Seymour Katz, M.D., Series Editor

Diagnosis and Management of IgG4-associated Pouchitis

by Darren N. Seril, Bo Shen

Chronic pouchitis is an inflammatory complication of total proctocolectomy with ileal pouch-anal anastomosis that can be difficult to manage. Pouchitis patients with elevated serum immunoglobulin G4 (IgG4) levels or increased numbers of IgG4-expressing plasma cells in the pouch mucosa are susceptible to chronic antibiotic-refractory pouchitis (CARP), as well as to having concomitant autoimmune diseases and extra-intestinal manifestations. Similar to autoimmune pancreatitis, IgG4-associated pouchitis may respond favorably to corticosteroid therapy. IgG4-related disease should be a consideration in patients with IgG4-associated pouchitis who have consistent histological changes and involvement of other organ sites. Pouch endoscopy with mucosal biopsy, and histological analysis with IgG4 immunostaining, are needed for the diagnosis. Oral budesonide may be an effective treatment option that should be considered early in the management of patients with IgG4-associated pouchitis, especially those with CARP. The effectiveness of B-cell targeting therapy, such as rituximab, has been established in principle in these patients.

INTRODUCTION

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is currently the surgical procedure of choice for medication-refractory ulcerative colitis (UC) and UC-associated colonic neoplasia as well as familial adenomatous polyposis. A large portion of UC patients with IPAA will develop inflammation of the ileal pouch reservoir, commonly known as pouchitis.[1] However, the exact etiology and pathogenesis of ileal pouch inflammation are not entirely clear. It is likely that pouchitis (especially chronic pouchitis) arises due to similar factors that cause inflammatory bowel disease (IBD): for example, predisposing genetic factors, aberrant microbiota-host interactions, and immune-dysfunction.[1] Indeed, this possible overlapping etio-pathogenesis has led to the notion that pouchitis can be useful as a model of IBD with a defined starting point (the exposure of the pouch to the fecal stream upon ileostomy reversal).[2] Given that pouchitis is responsive to antibiotic therapy in many cases, it is presumed that a disruption of the normal composition of commensal bacteria in the pouch ("dysbiosis") is a common causative factor.[3] A subgroup of pouchitis patients appears to have an immune-mediated inflammatory process characterized by an increase in the co-occurrence of autoimmune disorders (AImD),[4] extra-intestinal disease manifestations (EIM) such as primary sclerosing cholangitis (PSC),[5,6] and the presence of serum autoantibodies.[7–10] These patients

Darren N. Seril,[a] MD, PhD and Bo Shen,[b] MD
[a]Division of Gastroenterology/Hepatology, Albany Medical College, Albany, NY
[b]Department of Gastroenterology/Hepatology, The Cleveland Clinic Foundation, Cleveland, OH

with "immune-mediated pouchitis" (IMP) appear to have a greater tendency to having chronic antibiotic-refractory pouchitis (CARP) than patients without these features.[8–11]

The role of immunoglobulin G4 (IgG4) in immune function and disease pathology continues to be defined. IgG4 has unique properties that likely have a significant impact on its immuno-biology.[12] The part played by IgG4 in autoimmune pancreatitis (AIP) has been well characterized. It is now thought that AIP consists of at least 2 subtypes, AIP type 1 and type 2.[13] AIP type 1 is defined histologically by an IgG4-enriched lymphoplasmacytic tissue infiltrate. Elevated serum IgG4 and tissue infiltration by IgG4-expressing plasma cells are hallmarks of AIP type 1, and the histopathological measurement of IgG4-expressing cell infiltration is incorporated in some diagnostic criteria for AIP.[13,14] In contrast, AIP type 2 is marked by neutrophil infiltration and destruction of pancreatic ducts, as well as a lymphoplasmacytic infiltrate lacking a prominent IgG4-positive component.[13]

The association between IgG4 and AIP, as well as IgG4-associated manifestations at other organ sites, has led to the concept of IgG4-related disease (IgG4-RD), of which AIP type 1 is thought to be a pancreatic manifestation.[15] Nearly every organ system can be involved in the spectrum of this systemic disease, including the salivary glands, pancreaticobiliary system, and intestines.[15,16] Our group has reported that a subgroup of IPAA patients expressing elevated serum levels of IgG4 [17] or having a pouch inflammatory process associated with infiltration by IgG4-expressing plasma cells [18] is marked clinically by a propensity for antibiotic-refractory disease. While the exact role played by IgG4 in the pathogenesis of pouch dysfunction remains undefined, it is becoming clear that IgG4-associated pouchitis may have distinctive clinical characteristics and response to therapy. The focus of this review is on the emerging role of IgG4 in pouchitis and the implications for diagnosis and management.

IgG4 Immunobiology and Pathogenesis

Properties of IgG4

Our current understanding of the part played by IgG4 in disease is incomplete. Typically, IgG4 constitutes a minority of total IgG,[19] and its production requires long-term exposure to an inciting antigen.[20] Based on this observation, it has been suggested that IgG4 may take part in immune tolerance to chronic antigenic stimulation [21] and attenuation of the allergic reaction.[22] IgG4 is also notable for a poor ability to induce complement-mediated cytotoxicity.[23,24] In addition, IgG4 may have anti-inflammatory actions.[12,25] Based on these purported functions, the question of how IgG4 takes part in disease pathogenesis remains unanswered. Indeed, there is limited evidence of disease causation despite a well-documented association between IgG4 and diseases such as AIP.

IgG4 and Autoimmune Pancreatitis

Elevated IgG4 has been observed in multiple immune-mediated diseases, including known AImD such as rheumatoid arthritis (RA).[26,27] However, the association of IgG4 with disease has been most extensively studied in AIP. AIP type 1 is characterized by a prominent IgG4-positive lymphocyte infiltration as well as storiform fibrosis and obliterative phlebitis. Hypergammaglobulinemia is a common feature of AIP, and elevated serum IgG4 has been recognized in a high percentage of patients, specifically those with type 1.[28] The sensitivity of elevated serum IgG4 in diagnosing AIP was greater than 90% in some studies,[29] and had good accuracy in differentiating AIP from pancreatic cancer.[30] Serum IgG4 levels may also be useful as a marker of steroid response in AIP.[31] The infiltration of IgG4-expressing plasma cells is more frequently observed in pancreatic tissue from patients with AIP type 1 than other etiologies of pancreatic pathology, including pancreatic adenocarcinoma.[32] Validated criteria for the diagnosis of AIP, such as the Histology, Serology, other Organ involvement, and Response to therapy (HISORt) criteria, include the histological parameter of "abundant" IgG4-positive plasma cells on immunostaining (typically defined as >10 IgG4-positive plasma cells per high power microscopy field [HPF]).[14] However, a direct role of IgG4-expressing cells in the pathogenesis of AIP has not been established.

