X-linked form of Alport syndrome. Thin basement membrane nephropathy can be distinguished from IgAN only by renal biopsy with ultrastructural studies. Some persons undergoing renal biopsy for the evaluation of microscopic hematuria and modest proteinuria have no apparent immunohistologic abnormality.[123]

Disease Associations

The literature is replete with descriptions of associations of diseases with IgAN, although it is likely that many of these are chance occurrences.[124] Deposition of IgA in the mesangium is relatively common in severe liver disease due to alcoholic cirrhosis[125] and viral hepatitis.[126] Impaired clearance of IgA by the damaged hepatocytes is thought to contribute to this observation. IgAN has been associated with inflammatory bowel disease, more so ulcerative colitis than Crohn disease,[124] and with gluten sensitivity,[127] including celiac disease and dermatitis herpetiformis. Some investigators have postulated that intestinal inflammation leads to increased permeability of dietary antigens that induces synthesis of antigen-specific IgA antibodies to form immune complexes that later deposit in the mesangium.[128] Patients infected with human immunodeficiency virus (HIV) have increased circulating levels of immune complexes containing IgA and polymeric IgA1 rheumatoid factor. IgAN may be as frequent as 5% to 8% in these patients.[129,130] In this setting, IgA may bind to the viral capsid p24 protein to form immune complexes.

Clinical Course and Prognosis

IgAN is an important cause of end-stage renal disease in many countries, but predicting a patient's outcome at the time of diagnosis has been difficult. The clinical course is very clear at the time of diagnosis for those patients presenting with established renal impairment. An estimated glomerular filtration rate (eGFR[131]) $<$30 mL/min/1.73m^2 is generally deemed the "point of no return" whereby progression to end-stage renal failure is inevitable.[132] Patients with better eGFR at diagnosis usually follow one of four courses, although wide variations in screening and diagnosis approaches preclude a precise estimate of the frequency of each. The courses are: (1) clinical resolution of mild disease, (2) ongoing mild disease without progressive renal failure, (3) slowly progressive renal dysfunction, and (4) rapidly

progressive renal failure.[98,119,133,134] Hypertension is a frequent association; it is invariable and often severe in patients with progressive disease. As discussed previously, many individuals with benign, asymptomatic disease with good prognosis likely never come to medical attention.

An important minority, perhaps 15% of those diagnosed, has mild disease at presentation (i.e., normal renal function, minimal proteinuria [<500 mg per day], and microscopic hematuria) and with time undergoes spontaneous resolution of all signs of renal disease. This course is more common in children than older patients. Mesangial IgA sometimes disappears.[135] About 50% of patients diagnosed with IgAN have persistent but benign disease. The typical pattern is ongoing low-grade microscopic hematuria, minimal or absent proteinuria, normal eGFR, and normotension or easily controlled hypertension. Such individuals should be monitored regularly, as significant changes in disease status may occur over years. Many of the remaining patients will have slowly progressive renal impairment, over years to decades, eventually leading to end-stage renal failure if lifespan permits. A more malignant shorter course is uncommon but well recognized. A rapidly progressive course is often foretold by focal necrotizing glomerular lesions in the diagnostic renal biopsy.

