



IgG4 Tubulointerstitial Nephritis and its Role in the Diagnosis of Multi-Organ IgG4 Related Disease

Andrew Zaleski^{1*}, Nauzer Forbes¹, and Summit Sawhney²

¹Department of Internal Medicine, University of Calgary, Canada

²Department of Diagnostic Imaging, University of Calgary, Canada

Abstract

Our case demonstrates the classic imaging features of IgG4-related kidney disease, autoimmune pancreatitis, and sclerosing cholangitis through endoscopic retrograde cholangio-pancreatography (ERCP), ultrasound, CT, and MRI. Immunoglobulin G4 (IgG4) disease is gaining increasing recognition in the medical community as a result of its multi-system involvement. The pancreas remains the most common organ involved in autoimmune pancreatitis (AIP) although, pancreatic involvement is not necessary in order to have extrapancreatic manifestations. Due to its tumefactive nature, accurate diagnosis of IgG4 multi-organ related disease is vital in ensuring appropriate treatment and reduced morbidity associated with unnecessary investigation and intervention.

Keywords: IgG4 related disease; IgG4 tubulointerstitial nephritis; IgG4 biliary sclerosis, IgG4 autoimmune pancreatitis

Introduction

Immunoglobulin G4 (IgG4) disease is gaining increasing recognition in the medical community as a result of its multi-system involvement. One of the first studies to propose the presence of IgG4-related autoimmune disease beyond the confines of autoimmune pancreatitis (AIP) was Kamisawa et al. [1], in 2003. Since then, there has been a growing body of literature showing its widespread multi-organ involvement [1-4]. Though the precise pathophysiology of multi-system involvement is still under investigation, the established common feature amongst those with the condition is histopathological infiltration of IgG4-positive plasma cells and lymphocytes, which leads to fibrosis and tumefactive lesions in one or more organs [2,5].

The pancreas remains the most common organ involved, with autoimmune pancreatitis (AIP) accounting for 2 – 11% of chronic pancreatitis [2,6]. Though AIP may be one manifestation of IgG4 related disease, it has been demonstrated that pancreatic findings are not necessary for extrapancreatic disease manifestations to be present. Imaging with both computed tomography (CT) and magnetic resonance imaging (MRI) has become a key component in diagnosis of pancreatic and extrapancreatic IgG4-related disease. Diagnosis is made on the basis of (1) characteristic

imaging appearance, (2) IgG4 serum concentrations $\geq 135 \text{ mg/dl}$ and (3) histopathology showing marked lymphocyte and plasmocyte infiltration and fibrosis. Definite diagnosis is made when all of the above criteria are met, probable diagnosis is made when criteria (1) and (3) are met, and possible diagnosis is considered when criteria (1) and (2) are met [4]. Our case demonstrates the classic imaging features of IgG4-related kidney disease, AIP, and sclerosing cholangitis through endoscopic retrograde cholangio-pancreatography (ERCP), ultrasound, CT, and MRI. While the combination of classic imaging findings and elevated serum IgG4 levels is consistent with possible IgG4-related disease according to the 2011 guidelines [4], we propose that the presence of characteristic renal findings and the patient's response to steroid therapy should confirm a diagnosis of IgG4-related disease.

Case Report

The patient is a 65-year-old Caucasian male who initially presented to the emergency department with symptoms of right upper quadrant pain for several months and acute onset of jaundice for 3 days. A timeline of the patient's presentation and diagnostic work up are summarized in Figure (1). Ultrasound was initially performed to assess for biliary obstruction and demonstrated common bile duct (CBD) dilatation up to 10 mm with bilateral intrahepatic biliary duct dilation. The pancreatic head was also enlarged although not completely characterized due to overlying bowel gas (Figure 2). The distal CBD was also obscured by overlying bowel gas which limited assessment; further diagnostic testing involving CT imaging and endoscopic retrograde cholangio-pancreatography (ERCP) was recommended.

