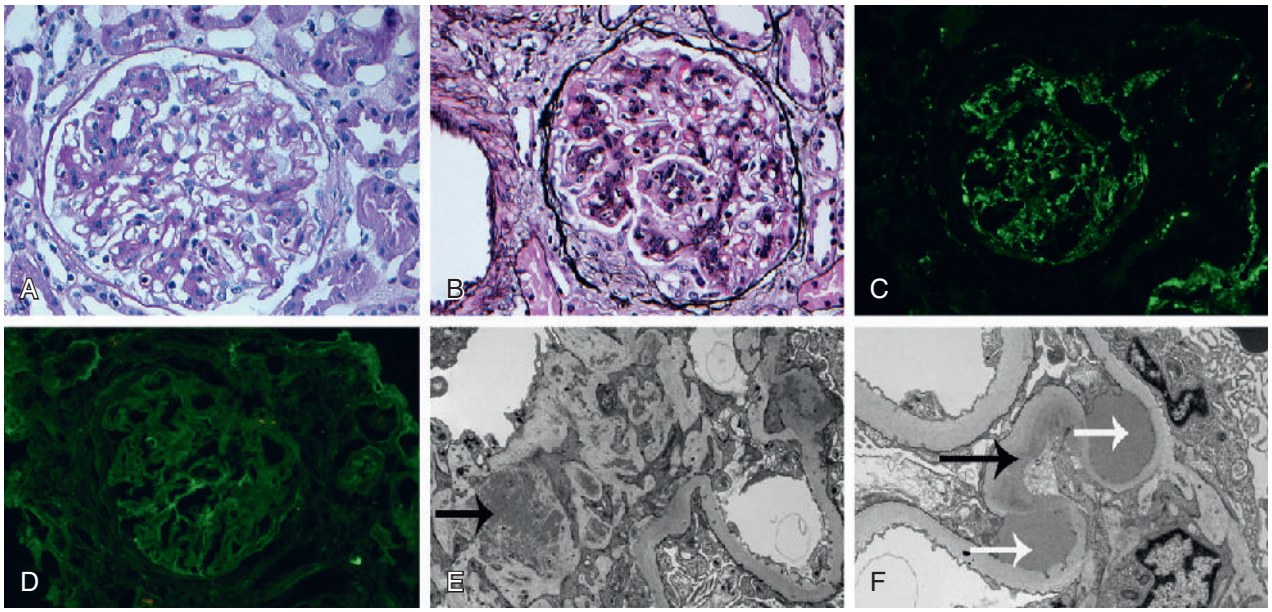

FIGURE 28-8 C3 glomerulonephritis. Light microscopy shows features of mesangial proliferative glomerulonephritis (**A**, periodic acid–Schiff, ×40) and membranoproliferative glomerulonephritis (**B**, silver methenamine stain, ×40) in the same biopsy. Immunofluorescence microscopy shows bright granular mesangial and capillary wall staining for C3 (**C**) and negative staining for immunoglobulin G (**D**). **E,** Electron microscopy shows a large accumulation of smudgy mesangial deposits *(arrow)* (×10,000). **F,** Electron microscopy shows subendothelial deposits *(black arrow)* and subepithelial humplike deposits *(white arrows)* (×150,000). The subepithelial deposits sometimes make it difficult to distinguish C3 glomerulonephritis from postinfectious glomerulonephritis. However, C3 glomerulonephritis may not show Ig (as in this case), and the term *atypical postinfectious glomerulonephritis* sometimes is applied in cases of C3 glomerulonephritis with subepithelial humplike deposits.

or acquired dysregulation of the alternative pathway of complement (C3 glomerulopathy) and can be further sub-classified as C3 glomerulonephritis and dense deposit disease (DDD) based on electron microscopy examination.

Immune complex–mediated MPGN precipitated by an infection is most commonly caused by HCV (i.e., cryoglobulinemic glomerulonephritis). The clinical presentation varies and can include nephrotic and nephritic features. In patients with cryoglobulinemic MPGN, the levels of C3, C4, and CH50 are persistently low, reflecting activation of both complement pathways. Patients with C3 glomerulonephritis or DDD may have a persistently low level of C3 but a normal level of C4. A C3 nephritic factor is found in many cases. C3 nephritic factor is an autoantibody to alternative pathway C3 convertase, resulting in persistent breakdown of C3.

The absence of well-designed studies based on current knowledge of the multiple pathogenic processes that impart a MPGN pattern of injury to the kidney make it impossible to give strong treatment recommendations. From a practical point of view, patients with MPGN due to chronic infections (e.g., HCV, endocarditis), autoimmune disease, and plasma cell dyscrasias should undergo treatment of the underling disease. Patients with normal kidney function, no active urinary sediment, and non–nephrotic-range proteinuria can be treated conservatively with angiotensin II blockade to control blood pressure and reduce proteinuria, because the long-term outcome is relatively benign in this setting. Follow-up is required to detect early deterioration in kidney function. Patients who have advanced renal insufficiency and severe tubulointerstitial fibrosis of renal biopsy are unlikely to benefit from immunosuppressive therapy.

GLOMERULAR DISEASES MANIFESTING WITH RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Antineutrophil Cytoplasmic Antibody–Associated Vasculitides

The ANCA-associated vasculitides (AAVs) are a group of three heterogeneous syndromes: granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss syndrome). The unifying feature is a necrotizing small vessel vasculitis with a predilection for the kidneys, lungs, and peripheral nervous system that occurs in association with autoantibodies against antigens in the cytoplasm of neutrophils (i.e., myeloperoxidase [MPO] and proteinase 3 [PR3]).

Approximately 75% of the patients with GPA are PR3-ANCA positive, and 20% are MPO-ANCA positive, whereas about 50% of patients with MPA are MPO-ANCA positive and about 40% are PR3-ANCA positive. Necrotizing granulomatous inflammation, which affects the upper and lower respiratory tract and frequently precedes other disease manifestations, separates GPA from MPA. EGPA is characterized by asthma and eosinophilia in addition to features of small vessel vasculitis such as mononeuritis multiplex. AAV is the most common cause of a RPGN in patients older than 60 years. AAV is associated with signs and symptoms ranging from limited renal disease to RPGN and pulmonary-renal syndrome (Table 28-3). Renal biopsy is characterized by a focal, necrotizing, and crescentic glomerulonephritis with pauci-immune immunofluorescence (Fig. 28-9).