Clinical and histologic features can be used to generate meaningful prognostic information.[18,98,119,134,136] Poorly controlled hypertension, decrement in eGFR over a short interval, proteinuria >500 mg per day for more than 6 months, hyperuricemia, hyperlipidemia, and obesity are clinical risk factors for a poor prognosis.[137,138] Alternatively, eGFR at the time of biopsy is a relatively poor predictor for clinical course.[138] The Oxford classification found that, in biopsy specimens without crescents, four light-microscopy pathologic variables, mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, and tubular atrophy/interstitial fibrosis, had independent value in predicting clinical outcome.[18,139] Furthermore, this value transcended age of the patient at biopsy and ancestry. If validated, this classification will better guide nephrologists in the care of individual patients.[18,139] The presence of cytotoxic T lymphocytes in the interstitium and within renal tubules was shown in a retrospective study to predict loss of renal clearance function in patients with normal or near-normal eGFR.[140] Also, increased urinary excretion of podocytes has been correlated with progressive glomerular scarring.[141] Glomerular crescents, even if relatively small, herald a poor clinical course[142] and the subset of patients with antineutrophil cytoplasmic autoantibodies (ANCA) exhibits particularly aggressive disease.[143] A calculated absolute renal risk for dialysis or death has been proposed, using hypertension, proteinuria ≥1 g per day, and severe histopathologic lesions at diagnosis.[144] Episodic macroscopic hematuria, initially deemed an unfavorable prognostic sign,[145] is now considered to indicate a benign prognosis, even after taking into account its higher frequency in children than adults. Individuals with continually normal blood pressure and proteinuria persistently <200 mg per day have a negligible risk of progression.[138] However, presentation with isolated microscopic hematuria may not be a reliable sign for a good long-term outcome.[146]

Disease Markers

Diagnosis of IgAN is based on evaluation of renal biopsy because of the absence of a valid alternative noninvasive test. As renal biopsy entails risk for serious complications, early detection of IgAN is frequently impossible and monitoring of the disease is compromised. Thus, a noninvasive diagnostic test will be very useful if it can detect subclinical IgAN, estimate the degree of activity, monitor the progression or abatement of renal injury, and assess response to treatment.

As the pathogenesis of IgAN is being uncovered and the roles of IgA1 and IgA1-containing immune complexes have been identified, serum levels of galactose-deficient IgA1 and antiglycan antibodies have been targeted as potential markers for diagnosis and disease progression.[39,60,82,105,111] Methodology includes lectin enzyme-linked immunosorbent assay (ELISA) for levels of galactose-deficient IgA1[60,105] or dot-blot test to semiquantitatively measure circulating IgG antibodies specific for galactose-deficient IgA1.[82] As these techniques are refined to improve sensitivity and specificity, they may become leading candidates to be developed into clinical assays.

Urine is another source of potential biomarkers, including galactose-deficient IgA1, immune complexes, or disease-specific peptides.[109,147–150] Several studies showed differential amounts of intact proteins and protein complexes in the urine of patients with IgAN, but no test has been developed into a clinically useful assay. More recently, it has been shown by modern proteomic/peptidomic techniques that urine includes many polypeptides and/or their proteolytic fragments that are disease-specific, including those specific for IgAN.[148,151–154] Thus, several approaches may be developed into clinically useful assays following the rules for clinical proteomics.[155,156]

Treatment

There is no known cure or disease-specific therapy for IgAN. Tactics to correct the glycosylation abnormality of IgA1 or to block the formation of nephritogenic IgA1-containing immune complexes remain at the conceptual stage and have yet to be tested in any disease model. Establishing efficacy of any treatment for IgAN is difficult because most patients have a benign course and the time course of progression is frequently slow, often measured in decades. As a result, the number of randomized controlled prospective clinical trials is quite limited and some trials have used reduction in proteinuria as a surrogate (proxy) endpoint, although the validity of this ploy has been questioned.[157] The therapeutic strategy for patients with glomerular renal diseases, including IgAN, is under review by a working group of the National Kidney Foundation in the United States, Kidney Disease: Improving

Global Outcomes (KDIGO), and its recommendations are slated to be published in 2012.

Preservation of Native Kidney Function

Current options mainly aim to control disease progression and, in general, do not differ significantly from recommended strategies for other progressive renal diseases. Patients with proteinuria <500 mg per day, normal blood pressure, normal eGFR, and little or no scarring on renal biopsy require regular observation and they should avoid use of tobacco,[158] maintain an appropriate weight, exercise regularly, and take aspirin 81 mg daily.