The observation that manifestations of AIP type 1 outside of the pancreas are also associated with the infiltration of IgG4-expressing plasma cells suggests that this type of AIP is a systemic IgG4-associated disease.[15] Indeed, over the last several years, IgG4 involvement at many different organ sites has been recognized, including the salivary glands,[33] biliary tree,[34] skin,[35] kidneys,[36] lungs,[37] and thyroid gland,[38] leading to the notion of IgG4-related disease (IgG4-RD). However,

(continued on page 70)

(continued from page 68)

evidence that directly links IgG4 to the causation of IgG4-RD is lacking, even though changes in serum IgG4 levels can correspond to corticosteroid treatment response.[31] There is evidence that elevations of IgG4 in the serum and at the tissue level can occur in association with inflammation at intestinal sites, including the ileal pouch, in the absence of other overt features of IgG4-RD.

IgG4 and Pouchitis

An association between ileal pouch inflammation and an elevated serum IgG4 level, or tissue infiltration by IgG4-expressing plasma cells, has been noted in a subgroup of IPAA patients. As will be discussed below, these associations may have implications for the classification and treatment of pouchitis in these patients. Our group reported a case of a 27 year-old man with IPAA and a background of UC and PSC, as well as Hashimoto's thyroiditis (but not AIP) that presented with diarrhea and findings of pouchitis on pouch endoscopy. He was noted to have an elevated serum IgG4 level (194 mg/dL), and histologic evaluation of pouch and afferent limb biopsies revealed a mixed lamina propria infiltrate of neutrophils and lymphocytes, with immunohistochemical staining of pouch biopsies showing greater than 10 IgG4-expressing plasma cells per HPF.[39] Of note, histologic analysis of the terminal ileum samples from the same patient obtained at the time of total colectomy showed no evidence of IgG4-positive cell infiltration. The patient responded clinically to budesonide therapy. This initial report indicated that IgG4-associated inflammation may take part in pouchitis, and also indicated that an IgG4-associated inflammatory process can arise *de novo* following surgery, and in association with other features of autoimmunity.[39] In addition, this case raised the possibility that IPAA patients with "IgG4-associated inflammation" may be more susceptible to CARP and benefit from corticosteroid therapy.

Pouchitis and Elevated Serum IgG4 Levels

The clinical characteristics of patients with pouchitis and concomitant serum elevation of IgG4 were further assessed in a prospective study of symptomatic IPAA patients. Among 124 pouch patients with underlying UC, serum IgG4 was reported to be elevated (>114 mg/dL) in 10 (8%) patients, of whom none had concurrent AIP.[17] The group of patients with pouchitis and elevated serum IgG4 had higher Pouchitis Disease Activity Index

ABBREVIATIONS

AImD	autoimmune disorder
AIP	autoimmune pancreatitis
CARP	chronic antibiotic-refractory pouchitis
CD	Crohn's disease
HISORt	Histology, Serology, other Organ involvement, and Response to therapy
EIM	extra-intestinal manifestation
HPF	high-power field
IBD	inflammatory bowel disease
Ig	immunoglobulin
IgG	immunoglobulin G
IgG4-RD	immunoglobulin G4-related disease
IgG4-SC	immunoglobulin G4-sclerosing cholangitis
IPAA	ileal pouch-anal anastomosis
IMP	immune-mediated pouchitis
mPDAI	modified Pouchitis Disease Activity Index
PDAI	Pouchitis Disease Activity Index
PSC	primary sclerosing cholangitis
PSC-UC	ulcerative colitis with concomitant primary sclerosing cholangitis
RA	rheumatoid arthritis
TNF-α	tumor necrosis factor-alpha
UC	ulcerative colitis

(PDAI) symptom sub-scores. In addition, significantly more patients with elevated serum levels of IgG4 (5/10 [50%]) had CARP compared to patients with a normal serum IgG4 level (23/114 [20%]).[17] In a subsequent study of 97 IPAA patients with underlying UC, a significantly higher median serum level of IgG4 was detected in patients with positive IgG4 histology (defined as >10 IgG4-expressing plasma cells per HPF on pouch biopsies) compared to those with negative IgG4 histology.[18] In that study, 4/28 (14%) patients with positive IgG4 histology versus 3/69 (4%) patients with negative IgG4 histology had elevated serum IgG4; however, the difference was not statistically significant. Overall, there was no correlation between elevated serum IgG4 and tissue infiltration by >10 IgG4-expressing plasma cells detected in the ileal pouch.[18] These studies indicate that serum IgG4 elevation may be a useful biological marker of an increased risk for CARP. However, it is apparent that an elevated IgG4 serology does not reliably correspond to increased IgG4-positive cell infiltration in the ileal pouch (and *vice versa*). This is similar to the observations in AIP type 1, in which a lack of concordance between IgG4 serology and histology has been noted in as many as one-third of cases.[15] As already mentioned, serum IgG4 levels mirrored corticosteroid response in some studies of AIP type 1,[31] but the reports have been conflicting. Similarly, serum IgG4 levels may be useful in predicting symptom relapse in some patients following successful treatment, but relapse has been noted in the presence of persistently normal post-treatment IgG4 levels as well.[40] Whether a higher concordance between serum IgG4 and tissue infiltration is characteristic of IgG4-RD (such as AIP type 1) compared to an "IgG4-associated" inflammatory process has yet to be addressed.

