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On the Cover
What is the diagnosis?
A 51-year-old male with normal baseline kidney function and a history of diabetes mellitus and arterial hypertension for 20 years presented with fatigue, edema, oligoanuria, and impaired kidney function 2 weeks after an upper respiratory tract infection. At admission, serum creatinine was 1.76 mg/dl (eGFR, 51 ml/min per 1.73 m²), with elevated white blood cells and C-reactive protein, positive antistreptolysin O antibodies test, active urine sediment, and proteinuria (9 g/day). The patient became anuric and dialysis dependent. The first kidney biopsy revealed acute, postinfectious glomerulonephritis with well-defined lesions of diabetic nephropathy. Serum C3 was initially low, with normal serum C4, rheumatoid factor, anti–nuclear autoantibodies, and anti–neutrophil cytoplasmic autoantibodies. No autoantibodies against complement factor H or C3 or C4 nephritic factors were detected, whereas C5b-9 was slightly increased. He received antimicrobial therapy, supportive care, dialysis, and pulses of glucocorticoids. The second biopsy a month later was unchanged. The patient remained on dialysis for 3 months and progressively improved. His serum C3 level returned to normal, and he ended dialysis with an eGFR of 20 ml/min per 1.73 m².

Image description
The first kidney biopsy revealed 8/26 globally sclerosed glomeruli (31%). In both biopsies, the dominant finding by light microscopy was diffuse proliferative and exudative glomerulonephritis with significant endocapillary proliferation and numerous neutrophils. In addition, diffuse mesangial expansion and well-defined mesangial Kimmelstiel-Wilson nodules were seen (left and left center images). Immunofluorescence revealed strong C3 expression (3–4+) in a diffuse, coarsely granular pattern along the glomerular capillaries and focally in the mesangium (right center image). There was no staining for IgA, and only trace IgM and IgG were found. Interstitial fibrosis and arteriosclerosis were moderate (30%). Electron microscopy revealed numerous, large subepithelial electron-dense deposits (humps) situated on moderately thickened basement membranes. Plentiful neutrophils were seen in the glomerular lumina (right image).

Teaching points
Poststreptococcal glomerulonephritis (PSGN) is an immunological-mediated glomerular lesion caused by prior infection, with specific nephritogenic stains of group A β-hemolytic streptococcus. Histologically, it is characterized by exudative glomerular injury, dominant C3 staining, and subepithelial humps. The clinical picture varies from asymptomatic to rapidly progressive glomerulonephritis. Although it is considered a self-limited condition, especially in children, it may occasionally follow a rather persistent course, leading to chronic kidney insufficiency. Patients with pre-existing pathology, where PSGN is superimposed, have been reported to have a poor outcome. Specifically, patients with comorbidities, such as diabetes mellitus, hypertension, smoking, and alcoholism, are more likely to end up on chronic dialysis.

For patients with PSGN who require or are progressing toward dialysis treatment, a kidney biopsy is mandatory in the acute phase to confirm the diagnosis and exclude other conditions that may present with acute glomerulonephritis and hypocomplementemia, such as C3 glomerulopathy, cryoglobulinemic glomerulonephritis, lupus nephritis, membranoproliferative glomerulonephritis, and IgA-dominant, staphylococcus-associated glomerulonephritis. The pattern of hypocomplementemia and its duration (the disease time-course), i.e., acute onset versus persistent-recurrent active glomerulonephritis over a prolonged period, in correlation with histopathology, depict the diagnosis. Clinically, a critical distinction pertains to the time of infection occurrence; prior to PSGN or coincidentally with the IgA-dominant, staphylococcus-associated glomerulonephritis.

Left image: A large glomerulus from the first biopsy with a significant number of inflammatory cells, mostly neutrophils, into distended capillary lumina. Thick basement membranes, diffuse mesangial matrix increase, and a well-formed mesangial nodule at the bottom right can be appreciated (H&E ×400).

Left center image: A large glomerulus from the second biopsy with extensive neutrophil infiltration in association with distension of glomerular lumina, superimposed on mesangial expansion caused by diabetes (H&E ×400).

Right center image: Diffuse, coarsely granular deposits along the glomerular capillary walls and focally in the mesangial regions, in a starry sky appearance (C3 ×400).

Right image: Electron microscopy revealed numerous and large subepithelial, electron-dense deposits (humps) situated on moderately thickened basement membranes. Plentiful neutrophils were seen in the glomerular lumina (uranyl acetate and lead citrate ×4400).

Images provided by Sophia Lionaki,* MD, Maria Pappa, MD, and John N Boletis, MD, Nephrology Department & Transplantation Unit, Laiko Hospital, National and Kapodistrian University of Athens, Faculty of Medicine, Greece, and George Liapis,* MD, Pathology Department, Laiko Hospital, National and Kapodistrian University of Athens, Faculty of Medicine, Greece, with acknowledgment to Sophia Haraki, PhD, Department of Histology and Embryology, National and Kapodistrian University of Athens, Faculty of Medicine, Athens, Greece, for technical support in electron microscopy.

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