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CASE REPORT | BILIARY

Successful Use of a Novel High-Dose Mycophenolate Mofetil and Rituximab Regimen for Progressive IgG4 Sclerosing Cholangitis With Multisystemic Involvement

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ABSTRACT

Immunoglobulin G4 (IgG4) sclerosing cholangitis is an immune-mediated fibroinflammatory disease of the biliary tree. It may be asymptomatic or cause abdominal pain, jaundice, or pruritus on presentation. While glucocorticoids and rituximab are regarded as initial treatment options, there is little guidance on the management of patients who either cannot tolerate these agents or are refractory to them. We discuss a case of IgG4 sclerosing cholangitis that required a novel treatment strategy of 1,000 mg oral mycophenolate mofetil twice daily and 375 mg/m^2 rituximab infusions every 3 months to achieve disease control and limit adverse effects.

KEYWORDS: IgG4 sclerosing cholangitis; immunosuppression; systemic involvement

INTRODUCTION

Immunoglobulin G4 (IgG4) sclerosing cholangitis is an immune-mediated fibroinflammatory disease of the biliary tree that can present with abdominal discomfort, jaundice, and pruritus, with most patients being asymptomatic on presentation.[1] Glucocorticoids are typically used for the first-line treatment, with rituximab preferred as the second-line.[1–3] Despite the availability of first-line and second-line therapies, there are no established guidelines for patients who cannot tolerate these options or develop disease progression. We present a complicated case of IgG4 sclerosing cholangitis with progressive multisystemic involvement due to poor tolerance of guideline-directed therapy.

CASE REPORT

This is a 53-year-old man who presented with 15 pounds weight loss and progressive jaundice over a month, pruritus for 5 days, and abdominal pain for 2 days. Admission laboratory results were aspartate transaminase 60, alanine transaminase 89, total bilirubin 18.2, and alkaline phosphatase 448. A computed tomography of the abdomen and pelvis with intravenous contrast showed intrahepatic and extrahepatic duct dilation with abrupt narrowing of the main duct. A subsequent endoscopic retrograde cholangiopancreatography (ERCP) was notable for multiple extrahepatic strictures (Figure 1), treated with dilation and biliary stent placement (Table 1). Serum IgG4 was found to be 1,030 mg/dL, with ampullary biopsies positive for IgG4. A presumptive diagnosis of Type III IgG4 sclerosing cholangitis was made, based on involvement of the distal bile ducts and ducts at the hepatic hilum.[4]

He was started on high-dose prednisone with a positive initial clinical response, but this was discontinued after the development of steroid-induced central serous chorioretinopathy within 8 weeks, during a slow taper. He was transitioned to azathioprine, but this was discontinued after 3 months due to the development of significant myelosuppression. He was then started on 375 mg/m^2 of rituximab monotherapy every 3 months, but this was quickly shortened to every 2 months and then every month dosing due to worsening extrahepatic biliary disease, requiring frequent biliary stent exchanges by ERCP. The frequent rituximab infusions were complicated by biopsy-confirmed lobular capillary hemangioma of the forehead and mild infusion reactions treated with diphenhydramine.

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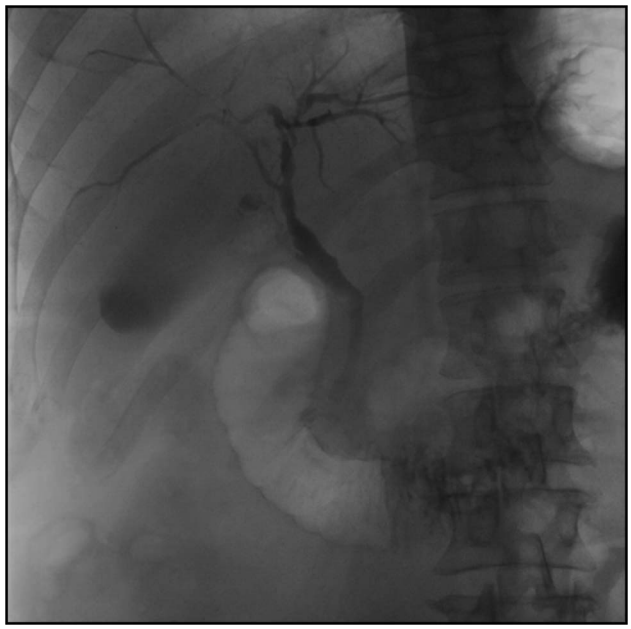

Figure 1. Cholangiogram obtained during index endoscopic retrograde cholangiopancreatography demonstrating multiple extrahepatic strictures.

