CLINICAL VIGNETTE

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS: The Case of the Missing Immunofluorescence Tissue

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Case Presentation

A 74-year-old Asian male with a medical history significant for stage III chronic kidney disease, gout, and nephrolithiasis presented to the emergency department with new onset hematuria, orthopnea, and lower extremity edema. He was noted to have new-onset acute kidney injury and proteinuria. His serum creatinine increased from 1.49 to 3.7 within 10 days, and he also had active urinary sediment.

In the ED, the patient's vitals included: Temperature 36.9°C, Blood Pressure 195/88 mmHg, Pulse 86, Respiratory Rate 18 and SpO2 96 % on room air. On examination, he appeared chronically ill with facial edema. His respiratory exam included bibasilar rales with normal respiratory excursion. Cardiac examination revealed a mid-systolic murmur at the left lower sternal border, elevated jugular venous pulsation, and 2+ pedal edema. Skin was notable for a surgically dressed right elbow with mild surrounding erythema and tenderness with palpation. The right elbow surgical wound had dehisced and probed to bone. Basic laboratory testing included: pancytopenia with white blood cells 3.07, hemoglobin 9.0 and platelets 60. Metabolic panel included sodium 138, potassium 5.6, chloride 111, total carbon dioxide 17, Glucose 127, BUN 77 and creatinine 3.7. Urinalysis was positive for 3+ protein 3+ blood and 15 RBC.

His past medical history includes chronic kidney disease III, hypertension, hyperlipidemia, tophaceous gout, nephrolithiasis, osteoarthritis and pancytopenia that was previously thought to be drug induced secondary to allopurinol and febuxostat. One month prior to presentation, the patient underwent right elbow tophi removal that was complicated by delayed wound healing and dehiscence. No wound infection was previously noted. He has no known drug allergies. Family history is significant for hypertension. He is married and a retired actor. He has a 70 pack year smoking history and previously abused alcohol. His daily medications include ibuprofen 200mg TID PRN, Lisinopril 20mg BID, baby aspirin, and steroid taper for recent gout flare.

He was admitted for acute kidney injury and proteinuria. Studies included absence of urine eosinophils; 24-hour-urine collection with 2.6 grams of protein, low C3 at 52, and elevated Anticardiolipin IgM at 28. Negative serologies included ANA, Rheumatoid Factor, ANCA, Anti-dsDNA, UPEP/IFE, SPEP/IFE, free light chain assay, C4, Anti-GBM, Hep C Ab, Anticardiolipin IgG, Hep B Surface Ab, Hep B surface Ag, HIV and RPR. Quantiferon Gold was indeterminate with no identified risk factors for tuberculosis. Serial blood cultures were negative as were serologies for endemic fungal antibodies, Brucella, Cryptococcus, Coxiella, Bartonella, Schistosoma, and Echinococcus serologies. His deep right elbow wound cultures returned positive for methicillin sensitive staphylococcus aureus.

EKG showed normal sinus rhythm at a rate of 84, LV and no acute ST or T wave changes. CXR was notable for bilateral pleural effusions. Echocardiogram noted global hypokinesis with depressed left ventricular ejection fraction to 45%, moderate to severe aortic insufficiency, severe pulmonary hypertension, and moderate tricuspid regurgitation. Transesophageal echocardiogram was negative for valvular vegetations. Imaging of the kidney by renal ultrasound noted a right kidney at 9.6cm with increased echogenicity and a left kidney at 11.8cm normal echogenicity. A bone marrow biopsy was performed for the pancytopenia, which confirmed low-grade myelodysplastic syndrome.

A renal biopsy was also obtained and reviewed by a renal pathologist. The Light Microscopy (LM) contained 22 to 25 glomeruli of which 60-65% were globally sclerotic or obsolescent. The remaining glomeruli noted a lobular pattern with many leukocytes, including numerous monocytes and occasional neutrophils with few lymphocytes within capillary lumina, causing occlusion of these structures. No crescents were noted. Mild tubular atrophy with interstitial fibrosis up to 25% was noted. Electron Microscopy (EM) evaluation noted a single glomerulus, which was lobular with mesangial hypercellularity and many leukocytes within capillary lumina. Tubular cells contained protein. Unfortunately, there was not sufficient tissue for immunofluorescence microscopy (IF). The final diagnosis, based on the LM and EM, was Membranoproliferative Glomerulonephritis, Acute Tubular Necrosis (ATN) and mild Acute Interstitial Nephritis (AIN). Unfortunately, the lack of immunofluorescence tissue made it difficult to further classify the MPGN. The pathologist noted

that the location and appearance of the deposits suggest an immune-complex mediated MPGN.

