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Unique Challenges in Diagnosing IgG4-Related Tubulointerstitial Nephritis with Arteritis

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INTRODUCTION

Tubulointerstitial nephritis (TIN) can be part of the systemic disease immunoglobulin G4 related disease (IgG4-RD).[1,2] IgG4-RD can affect an isolated organ, or it can involve multiple organs, synchronously or metachronously.[3,4] IgG4-RD diagnosis is challenging due to the presentations of nonspecific findings that mimic many diseases, including malignancy.[5]

Regarding IgG4-TIN, common laboratory abnormalities, outside of elevated creatinine (Cr) and blood urea nitrogen (BUN) included elevated serum total IgG or IgG4 (79% of patients), hypocomplementemia (56%), eosinophilia (33%), and positive ANA (31%).[6] Proteinuria (30%) and hematuria (22%) occurred less often.[3,6] On imaging, renal cortical nodules, round or wedge shaped lesions, or diffuse patchy involvement can be seen.[6] Outside of the kidneys, inflammatory masses can be seen in any organ in patients with IgG4-TIN, with autoimmune pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, sialadenitis, and aortic aneurysms constituting the more commonly reported extra-renal comorbidities.

Ultimately, renal biopsy, combined with supporting clinical, laboratory, and radiographic findings, is needed to diagnose IgG4-TIN. IgG4-TIN biopsies revealed plasma cell-rich TIN with over ten IgG4+ plasma cells/high power field (HPF).[6] Additional histological findings included tubular basement membrane immune complex deposits and an expansile or "storiform" interstitial fibroinflammatory process. One unusual case of IgG4-TIN with arteritis has been reported previously.[7]

In this report, a patient presented with an acute kidney injury (AKI) and heart failure and, after a complex workup, ultimately was diagnosed with IgG4-TIN with arteritis.

CASE REPORT

A 72-year-old man with past medical and social histories significant for rheumatoid arthritis (RA), anemia of chronic disease, resolved hepatitis C (HCV) infection, serum IgM kappa paraprotein, presented with two months of paroxysmal nocturnal dyspnea, night sweats, unintentional twenty-pound weight loss, fatigue, and a rash on his fingers. He had discontinued his RA disease modifying anti-rheumatic drugs (DMARDs), hydroxychloroquine, and leflunomide, secondary to ocular pain around the time of his symptom onset.

On exam, he was afebrile with blood pressure of 150/110 mmHg and heart rate of 92 beats per minute. Body mass index was 18.11 kg/m^2. Jugular venous distention was present. There were many punctuate, purple colored, non-tender, maculopapular 0.5 cm lesions on the palmar and dorsal surfaces of his fingers bilaterally. Laboratory abnormalities included: elevated Cr (1.89 mg/dL, increased from 1.0 mg/dL during a hospitalization for pneumonia one month prior), elevated BUN (25 mg/dL), decreased hemoglobin (10.1 g/dL), elevated B-type natriuretic peptide (1994 pg/mL), mildly elevated troponin (0.063 ng/dL), elevated erythrocyte sedimentation (54 mm/hr), and elevated C-reactive protein (12.9 mg/dL). Urinalysis was unremarkable, and fractional excretion of sodium was 1.50%.

An echocardiogram revealed an ejection fraction of 35% without valve vegetations. The patient received furosemide for decompensated heart failure. While his heart failure symptoms improved with diuresis, his Cr worsened to 2.53 mg/dL. Rehydration with lactated ringers minimally improved his Cr; however, this worsened his heart failure symptoms. Given the patient's medical history, discordant cardiac and renal function, and cutaneous lesions, further evaluation was pursued.

Infectious evaluation was negative. Rheumatological was negative except for a positive ANA with a 1:80 titer and a positive p-ANCA on indirect immunofluorescence assay. Notably, on multiplex immunoassay, anti-proteinase 3 (PR3) and anti-myeloperoxidase (MPO) antibodies were negative. Studies indicated the patient's anemia of chronic disease and elevated serum free kappa and lambda proteins were relatively unchanged from previous studies.

Renal ultrasound was without abnormalities. Skin biopsy indicated keratosis with granuloma annulari and nonspecific chronic inflammation. Given the lack of a clear diagnosis after this workup and the patient's persistently elevated Cr with unremarkable urinalyses, a renal biopsy obtained. A renal biopsy initially was interpreted as pauci-immune crescentic glomerulonephritis (PICGN) and arteritis/arteriolitis based on the presence of a crescent-like structure in one glomerulus (of 20 glomeruli on the light microscopy sample) and associated arteritis. The patient was started on methylprednisolone 1000 mg followed by prednisone 50 mg/day.

