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Immunoglobulin A Nephropathy and Henoch-Schönlein Purpura

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Introduction/Clinical Setting

Immunoglobulin A (IgA) nephropathy was first described by the pathologist Jean Berger (1,2) and thus is sometimes called Berger's disease. Immunoglobulin A nephropathy is defined by the presence of IgA-dominant or co-dominant mesangial immunoglobulin deposits (Fig. 6.1) (3). Lupus glomerulonephritis, which may have IgA dominant or co-dominant deposits, is excluded from this diagnostic category. Immunoglobulin A nephropathy occurs as a primary (idiopathic) disease, as a component of Henoch-Schönlein purpura small-vessel vasculitis, secondary to liver disease (especially alcoholic cirrhosis), and associated with a variety of inflammatory diseases including ankylosing spondylitis, psoriasis, Reiter's disease, uveitis, enteritis (e.g., *Yersinia enterocolitica* infection), inflammatory bowel disease, celiac disease, dermatitis herpetiformis, and HIV infection (4–6).

Pathologic Findings

Light Microscopy

Immunoglobulin A nephropathy and Henoch-Schönlein purpura nephritis can have any of the histologic phenotypes of immune complex-mediated glomerulonephritis other than pure membranous glomerulopathy, including no lesion by light microscopy with immune deposits by immunohistology, mesangioproliferative glomerulonephritis with mesangial but no endocapillary hypercellularity (Figs. 6.2 and 6.3), focal or diffuse proliferative glomerulonephritis with endocapillary hypercellularity (with or without crescents) (Fig. 6.4), overt crescentic glomerulonephritis with 50% or more crescents, type I membranoproliferative (mesangiocapillary) glomerulonephritis (rare), and focal or diffuse sclerosing glomerulonephritis (7–10).

A variety of classification systems have been used to categorize the light microscopic phenotypes of IgA nephropathy, such as those proposed by

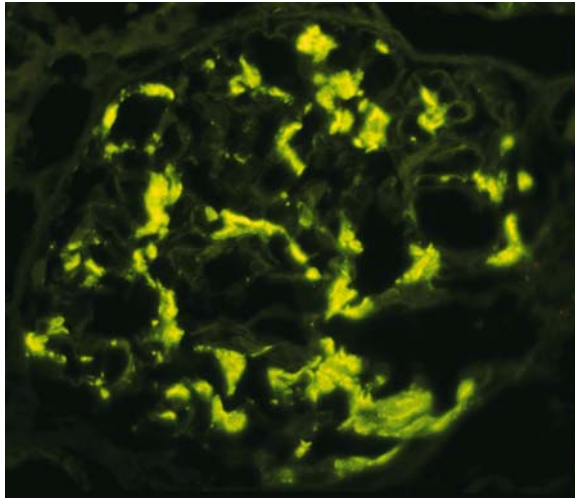


FIGURE 6.1. Immunofluorescence microscopy demonstrating glomerular mesangial staining for immunoglobulin A (IgA) in a patient with IgA nephropathy.

Kurt Lee et al (7) and by Mark Haas (8) (Table 6.1). Another approach is to use the same descriptive terminology that is in the World Health Organization (WHO) lupus classification system to categorize IgA nephropathy as well as other forms of immune complex glomerulonephritis. This system works as well for IgA nephropathy as it does for lupus, and also has the

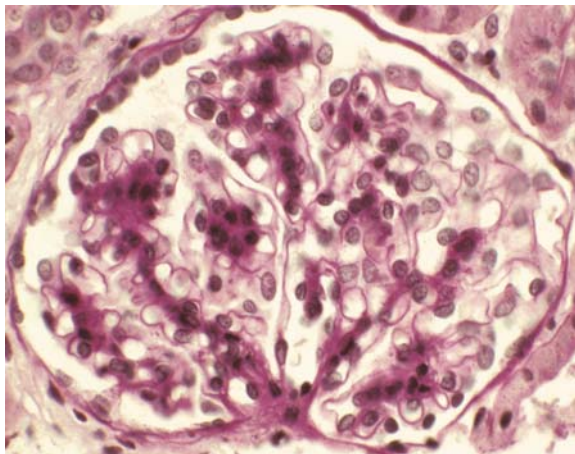


FIGURE 6.2. Glomerulus from a patient with IgA nephropathy showing mild segmental mesangial hypercellularity in the upper left quadrant of the glomerulus [periodic acid-Schiff (PAS) stain].