For children and adults at risk for progressive renal injury, additional therapy is indicated. There is an evidence-based consensus that the initial approach should be suppression of the renin-angiotensin-aldosterone system (RAAS[159–163]). This treatment is appropriate for control of hypertension and proteinuria. The target blood pressure for adults is <125/75 mm Hg. Proteinuria should be reduced to <500 mg per day. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor type 1 blockers (ARBs) act synergistically and this therapy delays loss of eGFR.[164] To attain these goals, additional measures may be necessary, such as restricting dietary sodium intake to <2.4 g per day and/or use of aldosterone antagonists or other diuretic agents. Importantly, patients with severe proteinuria (≥3 g per day) for whom treatment reaches and maintains excretion at ≤1 g per day have a clinical course similar to that for patients whose proteinuria was always <1 g per day.[137]

For patients with preserved renal function (e.g., eGFR >70 mL/min/1.73 m^2) who fail to reach the above treatment targets, immunosuppressive therapy has been recommended by some investigators based on a modest number of controlled prospective clinical trials.[165] Enthusiasm must be tempered by recalling that IgAN frequently recurs in renal allografts despite the use of corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine, and tacrolimus in two- or three-drug combinations starting at the initial exposure of the kidney to a nephritogenic milieu. Glucocorticoids may be considered in a single-agent regimen using oral and parental therapy over a 6-month interval.[166] Clinical investigations under way in Germany will assess the efficacy of glucocorticoids added to suppression of RAAS.[167] Combining glucocorticoids with azathioprine was not helpful for adult patients at risk for progression and with eGFR >50 mL per min.[168] Cyclosphosphamide followed by azathioprine benefited patients with impaired renal function in a controlled prospective trial (serum creatinine >1.48 mg per dL [130 mmol per L] and higher by >15% in the prior year).[169] Patients with focal necrotizing glomerular lesions or cellular crescents frequently exhibit a rapid loss of eGFR and are often treated with cyclophosphamide, intravenous methylprednisolone, and oral prednisone (± plasmapheresis and ± antiplatelet agents), in a fashion similar to that for other forms of rapidly progressive, crescentic renal disease.[170,171] Unfortunately, high quality, randomized clinical trials have not been done, and there likely will be none in the near future. Small studies have shown an early response to treatment but a disappointing outcome for many patients over longer intervals. In weighing treatment with potent immunomodulating agents, it is important to respect the potentially serious toxicities and side effects. The occasional patient with nephrotic syndrome and histologic features of minimal change disease will respond well to standard glucocorticoid treatment for isolated minimal change disease.

Some investigators have advocated adjunctive therapy with omega-3 fatty acids (fish oil). Although the antiinflammatory, antihypertensive, and antithrombotic effects may reduce proteinuria, its value for preserving renal clearance function is unproven.[172–174] Other agents have shown little benefit. Mycophenolate mofetil has been efficacious for patients with systemic lupus erythematosus, but treatment of patients with IgAN has shown mixed results.[175,176] Studies using a calcineurin inhibitor have been inconclusive.[160] Phenytoin, which reduces serum IgA levels, showed no usefulness.[177] There is also no advantage with methods to reduce antigen or antibody load, such as dietary gluten restriction or prophylactic antibiotics.

The dramatic presenting symptom of synpharyngitic hematuria has popularized tonsillectomy as a treatment option, particularly in Japan. Unfortunately, reports describing a clinical effectiveness for hematuria and proteinuria are limited to case series or nonrandomized trials, and patients were often concomitantly treated with immunosuppressive therapy.[178,179] There is little evidence that tonsillectomy ameliorates progression to end-stage renal failure.[180] Prospective randomized clinical trials are sorely needed before this surgical therapy can be recommended. Supportive therapy, including analgesia as required, is all that is required for acute episodes of macroscopic hematuria associated with biopsy-proven acute tubular injury not associated with crescentic glomerulonephritis.[181]

