IgG4-Related Disease of the Gastrointestinal Tract

A 21st Century Chameleon

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Context.—Immunoglobulin G4 (IgG4)–related disease is a systemic fibroinflammatory disease capable of affecting virtually any organ. Although the pancreas and hepatobiliary system are commonly affected, involvement of the tubular gut is unusual. The pancreatic manifestations of this disease (autoimmune pancreatitis) often mimic pancreatic carcinoma, whereas the hepatobiliary manifestations are mistaken for cholangiocarcinoma or primary sclerosing cholangitis. The characteristic histologic features include a dense lymphoplasmacytic infiltrate, storiform-type fibrosis, and obliterative phlebitis. An increase in IgG4+ plasma cells and an IgG4 to IgG ratio of more than 40% are considered obligatory components of the diagnostic algorithm.

Objective.—To review the challenges associated with the diagnosis of IgG4-related disease of the gastrointestinal tract.

Data Sources.—A review of pertinent literature, along with the author’s personal experience, based on institutional and consultation materials.

Conclusion.—The complete spectrum of histologic changes is seldom captured in a biopsy specimen, and thus, the histopathology findings are best interpreted within the overall clinical context. Increased IgG4+ plasma cells are identified in a variety of benign and malignant diseases of the gastrointestinal tract.

IgG4-related disease, a systemic, immune-mediated inflammatory disease, is notable for its ability to affect virtually every organ and, on imaging, mimics a variety of benign and neoplastic diseases.1–4 Although the initial wave of discovery signaled a predilection for the pancreas and liver, an intensive decade-long study suggests that patients with the nongastrointestinal forms of the disease outnumber those with disease involving the gastrointestinal tract.

Nevertheless, the pancreatic and hepatic manifestations of this disease are far better characterized than are other forms of IgG4-related disease. Guidelines for the diagnosis of IgG4-related disease have been proposed, including those for autoimmune pancreatitis, as well as strategies to assist the histopathologist.5–7 These guidelines emphasize the need for close collaboration between the various subspecialties involved in the diagnosis and treatment of this disease, a group that includes radiologists and pathologists. Although pathology remains the gold standard for the diagnosis of IgG4-related disease, generally, pathology constitutes one element in an otherwise complex diagnostic algorithm.

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DEMOGRAPHIC ASPECTS OF THE DISEASE

The prototypic patient with IgG4-related disease is an elderly male. However, as our understanding of this disease has matured, we’ve learned to recognize a more-complex demographic picture, and at some locations, such as the head and neck region, the disease is just as common in women as it is in men.8 Furthermore, the disease may present as early as the third decade and, rarely, in children as well.9

ETIOLOGY

Several recent reviews1,2 take a critical look at the etiopathogenesis of this disorder. Although a detailed review of the pathogenesis of IgG4-related disease is not the primary intent of this review, a few comments are necessary to set the stage for an understanding of this systemic disease. Although the available data suggest that the disease is an autoimmune disorder, given its predilection for men and the propensity to present as a tumefactive lesion, IgG4-related disease is unlike most conventional autoimmune diseases.2,3,10 Although no universally accepted and validated target antigen has been identified, the association with IgG4 suggests that the humoral response is an important component of this disease. The relevance of the humoral immune system has been further underscored by recent efforts that have interrogated the B-cell repertoire: Next-generation sequencing performed on peripheral blood lymphocytes suggests that the B-cell repertoire is dominated by a small group of B-cell clones, which decline following immunosuppressive therapy.13,12 Recent data generated at the author’s institution suggest that T cells may also have a major role in this disorder (S.
likely accounts for the characteristic pattern of fibrosis seen though inflammatory cells dominate the histologic appearance. Regardless, the appearance is similar to that region. A resemblance to a

