A Case of IgG4-Related Kidney Disease Developing While on Steroid Treatment for Autoimmune IgG4 Pancreatitis

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Abstract
IgG4 (immunoglobulin G4)-related systemic disease is an autoimmune process affecting multiple organ systems. This inflammatory process can present as but not limited to pancreatitis, cholangitis, or unspecified kidney disease. In this case, our patient developed IgG4-related kidney disease while already on a prolonged steroid course for IgG4-related pancreatitis. The patient ultimately had renal recovery after starting a higher dose of prednisone, but also developed steroid-related complications. This case further highlights the relationship between IgG4 diseases now termed IgG4-related systemic disease. This case brings to light the need for further investigative research into ideal steroid dosing, as well as steroid-sparing agents for IgG4-related systemic disease.

Keywords
nephrology, gastroenterology, IgG4, IgG4-related systemic disease

Introduction
IgG4 (immunoglobulin G4)-related systemic disease is a recently discovered autoimmune disease that affects several organ systems.1 While the disease typically responds well to steroids, the ideal dose remains unclear.2,3,5 Given its relatively recent discovery in 2003, the literature on IgG4-related systemic disease is limited.6 While it frequently responds to steroids, the appropriate regimens and doses have yet to be determined.5 The following report describes a novel case of IgG4-related kidney disease that developed while the patient was already on steroids for autoimmune IgG4 pancreatitis.

Case Presentation
A 57-year-old male with a medical history significant for well-controlled diabetes mellitus type 2 without retinopathy, autoimmune IgG4 pancreatitis, and benign prostate hyperplasia presented to nephrology clinic for worsening creatinine.

Two years prior to the kidney biopsy, the patient was admitted for acute pancreatitis (AP). Investigation for common causes of AP was negative. IgG4 levels were elevated more than 1000, with peak level of 1270. Pancreatic biopsy was performed in October 2018, and immunostaining revealed increased IgG4 plasma cells.

Family history was significant for unspecified autoimmune diseases, end-stage renal disease, and unspecified kidney disease.

The patient’s last episode of AP was in 2018. At that point, he was initiated on a prolonged steroid course of prednisone 40 mg daily starting in August 2018, which was gradually tapered off by September 2020.

While creatinine was normal (0.8) in May 2019 (Figure 1), it was noted to progressively worsen over the course of steroids, reaching 2.08 by November 2020 (Figure 2). Urinalysis revealed no red blood cells, blood, white blood cells, eosinophils, or protein. Urine protein/creatinine ratio initially was 0.1 mg/g in May 2019, and remained minimal at 0.3 mg/g by November 2020. No nephrotoxic medications were given during this rise of creatinine besides steroids, and the patient denied any use of nonsteroidal anti-inflammatory drugs for his pancreatitis pain.

Of note, the patient underwent a right submandibular mass biopsy 4 years prior to kidney biopsy, which demonstrated florid follicular lymphoid hyperplasia, lymphoplasmacytic infiltration, and stromal fibrosis. The immunostaining

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ratio of IgG versus IgG4 was only 1:1, which, per the pathology report, did not support IgG4 disease.

In the setting of progressively worsening creatinine, kidney biopsy was planned for November 2020 with the expectation that it would differentiate steroid-induced acute interstitial nephritis from IgG4-related kidney disease. Kidney biopsy demonstrated chronic active tubulointerstitial nephritis on light microscopy, and immunofluorescence staining confirmed positive IgG4 staining (Figures 3-6).

Because the kidney biopsy confirmed the presence of IgG4-related kidney disease that developed during steroid treatment, he was restarted on steroids at a higher dose than previously prescribed. Prednisone 1 mg/kg was initiated in December 2020 (Figure 7), with immediate improvement in renal function as evidenced by downtrending creatinine following initiation of high-dose steroids to 1.85 mg/kg even just a few weeks later. He continues to have renal recovery as of March 2021.

Discussion

IgG4-related systemic disease has only recently been described in the literature, first mentioned in 2003. Patients have been observed to demonstrate a constellation of manifestations including autoimmune pancreatitis, kidney disease, and sclerosing cholangitis. The mechanism behind the development of IgG4-related systemic disease remains unclear: whether elevated IgG4 levels are the cause as
opposed to simply a result of the disease has yet to be definitively determined, although immune complex formation has been proposed as a potential mechanism, perhaps by complement fixation via the lectin pathway or via the classical pathway.

The most common manifestation of IgG4-related kidney disease is tubulointerstitial disease, as seen in our patient. Membranous glomerulonephropathy is less frequently seen and was considered less likely in our patient even prior to biopsy given the low urine protein-creatinine ratio. Typical biopsy findings in IgG4-related tubulointerstitial disease include dense infiltration of IgG4-positive mononuclear cells, well-demarcated borders between involved and uninvolved regions, and storiform fibrosis, all of which were seen in our patient.

Concomitant pancreatitis and IgG4-related kidney disease has been reported: a retrospective study from Sweden evaluating 71 patients with autoimmune pancreatitis type 1 found that 27.4% of those patients also had concomitant IgG4-related kidney disease with a male predominance.

While there are currently no randomized controlled trials investigating the management and treatment of IgG4-related systemic disease, review of the current literature supports the use of glucocorticoids. Data suggest a favorable response to steroids, as demonstrated in our patient. Unlike in other kidney diseases, the presence of extensive fibrosis on biopsy surprisingly does not portend resistance to steroids. Several potential contenders to steroid treatment have been identified (including rituximab, mycophenolate mofetil, azathioprine, and bortezomib), evidence on the utility of these agents is limited to preliminary data based on a few case reports. Identification of a steroid-sparing agent is crucial given the detrimental effects that high-dose steroids can have on the kidneys. In our patient, high-dose steroids raised his
A1C from 7.2 to 11.5 within 2 months, unfortunately increasing his risk for diabetic-related kidney disease. Patients like ours would benefit tremendously from steroid-sparing agents, highlighting the need for additional investigative research into treatment strategies.

Conclusion
Patients presenting with one form of IgG4 disease may be predisposed to developing other IgG4 disease manifestations. Increased awareness of this diagnosis will allow clinicians to screen patients appropriately and anticipate possible complications. Given the risks and complications associated with steroid treatment, particularly at high doses, further research into steroid-sparing agents is vital to provide clinicians with the tools necessary to optimize the medical management of this disease process.

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Ethics Approval
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Informed Consent
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