IgG4 Histology in Pouchitis

The identification of increased numbers of infiltrating IgG4-positive plasma cells in pouch biopsies appears to be associated with an increased propensity for refractoriness to antibiotic therapy. In the study by our group noted above, 28/97 (29%) symptomatic IPAA patients had >10 IgG4-expressing plasma cells in the ileal pouch mucosa. Nineteen of these patients (68%) with IgG4-positive immunostaining of pouch mucosal biopsies had CARP, as compared to 30/69 (43.5%) patients without IgG4-positive cells in the pouch.[18] It is noteworthy that there was no difference in regards to the incidence of Crohn's disease (CD) of the pouch or irritable pouch syndrome (IPS) between patients with and without increased numbers of infiltrating IgG4-expressing cells in pouch tissues. In addition, the incidence of PSC (29%) and concomitant AImD (39%) were significantly greater among IPAA patients with elevated tissue IgG4-expressing plasma cells than those without elevated IgG4 histology (10% and 19%, respectively).[18] Thus, IgG4-associated pouchitis (as defined by an increased number of infiltrating IgG4-positive plasma cells) is characterized clinically by an increased incidence of CARP as well as a concurrence with clinical markers of an immune-mediated process.

The presence of IgG4-expressing plasma cells in pouch biopsy specimens is relatively common in symptomatic IPAA patients. In a recent study, among 98 IPAA patients with symptoms of pouch dysfunction and immunohistochemical staining for IgG4-positive cells, 76 (78%) had one or more IgG4-positive plasma cells per HPF in biopsy specimens.[41] Tissue infiltrations by >10 IgG4-expressing plasma cells per HPF was detected in biopsy specimens from 27/98 (28%) patients. In addition, similar to the prior study by Navaneethan et al.,[18] a significantly greater proportion of patients with CARP had elevated IgG4 histology (17/31, 55%) as compared to all other etiologies of pouch dysfunction (10/67, 15%).[41] It is tempting to conclude that elevated IgG4 in these patients is a by-product of an underlying aberrant immune response. However, we have found that while there is marked overlap between elevated IgG4 expression (either in the serum or in plasma cells infiltrating the pouch tissue) and other immune markers, there is more pronounced concurrence with autoimmune thyroid disease, microsomal antibody expression, and PSC in patients with CARP. This association between certain immune markers may explain the observation that microsomal antibody expression and increased tissue infiltration by IgG4-expressing plasma cells are risk factors for CARP rather than an increasing number of immune markers *per se*.[41] A summary of the studies investigating the association between elevated IgG4 and pouch dysfunction is shown in Table 1.

Pouchitis and IgG4-related Disease

It is not clear if any of the cases of "IgG4-associated pouchitis" represent an ileal pouch manifestation of IgG4-RD. As alluded to above, IgG4-RD is comprised of an ever-increasing group of systemic inflammatory disorders whose diagnosis depends primarily on the finding of characteristic histologic features (including

Table 1. Studies Investigating Immunoglobulin G4 in Patients with Ileal Pouch-Anal Anastomosis

Study	Patients and Design	Patient Characteristics[a]	Elevated Serum IgG4[b]	Elevated IgG4 Histology[c]	Findings or Outcome
Shen et al. 2011[39]	27 y/o M (case report)	UC background, Hashimoto's thyroiditis; diarrhea	Yes	Yes	Pouchitis; clinical response to budesonide (Serum IgG4 level did not respond to therapy)
Navaneethan et al. 2011a[17]	124 patients (prospective)	UC background; symptomatic[d]	10 (8%)	NP	IgG4+ serology: higher PDAI symptom sub-score, 50% CARP IgG4-serology: 20%
Navaneethan et al. 2011b[18]	97 patients (prospective)	91% UC background, 9% indeterminate colitis or Crohn's colitis; symptomatic	7 (7.2%)	28 (29%)	IgG4+ histology: 68% CARP, 29% PSC, 39% AImD IgG4- histology: 43.5% CARP, 10% PSC, 19% AImD
Seril et al. 2014[41]	98 patients (retrospective)	UC background; symptomatic	5 (5.1%)	27 (28%)	IgG4+ histology: 63% CARP, 15% PSC, 15% AImD IgG4- histology: 20% CARP, 8.5% PSC, 24% AImD

[a] No patients had concomitant autoimmune pancreatitis
[b] Defined as a serum IgG4 level greater than 114 mg/dL
[c] Defined as tissue infiltration by greater than 10 IgG4-expressing plasma cells per high power microscopy field in pouch biopsies
[d] Diarrhea, blood in stool, abdominal pain, pelvic pain, or fatigue
Abbreviations: AImD, autoimmune disorder; AIP, autoimmune pancreatitis; IgG4, immunoglobulin G4; NP, not performed; PDAI, Pouchitis Disease Activity Index; PSC, primary sclerosing cholangitis; UC, ulcerative colitis

elevated IgG4-expressing plasma cells), and often multi-organ involvement. The frequent use of corticosteroids in patients with pouchitis may confound the signature histological findings of IgG4-RD. To date, none of the cases of pouchitis with elevated IgG4 that have been reported had extra-intestinal features that can be defined as IgG4-RD.[17,18,41] The exception may be the concurrence of "IgG4-associated pouchitis" with PSC.[18,41] It is possible that some of these cases had undiagnosed IgG4-sclerosing cholangitis (IgG4-SC) rather than PSC,[42,43] thus establishing a case for IgG4-RD in pouchitis. The distinction may be more than semantic in nature. The prominence of IgG4-expressing plasma cells may imply corticosteroid sensitivity as well as responsiveness to therapy targeting B-cells, analogous to the case in AIP and other IgG4-RD. However, whether "IgG4-pouchitis" and "IgG4-associated pouchitis" are distinct entities with differing clinical features and response to therapy has yet to be established.

Diagnosis Of IgG4-Associated Pouchitis

Measurement of Serum IgG4 Levels

If there is sufficient clinical suspicion for IgG4-associated pouch inflammation, screening for IgG4 levels can be sought by checking of serum IgG

(continued on page 74)

(continued from page 72)

subclasses. In published studies, the cut-off value for elevated serum IgG4 has varied from 114 to 140 mg/dL. However, the incidence of elevated serum IgG4 underestimates the frequency of IgG4-associated inflammation as defined by tissue infiltration by IgG4-expressing plasma cells,[18,41] which is used in the criteria for IgG4-RD. The response of IgG4 serum levels to treatment has yet to be studied in patients with pouchitis. Prospective studies are needed to determine if changes in IgG4 levels correspond to clinical response to therapy, as well as loss of response or relapse, as was the case in some reports of AIP.[31] However, in a case report of an IPAA patient with pouchitis and elevated IgG4, clinical response to budesonide therapy was not associated with a reduction in the serum IgG4 level.[39]