and B). A diagnostically useful analogy is that of a erroneous diagnosis of IgG4-related disease (Figure 3, A and B). A needle biopsy. A definitive diagnosis generally requires the presence of at least 10 IgG4+ plasma cells (Figure 6), and a secure diagnosis often necessitates an IgG4 to IgG ratio of greater than 40%. However, overreliance on IgG4+ plasma cells is discouraged: IgG4+ plasma cells are identified in a variety of connective tissue as well as neoplastic diseases, including pancreatic ductal adenocarcinoma.23 In fact, some pancreatic adenocarcinomas show a dense, peritumoral, IgG4+ plasma cell infiltrate, and inadvertent sampling of that zone could prompt a diagnosis of IgG4-related disease.24 A delay in the diagnosis of cancer could potentially close the already narrow window for surgical resection. Histopathology is best viewed as one element in a larger algorithm, the other elements being increased serum IgG4, characteristic imaging appearance, and the presence of other organ involvement (see below).25 Finally, when all else fails, a trial of steroids can be embarked upon: Lack of a swift response should prompt a thorough reassessment of all material, including imaging and histologic material.2 In some instances, a surgical resection may represent the only means of excluding a malignant process.

The diagnostic of autoimmune pancreatitis on a fine-needle aspiration biopsy poses an even more significant challenge.26 The reactive ductal atypia can be mistaken for a malignant process.25 The inflammatory cells are invariably in type-1 autoimmune pancreatitis and IgG4-related disease. The vascular lesions of type-1 autoimmune pancreatitis are virtually pathognomonic—with one major caveat: Unless strictly defined, they lose their diagnostic value. For example, aggregates of lymphocytes adjacent to a venous channel do not constitute obliterator phlebitis. Instead, the lumen in obliterator phlebitis is partially or completely obliterator by the fibroinflammatory process (Figure 4). An elastic stain is often helpful in uncovering totally obliterator vascular structures. However, obliterator venous structures are also readily identified by tracking intact arterial channels: The arterial and venous structures in the pancreas (and in many other organs as well) tend to run in parallel. In addition to the obliterator veins, a careful evaluation will occasionally uncover obliterator arteries. Interestingly, in spite of the presence of obliterator vascular structures, there is no evidence of infarct-type necrosis. Although most of the inflammatory infiltrate is composed of lymphocytes and plasma cells, a modest eosinophil cells infiltrate is invariably found (Figure 5). The image generated by the presence of storiform-type fibrosis and obliterator phlebitis is diagnostic of IgG4-related disease. Parameters usually absent in type-1 autoimmune pancreatitis include neutrophilic abscesses and granulomas.21

Diagnosis of Type-1 Disease on Biopsy.—A tissue diagnosis is required only in those cases with an atypical presentation, such as individuals with normal serum IgG4 (approximately 20% of all cases), focal enlargement of the pancreas, or atypical imaging features that raise concern for malignancy.22 Thus, in most cases, the diagnosis of type-1 autoimmune pancreatitis is based on clinical, imaging, and serologic data alone. Interpreting pancreatic biopsy samples is a challenge because the disease does not uniformly affect the organ, and thus, a biopsy specimen may not capture the diseased portion of the pancreas. The presence of storiform fibrosis and a dense lymphoplasmacytic infiltrate is highly suggestive of IgG4-related disease; however, obliterator phlebitis is seldom identified on a needle biopsy. A definitive diagnosis generally requires the presence of at least 10 IgG4+ plasma cells (Figure 6), and a secure diagnosis often necessitates an IgG4 to IgG ratio of greater than 40%. However, overreliance on IgG4+ plasma cells is discouraged: IgG4+ plasma cells are identified in a variety of connective tissue as well as neoplastic diseases, including pancreatic ductal adenocarcinoma.23 In fact, some pancreatic adenocarcinomas show a dense, peritumoral, IgG4+ plasma cell infiltrate, and inadvertent sampling of that zone could prompt a diagnosis of IgG4-related disease.24 A delay in the diagnosis of cancer could potentially close the already narrow window for surgical resection. Histopathology is best viewed as one element in a larger algorithm, the other elements being increased serum IgG4, characteristic imaging appearance, and the presence of other organ involvement (see below).25 Finally, when all else fails, a trial of steroids can be embarked upon: Lack of a swift response should prompt a thorough reassessment of all material, including imaging and histologic material.2 In some instances, a surgical resection may represent the only means of excluding a malignant process.