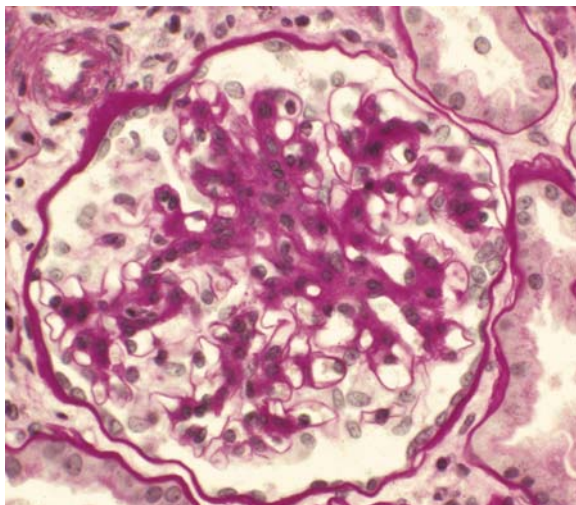


FIGURE 6.3. Glomerulus from a patient with IgA nephropathy showing moderate segmental mesangial hypercellularity and increased mesangial matrix in the upper portion of the tuft (PAS stain).

advantage of not requiring knowledge of multiple different classification systems.

In patients whose renal biopsy specimens are referred to the University of North Carolina for evaluation, crescents are observed in about a third of patients with IgA nephropathy and two thirds of patients with Henoch-

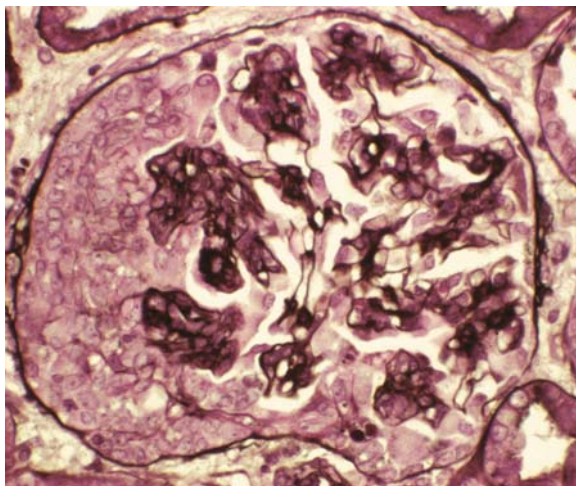


FIGURE 6.4. Glomerulus from a patient with Henoch-Schönlein purpura showing a proliferative glomerulonephritis with endocapillary hypercellularity adjacent to a cellular crescent on the right of the tuft (Jones silver stain).

TABLE 6.1. Three different approaches to the histologic classification of IgA nephropathy

Lee system	Haas system	WHO lupus terminology
I: Focal mesangioproliferative	I: Focal mesangioproliferative	I: Normal by light microscopy
II: Moderate focal proliferative	III: Focal proliferative	II: Focal mesangioproliferative
III: Mild diffuse proliferative	II: Focal sclerosing	III: Focal proliferative
IV: Moderate diffuse proliferative	IV: Diffuse proliferative	IIIC: Focal sclerosing
V: Severe diffuse proliferative	V: Chronic sclerosing	IV: Diffuse proliferative
		VI: Chronic sclerosing

Note: The Lee and Haas systems were specifically designed for IgA nephropathy, whereas the terminology for the World Health Organization (WHO) system was designed for lupus glomerulonephritis but can be used to describe the pathology of IgA nephropathy.

Schönlein purpura nephritis (11). However, overt crescentic glomerulonephritis with 50% or more of glomeruli with crescents is uncommon (<5% in IgA nephropathy and <10% in Henoch-Schönlein purpura nephritis). When substantial crescent formation is present, especially with conspicuous fibrinoid necrosis, the possibility of concurrent antineutrophil cytoplasmic antibody (ANCA) disease should be considered (12).

Between 5% and 10% of specimens with IgA nephropathy identified by immunohistology have focal segmental glomerular sclerosis as seen on light microscopy that is indistinguishable from idiopathic focal segmental glomerulosclerosis (8).

Immunofluorescence Microscopy

The sine qua non for a diagnosis of IgA nephropathy is immunohistologic detection of dominant or co-dominant staining for IgA in the glomerular mesangium (Fig. 6.1). A caveat to this is that the staining for IgA should at least be 1+ on a scale of 0 to 4+ or 0 to 3+. Trace amounts of IgA are not definitive evidence for IgA nephropathy. The IgA is predominantly IgA1 rather than IgA2. Capillary wall staining is observed in about a third of patients, and is more common in Henoch-Schönlein purpura nephritis (10). The mesangial immune deposits of IgA nephropathy stop abruptly at the glomerular hilum and are not observed along tubular basement membranes. Rare patients have IgA nephropathy concurrent with membranous glomerulopathy, and thus their specimens show granular capillary wall IgG staining and mesangial IgA dominant staining (13).