Pouch Endoscopy and IgG4 Histology

While serum IgG4 level can be used as a non-invasive screening test, endoscopy with biopsies should be performed in IPAA patients in whom IgG4-associated inflammation (as well as IgG4-RD) is suspected. In the case of the ileal pouch, biopsies of the afferent limb, pouch body, and the anal transition zone (or cuff) should be obtained. Infiltrating IgG4-expressing plasma cells are detected in biopsy specimens by standard immunohistochemical staining methods, and

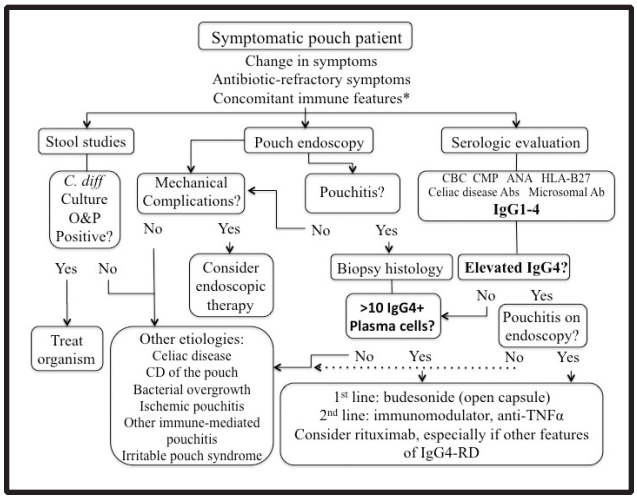

Figure 1. Proposed algorithm for the diagnosis and management of immunoglobulin G4-associated pouchitis. Abbreviations: ANA, antinuclear antibody; CD, Crohn's disease; Cdiff, Clostridium difficile; HLA-B27, human leukocyte antigen B27; IgG, immunoglobulin G; IgG4-RD, immunoglobulin G4-related disease; O&P, ova and parasites. *Concomitant immune features: concurrent autoimmune disorders, extra-intestinal manifestations of inflammatory bowel disease, or serum autoantibody expression.

are typically expressed as the number of immunostain-positive cells per HPF. There are currently no standardized criteria for the number of HPF that should be viewed to obtain the number of infiltrating IgG4-positive plasma cells. Similarly, the number of infiltrating IgG4-expressing plasma cells that is used to define a "positive" sample has for the most part been extrapolated from the reports in AIP. Some studies in AIP have utilized a 4-tiered scoring system of IgG4-positive cell numbers: for example, 0 to 5 IgG4-positive cells per HPF (regarded as negative), 6 to 10 cells (mild), 11 to 30 cells (moderate), and greater than 30 cells (severe). IgG4-expressing plasma cell levels defined as "moderate to severe" (i.e., >10 positive cells/ HPF) have been associated with a diagnosis of AIP.[32] The Mayo Clinic HISORt criteria for AIP utilizes a cut-off of >10 IgG4-positive cells/HPF.[14] However, the recommended cut-off for IgG4-positive cell number used in defining IgG4-RD varies bases on the organ site, with the number varying from >10 IgG4-positive cells/HFP in the liver and bile duct to greater than 200 in the skin.[16] In addition, an IgG4-RD consensus group recommended an IgG4-to-total IgG-positive cell ratio greater than 0.4 in establishing the diagnosis of IgG4-RD.[16] It is not clear if these same thresholds are valid in the small intestine and ileal pouch. Furthermore, the usefulness of these cut-offs in the setting of "IgG4-associated" inflammation in the absence of other features of IgG4-RD (i.e., other characteristic histological features and multi-organ involvement) is undefined. The diagnostic value of the IgG4-to-total IgG-positive cell ratio in those organ sites is also unknown. The studies examining IgG4 histology in pouchitis reported on IgG4-positive cell numbers alone. Further prospective studies are needed to correlate IgG4-positive plasma cell numbers with disease activity and relevant clinical endpoints in IPAA patients. This would permit a standardized approach to the quantitation of IgG4-expressing cell numbers, including the quantitation of total IgG-expressing cells and the number of HPF utilized in the analysis. Still, based on the studies to date, the use of greater than 10 IgG4-expressing plasma cells as a definition of elevated IgG4-positive cell infiltration appears to delineate a group of pouchitis patients at increased risk for CARP.[18,41]

While useful for diagnosing IgG4-associated inflammation, mucosal biopsies may underestimate the prevalence of IgG4-positive cell infiltration. In a report

by Hartman et al. in IBD patients, IgG4-expressing plasma cells were present in the submucosa or muscularis mucosa in 86% of resection samples, but were detected in the lamina propria in 23% of resection samples, and in only 25% of biopsy samples.[44] Despite this possible limitation, immunohistochemical staining for IgG4-expressing plasma cells in biopsy samples is likely a more sensitive measure of IgG4-associated inflammation in the ileal pouch than IgG4 serology. Indeed, our group has noted a lack of correlation between the presence of elevated IgG4-expressing plasma cells in the ileal pouch and serum IgG4 levels.[18] Furthermore, in the recent study of 98 IPAA patients with IgG4 immunostaining mentioned above, 27 (27.5%) patients had greater than 10 IgG4-expressing plasma cells per HPF on biopsy histology, and only 2/27 (7%) patients with elevated tissue infiltration by IgG4-expressing plasma cells had concomitantly elevated serum IgG4 (including 1/17 (6%) patients with CARP).[41] Thus, pouch endoscopy with biopsy and staining for IgG4 is warranted if serum IgG4 is normal (or low) but suspicion for an IgG4-associated process remains. Of course, the diagnosis of "IgG4-associated pouchitis" is not complete in the absence of endoscopic findings consistent with ileal pouch inflammation. The modified Pouchitis Disease Activity Index (mPDAI) is useful in this regard, with a score of greater than 5 being diagnostic of pouchitis.[45] In addition to facilitating a diagnosis of pouchitis and IgG4-associated inflammation, pouch endoscopy can also be used to assess for mechanical abnormalities of the pouch (e.g., pouch strictures and sinuses) that may be alternative causes of symptoms or suggestive of an alternate diagnosis, such as Crohn's disease (CD) of the pouch.[1] It should also be noted that inflammation of the anal transition zone (cuffitis) can be a cause of symptoms in IPAA patients and can also be associated with a prominent IgG4-associated inflammatory process, although this relationship has yet to be studied in depth.