During the initial treatment, a second opinion of the renal biopsy was interpreted as a primary tubulointerstitial disease pattern of injury with associated arteritis and a glomerular "pseudo-crescent". Light microscopy revealed 20 glomeruli, with one being globally sclerotic. There was moderate interstitial fibrosis and tubular atrophy with a multifocal interstitial inflammatory cell infiltrate of mononuclear cells, numerous plasma cells, occasional eosinophils, and associated mononuclear cell tubulitis. There was a well demarcated border between normal kidney parenchyma and tissue with interstitial fibrosis and inflammation (which can be a feature of IgG4-TIN).[6] Within an area of interstitial inflammation and fibrosis, there was inflammation surrounding one glomerulus, which showed one pseudo-crescent (also known as an "interstitial crescent") associated with capsulitis, without rupture of the glomerular basement membrane or Bowman's capsule; this type of pseudo-crescent is an unusual but characteristic feature of IgG4-TIN.[8] No true crescents were identified. Three arteries showed mononuclear

cells and plasma cells in the thickened intima, and some arteries showed inflammation in the media and adventitia (Figures 1 and 2). No vessel fibrinoid necrosis was identified. No renal parenchyma was available for immunofluorescence. By electron microscopy, no immune deposits were identified. Immunoperoxidase staining for IgG4 showed over 50 IgG4+ plasma cells/HPF.

Based on these renal biopsy findings, the patient was diagnosed with IgG4-TIN. Because the initial treatment for both PICGN and IgG4-TIN involves steroid immunosuppression,[9,10] his steroids were continued. Serum IgG4 levels were within normal limits, although these were collected during immunosuppression, which can decrease serum IgG4 levels.[11]

During follow-up, the patient's Cr remained stable around 2.0 mg/dL despite readmissions for steroid related side effects. Three months after diagnosis, his steroids were tapered to 20 mg/day and hydroxychloroquine and leflunomide were resumed for RA control.

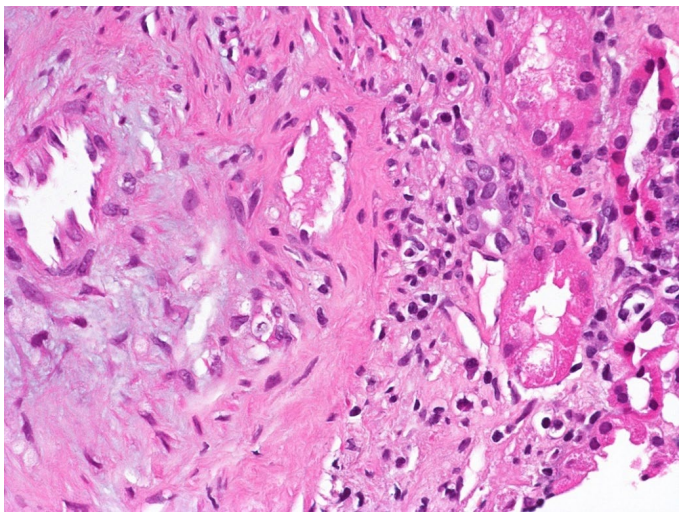

Figure 1. Tubulointerstitial disease pattern of injury with associated arteritis.

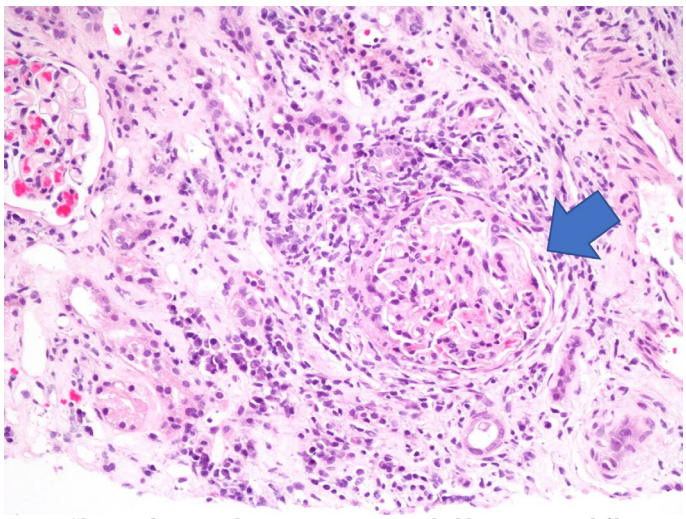

Figure 2. Glomerular pseudo-crescent surrounded by interstitial fibrosis and tubular atrophy with a multifocal interstitial inflammatory cell infiltrate of mononuclear cells, numerous plasma cells, occasional eosinophils, and associated mononuclear cell tubulitis.

