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A 36-Year-Old Man with Renal Failure, Fevers, and Hypocomplementemia

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CASE PRESENTATION

Chief Complaint

A 36-year-old man with recently diagnosed renal injury presented with fevers and dental pain.

History of Present Illness

For 15 months the patient had decreased appetite and malaise. He had missed work due to his symptoms. Two months prior, cough and ongoing malaise prompted an Emergency Department visit. At that time, routine laboratory evaluation revealed blood urea nitrogen 105 mg/dL and creatinine 7.01 mg/dL with estimated glomerular filtration rate of 9 mL/min/1.73m². A work-up was initiated and renal biopsy was performed. A 16-day trial of oral prednisone was prescribed for presumed acute interstitial nephritis. The patient was discharged without dialysis and seen a week later in renal clinic for follow-up. Seven weeks later, he returned to the Emergency Department with fevers and dental pain of 6 days' duration and was admitted. The initial renal biopsy, since resulted, was limited by a small sample. It showed non-specific findings of extensive interstitial fibrosis and tubular atrophy with scattered lymphoplasmacytic inflammation and a few globally sclerotic glomeruli.

Past Medical History

Past medical history was notable for a gunshot wound to the left upper extremity requiring exploratory surgery seven years earlier. At the time of the current admission, the patient had completed a course of oral prednisone (40 mg twice a day for 4 days, 30 mg twice a day for 4 days, 40 mg daily for 4 days, 20 mg daily for 4 days) and was taking sevelamer carbonate 800mg orally three times daily.

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Social and Family History

The patient was Hispanic. He was married with one child and worked as a dishwasher at a restaurant. He did not consume alcohol, use tobacco, or illicit drugs. There was no family history of autoimmune disease, renal disease, or malignancy. His mother died at a young age of “cirrhosis” of unclear etiology; she did not consume alcohol.

Review of Systems

He had anorexia but no weight change. He denied pharyngitis, visual changes, oral or nasal ulcers, rash or nodules, weight loss, abdominal pain, dysuria, hematuria, flank pain, or edema. He had no history of tuberculosis, incarceration, or homelessness. He denied sick contacts, recent travel, and occupational exposures.

Physical Examination

He was febrile with temperature 39.4°C. His blood pressure was 138/84 mm Hg, pulse was 132 beats per minute, respiratory rate was 22 breaths per minute, and oxygen saturation was 96% on room air. Conjunctival pallor was noted, and oral examination was significant for dental caries with normal salivary pool. There was no lacrimal gland swelling and no pain with extraocular movements. Neck examination revealed shotty, subcentimeter submandibular and anterior cervical lymphadenopathy without diffuse parotid or submandibular swelling. Cardiopulmonary exam demonstrated tachycardia with regular rate and rhythm. His carotid, brachial, radial, and femoral pulses were 2+. His lungs were clear to auscultation. His abdomen was soft and non-distended. Hepatosplenomegaly was not appreciated. Neurological exam revealed 5/5 strength bilaterally in flexors, extensors, abductors, and adductors of upper and lower extremities. Reflexes were 2+ throughout. There were no sensory deficits. Gait was normal. He had no synovitis or joint effusions and had full range of motion in all of his joints. His extremities were non-edematous. No rash was present.

Initial laboratory evaluation and studies

Initial laboratory evaluation revealed normal peripheral smear and lactate dehydrogenase, non-reactive HIV 1/2 antigen/antibody combo test, hepatitis C antibody, and normal cryoglobulins and serum protein electrophoresis with immunofixation. Additional results are shown in Table 1. Chest radiograph did not show hilar lymphadenopathy. Abdominal and renal ultrasonography demonstrated normal liver without nodularity or masses and was notable for bilateral nephromegaly with marked echogenicity in the medullary pyramids (Figure 1) and splenomegaly. Transthoracic echocardiogram (TTE) showed normal systolic, diastolic, and valvular function without vegetations.

CASE SUMMARY

This is a 36-year-old man with acute fevers in the setting of fibrotic kidney injury, nephromegaly, and hypocomplementemia.

DIFFERENTIAL DIAGNOSIS

To synthesize this case, each of three key characteristics—fibrotic renal disease, nephromegaly, and hypocomplementemia—has a separate differential diagnosis to be considered. A unifying diagnosis will explain all features and guide further investigation.