Other Serologic and Radiologic Evaluations

Other serologic measures are for the most part of limited value in evaluating a patient with suspected or confirmed IgG4-associated pouchitis. However, given the overlap between IgG4 and PSC in a subgroup of patients, it would be appropriate to check a comprehensive metabolic panel to assess for liver enzyme or total bilirubin abnormalities that may be due to an early onset of hepato-biliary disease.[42,43] It may also be useful to measure select autoimmune serology, especially if there is clinical suspicion for concomitant AImD; for example, anti-nuclear antibody, rheumatoid factor, and (in the case of joint symptoms) HLA-B27. Furthermore, assessment for microsomal antibody expression may be particularly useful. Our group has found that microsomal antibody expression [17] and concomitant autoimmune thyroid diseases [4] are increased in symptomatic IPAA patients with CARP as compared to those without CARP, and there appears to be an overlap of these immune markers with IgG4 in some patients with refractory pouchitis.[41]

As is the case for other etiologies of pouchitis, imaging studies are not routinely used in the diagnosis of IgG4-associated pouchitis. If there is concern for pouch-related obstruction or a mechanical pouch complication, then abdominal x-ray, computed tomography, or pelvic magnetic resonance imaging may be indicated.

Clinical Presentation and Disease Course

Patients with IPAA and IgG4-associated inflammation can present with typical symptoms of pouchitis, including increased stool frequency, urgency, stool blood, abdominal pain, pelvic pain, and fatigue. Other systemic features such as fevers, night sweats, and weight loss would be atypical findings, and should raise concern for a superimposed infectious process such as *Clostridium difficile* infection of the pouch [46] or cytomegalovirus infection of the pouch,[47] as well as pouch-associated sinus tract or fistula with abscess. As noted above, mechanical complications of the pouch can mimic some of the clinical features of pouchitis;[48] however, pain in the region of the sacrum and coccyx that sometimes accompanies a posterior pouch sinus tract would not be typical of IgG4-associated pouchitis. If IgG4-associated pouchitis occurs in the setting of IgG4-RD, the patient may have diverse symptoms based on the involvement of other organs in the IgG4-related disease process.[15] For example, IgG4-SC may present more often with obstructive jaundice than PSC.[49]

The natural history of IgG4-associated pouchitis has yet to be fully characterized. There is some evidence that IgG4-associated pouchitis is marked by a more severe clinical presentation: pouchitis patients with elevated serum IgG4 had significantly greater PDAI symptom sub-scores as compared to those with normal serum IgG4.[17] Furthermore, as described above, there is evidence that IPAA patients having an elevated serum IgG4 level or increased tissue infiltration by

IgG4-expressing plasma cells are at increased risk for CARP, and therefore more frequently require anti-inflammatory or immunosuppressive therapy.[18,41] Whether these patients are at risk for other adverse outcomes, including more frequent hospitalization or pouch failure,[50] is an area of ongoing research. It has been reported that elevated serum IgG4 adversely impacts the disease course of PSC: IgG4-positive individuals had a shorter interval until liver transplantation,[42,51] and patients with PSC-UC were reported to have reduced colectomy-free survival.[52] The impact of IgG4-associated pouchitis on the occurrence of mechanical complications of the pouch has yet to be studied as well.

IgG4 and Implications for Treatment

Corticosteroid Therapy

A characteristic feature of AIP (as well as other IgG4-RD) is responsiveness to corticosteroid therapy.[40,53] Indeed, corticosteroid responsiveness is among the criteria for AIP.[14] This may have implications for the treatment of IgG4-associated inflammation in intestinal sites, including in pouchitis. As noted above, pouchitis patients with elevated serum IgG4 and increased tissue infiltration by IgG4-expressing plasma cells are at an increased risk for CARP and the need for immunosuppressive therapies in order to achieve symptom remission.[18,41] While the efficacy of corticosteroid therapy in this context has yet to be substantiated by large clinical studies, our group reported a case of IgG4-associated pouchitis that responded clinically to budesonide therapy.[39] Furthermore, observation in our clinical practice indicates that, in general, these patients respond favorably to budesonide therapy, such that in many cases it is considered the 2nd line of therapy if they have demonstrated dependence on or refractoriness to standard antibiotic regimens. An area of ongoing study is the clinical response of IPAA patients with IgG4-associated pouchitis to oral budesonide therapy. The response of serum IgG4 levels to corticosteroid therapy has not been studied in pouchitis patients; however, our group has observed that budesonide therapy may be associated with a reduction in the number of IgG4-expressing plasma cells infiltrating the pouch mucosa (unpublished data).

The rate of clinical relapse following corticosteroid therapy is similarly unexplored in pouchitis patients. The reports in AIP patients indicate that relapse is common following treatment with corticosteroids. In a large study in Japan, more than 90% of AIP patients treated with corticosteroids had experienced disease relapse at 3 years of follow-up.[40] Patients with AIP type 1 have been reported to be more susceptible to disease relapse following corticosteroid treatment compared to those with AIP type 2.[54] Similarly, in one study, half of the corticosteroid-responsive PSC patients with elevated IgG4 had biochemical relapse after treatment.[43] In the study of a French cohort of patients with IgG4-RD, 90% (19/21) had response to corticosteroid therapy as defined by clinician survey responses, but 12 of the corticosteroid-responsive patients eventually required other immunosuppressive therapies.[55] Thus, perhaps analogous to other chronic inflammatory diseases such as IBD, corticosteroids are useful in inducing IgG4-RD remission but not in maintaining remission.