DISCUSSION

The patient was similar to the average demographic profile of an IgG4-TIN patient (a male near age 65).[6] His presentation of decompensated heart failure and cutaneous lesions concerning for endocarditis or vasculitis, combined with his DMARD non-adherence, imaging limitations due to retained shrapnel, and false positive p-ANCA created diagnostic challenges. Notably, the patient's renal biopsy contained a pseudo-crescent and arteritis, which are uncommon features of IgG4-TIN.[7,8]

While renal failure is the most common presentation of IgG4-TIN,[6] this patient's AKI initially was thought to be due to a prerenal etiology based on his cardiac symptoms. While IgG4-RD is associated with coronary arteritis, periaortitis, and pericarditis,[12-14] it has not been associated with heart failure, as in this patient. Whether correlation between the diagnoses of heart failure and IgG4-TIN implied causation is difficult to discern without cardiac magnetic resonance imaging (MRI),[14] which was intolerable due to the patient's retained shrapnel. Therefore, it remains unknown if this patient's heart failure was related to IgG4-RD or was a coincidental co-occurrence.

The cutaneous lesions were considered during the cardiac evaluation. There was concern for endocarditis; however, this was deemed unlikely with a low modified Duke score.[15] After ruling out endocarditis, the skin lesions, combined with the patient's history of RA and HCV, which are associated with systemic vasculitis,[16,17] prompted additional studies. Cutaneous lesion biopsies revealed granuloma annulare, effectively excluding vasculitis associated lesions. Granuloma annulare is a common condition associated with a variety of diseases ranging from diabetes mellitus to autoimmune thyroiditis,[18] but it has not been associated with IgG4-TIN.[19,20] While the cutaneous lesions resolved with corticosteroid treatment, it is difficult to determine if this patient's granuloma annulari was related to IgG4-RD.

The patient's RA with DMARD non-adherence further complicated the evaluation. Half of RA patients have elevated serum IgG4 levels,[21] but it is unusual for RA patients to experience IgG4-TIN.[9] This patient's symptom onset near the discontinuation of DMARDs created questions: Were the patient's DMARDs suppressing IgG4-RD? Does abrupt cessation of DMARDs predispose to rebound development of IgG4-RD? Are hydroxychloroquine or leflunomide possible treatments for IgG4-TIN? Continued research into IgG4-TIN, RA, and ideal immunosuppression regimens are needed.

While this patient had unusual extra-renal findings possibly related to IgG4-RD that complicated the workup, the most striking finding was his kidney biopsy, specifically the arteritis and interstitial plasma cell infiltrates with over 40 IgG4+ plasma cells/HPF. These interstitial inflammatory infiltrates met the first criteria to diagnose IgG4-TIN.[6] Besides renal histological findings, definitive diagnosis of IgG4-TIN required elevated serum IgG4, renal imaging abnormalities, or specific secondary organ involvement. Determining if the patient met criteria to diagnose IgG4-TIN was challenging. The patient received steroids

before his serum IgG and IgG4 levels were evaluated; therefore, these values could have been falsely normal.[11] Definitive evaluation for renal abnormalities would be aided by MRI,[22] which was intolerable. Imaging via contrast computed tomography is a possible alternative,[23,24] but the patient was reluctant to receive contrast. The patient did not have a history of extra-renal diseases associated with IgG4-TIN,[6] but evaluation for inflammatory lesions in the heart was unable to be performed. Thus, while the patient did not meet a second diagnostic criteria for IgG4-TIN, given the renal biopsy findings with lack of a more likely diagnosis, the patient was diagnosed with and treated for IgG4-TIN.

Outside of the imaging limitations in the patient's evaluation, this case highlighted the clinical and histopathological overlap of two distinct diseases: IgG4-TIN and ANCA-associated disease. This patient had a positive ANA and indirect immunofluorescence p-ANCA test with negative anti-MPO and anti-PR3. ANA can produce a "false positive" p-ANCA result due to the indirect immunofluorescence technique.[25] Anti-MPO and anti-PR3 studies are more specific for PICGN and were negative, making this diagnosis unlikely.[26] Still, like IgG4-TIN, ANCA-associated disease can show increased IgG4+ plasma cells.[6] Recognition of "pseudo-crescents" that may occur in IgG4-TIN, rather than true crescents, and recognition of associated non-necrotizing plasma cell arteritis, facilitate diagnosis of IgG4-TIN rather than PICGN.[8] Conversely, increased IgG4+ plasma cells in an infiltrate are insufficient to diagnose IgG4-TIN. These diseases may be treated similarly, with steroids and rituximab, although the first line treatment for IgG4-TIN is generally steroids alone, which is an insufficient treatment for ANCA-associated disease.[27]

CONCLUSIONS

IgG4-RD remains an underdiagnosed, immune-medicated condition that can affect the kidneys. IgG4-TIN should be included in the differential diagnosis for patients presenting with an intrinsic AKI. Ultimately, biopsy is required for diagnosis, and unique histological findings, including pseudo-crescents and non-necrotizing plasma cell arteritis, may aid the diagnostic process. Recognizing the unusual presentations of IgG4-TIN can aid in the diagnostic distinction between PICGN and IgG4-TIN, which is necessary for optimal treatment.

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