Tubulointerstitial Nephritis

Tubulointerstitial nephritis (TIN) is an important cause of chronic kidney disease. Acutely, TIN is often reversible. Yet chronic disease can result in irreversible scarring due to interstitial fibrosis and tubular atrophy. These pathologic changes are a consequence of inflammatory and tissue repair mechanisms that promote fibrosis via cytokine production and recruitment of fibroblasts (1,2). Progressive loss of functional renal parenchyma due to interstitial fibrosis and tubular atrophy (IFTA) ultimately leads to end stage renal disease. The degree of IFTA is an important predictor of long-term renal survival (2).

Drug-induced TIN is the most common cause and typically associated with beta-lactamase antibiotics, NSAIDs, and other medications including rifampin, sulfonamides, and allopurinol. Clinical presentation is often allergic and can include fever (36%), eosinophilia (35%), rash (22%), or the full triad (11%) (3). Although our patient was exposed to NSAIDs and presence of WBC in the urine supported this diagnosis, hypocomplementemia and nephromegaly are not seen in cases of TIN due to NSAID use.

Autoimmune disease-associated TIN can be associated with systemic lupus erythematosus (SLE), sarcoidosis, Sjögren's syndrome, and granulomatosis with polyangiitis (GPA) (formerly known as Wegener's granulomatosis) (4,5). Patients with SLE and GPA often have an interstitial nephritis accompanying the characteristic glomerular disease and may rarely present with AIN, even in the absence of glomerular disease. Amyloidosis and IgG4-related disease (IgG4-RD) can also cause TIN (6,7). Despite hypocomplementemia, renal injury, and anemia, there was no other specific symptom, sign, positive ANA, or positive ANCA to suggest SLE, Sjögren's syndrome, or GPA. Although the patient had poor dentition, Sjögren's syndrome was unlikely given lack of xerostomia or xerophthalmia. Infiltrative processes such as sarcoidosis, amyloidosis, and IgG4-RD can go undiagnosed for months to years given potential relative paucity of clinical symptoms until end-organ damage is manifested. On renal biopsy there were no granulomas to suggest sarcoidosis, and Congo red-stain with birefringence was negative for amyloid.

Tubulointerstitial nephritis and uveitis (TINU) is an uncommon entity encountered by ophthalmologists and pediatric nephrologists. It is seen typically in young women and the pathogenesis is unknown. Patients with TINU may make autoantibodies against modified-C-reactive protein which is found both in uveal and renal tubular cells (8). Uveitis is initially treated with glucocorticoids and renal disease can be self-limited though may require additional immunosuppression (9). Our patient lacked ocular findings and his male gender and age made this diagnosis unlikely.

Infectious causes of TIN include bacterial (streptococcal species, legionella, leptospira), viral (cytomegalovirus, adenovirus, polyomavirus), and fungal (histoplasma, candida)

pathogens. Although our patient was found to have *Streptococcus pneumoniae* in the blood and urine, which could raise suspicion for subacute bacterial endocarditis in the setting of hypocomplementemia, TTE was negative for vegetations, effectively ruling out endocarditis. However, his profound hypocomplementemia and splenomegaly may have contributed increased susceptibility to encapsulated organisms, rather than the streptococcal species directly causing tubulointerstitial injury (10).

Nephromegaly

Causes of nephromegaly are broad and can be categorized by type (Table 2). The most common cause of nephromegaly is diabetes (11). Rheumatologists are most likely to encounter nephromegaly in patients with urate nephropathy from gout, some cases of lupus nephritis, and organ infiltration from sarcoidosis, amyloidosis, or IgG4-RD (12). As mentioned previously, the diagnoses of SLE, sarcoidosis, and amyloidosis were not suspected.

Hypocomplementemia

Complement is activated in several rheumatologic diseases, such as SLE. Complement defends against pathogens, promotes antibody responses, and clears immune complexes in concert with the innate and adaptive immune systems (13). In SLE, complement contributes to inflammation, reducing plasma complement levels while depositing in tissues (14). Other rheumatologic entities in which complement is activated include hypocomplementemic urticarial vasculitis syndrome (HUVS) as well as cryoglobulinemic vasculitis, seen in patients with Type I (monoclonal IgG or IgM eg. multiple myeloma/Waldenstrom's macroglobulinemia), Type II (mixed polyclonal IgG with monoclonal IgM rheumatoid factor eg. hepatitis B or C), or Type III (polyclonal IgG and IgM rheumatoid factor eg. SLE, Sjögren's syndrome, hepatitis C) (14). As the name suggests, HUVS necessitates hypocomplementemia as well as intermittent presence of urticarial wheals of at least 6 months' duration (15). The patient's lack of urticarial wheals, arthritis, uveitis, and abdominal pain made this an unlikely cause. The patient had no clinical or laboratory findings consistent with cryoglobulinemic vasculitis (16). Hypocomplementemia can also be seen in IgG4-RD (17).