A multi-phase contrast-enhanced CT scan of the abdomen and pelvis supported the presence of intrahepatic and extrahepatic biliary duct dilation, with the CBD measuring up to 7mm. The distal CBD demonstrated marked peribiliary wall enhancement and abrupt tapering as it traversed the pancreatic head, with a stricture spanning 1.5 cm. The distal CBD could be traced to the

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***Corresponding author:** Andrew Zaleski, Department of Internal Medicine, University of Calgary, Foothills Medical Center, Calgary, 312 – 328 21 Avenue SW, Calgary Canada, Canada, Tel: 403-369-9578; Email: azaleski2017@gmail.com

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ampulla of vater, and there was no concurrent main pancreatic duct dilation. The pancreas itself demonstrated effacement of the lobulations within the pancreatic head and progressive parenchymal enhancement. Not previously seen on ultrasound, the kidneys were diffusely abnormal, with bilateral symmetric wedge-shaped ill-defined hypoattenuating lesions along the renal cortices on arterial phase which were less distinct on portal venous phase with progressive enhancement. Laboratory results at the time of presentation demonstrated a cholestatic picture with elevated gamma glutamyl transferase (GGT) of 1,527 units/L and total bilirubin of 52 mmol/L. In addition, there was evidence of mild to moderate hepatitis, with elevation of ALT and AST to within 5-6 times the upper limit of normal. Based on the imaging appearance, correlation with serum biochemistry for IgG4-related disease and referral to gastroenterology for ERCP was recommended (Table 1).

ERCP was performed 3 days later. ERCP also demonstrated a focal stricture in the distal CBD (Figure 3). Sphincterotomy and CBD stenting was performed along with brushing of the CBD for cytology. No biliary duct stones were found. The stent was removed 2 weeks later. Cytology was negative for malignancy and inconclusive for IgG4 immunohistochemistry. Laboratory

Table 1: Summary of laboratory results at the time of diagnosis. H (High), N (Normal), L (Low).

White Blood Cell (WBC)	6.4 (N)
Alanine Aminotransferase (ALT)	343 Units/L (H)
Aspartate Aminotransferase (AST)	112 Units/Li (H)
Bilirubin, Total	52 mmol/L (H)
Bilirubin, Direct	38 mmol/L (H)
Creatinine	142 umol/L (H)
Estimated Glomerular Filtration Rate (eGFR)	45 mL/min (L)
Gamma Glutamyl Transferase (GGT)	1527 Units/L (H)
Lipase	149 Units/L (H)
CA 19-9	5 Units/mL (N)

Timeline
Day 0: Presentation to ED with jaundice and abdominal pain
Day 0: US showing CBD and intrahepatic biliary duct dilatation
Day 1: CT abdomen pelvis showing pancreatic, biliary duct, and renal involvement
Day 4: ERCP with placement of CBD stent
Day 5: Serum biochemistry for IgG4
Day 7: Initiation of 4 week course of high dose steroids
Week 5: Steroid taper
Week 13: Discontinuation of steroid taper
Month 10: Follow up MRI showing improvement in biliary, renal, and pancreatic findings

Figure 1 Timeline illustrating the progression through presentation, diagnostic workup, treatment and follow up.



Figure 2 Doppler ultrasound showing dilation of the common bile duct with structuring near the pancreatic head.



Figure 3 ERCP confirming stenosis of the intrapancreatic common bile duct with post-stenotic biliary duct dilatation.

testing revealed marked elevation of IgG4 at 8.60 g/L (normal 0.04 – 0.86 g/L) and total immunoglobulin G level of 18.81 g/L (normal 6.80 – 18.00 g/L).

The combination of the imaging findings and biochemistry was highly suggestive of IgG4-related disease and the patient was started on a course of oral prednisone (40 mg daily for 4 weeks, followed by 8 week taper off by 5 mg daily per week). His clinical symptoms improved on prednisone and he underwent routine follow up with serum biochemistry including IgG4, liver panel, lipase, and complete blood count. AST, ALT, bilirubin and lipase normalized following first follow up repeat bloodwork 1 month after initial presentation. The patient was then initiated on azathioprine 100 mg daily following his taper. IgG4 levels initially did not respond to therapy, so azathioprine was increased to 150 mg daily and accompanied by prednisone 20 mg daily. IgG4 levels gradually decreased and plateaued at approximately 4 g/L, with

ongoing normalization of liver enzymes for over 18 months.