Staining for IgA essentially always is accompanied by staining for other immunoglobulins and complement components (3). Staining for IgG and IgM often is present, but at low intensity compared to IgA. A very distinc-

tive feature of IgA nephropathy compared to other immune complex diseases is the predominance of staining for lambda over kappa light chains in many specimens. C3 staining is almost always present and usually relatively bright. However, staining for C1q is uncommon and when present is typically of low intensity. The presence of substantial C1q should raise the possibility of lupus nephritis with conspicuous IgA deposition. This suspicion would be supported further by finding endothelial tubuloreticular inclusions by electron microscopy and antinuclear antibodies serologically. As in other forms of glomerulonephritis, staining for fibrin is seen at sites of necrosis and crescent formation. Depending in part on what reagent antibody is used, the immune deposits occasionally stain for fibrin, especially in patients with Henoch-Schönlein purpura nephritis (10).

Electron Microscopy

The typical ultrastructural finding is immune complex-type electron-dense deposits in the mesangium (Figs. 6.5 and 6.6). Dense deposits most often are found immediately beneath the paramesangial glomerular basement membrane. The amount of deposits varies substantially, with occasional specimens having massive replacement of the matrix by the dense material (Fig. 6.6). Rare specimens that have well-defined IgA deposits by immunofluorescence microscopy do not have detectable mesangial dense deposits, which does not rule out a diagnosis of IgA nephropathy because the

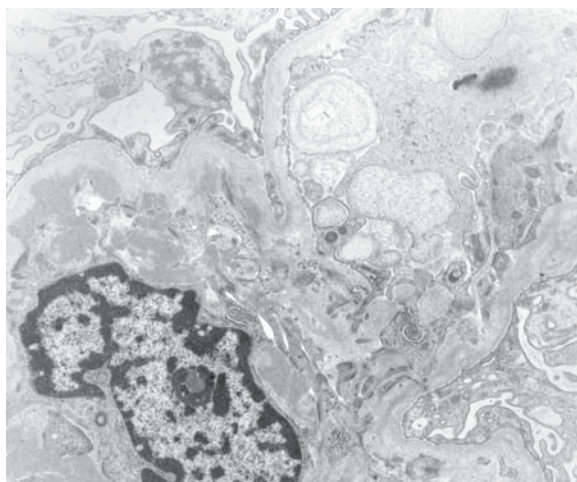


FIGURE 6.5. Electron micrograph of a glomerulus from a patient with IgA nephropathy showing a moderate amount of electron-dense deposits within the mesangium. The mesangium is on the left of the image and a portion of the capillary loop is on the right.

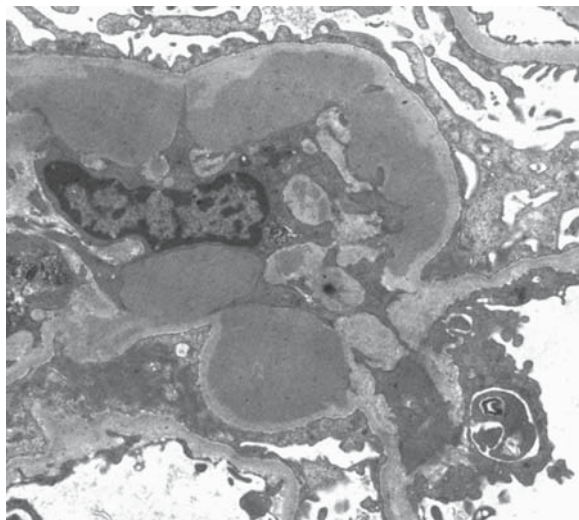


FIGURE 6.6. Electron micrograph of a glomerulus from a patient with IgA nephropathy showing massive electron-dense deposits within the mesangium. The mesangium is on the left of the image and a portion of the capillary loop is on the right.

immunohistology is the defining feature. Capillary wall subepithelial, sub-endothelial, and intramembranous deposits are identified in approximately a quarter to a third of specimens with IgA nephropathy (3), and are more frequent in patients with Henoch-Schönlein purpura nephritis (10). Capillary wall deposits are least frequent in histologically mild disease and most frequent in histologically severe disease, especially when crescents are present.

Focal areas of glomerular basement membrane thinning are observed in many specimens with IgA nephropathy (14). This structural abnormality may contribute to the hematuria. Focal or diffuse podocyte foot process effacement often is present, especially in patients with nephrotic range proteinuria. Foot process effacement is particularly prominent in patients who have the syndrome of histologically mild IgA nephropathy with minimal change glomerulopathy-like features clinically (15). Mesangial matrix expansion and mesangial hypercellularity parallel the mesangial changes seen by light microscopy.