Despite a noted improvement in his serum IgG4 levels from 1,030 to 634 over the following months, his disease progressed based on relapsing clinical symptoms and the eventual findings of diffuse intrahepatic duct involvement on subsequent ERCPs, with eventual reclassification to Type II IgG4 sclerosing cholangitis based on the involvement of the distal bile duct and diffuse intrahepatic ducts (Figure 2).[4] During this time course, he had recurrent episodes of (presumed autoimmune) acute pancreatitis as evidenced by radiologic findings and a lipase elevated above 3 times the upper limit of normal, with no other risk factors. During this period, he also had 1 documented episode of ascending cholangitis 18 months after diagnosis, IgG4-related involvement of his orbital and lacrimal glands 3 years after diagnosis, as well as development of IgG4-related Stage 3b chronic kidney disease with nephrotic range proteinuria with a protein/creatinine ratio of 15,513 mg/g and peripheral edema and ascites 42 months after diagnosis. He eventually progressed to chronic pancreatitis.

Based on continued disease progression on rituximab monotherapy along with multiple medication-related adverse events as documented above over a period of 2 and a half years from diagnosis, the decision was made at a multidisciplinary meeting to add 1,000 mg twice daily of oral mycophenolate mofetil to his q3 month rituximab infusion dosed at 700 mg (375 mg/m^2). This was clinically effective with rapid resolution of biliary strictures (Figure 3) and normalization of biochemical parameters. A slow taper of this novel treatment regimen was initiated 2 years afterward, with gradual reduction of his rituximab dosing frequency. At his last clinic visit, his hepatic function panel was still within normal limits—aspartate transaminase 18, alanine transaminase 27, alkaline phosphatase 86, and total bilirubin 0.3. IgG4 was 129, creatinine was within normal limits at 1.13, and his protein/creatinine ratio downtrended to 553.2 mg/g.

DISCUSSION

We present a novel combination regimen for the management of progressive IgG4-related sclerosing cholangitis, which has not been reported anywhere else to the best of our knowledge.

The incidence of IgG4-related sclerosing cholangitis in the United States has not been accurately determined due to its rarity. Patients with IgG4-related sclerosing cholangitis often have extrabiliary manifestations of IgG4-related disease (IgG4-RD), like our patient. The first-line treatment for IgG4-RD in all guidelines is the use of daily prednisone therapy for 4–6 weeks, followed by a gradual taper.[2] Most patients typically improve rapidly with steroid monotherapy, but some patients may require the addition of or substitution with rituximab, a monoclonal CD20-targeted antibody.[3] Azathioprine and mycophenolate mofetil are reasonable alternative choices if rituximab cannot be used.[2] Both of these agents may also be used for maintenance treatment in patients who are at a high risk for relapse of symptoms, such as patients with type 1 autoimmune pancreatitis with diffuse pancreatic enlargement, more than 2 organs

Table 1. Laboratory values for patient from presentation till date

	Index presentation	Just before initiation to novel combination therapy (2.5 y after diagnosis)	Most recent (4.5 y after diagnosis)
Alkaline phosphatase (range: 45–117 IU/L)	448	601	86
Total bilirubin (Range: 0.2–1 mg/dL)	18.2	3	0.3
Alanine transaminase (range: 12–78 IU/L)	89	74	27
Aspartate transaminase (range: 15–37 U/L)	60	66	18
Serum IgG4 (range: 1–123 mg/dL)	1,030	634	129
Creatinine (range: 0.67–1.17 mg/dL)	0.85	1.89	1.13
Protein/Creatinine ratio (range: 22–128 mg/g)	Not checked	15,513	553.2

IgG4, Immunoglobulin G4.