Follow up gadolinium enhanced MRI performed 10 months after initial presentation demonstrated resolution of intrahepatic and CBD dilatation with some residual enhancement and circumferential thickening of the CBD at the site of previous stricture. The focal edema involving the pancreatic head had also resolved. The kidneys retained some perinephric stranding and patchy bilateral renal cortical enhancement, although this had also improved compared to the initial CT.

Discussion

IgG4-related disease is a complex systemic process that is becoming increasingly recognized for its multi-organ effects. Organs that have been associated with IgG4-related disease include the pancreas, biliary tree, salivary and lacrimal glands, periorbital tissues, lungs, lymph nodes, thyroid gland, kidneys, prostate gland, testicles, breasts, and pituitary gland. Our case demonstrates involvement of the pancreas, biliary tree, and kidneys. IgG4-related renal disease is commonly associated with AIP in up to 35% of cases [2,6]. The concomitant presence of classic renal findings in the setting of pancreatic involvement makes diagnosis of IgG4-related disease much more likely. In cases of isolated renal involvement, it is important to recognize the classic imaging findings in IgG4-related kidney disease as demonstrated in our case to better differentiate it from other differential diagnosis with similar findings such as lymphoma, extramedullary hematopoiesis, Erdheim-Chester disease, xantho-granulomatous pyelonephritis, and other autoimmune diseases. The renal manifestations of IgG4-related disease can be subdivided based on anatomic involvement of the kidney. These include tubulointerstitial nephritis (TIN) involving the renal cortex, renal pyelitis involving the renal collecting system urothelium, or retroperitoneal fibrosis leading to ureteric obstruction and hydronephrosis [7,8]. If recognition of IgG4-related renal disease is delayed, the process can progress to renal failure. Contrast enhanced CT imaging features of IgG4-TIN are described as bilateral round or wedge-shaped peripheral cortical hypo-attenuating lesions on arterial phase [7,8]. Solitary lesions are rarer and usually require further workup to exclude malignancy. In some cases, similarly to AIP a hypoattenuating rim of fibrosis is seen along the renal capsule [7,8]. In later phases such as portal venous, the cortical lesions demonstrate progressive enhancement and can become isoattenuating to the renal cortex. On non-enhanced CT these are not visible making IV contrast necessary for diagnosis [2]. The non-contrast CT series from our case demonstrates how occult renal IgG4-related disease is without IV contrast (Figure 4). Along with the cortical lesions, enlargement of the kidneys is often associated with TIN. On MRI, the cortical lesions are well defined on T2-weighted sequences and contrast-enhanced T1-weighted sequences in which they appear as areas of low signal [2,6]. In the case of our patient, the kidneys bilaterally demonstrated ill-defined wedge-shaped hypoattenuating areas on arterial phase (Figure 5) with progressive enhancement on portal venous phase (Figure 6),



Figure 4 Coronal non-contrast series demonstrating the occult nature of renal findings without IV contrast. Perinephric stranding on these images is entirely non-specific..

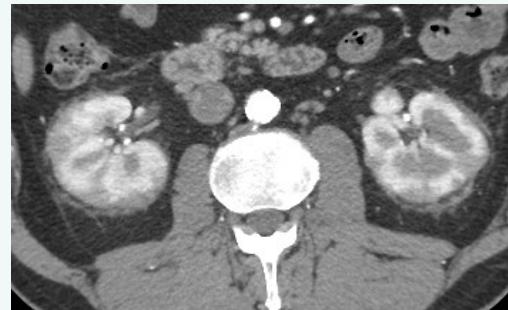


Figure 5 Arterial phase axial (A) and coronal (B) enhanced CT images showing peripheral wedge-shaped hypoattenuating cortical lesions. Thick hypoattenuating rim around the kidney consistent with fibrosis of the renal capsule.