Immunomodulators and Anti-TNF-α Therapy

Medications that are routinely used in the management of IBD, including immunomodulators (e.g., azathioprine, methotrexate, and mycophenolate mofetil), have also been employed in patients with IgG4-RD.[56] However, assessments of their efficacy have been limited to case reports and series, and the usefulness of these agents in the treatment of IgG4-associated pouchitis has not been explored. Anti-tumor necrosis factor-α (TNFα) therapy has been employed in the treatment of IgG4-RD as well. For example, a patient with features suggestive of IgG4-RD consisting of pancreatic pseudo-tumor (likely AIP type 1), elevated serum IgG4, and severe IgG4-associated pan-colitis experienced symptom relapse following corticosteroid and azathioprine therapy, and had lost response to infliximab. The patient was eventually treated successfully with adalimumab.[57] Similarly, a case of severe IgG4-related ocular adnexal disorder, refractory to corticosteroids, was responsive to infliximab.[58] In a report by Hartman et al., greater than 80% of surgical resection specimens from IBD patients who were refractory or intolerant of anti-TNFα therapy contained elevated IgG4-expressing plasma cells.[44] This may suggest that IBD with IgG4-associated inflammation is prone to treatment refractoriness, similar to the case of IgG4-associated pouchitis. Alternatively, the IgG4-expressing plasma cells in these patients may play a role in the host response to biological therapy. The elaboration of antibodies against anti-TNFα biologics (especially infliximab, as well as adalimumab) is a cause of infusion reactions

(continued on page 78)

(continued from page 76)

and loss of treatment response.[59] The host response to those biologics may be mediated in part by an IgG4 response. For example, IgG4 was reported to constitute a considerable portion of anti-adalimumab antibodies in patients with RA.[60] It remains to be determined if elevated IgG4 in pouchitis patients is a determinant of reduced responsiveness to anti-TNFα therapy, or is itself a response to therapy that results in medication-neutralization and loss of response.

B-cell Targeting Therapy

The presence of an IgG4-associated inflammatory process in the pouch, including in the setting of IgG4-RD, suggests that a B-cell targeting approach would be useful. In fact, rituximab therapy was successful in the treatment of 9 of 10 patients with IgG4-RD who had persistence of disease despite diverse immunosuppressive therapies (including prednisone, azathioprine, 6-mercaptopurine, methotrexate, and mycophenolate mofetil).[61] Treatments like rituximab may be particularly beneficial in IgG4-associated diseases by reducing memory B-cells.[62] Further studies are needed to explore the effectiveness of targeted therapies in patients with IgG4-associated pouchitis, including rituximab. This approach has been established in principle by the favorable response of an IPAA patient with IgG4-expressing plasma cell infiltration of the pouch and the thyroid to rituximab therapy (unpublished data).

SUMMARY

The role of IgG4-associated inflammation in pouchitis is continuing to emerge. A proposed algorithm for the diagnosis and management of IgG4-associated pouchitis is shown in Figure 1. Elevated serum levels of IgG4 occur in a minority of symptomatic ileal pouch patients, but are associated with an increased prevalence of CARP. Similarly, a subgroup of chronic pouchitis patients has increased pouch tissue infiltration by IgG4-expressing plasma cells and a predilection for CARP. However, the correspondence between IgG4 serology and IgG4 histology is poor. "IgG4-associated pouchitis" appears to have clinical features of an immune-mediated process, having a greater prevalence of concomitant AImD, as well as extra-intestinal manifestations of IBD (notably PSC) than those without elevated IgG4. IgG4-RD should be a consideration in patients with IgG4-associated pouchitis with typical histologic changes and involvement of other organ sites. Pouch endoscopy with mucosal biopsy, and histologic analysis with IgG4 immunostaining, are essential for the diagnosis of IgG4-associated pouchitis. The implications of an IgG4-associated inflammatory process for the treatment of pouchitis are continuing to be studied. Budesonide therapy may be an effective option that should be considered early in the management of pouch patients with established IgG4-associated pouchitis. ■

The authors declare no financial conflicts of interest.

Acknowledgement

Bo Shen, MD is supported by the Ed and Joey Story Endowed Chair.

References

1. Shen B. Pouchitis: what every gastroenterologist needs to know. *Clin. Gastroenterol. Hepatol.* 2013;11(12):1538-1549. doi:10.1016/j.cgh.2013.03.033.
2. Wu H, Shen B. Pouchitis: lessons for inflammatory bowel disease. *Curr. Opin. Gastroenterol.* 2009;25(4):314-322. doi:10.1097/MOG.0b013e32832b36eb.
3. Shen B, Achkar JP, Lashner BA, et al. A randomized clinical trial of ciprofloxacin and metronidazole to treat acute pouchitis. *Inflamm. Bowel Dis.* 2001;7(4):301-305.
4. Shen B, Remzi FH, Nutter B, et al. Association between immune-associated disorders and adverse outcomes of ileal pouch-anal anastomosis. *Am. J. Gastroenterol.* 2009;104(3):655-664. doi:10.1038/ajg.2008.76.
5. Lohmuller JL, Pemberton JH, Dozois RR, Ilstrup D, van Heerden J. Pouchitis and extraintestinal manifestations of inflammatory bowel disease after ileal pouch-anal anastomosis. *Ann. Surg.* 1990;211(5):622-627; discussion 627-629.
6. Hata K, Watanabe T, Shinozaki M, Nagawa H. Patients with extraintestinal manifestations have a higher risk of developing pouchitis in ulcerative colitis: multivariate analysis. *Scand. J. Gastroenterol.* 2003;38(10):1055-1058.
7. Fleshner PR, Vasiliauskas EA, Kam LY, et al. High level perinuclear antineutrophil cytoplasmic antibody (pANCA) in ulcerative colitis patients before colectomy predicts the development of chronic pouchitis after ileal pouch-anal anastomosis. *Gut* 2001;49(5):671-677.
8. Fleshner P, Ippoliti A, Dubinsky M, et al. Both preoperative perinuclear antineutrophil cytoplasmic antibody and anti-CBir1 expression in ulcerative colitis patients influence pouchitis development after ileal pouch-anal anastomosis. *Clin. Gastroenterol. Hepatol.* 2008;6(5):561-568. doi:10.1016/j.cgh.2008.01.002.
9. Lian L, Remzi FH, Kiran RP, Fazio VW, Shen B. Clinical implication of false-positive celiac serology in patients with ileal pouch. *Dis. Colon Rectum* 2010;53(10):1446-1451. doi:10.1007/DCR.0b013e3181eba46c.
10. Navaneethan U, Venkatesh PGK, Manilich E, Kiran RP, Remzi FH, Shen B. Prevalence and clinical implications of positive serum anti-microsomal antibodies in symptomatic patients with ileal pouches. *J. Gastrointest. Surg.* 2011;15(9):1577-1582. doi:10.1007/s11605-011-1586-7.
11. Seril DN, Yao Q, Shen B. The association between autoimmunity and pouchitis. *Inflamm. Bowel Dis.* 2014;20(2):378-388. doi:10.1097/01.MIB.0000435761.82705.6a.
12. Van der Neut Kolfschoten M, Schuurman J, Losen M, et al. Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange. *Science* 2007;317(5844):1554-1557. doi:10.1126/science.1144603.
13. Zhang L, Chari S, Smyrk TC, et al. Autoimmune pancreatitis (AIP) type 1 and type 2: an international consensus study on histopathologic diagnostic criteria. *Pancreas* 2011;40(8):1172-1179. doi:10.1097/MPA.0b013e318233bec5.
14. Chari ST. Diagnosis of autoimmune pancreatitis using its five cardinal features: introducing the Mayo Clinic's HISORt criteria. *J. Gastroenterol.* 2007;42 Suppl 18:39-41. doi:10.1007/s00535-007-2046-8.
15. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N. Engl. J. Med.*