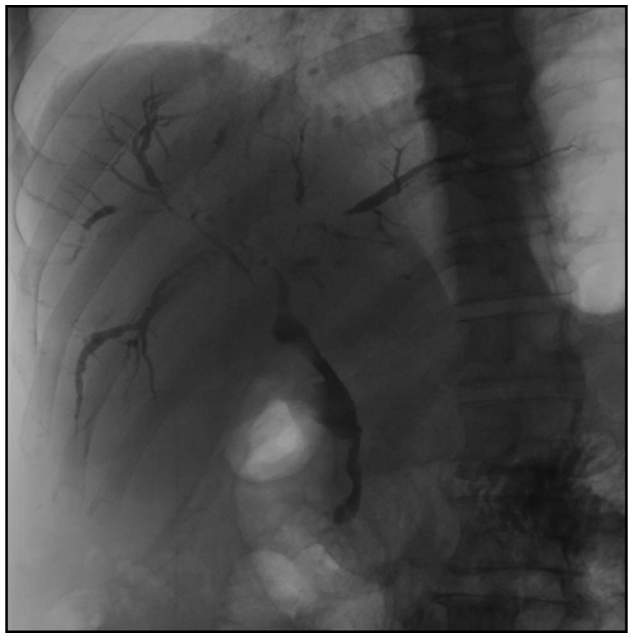

Figure 2. Cholangiogram obtained during follow-up endoscopic retrograde cholangiopancreatography 14 months after diagnosis, with diffuse progressive intrahepatic duct involvement.

involved in IgG4-RD, delayed radiologic improvement with treatment, or refractory high levels of IgG4 after treatment.[2,5] Other predictors of relapse are severe bile duct strictures, low-dose steroids or interruption in steroid treatment, prolonged period between diagnosis and treatment, personal history of allergy, and high serum tumor necrosis factor-alpha and soluble interleukin-2 receptor levels.[6,7]

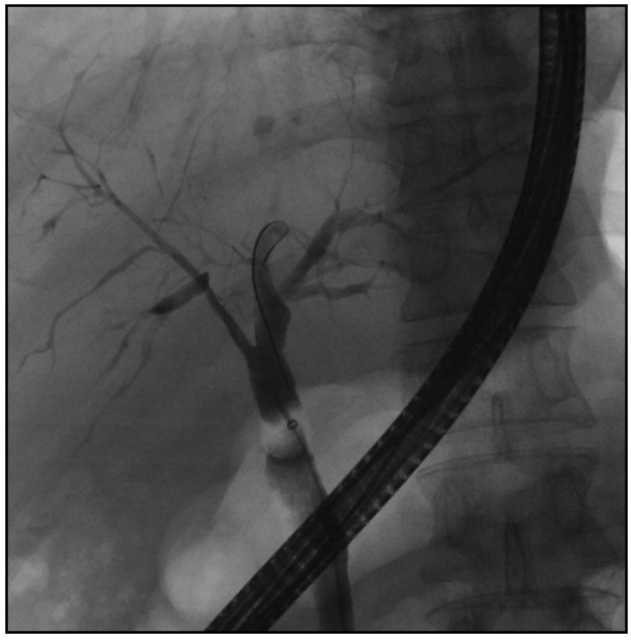

Figure 3. Cholangiogram from most recent endoscopic retrograde cholangiopancreatography showing improvement in biliary strictures after initiation of the novel combination regimen of 1,000 mg oral mycophenolate mofetil twice daily and rituximab infusion every 3 months.

Our patient was started on various guideline-recommended immunosuppression agents with various adverse events as described. Owing to a scarcity of evidence-based guidelines for cases of progressive IgG4 sclerosing cholangitis due to medication intolerance and relapse, a combination regimen of mycophenolate mofetil and rituximab was trialed, which achieved our desired outcomes of disease control.

Our case highlights the importance of more medical literature addressing successful management strategies for complicated IgG4-RD cases. Having a defined algorithmic guide to therapeutic options in this patient would have allowed for more rapid clinical remission without progressive multiorgan involvement and multiple procedures. We hope our successful management approach will aid clinicians treating patients in this same predicament. Further studies are needed to validate this treatment strategy in this niche patient population.

DISCLOSURES

Author contributions: U. Pamidimukkala: manuscript writing; G. Aitcheson and H. Fatima: manuscript editing; I. Obaitan: manuscript writing, editing, provision of images. Dr. Itegbemie Obaitan is the article guarantor.

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Informed consent was obtained for this case report.

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