Unifying diagnosis

Of the etiologies reviewed above, only IgG4-RD was a constant among the triad of fibrotic renal disease, bilateral nephromegaly, and hypocomplementemia. To confirm IgG4-RD, additional laboratory measures and tissue staining were essential.

PATIENT'S COURSE

The serum IgG4 was 1260 mg/dL, which measures more than nine times the upper limit of normal (86–135 mg/dL). Given the concern for IgG4-RD, serum plasma IgG4 levels were obtained and a repeat renal biopsy was performed. The biopsy (Figure 2) showed storiform fibrosis, dense interstitial lymphoplasmacytic infiltrates with up to 40 IgG4+ plasma cells/high-power field (hpf), and IgG4+/total IgG+ plasma cell ratio of >80%, which strongly suggested a diagnosis of IgG4-RD TIN. Electron microscopy and immunofluorescence

studies performed on the biopsy tissue did not reveal evidence of an immune complex mediated glomerulonephritis or paraprotein deposition. Blood cultures grew *Streptococcus pneumoniae* in 2 out of 2 bottles, and urine culture grew *Streptococcus viridans*. The patient was started on antibiotics for his acute infection. After he completed the course of antibiotics, he was started on prednisone 60 mg daily and rituximab 1000 mg intravenously at week 0 and week 2 for IgG4-RD TIN. C4 was checked after 15 months and had normalized from <1 to 24. Fifteen months after initial presentation, his creatinine (4.91 mg/dL) and urine protein to creatinine ratio (0.5) remained elevated despite a second cycle of rituximab and a slow prednisone taper.

DISCUSSION

IgG4-RD is a multi-organ, fibrotic, inflammatory condition that can affect nearly every organ. (6). Renal involvement in IgG4-RD occurs in 15%, most commonly as TIN or membranous glomerulonephritis (MGN) (18). Another renal manifestation of IgG4-RD includes retroperitoneal fibrosis causing impingement-related hydronephrosis (18,19).

IgG4-RD TIN is an increasingly recognized manifestation of IgG4-RD, although existing study sample sizes are small. IgG4-RD TIN is more common in men than women with an average age of onset at 65 years. Concomitant extrarenal disease is frequent (18,20). Onset is typically insidious rather than rapidly progressive, as reflected by a slowly rising creatinine. Mild proteinuria is more common than nephrotic range proteinuria (18). Frequently, urinalysis with microscopy demonstrates mild hematuria; pyuria and white blood cell casts are uncommon. Hypocomplementemia of C3, C4, and CH50 occurs in 60% of patients with IgG4-RD TIN (21). C4 deficiency from IgG4-RD TIN may have increased the patient's susceptibility to infection with encapsulated organisms. Low complement is unusual in IgG4-RD unless there is tubulointerstitial renal involvement. Therefore, hypocomplementemia in IgG4-RD should raise suspicion for IgG4-RD TIN (18). One hypothesis for hypocomplementemia in IgG4-RD TIN is that although IgG4 itself may not bind complement, other IgG subclasses, which are often elevated in patients with IgG4-RD, bind complement (21,22). A weakly positive antinuclear antibody may be present, although specific serologies for SLE and Sjögren's syndrome are typically negative. Elevated serum IgG4 greater than 6–8 times the normal upper limit should raise concern for IgG4-RD; multiorgan disease may elevate IgG4 levels to 40–50 times normal (18). Normal serum IgG4 does not exclude the diagnosis and an elevated IgG4 level requires clinicopathological correlation.

Radiographic features of IgG4-RD TIN include bilateral nephromegaly in 20% of patients as well as bilateral lesions of the renal cortices in 40%. These hypodense masses can mimic renal cell carcinoma. Two features of renal parenchymal lesions in IgG4-RD TIN include 1) clear demarcation between affected and unaffected parenchyma and 2) infiltration that invades into and beyond the renal capsule (19).