Discussion

The diagnosis and work-up of MPGN has evolved as the underlying etiologies of MPGN are better understood. As a result, classification for Membranoproliferative Glomerulonephritis (MPGN) has been updated. In the past, the diagnosis for MPGN was determined on the structural appearance of the glomerulus on LM with classification based on the EM. The original classification of MPGN was based on the location of deposits seen on EM. After confirmation of mesangial hypercellularity, endocapillary proliferation and capillary-wall remodeling on LM, tissue from EM was used to classify subtype of MPGN.[1] Originally, MPGN was organized into 3 subtypes based on location of deposits: Type I for subendothelial deposits, type II for dense deposits in the glomerular basement membrane, and type III for subepithelial and subendothelial deposits.[2] These deposits are a result of immunoglobulins, complement factors or both.[1]

The current MPGN classification is focused on gathering additional information from the IF rather than EM. It is standard for all kidney biopsy tissues to be sent for LM, EM, and IF, assuming sufficient tissue is available. IF is used for detection of immunoglobulins and complements. This includes IgG, IgA, IgM, C3 C1q, kappa Ig light chains, lamda Ig light chains, fibrinogen, and albumin.[3] This allows a detailed evaluation for the presence of immune-complex deposits or autoantibodies against the glomerular basement membrane. EM on the other hand is used to detect abnormal material such as immune-complex or fibrils such as amyloid. Because EM is less sensitive for the detection of immune-complex deposits, IF is needed to confirm its presence; however, EM can help locate the immune-complexes.

Based on the updated recommendations, MPGN is now divided into 3 categories based on the presence or absence of immunoglobulins and complements on IF portion of the kidney biopsy (see Figure 1).[1] An IF pattern that is positive for C3 and immunoglobulins suggests an immune-complex mediated process. The three main causes of an immune-complex mediated process are infection, autoimmune disease, and monoclonal gammopathy.[1] The presence of isolated C3 on IF suggests Dense Deposit Disease or C3 glomerulonephritis (C3GN).[1] If there is no staining on IF then thrombotic microangiopathy is implicated and diseases such as HUS and TTP need to be ruled out.

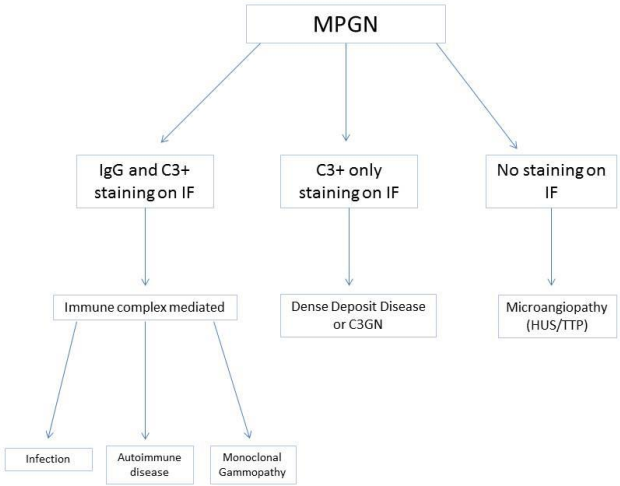
Immune-complex mediated MPGN is a result of overproduction of antibodies leading to immune complexes. This leads to activation of the classical complement pathway and deposition of complement factors from both the classical and terminal complement pathways.[1] Chronic viral or bacterial infections, including carrier states, can precipitate such immune-complex formation. Hepatitis B and C viral infections are the most common causes of immune-complex mediated MPGN.[4] Chronic bacterial infections including endocarditis, shunt nephritis and abscess, or in the case of this patient, chronic osteomyelitis.[5] Specifically, infections with staphylococcus, streptococci, Mycobacterium tuberculosis, Mycoplasma pneumoniae, and meningococcus have been associated with low grade circulating antibodies.[1] Autoimmune diseases such as Systemic Lupus Erythematous, Rheumatoid Arthritis, Mixed Connective Tissue Disorder also needed to be considered.[5] Monoclonal gammopathy can also lead to immune-complex-formation.[1,5]

Conclusion

The importance of Immunofluorescence in the evaluation of proteinuria and hematuria in the diagnosis of MPGN is vital. Data obtained from the IF portion of the renal biopsy organizes MPGN based on the presence or absence of immunoglobulins and/or complements. This provides the nephrologist with clinically relevant information to narrow therapy for the MPGN. Unfortunately, the kidney biopsy for our patient did not have enough tissue for fixation for IF. However, the pathologist was able to note that the location and appearance of the deposits suggested an immune-complex mediated MPGN. Focusing on an immune complex mediated MPGN, we then did an extensive evaluation for monoclonal gammopathy, autoimmune, and infectious pathology. Although UPEP, SPEP, immunofixation, and free light chain assay were all normal, a bone marrow aspirate negative for pathologic plasma cells definitively ruled out a monoclonal gammopathy. The patient's screening autoimmune pattern was negative. After further investigation, it was discovered that the patient's right elbow, which had recently undergone tophi removal, was superinfected with MSSA, leading to chronic osteomyelitis. This chronic osteomyelitis was likely the source of the low-grade antibody production. Infectious disease recommended a 6-week course of IV vancomycin. The patient ultimately was placed on hemodialysis but, unfortunately, never regained kidney function.

Figures

Figure 1. New MPGN Classification system based on Immunofluorescence



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