- **Membranoproliferative glomerulonephritis** (MPGN) in most cases is the result of immune complex deposition in both mesangial regions and capillary walls. It may be associated with systemic infections.
- **Dense deposit disease (type II MPGN),** defined by a unique permeation of glomerular basement membranes by electron dense material, primarily affects children and young adults. It is associated with acquired or genetic dysregulation of the alternate pathway of complement.

Isolated Glomerular Abnormalities

IgA Nephropathy (Berger Disease)

IgA nephropathy, characterized by the presence of prominent IgA deposits in the mesangial regions and recurrent hematuria, is the most common type of glomerulonephritis worldwide. The disease can be suspected by light microscopic examination, but the diagnosis is made only by the detection of glomerular IgA deposition (Fig. 20-19). Mild proteinuria is usually present, and the nephrotic syndrome may occasionally develop. Rarely, patients may present with crescentic RPGN.

Whereas IgA nephropathy is typically an isolated renal disease, similar IgA deposits are present in a systemic disorder of children, *Henoch-Schönlein purpura*, to be discussed later, which has many overlapping features with IgA nephropathy. In addition, *secondary IgA nephropathy* occurs in patients with liver and intestinal diseases, as discussed later.

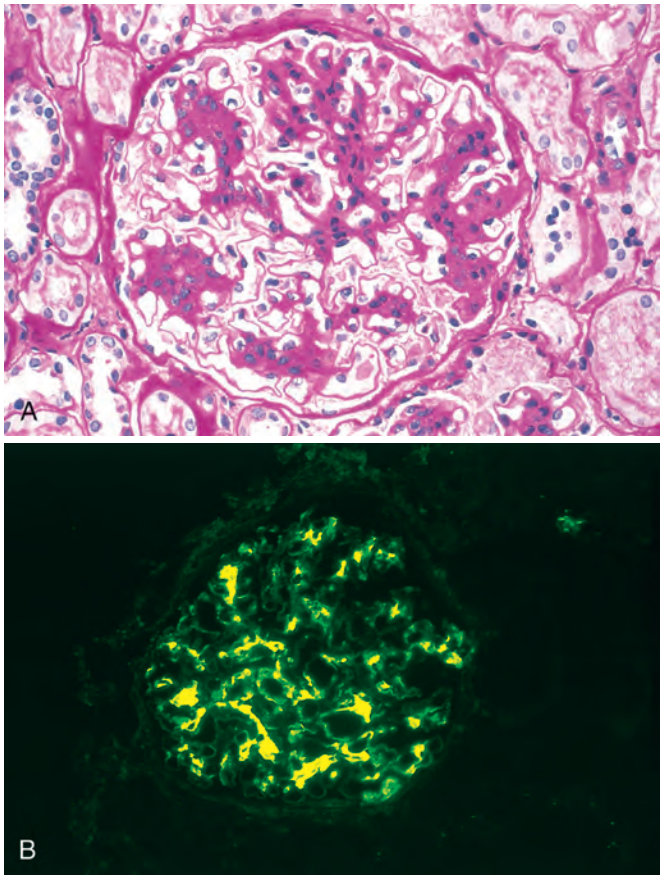

Figure 20-19 IgA nephropathy. **A,** Light microscopy showing mesangial proliferation and matrix increase. **B,** Characteristic deposition of IgA, principally in mesangial regions, detected by immunofluorescence.

Pathogenesis. Current evidence favors a "multi-hit" etiology for this disorder involving several steps. IgA, the main Ig in mucosal secretions, is present in plasma at low concentrations, mostly in monomeric form, the polymeric forms being catabolized in the liver. In patients with IgA nephropathy, levels of plasma polymeric IgA are increased, but increased production is not sufficient to cause this disease. A clue comes from the observation that in IgA nephropathy, the glomerular deposits consist predominantly of polymeric IgA molecules with aberrant glycosylation. It is believed that a key facet of IgA nephropathy is a hereditary or acquired defect in the normal formation or attachment of galactose-containing sugar chains called O-linked glycans to the hinge region of the IgA molecule (particularly to those of the IgA1 subclass) prior to their secretion by B cells. This aberrantly glycosylated IgA1 is either deposited by itself in glomeruli or it elicits an autoimmune response and forms immune complexes in the circulation with IgG autoantibodies directed against the abnormal IgA molecules. The immune complexes are deposited in the mesangium; alternatively, the abnormal IgA1 is deposited in the mesangium with subsequent formation of immune complexes in situ. The mesangial immune deposits then activate mesangial cells to proliferate, produce increased amounts of extracellular matrix, and secrete numerous cytokines and growth factors. These secreted mediators may not only participate in further mesangial cell activation but may also recruit inflammatory cells into the glomeruli. The recruited leukocytes contribute to glomerular injury and also to a reparative response, which can include opsonization and removal of the immune complexes. The deposited IgA and IgA-containing immune complexes activate the complement system via the alternate pathway, and hence the presence of C3 and the absence of C1q and C4 in glomeruli are typical of this disorder. A genetic influence is suggested by the occurrence of this condition in families and in HLA-identical siblings, the increased frequency of certain HLA and complement genotypes in some populations, and the findings of genome wide association studies linking specific MHC Class II loci to disease susceptibility.

Epidemiologic features of this disorder indicate that the increased synthesis of abnormal IgA may occur in response to respiratory or gastrointestinal exposure to environmental agents (e.g., viruses, bacteria, food proteins). The specific initiating antigens are unknown, and several infectious agents and food products have been implicated. IgA nephropathy occurs with increased frequency in individuals with *gluten enteropathy* (celiac disease), in whom intestinal mucosal defects are well defined, and in *liver disease*, in which there is defective hepatobiliary clearance of IgA complexes *(secondary IgA nephropathy)*.

MORPHOLOGY

On histologic examination the lesions vary considerably. The glomeruli may be normal or may show mesangial widening and endocapillary proliferation (mesangioproliferative glomerulonephritis), segmental proliferation confined to some glomeruli