Etiology/Pathogenesis

Immunoglobulin A nephropathy probably can result from multiple different etiologies and pathogenic processes, such as (1) abnormal structure and function of IgA molecules, (2) reduced clearance of circulating IgA com-

plexes, (3) increased affinity for or reduced clearance of IgA deposits from the glomerular mesangium, (4) excessive IgA antibody production in response to mucosal antigen exposure, (5) excessive mucosal exposure to antigens, (6) increased permeability of mucosa to antigen, or (7) combinations of these factors.

Some secondary forms of IgA nephropathy appear to be caused by either decreased clearance of IgA from the circulation (e.g., reduced hepatic clearance caused by cirrhosis) or increased entry of IgA complexes into the circulation (e.g., caused by increased synthesis and greater access to the circulation in inflammatory bowel disease).

However, an important pathogenic mechanism in many patients with IgA nephropathy and Henoch-Schönlein purpura nephritis appears to derive from abnormally reduced galactosylation of the O-linked glycans in the hinge region of IgA1 molecules (6,16). This abnormality could result in mesangial IgA deposition by a variety of mechanisms including reduced clearance from the circulation because of lack of receptor engagement by the abnormal IgA, increased aggregation of IgA in the circulation resulting in mesangial trapping, development of immune complex-forming autoantibodies directed against the abnormal IgA, increased affinity of the abnormal IgA for mesangial matrix, or combinations of these processes.

Clinicopathologic Correlations

Immunoglobulin A nephropathy is said to be the most common form of glomerulonephritis in the world (4). The prevalence of IgA nephropathy varies among different racial groups, with the highest prevalence among Asians and Native Americans, intermediate prevalence among Caucasians, and lowest prevalence among individuals of African descent (4). Immunoglobulin A nephropathy and Henoch-Schönlein purpura nephritis are twice as common in males as females. On average, Henoch-Schönlein purpura nephritis occurs at an earlier age than IgA nephropathy (9). The onset and diagnosis of IgA nephropathy usually is in late childhood or early adulthood, whereas Henoch-Schönlein purpura usually occurs in children younger than 10 years of age. Immunoglobulin A nephropathy can manifest any of the signs and symptoms caused by glomerular disease. The most common initial manifestations are asymptomatic microscopic hematuria or intermittent gross hematuria or both. Approximately 10% of patients present with nephrotic syndrome and approximately 10% have renal failure at initial presentation. Rare patients present with rapidly progressive glomerulonephritis (17) or advanced chronic renal failure. Approximately 10% to 15% of patients reach end-stage renal disease within 10 years of diagnosis, and approximately 25% to 35% within 20 years (5,10). Immunoglobulin A nephropathy has a recurrence rate of greater than 50% in renal transplants. Recurrent IgA nephropathy causes

some graft dysfunction in approximately 15% of patients after 5 years and graft loss in approximately 5% after 5 years (18).

The glomerulonephritis of Henoch-Schönlein purpura is not pathologically distinguishable from IgA nephropathy, although, as noted earlier, on average, Henoch-Schönlein purpura nephritis tends to be more severe with a higher frequency of crescent formation (10). In addition to nephritis, common clinical manifestations of Henoch-Schönlein purpura include arthralgias, purpura caused by leukocytoclastic angiitis of dermal capillaries, and abdominal pain caused by involvement of small vessels in the gut and other abdominal viscera (19). The presence of IgA deposits without vasculitis in systemic vessels is not adequate for a diagnosis of Henoch-Schönlein purpura because some patients with IgA nephropathy have no evidence for systemic vasculitis. IgA deposits in extrarenal vessels, such as dermal venules. Patients with Henoch-Schönlein purpura usually have only one episode of purpura that resolves completely. Persistent and progressive nephritis is the most important long-term complication and results in end-stage disease in 5% to 20% of patients after 20 years (9).

The outcome of IgA nephropathy cannot be accurately predicted on the basis of clinical or pathologic features; however, as with other glomerular diseases, there are trends toward worse outcomes with more severe renal insufficiency at presentation, greater proteinuria, extensive crescent formation, or more extensive glomerular or tubulointerstitial scarring (6).

The treatment for IgA nephropathy remains controversial (4–6). There is general agreement that angiotensin-converting enzyme inhibitors are beneficial. Fish oil supplements with high concentrations of omega-3 fatty acids have been advocated by some investigators, but the evidence of their benefit is not conclusive. As with other forms of glomerulonephritis, corticosteroid treatment may be helpful, especially when there is substantial active glomerular inflammation or the syndrome with concurrent minimal change-like glomerulopathy. Treatment with cytotoxic agents generally has been reserved for patients with severe crescentic IgA nephropathy or Henoch-Schönlein purpura nephritis (17). It is hoped that the emerging knowledge of the pathogenesis of IgA nephropathy and Henoch-Schönlein purpura will lead to more effective treatment strategies.

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