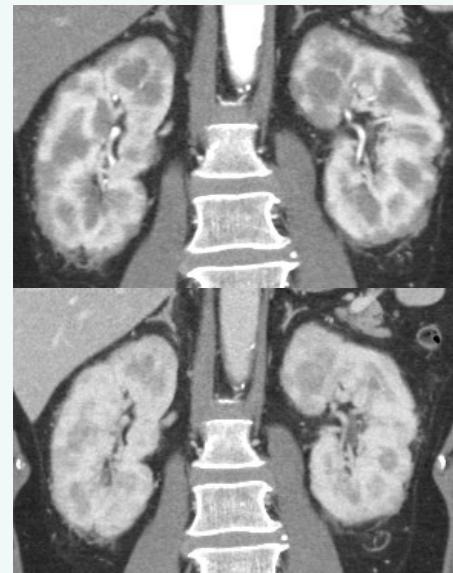


Figure 6 Arterial (A) and portal venous (B) phase coronal images through the kidneys that demonstrates wedge-shaped cortical hypoattenuating lesions that progressively enhance on portal venous phase.

which as previously described is the classic presentation of IgG4 TIN. A hypoattenuating rim was also seen around the kidneys consistent with fibrosis of the renal capsule. The MRI in our case was performed as a follow-up study and lacks these acute findings although still demonstrates the peripheral capsular renal fibrosis. Renal pyelitis on CT presents as diffuse wall thickening of the renal pelvis. Occasionally this can become more nodular and transitional cell carcinoma must be excluded. The presence of AIP often aids in differentiating more nodular renal lesions from primary renal cancers as it makes IgG4 disease much more likely [2,6,7]. The presence of the classic IgG4-related renal tubulointerstitial nephritis findings in this case was the key finding which allowed for differentiating multi-organ involved IgG4 disease from a primary pancreatic or biliary malignancy which was later confirmed on endoscopic brushings of the main pancreatic duct. In addition, the presence of pancreatic and biliary findings made renal biopsy unnecessary in reaching diagnosis reducing patient morbidity and mortality.

Autoimmune pancreatitis is the most common organ manifestation IgG4-related disease [2]. It is an important diagnosis to recognize as occasionally it is found post pancreateoduodenectomies for suspected pancreatic cancers. One study by Hardacre et al., listed the rate of IgG4 pancreatitis found incidentally in surgical pathology for suspected pancreatic cancer in 2.5% of surgical cases [9]. Autoimmune pancreatitis can be subdivided by both histopathology and imaging characteristics. From a histopathological stand point autoimmune pancreatitis can be subdivided into Type 1 lymphoplasmacytic sclerosing pancreatitis (IgG4-related) and Type 2 idiopathic duct-centric chronic pancreatitis (no IgG4 elevation) [2,10]. AIP has two main imaging subtypes: diffuse and focal. The diffuse form is the more common disease pattern and involves uniform enlargement of the pancreas with effacement of the normal interdigitated fat within the pancreatic clefts. This forms the characteristic featureless "sausage-like" pancreatic appearance. The focal form of the disease mainly presents as focal enlargement of the pancreatic head and less often the body and tail. This forms a "mass-like" appearance making it difficult to differentiate from pancreatic carcinoma [2,8,11]. Our case demonstrated the focal form of IgG4 pancreatitis with nodular enlargement of the uncinate process (Figure 7) with focal stenosis of the traversing common bile duct. Unfortunately, in the case of our patient the encapsulated rim or halo of low attenuation surrounding the pancreas was not present which has been described as a more specific finding of autoimmune pancreatitis due to fluid, phlegmon, or fibrosis [2]. The MRI in our case had been performed in follow-up months after the initial onset of symptoms and did not demonstrate the characteristic findings associated with autoimmune pancreatitis. Autoimmune pancreatitis on MRI commonly shows a low T1/T2 signal peripancreatic capsule, pancreatic ductal stenosis over a long segment, and a duct penetrating sign with restricted diffusion corresponding low ADC values. In contrast, pancreatic cancers lack the peripancreatic capsule, often cause shorter pancreatic ductal stenoses, and have higher associated ADC values than

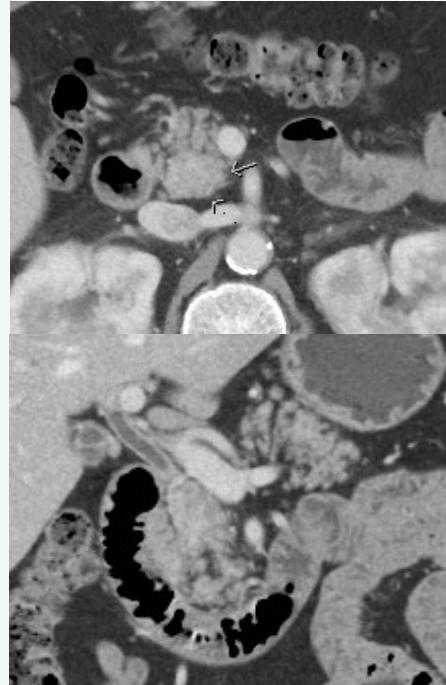


Figure 7 Axial (A) and coronal (B) images from enhanced CT showing focal thickening and edema of the pancreatic uncinate process in keeping with nodular subtype of IgG4 pancreatitis.