Transplantation

Kidney transplantation should be offered to all patients with IgAN without a contraindication, but it is not curative. The rate of recurrence (at least the appearance of IgA deposits) is at least 50% at 5 years after engraftment.[25,181] The risk of recurrence is higher if a prior allograft was lost to recurrent disease or the pretransplant course of disease was rapidly progressive and the biopsy showed crescentic glomerulonephritis.[182] The merit of three other factors to predict recurrence are more controversial: allografts from a genetically related donor, the lack of induction therapy with an antilymphocyte or antithymocyte agent, and presence of IgA deposits on biopsy at engraftment.[162]

Recurrent disease may be subclinical[25] and was often considered to be of little clinical significance,[183] but may have serious consequences.[184,185] Allograft loss due to recurrent IgAN is likely under-reported; unless immunofluorescence studies are routinely performed for transplant biopsy and

nephrectomy specimens, losses may be erroneously attributed to chronic rejection or transplant glomerulopathy. High serum levels of aberrantly glycosylated IgA1 have not been associated with recurrent disease. Some genetic variants, including polymorphisms of TNF-α and interleukin-10, may be protective.[186] Despite these risks, the prognosis after transplantation for patients for IgAN is comparable with that for patients with other glomerulonephritis causes of end-stage renal failure.

Animal Models

The IgA1 isotype is present in only humans and hominoid primates. Consequently, progress in understanding the pathogenesis of IgAN has been hampered by the lack of animal models that recapitulate human disease. In spite of that, animal studies have identified multiple factors, including defective immunoregulation, mononuclear phagocyte function, and the role of antigen and complement, in the development of glomerular disease resembling human IgAN.

HIGA and ddY strains of mice develop IgAN-like deposits spontaneously with age.[187–192] ddY mice show mild proteinuria without hematuria and mesangioproliferative glomerulonephritis with glomerular IgA deposits, associated with increased serum IgA levels and some syntenic genetic loci.[191–193] These two models may offer opportunities to test some therapeutic approaches.[190,194] Another spontaneous model uses marmosets that exhibit wasting syndrome with glomerulonephritis and IgA deposits.[195]

Various genetic manipulations of mice induce renal pathology resembling IgAN.[196] A back-pack murine model used antigen-specific dimeric- and monomeric-IgA-producing hybridomas and the antigen to induce formation of immune complexes.[197] Only dimeric-IgA-containing complexes formed glomerular deposits. In other studies, assorted types of IgA-containing complexes have been used to generate passive models of IgAN that would be suitable for testing potential therapeutic strategies.[36,66,77,190,198–201]

HENOCH-SCHÖNLEIN PURPURA

HSP is a common vasculitis with IgA-dominant immune deposits affecting small vessels in skin, joints, and gut.[9,202–207] Historically, HSPN is a much older disease than IgAN, as it is a clinical syndrome readily recognized with its overt nonthrombocytopenic purpuric rash, arthritis, gut manifestations, and glomerulonephritis. Whereas Schönlein[6] in 1837 associated purpura and arthritis, and Henoch in 1874[7] recognized gastrointestinal and renal manifestations, the first clinical description of the disease was probably by Heberden in 1806.[208] Until the 1970s, most accounts of HSPN were descriptive, but the arrival of immunofluorescence technology allowed exploration of possible immunopathogenetic mechanisms. IgA immunofluorescence staining occurs in the glomerular mesangium and leukocytoclastic vasculitis lesions in the skin (especially purpuric lesions).[8]

Clinical Features

HSP most often manifests in the first decade of life (with male to female ratio of ~2 to 3:1) and has an increased prevalence in patients with familial Mediterranean fever. Susceptibility to disease or clinical features in some populations may be influenced by alleles at several genetic loci, including those for HLA, interleukin-8, and Toll-like receptors.[209–214] Most children exhibit a self-limited course with complete resolution, although a third of patients have a recurrence.[215] About 40% to 50% of patients with HSP develop glomerulonephritis, HSPN, and a nephritic or nephrotic syndrome and acute renal failure are more common manifestations than in IgAN. The renal disease is likely to be more severe in adults than in children[216]; skin involvement may include ulcers and renal disease more frequently progresses to end-stage renal disease.[203] As with IgAN patients, proteinuria carries significant weight in assessment of prognosis. Higher mean proteinuria over time[217] or proteinuria at 1 year after diagnosis[218] predicts a worse long-term outcome.