2012;366(6):539-551. doi:10.1056/NEJMra1104650.
16. Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. *Mod. Pathol.* 2012;25(9):1181-1192. doi:10.1038/modpathol.2012.72.
17. Navaneethan U, Venkatesh PGK, Kapoor S, Kiran RP, Remzi FH, Shen B. Elevated serum IgG4 is associated with chronic antibiotic-refractory pouchitis. *J. Gastrointest. Surg.* 2011;15(9):1556-1561. doi:10.1007/s11605-011-1587-6.
18. Navaneethan U, Bennett AE, Venkatesh PGK, et al. Tissue infiltration of IgG4+ plasma cells in symptomatic patients with ileal pouch-anal anastomosis. *J. Crohns Colitis* 2011;5(6):570-576. doi:10.1016/j.crohns.2011.05.011.
19. Nirula A, Glaser SM, Kalled SL, Taylor FR, Taylora FR. What is IgG4? A review of the biology of a unique immunoglobulin subtype. *Curr. Opin. Rheumatol.* 2011;23(1):119-124. doi:10.1097/BOR.0b013e3283412fd4.
20. Aalberse RC, van der Gaag R, van Leeuwen J. Serologic aspects of IgG4 antibodies. I. Prolonged immunization results in an IgG4-restricted response. *J. Immunol. Baltim. Md 1950* 1983;130(2):722-726.
21. Adjobimey T, Hoerauf A. Induction of immunoglobulin G4 in human filariasis: an indicator of immunoregulation. *Ann. Trop. Med. Parasitol.* 2010;104(6):455-464. doi:10.1179/136485910X12786389891407.
22. Wood N, Bourque K, Donaldson DD, et al. IL-21 effects on human IgE production in response to IL-4 or IL-13. *Cell. Immunol.* 2004;231(1-2):133-145. doi:10.1016/j.cellimm.2005.01.001.
23. Van der Zee JS, van Swieten P, Aalberse RC. Inhibition of complement activation by IgG4 antibodies. *Clin. Exp. Immunol.* 1986;64(2):415-422.
24. Tao MH, Canfield SM, Morrison SL. The differential ability of human IgG1 and IgG4 to activate complement is determined by the COOH-terminal sequence of the CH2 domain. *J. Exp. Med.* 1991;173(4):1025-1028.
25. Van de Veen W, Stanic B, Yaman G, et al. IgG4 production is confined to human IL-10-producing regulatory B cells that suppress antigen-specific immune responses. *J. Allergy Clin. Immunol.* 2013;131(4):1204-1212. doi:10.1016/j.jaci.2013.01.014.
26. Lin G, Li J. Elevation of serum IgG subclass concentration in patients with rheumatoid arthritis. *Rheumatol. Int.* 2010;30(6):837-840. doi:10.1007/s00296-009-1330-8.
27. Reddi DM, Cardona DM, Burchette JL, Puri PK. Scleroderma and IgG4-related disease. *Am. J. Dermatopathol.* 2013;35(4):458-462. doi:10.1097/DAD.0b013e318276cbac.
28. Okazaki K, Tomiyama T, Mitsuyama T, Sumimoto K, Uchida K. Diagnosis and classification of autoimmune pancreatitis. *Autoimmun. Rev.* 2014;13(4-5):451-458. doi:10.1016/j.autrev.2014.01.010.
29. Hirano K, Kawabe T, Yamamoto N, et al. Serum IgG4 concentrations in pancreatic and biliary diseases. *Clin. Chim. Acta Int. J. Clin. Chem.* 2006;367(1-2):181-184. doi:10.1016/j.cca.2005.11.031.
30. Morselli-Labate AM, Pezzilli R. Usefulness of serum IgG4 in the diagnosis and follow up of autoimmune pancreatitis: A systematic literature review and meta-analysis. *J. Gastroenterol. Hepatol.* 2009;24(1):15-36. doi:10.1111/j.1440-1746.2008.05676.x.
31. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N. Engl. J. Med.* 2001;344(10):732-738. doi:10.1056/NEJM200103083441005.
32. Zhang L, Notohara K, Levy MJ, Chari ST, Smyrk TC. IgG4-positive plasma cell infiltration in the diagnosis of autoimmune pancreatitis. *Mod. Pathol.* 2007;20(1):23-28. doi:10.1038/modpathol.3800689.
33. Kitagawa S, Zen Y, Harada K, et al. Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Küttner's tumor). *Am. J. Surg. Pathol.* 2005;29(6):783-791.
34. Kawakami H, Zen Y, Kuwatani M, et al. IgG4-related sclerosing cholangitis and autoimmune pancreatitis: histological assessment of biopsies from Vater's ampulla and the bile duct. *J. Gastroenterol. Hepatol.* 2010;25(10):1648-1655. doi:10.1111/j.1440-1746.2010.06346.x.
35. Khosroshahi A, Carruthers MD, Deshpande V, Leb L, Reed JI, Stone JH. Cutaneous immunoglobulin G4-related systemic disease. *Am. J. Med.* 2011;124(10):e7-8. doi:10.1016/j.amjmed.2011.03.011.
36. Saeki T, Nishi S, Imai N, et al. Clinicopathological characteristics of patients with IgG4-related tubulointerstitial nephritis. *Kidney Int.* 2010;78(10):1016-1023. doi:10.1038/ki.2010.271.
37. Sekiguchi H, Horie R, Aksamit TR, Yi ES, Ryu JH. Immunoglobulin G4-related disease mimicking asthma. *Can. Respir. J.* 2013;20(2):87-89.
38. Kakudo K, Li Y, Taniguchi E, et al. IgG4-related disease of the thyroid glands. *Endocr. J.* 2012;59(4):273-281.
39. Shen B, Bennett AE, Navaneethan U. IgG4-associated pouchitis. *Inflamm. Bowel Dis.* 2011;17(5):1247-1248. doi:10.1002/ibd.21441.
40. Kamisawa T, Shimosegawa T, Okazaki K, et al. Standard steroid treatment for autoimmune pancreatitis. *Gut* 2009;58(11):1504-1507. doi:10.1136/gut.2008.172908.