Hallmark histopathologic features in IgG4-RD are dense inflammatory lymphoplasmacytic infiltrates composed of polyclonal CD20 B-lymphocytes, T-cells, and IgG4+ plasma cells and storiform fibrosis, so-called for its irregular whorled appearance. A third pathologic

feature, obliterative phlebitis, is uncommon in renal biopsy. Mild tissue eosinophilia may be present but is not required for diagnosis (6). Two or more of the above pathologic features on kidney biopsy in combination with >10 IgG4+ plasma cells/hpf is highly suggestive of IgG4-RD and confirmed when a background of >40% IgG4+/IgG+ plasma cell ratio is also met (6,23).

IgG4-RD MGN is rare and can co-occur with IgG4-RD TIN (7%) (17). Patients with IgG4-RD MGN tend to be older males with elevated creatinine, hypoalbuminemia, and nephrotic range proteinuria at diagnosis (24). Typically, in IgG4-RD MGN, complements are normal and nephromegaly is not a feature. Table 3 compares IgG4-RD TIN and MGN.

Prompt treatment of IgG4-RD TIN is crucial to prevent progression of fibrosis and to preserve long-term renal function. Randomized controlled trials are lacking owing to the rarity of the disease. Glucocorticoids are first line, and in some cases monotherapy has led to renal improvement (25). Despite treatment with steroids, relapse can occur (15–20%) leading to progressive chronicity and end stage renal disease (7,25).

In cases of IgG4-RD, rituximab has been used with the rationale that it will interfere with short-lived plasma-cells, plasmablasts, and B-cells contributing to IgG4-RD pathology (26). An open-label prospective, single-arm trial of rituximab in 30 individuals with varied organ involvement resulted in complete remission of 40% at 12 months. In that cohort, 4 of 30 (13%) had IgG4-RD TIN (27). Refractory cases of IgG4-RD may fail to recover organ function if fibrosis is too extensive, despite aggressive treatment with multiple cycles of rituximab (28).

Although glucocorticoids are first line for IgG4-RD due to lack of randomized controlled trials providing evidence for other therapies, there were several reasons for concurrent treatment with prednisone and rituximab. The major concern in this patient with severe disease and delayed diagnosis was the inability to predict long-term renal response. With both inflammation and fibrosis on biopsy, there was some possibility of reversibility. Frequency of relapse on glucocorticoid monotherapy in IgG4-RD is well-described (22) as is long-term renal atrophy in those with IgG4-RD renal disease who present with low eGFR at baseline (29).

Case-series and open-label data suggest that rituximab may be well-tolerated and effective for active inflammation in IgG4-RD (27,28), even in the absence of glucocorticoid therapy (27). Results are less clear in cases of advanced fibrosis, and no trials have specifically addressed IgG4-RD TIN. In hopes of avoiding irreversible end stage renal disease leading to dialysis, we treated simultaneously with glucocorticoid and rituximab.

FINAL DIAGNOSIS

IgG4-Related Disease Tubulointerstitial Nephritis with Associated Hypocomplementemia leading to *Streptococcus Pneumoniae* Sepsis and *Viridans Streptococci* Urinary Tract Infection.

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Figure 1. Renal Ultrasound of Left Kidney

Markedly echogenic kidneys bilaterally, primarily within the medullary pyramids. Bilateral nephromegaly; Left = 14.6cm, Right = 13.8cm (not shown), (normal range 10–13cm).

Figure 2. Renal Biopsy Findings

(A) Several globally sclerotic glomeruli are seen within dense interstitial fibrosis without recognizable tubules; scattered interstitial inflammatory cells are noted (periodic acid Schiff; 100x). (B) Storiform fibrosis (pink collagenous background) was diffuse with associated lymphoplasmacytic infiltrate (hematoxylin and eosin, 200x). Immunohistochemical staining for IgG4 (C) and total IgG (D) show that most (>80%) of IgG+ plasma cells are also positive for IgG4 (400x).

Table 1.