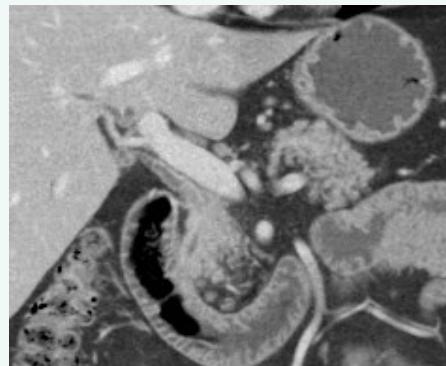


Figure 8 Enhanced abdominal CT showing focal stricture (short arrow) of the CBD with biliary duct wall thickening and enhancement (long arrow).

AIP. FDG PET/CT is also another modality occasionally used for distinguishing AIP from pancreatic neoplasms. AIP demonstrates a more heterogeneous and diffuse FDG uptake with increased uptake at extrapancreatic sites of disease while pancreatic cancer is characterized by more focal nodular uptake [2,11]. Pancreatic cancer cannot be excluded based on imaging appearance alone and as a result ERCP is often used to provide a pathological confirmation. The ERCP in our case was both therapeutic in stenting the CBD stenosis but also provided tissue sampling which excluded pancreatic malignancy. As previously discussed, according to the 2011 Comprehensive diagnostic criteria for IgG4-

related disease, our case would fall into the possible category as it possesses both classic imaging findings and serum elevated IgG4. However, the multi-organ involvement and response to steroid therapy makes the diagnosis of multi-organ IgG4-related disease more conclusive.

IgG4-related sclerosing cholangitis is the second most commonly affected organ following the pancreas in IgG4-related disease. It is associated with approximately 60-80% of cases of IgG4-related autoimmune pancreatitis [2]. It can be found both concurrently with AIP as well as in isolation which can result in difficulty coming to a diagnosis. The biliary involvement in our case was the most common manifestation of IgG4 sclerosing cholangitis in which the intrapancreatic portion of the CBD as a result of diffuse bile duct thickening, stenosis and upstream dilatation (Figure 8). In our case this lead further to result in a cholestatic biochemical picture and clinical jaundice [5,12]. As a contrast to primary sclerosing cholangitis, sclerosing cholangitis associated with IgG4 disease is highly responsive to steroid therapy as was seen in our case in which the clinical jaundice and elevated cholestatic biomarkers returned to normal following steroid therapy. Our case is confounded in this improvement however but the placement of a biliary stent during ERCP. Again, unfortunately endoscopic brushings did not demonstrate the dense infiltration of IgG4-positive plasma cells within the bile duct wall and periportal region that is characteristic histological finding [5,12]. Pathology results did not find the presence of pancreatic malignancy however which is an important diagnosis to exclude especially in focal type AIP. The lack of pathological correlation in this case may have been to inadequate tissue sampling or a false negative biopsy as the serum biochemistry and imaging characteristics are so supportive of IgG4 sclerosing cholangitis.

Treatment with a course of oral prednisone 40 mg/daily for 4 weeks followed by gradual taper is in accordance with the

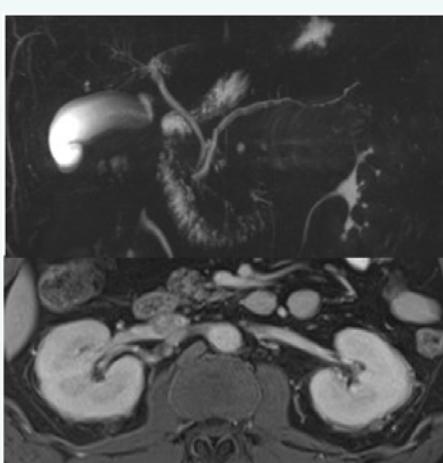


Figure 9 Follow up MRI images through the biliary tree (A) and kidneys (B) showing resolution of the tumefactive IgG4-related findings as a response to steroid therapy.

