Solutions to Test Your Knowledge: The Rise of C3 Glomerulopathies

1. D
2. C
3. B
4. B
5. B

1D. Based on the initial presentation of the patient, the diagnosis of acute post-infectious glomerulonephritis (PIGN) was made. There are 5 characteristic clinical and pathologic features used to establish the diagnosis. These features include a history of recent infection, hypocomplementemia, light microscopic findings of an exudative glomerulonephritis, C3-dominant staining by immunofluorescence, and subepithelial “hump-shaped” deposits on electron microscopy. However there were multiple findings that were atypical for PIGN including the presence of segmental membranoproliferative features, the clinical presentation of nephrotic syndrome, and the absence of definitive "hump-shaped” deposits. Initiating pulse dose steroids without knowing the underlying lesion would not be appropriate. Patients with evidence of persistent group A streptococcal infection should be given a course of antibiotic therapy; however, we have no such evidence in this patient. This patient is already on lisinopril, thus the addition of losartan is not warranted.

Reference: Nasr SH, Markowitz GS, Stokes MB, et al. Acute postinfectious glomerulonephritis in the modern era: experience with 86 adults and review of the literature. Medicine (Baltimore). 2008; 87(1):21-32.

2C. The biopsy is not consistent with PIGN. The features of the biopsy are more consistent with an MPGN pattern of injury. Laboratory evaluation failed to show the presence of a monoclonal gammopathy. In C3 glomerulonephritis, immunofluorescence microscopy shows C3 deposition along the capillary walls and mesangium with no significant immunoglobulin deposition. Note that this pattern is also seen with dense deposit disease (DDD). Class V lupus (membranous) is characterized by diffuse thickening of the glomerular capillary wall on light microscopy and subepithelial immune deposits on immunofluorescence or electron microscopy.

Reference: Fakhouri F, Frémeaux-Bacchi V, Noël LH, Cook HT, Pickering MC. C3 glomerulopathy: a new classification. Nat Rev Nephrol. 2010; 6(8):494.

3B. Podocin is a protein component of the slit diaphragm of podocytes. Mutations in the podocin gene NPHS2 have been associated with focal segmental glomerulosclerosis. Mutations in platelet-activating factor acetylhydrolase have been associated with IgA nephropathy. Mutations in the TRPC6 cation channel have been associated with familial focal segmental glomerulosclerosis. In patients of Cypriot origin, a familial form of C3 glomerulonephritis has been described. The mutation is in the gene for complement factor H-related protein 5 (CFHR5).

Reference: Gale DP, de Jorge EG, Cook HT, et al. Identification of a mutation in complement factor H-related protein 5 in patients of Cypriot origin with

glomerulonephritis. Lancet. 2010; 376(9743):794.

4B. The EM is consistent with the diagnosis of DDD. This ribbon-like appearance of subendothelial and intramembranous material is diagnostic.

5B. Both C3 glomerulonephritis and DDD are caused by excessive activation of the alternative complement cascade. C4 is not part of the alternative complement cascade.