Results of laboratory evaluation at initial visit, 3 months, and 15 months later

	Initial ED visit	3 months after initial visit	15 months after initial visit	Normal Range
WBC count, cells/mm ³	10.3	12.2	5.5	3,900–11,700
Hemoglobin, g/dL	9.5	9.3	10.8	13.3–17.1
Hematocrit, %	30.2	28.0	30.7	39.8–52.2
Platelet count, cells/mm	135	138	125	150,000–400,000
Sedimentation Rate, mm/hr	122	106	26	0–15
Sodium, mmol/L	136	142	145	136–145
Potassium, mmol/L	4.5	4.0	4.4	3.5–5.1
Chloride, mmol/L	112	105	113	98–109
Co2, mmol/L	11	22	22	22–29
BUN, mg/dl	105	48	59	6–20
Creatinine, mg/dL	7.01	4.44	4.91	0.7–1.3
Glucose, mg/dL	86	103	101	70–199
AST, U/L	87	40	..	10–48
ALT, U/L	52	13	..	10–40
Total Bilirubin, mg/dL	0.3	0.3	..	0.1–1.1
Alkaline Phosphatase, U/L	165	313	..	56–119
Albumin, g/dL	2.6	3.6	4.1	3.2–4.6
Total Protein, g/dL	9.4	7.5	..	6.2–8.1
C-reactive protein, mg/L	161.5	26.8	..	<3.1
Complement 3, mg/dL	40	12	103	86–184
Complement 4, mg/dL	<1	1	24	12–40
IgG4, mg/dL	1260	437	..	86–135
Urine Protein, mg/dL	93	68	195	0–15
Urine Creatinine	101.4	58.6	91.6	..
Protein to Creatinine ratio	1.1	0.9	0.5	<0.02
Complement activity, CAE units	..	1	..	60–144
Urine Specific Gravity	1.011	1.006	1.011	1.003–1.030
Urine pH	7.0	7.0	6.5	5.0–7.0
Urine Protein	1+	1+	1+	0
Urine Nitrites	Negative	Negative	Negative	Negative
Urine Leukocyte Esterase	Negative	Positive	Negative	Negative
Urine Glucose	Negative	Negative	Negative	Negative
Urine Ketones	Negative	Negative	Negative	Negative
Urine Blood	1+	..	..	0
Urine WBC cells/high powered field	10–20	0–2	20–50	0–2

	Initial ED visit	3 months after initial visit	15 months after initial visit	Normal Range
Urine RBC cells/high powered field	10–20	2–5	0–3	0–3
Blood cultures 2/2 bottles	..	<i>S. pneumoniae</i>	..	Negative
Urine culture, colonies/mL	..	<i>S. viridans</i> 15,000	..	Negative

WBC = white blood cells; CO₂ = Carbon dioxide; RBC = red blood cells; *S.* = *Streptococcus*

.. = No data

Table 2.**Causes of bilateral nephromegaly**

Obstructive	Hematologic
Urate nephropathy	Sickle Cell Disease
Myoglobinuria	Renal Vein Thrombosis
Hemoglobinuria	Oncologic
Cystic	Leukemia/Lymphoma
Polycystic kidney disease	Multiple Myeloma
Tuberous sclerosis	Renal Cell Carcinoma
Multicystic dysplastic kidney	Infiltrative
Metabolic	Sarcoidosis
Diabetes mellitus (most common)	Amyloidosis
Acromegaly	IgG-4 RD
Storage diseases (GSD)	Malakoplakia (histiocytic infiltration)
Inflammatory	Infectious
Acute tubulointerstitial nephritis	Viral – HIV
Acute glomerulonephritis	Fungal – histoplasmosis
Acute nephrotic syndrome	Bacterial – TB, PJP
Abscess	
Kawasaki Disease	

GSD = glycogen storage disease; IgG4-RD = IgG4-Related Disease; HIV=Human immunodeficiency virus; TB = tuberculosis; PJP = pneumocystis jirovecii pneumonia

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Table 3.

Comparison of IgG4-RD Renal Disease: Tubulointerstitial vs Membranous Nephritis

Characteristic	Tubulointerstitial Nephritis	Membranous Nephritis
Males	Common 80%	Common
Age >65 years	Common	Common
Proteinuria	<3.5 g	>3.5 g
Hypocomplementemia anti-PLA ₂ R autoantibodies	Common 60% Absent	Rare Absent
Bilateral nephromegaly	Common	Rare
Renal mass lesions	25%	Rare
TBM immune complex deposits	80%	30%
Proteinuria resolution with treatment	Brisk	Delayed
Other IgG4-RD organ involvement	80%	80%
Acute or progressive chronic renal failure	75%	Reported, unknown %

Anti-PLA₂R: Anti-Phospholipase-A2-Receptor; TBM: tubular basement membrane

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