International Consensus Guidance Statement on Management and Treatment of IgG4-Related Disease [13]. In cases with multiorgan disease, significant elevation in serum IgG4, involvement of proximal bile ducts, or a history of relapse maintenance low dose steroid therapy (2.5 – 5 mg/day of prednisolone) is beneficial in decreasing morbidity associated with relapsing episodes [13]. Even though based on these criteria the patient would be at high risk for relapse, maintenance therapy was not initiated at this time. Biochemical follow up of serum IgG4 and total IgG, liver enzymes, lipase, and bilirubin showed complete normalization aside from persistent mild elevation of serum IgG4 which continues to be followed. Follow up MRI imaging demonstrated interval improvement of the biliary, pancreatic and renal findings seen on the earlier CT (Figure 9).

Conclusion

IgG4-related disease since its first description in 2003 by Kamisawa et al. [1], has been gaining recognition in linking multiorgan autoimmune inflammation via accumulation of IgG4-positive plasma cells. Due to its tumefactive nature, accurate disease diagnosis especially recognition of the classic imaging appearance is vital in appropriate treatment and reducing morbidity associated with unnecessary intervention. The case presented demonstrated classical findings involving type 1 autoimmune pancreatitis, IgG4-related sclerosing cholangitis, and IgG4- tubulointerstitial nephritis with associated marked elevation in serum IgG4 and treatment response both imaging and biochemically to steroid therapy.

References

1. Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, et al. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol*. 2003; 38: 982–984.
2. Martínez-de-Alegria A, Baleato-González S, García-Figueiras R, Bermúdez-Naveira A, Abdulkader-Nallib I, Díaz-Peromingo JA, et al. IgG4-related disease from head to toe. *Radiographics*. 2015; 35: 2007–2025.
3. Hedigre SS, McDermott S, Borczuk D, Elmi A, Saini S, Harisinghani MG. The Spectrum of IgG4-Related Disease in the Abdomen and Pelvis. *AJR*. 2013; 201: 14–22.
4. Umehara H, Nakajima A, Nakamura T, Kawanami T, Tanaka M, Dong L, et al. IgG4-related disease and its pathogenesis—cross talk between innate and acquired immunity. *Int Immunol*. 2014; 26: 585–595.
5. Kamisawa T, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. *J Gastroenterol*. 2006; 41: 613–625.
6. Horger M, Lamprecht HG, Bares R, Spira D, Schmalzing M, Claussen CD, et al. Systemic IgG4-Related Sclerosing Disease: Spectrum of Imaging Findings and Differential Diagnosis. *2012; 199: 76-82*.
7. Takahashi N, Kawashima A, Fletcher JG, Chari ST. Renal involvement in patients with autoimmune pancreatitis: CT and MR imaging findings. *Radiology*. 2007; 242: 791–801.
8. Kawano M, Saeki T. IgG4-related kidney disease – an update. *Curr Opin Nephrol Hypertens*. 2015; 24: 193–201.
9. Hardacre JM, Iacobuzio-Donahue CA, Sohn TA, Abraham SC, Yeo CJ, Lillemoe KD, et al. Results of pancreaticoduodenectomy for



- lymphoplasmacytic sclerosing pancreatitis. Ann Surg. 2003; 237: 853-858.
10. Sato Y, Notohara K, Kojima M, Takata K, Masaki Y, Yoshino T. IgG4-related disease: Historical overview and pathology of hematological disorders. Pathology International. 2010; 60: 247-258.
11. Tang CSW, Sivarasan N, Griffin N. Abdominal manifestations of IgG4-related disease: a pictorial review. Insights Imaging. 2018; 9: 437-448.
12. Hirano K, Tada M, Isayama H, Yamamoto K, Mizuno S, Yagioka H, et al. Endoscopic evaluation of factors contributing to intrapancreatic biliary stricture in autoimmune pancreatitis. Gastrointestinal Endoscopy; 2010; 71: 85-90.
13. Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, et al. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. Arthritis & Rheumatology. 2015; 67: 1688-1699.