41. Seril DN, Yao Q, Lashner BA, Shen B. Autoimmune Features Are Associated with Chronic Antibiotic-Refractory Pouchitis. *Inflamm. Bowel Dis.* 2014:Epub ahead of print.
42. Zhang L, Lewis JT, Abraham SC, et al. IgG4+ plasma cell infiltrates in liver explants with primary sclerosing cholangitis. *Am. J. Surg. Pathol.* 2010;34(1):88-94. doi:10.1097/PAS.0b013e3181c6c09a.
43. Björnsson E, Chari S, Silveira M, et al. Primary sclerosing cholangitis associated with elevated immunoglobulin G4: clinical characteristics and response to therapy. *Am. J. Ther.* 2011;18(3):198-205. doi:10.1097/MJT.0b013e3181c9dac6.
44. Hartman DJ, Binion DG. Distribution of IgG4 cells in medically refractory patients with inflammatory bowel disease. *Gastroenterology* 2012;142(5).
45. Shen B, Achkar J-P, Connor JT, et al. Modified pouchitis disease activity index: a simplified approach to the diagnosis of pouchitis. *Dis. Colon Rectum* 2003;46(6):748-753. doi:10.1097/01.DCR.0000070528.00563.D9.
46. Seril DN, Shen B. *Clostridium difficile* Infection in Patients With Ileal Pouches. *Am. J. Gastroenterol.* 2014;109(7):941-947. doi:10.1038/ajg.2014.22.
47. He X, Bennett AE, Lian L, Shen B. Recurrent cytomegalovirus infection in ileal pouch-anal anastomosis for ulcerative colitis. *Inflamm. Bowel Dis.* 2010;16(6):903-904. doi:10.1002/ibd.21121.
48. Shen B, Remzi FH, Lavery IC, Lashner BA, Fazio VW. A proposed classification of ileal pouch disorders and associated complications after restorative proctocolectomy. *Clin. Gastroenterol. Hepatol.* 2008;6(2):145-158; quiz 124. doi:10.1016/j.cgh.2007.11.006.
49. Nakazawa T, Naitoh I, Hayashi K, Miyabe K, Simizu S, Joh T. Diagnosis of IgG4-related sclerosing cholangitis. *World J. Gastroenterol.* 2013;19(43):7661-7670. doi:10.3748/wjg.v19.i43.7661.
50. Tulchinsky H, Hawley PR, Nicholls J. Long-term failure after restorative proctocolectomy for ulcerative colitis. *Ann. Surg.* 2003;238(2):229-234. doi:10.1097/01.sla.0000082121.84763.4c.
51. Mendes FD, Jorgensen R, Keach J, et al. Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis. *Am. J. Gastroenterol.* 2006;101(9):2070-2075. doi:10.1111/j.1572-0241.2006.00772.x.
52. Navaneethan U, Venkatesh PGK, Choudhary M, Shen B, Kiran RP. Elevated immunoglobulin G4 level is associated with reduced colectomy-free survival in patients with primary sclerosing cholangitis and ulcerative colitis. *J. Crohns Colitis* 2013;7(2):e35-41. doi:10.1016/j.crohns.2012.04.006.
53. Kamisawa T, Yoshiike M, Egawa N, Nakajima H, Tsuruta K, Okamoto A. Treating patients with autoimmune pancreatitis: results from a long-term follow-up study. *Pancreatol.* 2005;5(2-3):234-238; discussion 238-240. doi:10.1159/000085277.
54. Sah RP, Chari ST, Pannala R, et al. Differences in clinical profile and relapse rate of type 1 versus type 2 autoimmune pancreatitis. *Gastroenterology* 2010;139(1):140-148; quiz e12-13. doi:10.1053/j.gastro.2010.03.054.
55. Ebbo M, Daniel L, Pavic M, et al. IgG4-related systemic disease: features and treatment response in a French cohort: results of a multicenter registry. *Medicine (Baltimore)* 2012;91(1):49-56. doi:10.1097/MD.0b013e3182433d77.
56. Ghazale A, Chari ST, Zhang L, et al. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. *Gastroenterology* 2008;134(3):706-715. doi:10.1053/j.gastro.2007.12.009.
57. Naghibi M, Ahmed A, al Badri AM, Bateman AC, Shepherd HA, Gordon JN. The successful treatment of IgG4-positive colitis with adalimumab in a patient with IgG4-related sclerosing disease--a new subtype of aggressive colitis? *J. Crohns Colitis* 2013;7(3):e81-84. doi:10.1016/j.crohns.2012.05.003.
58. Balaskas K, de Leval L, La Corte R, Zografos L, Guex-Crosier Y. Infliximab therapy for a severe case of IgG4-related ocular adnexal disorder recalcitrant to corticosteroid treatment. *Ocul. Immunol. Inflamm.* 2012;20(6):478-480. doi:10.3109/09273948.2012.714045.
59. O'Meara S, Nanda KS, Moss AC. Antibodies to infliximab and risk of infusion reactions in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm. Bowel Dis.* 2014;20(1):1-6. doi:10.1097/01.MIB.0000436951.80898.6d.
60. Van Schouwenburg PA, Krieckaert CL, Nurmohamed M, et al. IgG4 production against adalimumab during long term treatment of RA patients. *J. Clin. Immunol.* 2012;32(5):1000-1006. doi:10.1007/s10875-012-9705-0.
61. Khosroshahi A, Carruthers MN, Deshpande V, Unizony S, Bloch DB, Stone JH. Rituximab for the treatment of IgG4-related disease: lessons from 10 consecutive patients. *Medicine (Baltimore)* 2012;91(1):57-66. doi:10.1097/MD.0b013e3182431ef6.
62. Iwata S, Saito K, Hirata S, Tanaka Y. Phenotypic changes of lymphocyte in a patient with IgG4-related disease after corticosteroid therapy. *Ann. Rheum. Dis.* 2012;71(12):2058-2059. doi:10.1136/annrheumdis-2012-201657.