HSP commonly occurs soon after an upper respiratory tract infection. In one series, the prevalence of the major symptoms in children was purpura (100%), arthritis (82%), abdominal pain (63%), renal disease (40%), and gastrointestinal bleeding (33%).[33] The rash is distributed symmetrically, usually with greater involvement below the waist. Pain in multiple large joints (knees and ankles) without frank arthritis or permanent damage is typical, and abdominal pain may be disabling and accompanied by visibly bloody stools. Although these symptoms may cause much acute morbidity, recovery is usual. For those who develop renal involvement, it is generally apparent within 4 weeks of diagnosis.[219] As with IgAN, intermittent macroscopic hematuria or persisting microscopic hematuria are common.[11,203] Diagnosis of HSPN relies mostly on clinical signs and symptoms; because of risk of complications, only a few patients undergo renal biopsy to document the immunohistology.[220] Currently, no test predicts development of nephritis in HSP patients.

Renal Pathology

For those HSPN patients who undergo renal biopsy, the renal immunohistologic findings are indistinguishable from those of IgAN.[13,181,202,221] Clinical and laboratory evidence support a close relationship between IgAN and HSPN.[11,181,222] Proliferation of mesangial cells and expansion of extracellular matrix are found in patients with mild clinical disease, but progressive glomerular sclerosis and interstitial fibrosis lead to end-stage renal disease in 30% to 40% patients within 20 years after diagnosis.[202] HSPN recurs as IgA deposits in approximately 50% to 60% of renal allografts, usually without nonrenal manifestations.[23,24,223]

Pathogenesis

Aberrant glycosylation of IgA1 and IgA1-IgG circulating immune complexes of high molecular mass have been shown for patients with HSPN, similar to the findings for patients with

IgAN but not for patients with HSP without nephritis or with any other type of glomerulonephritis.[45,70,71,74,181,203,224,225] As in IgAN patients, high circulatory levels of galactose-deficient IgA1 in HSPN patients are inherited.[94] To date, no longitudinal study has examined whether this laboratory finding persists after resolution of clinical symptoms. HSPN patients, compared with HSP patients, have higher whole blood and urinary levels of leukotriene B_4 and lower levels of lipoxin A_4.[226] These findings may explain the prominent role of neutrophils in the vasculitis.

Treatment

To date, studies of children have failed to show that any therapy shortens duration of disease or prevents recurrence,[215] although a short course of glucocorticoids can reduce severity of abdominal pain or joint pain.[227] Anecdotal reports have described improvement after treatment with colchicine (as is used for familial Mediterranean fever) but this approach has not been systematically studied.[228] Glucocorticoids are not effective in preventing HSPN.[227,229–232] Despite the poor prognosis for HSPN in children, there is no firm evidence that treatment with glucocorticoids, azathioprine, cyclosphosphamide, cyclosporine, warfarin, dipyridamole, or mycophenolate mofetil, alone or in combination, confers benefit. Although randomized controlled trials have not been done, there is a general consensus that ACE inhibitors and ARBs should be used to treat hypertension and proteinuria in patients with HSPN.[233] Recent case reports indicated improvement in three children with refractory HSP treated with rituximab[234] and 14 children with HSPN treated with plasmapheresis alone[235] but neither approach has been rigorously tested. For adults, randomized trials to evaluate efficacy of any treatment are rare. One study found that adding cyclophosphamide to glucocorticoids for treatment of patients' severe HSP (most of whom had proteinuria ≥1 g/day and microscopic hematuria) was not advantageous.[236] As for patients with IgAN, renal transplantation is an excellent option for renal replacement therapy.[185]

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