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entrapped within collagen bundles, and those cellular fibrinflammatory fragments may provide evidence to support a diagnosis of autoimmune pancreatitis. Nevertheless, the primary role of a fine-needle aspiration biopsy is to exclude malignancy.

**Type-2 Autoimmune Pancreatitis**

Type-2 autoimmune pancreatitis affects middle-aged individuals and does not show the marked predilection for men seen in type-1 disease. Similar to type-1 disease, patients with type-2 disease may present with obstructive jaundice and a tumefactive lesion in the pancreas, a picture that mimics pancreatic carcinoma. Some patients show symptoms that mimic other forms of chronic pancreatitis. Unfortunately, there is no biomarker for the diagnosis of the type-2 variant of autoimmune pancreatitis: Serum IgG4 levels are generally not elevated. Histopathologic evaluation of the pancreas remains the only secure means of establishing a diagnosis of type-2 autoimmune pancreatitis.

Pathology of Type-2 Autoimmune Pancreatitis—Type-2 autoimmune pancreatitis has little in common with type-1 disease (Table). The 2 hallmarks of type-2 autoimmune pancreatitis are (1) a brisk, periductal, lymphoplasmacytic infiltrate (Figure 7); and (2) neutrophils within ducts, the so-called granulocytic epithelial lesions (Figure 8). These neutrophils are also identified within acinar epithelium, a helpful clue on needle biopsy samples. These neutrophils may also be seen on a fine-needle aspiration biopsy specimen. The disease is also accompanied by marked pancreatic atrophy and fibrosis, both in the interlobular septa and within the lobules. However, with the exception of the infiltrate immediately adjacent to the

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**Figure 1.** Type-1 autoimmune pancreatitis with characteristic storiform-type fibrosis. Note the bands of fibrosis radiating from the center of the photograph. A dense, lymphoplasmacytic infiltrate is also present (hematoxylin-eosin, original magnification $\times 100$).

**Figure 2.** Type-1 autoimmune pancreatitis. This low-power image shows an accentuated lobular pattern. The interlobular stroma is expanded by a fibroinflammatory infiltrate. Note the focus of periductal inflammation (arrow). The cystically dilated islets show ductuloinsular complexes; such neuroendocrine hyperplasia is occasionally seen in autoimmune pancreatitis (hematoxylin-eosin, original magnification $\times 40$).

**Figure 3.** A, Storiform pattern of fibrosis. However, this example lacks the dense inflammatory infiltrate typically seen with autoimmune pancreatitis. This image is from a pancreatectomy from an individual with alcohol-related pancreatitis. B, Keloidal-type fibrosis associated with alcohol-related pancreatitis. This form of fibrosis is not seen in autoimmune pancreatitis (hematoxylin-eosin, original magnifications $\times 100$ [A] and $\times 200$ [B]).
ducts, there is much less lymphoplasmacytic infiltrate than that seen in type-1 autoimmune pancreatitis. The fibrosis also lacks the characteristic storiform-type pattern of type-1 autoimmune pancreatitis. Although foci of phlebitis are identified, obliterative phlebitis is not seen. The IgG4- plasma cells are not a feature of type-2 autoimmune pancreatitis, although some cases may show slightly more IgG4- plasma cells.

### IgG4-RELATED SCLEROSING CHOLANGITIS

Until the appreciation of IgG4-related disease as a distinct entity, the biliary manifestations of this disease were often mistaken for a variety of benign and malignant conditions, including primary sclerosing cholangitis as well as bile duct carcinoma and cholangiocarcinoma. It is imperative to consider this diagnosis in all suspected cases of primary sclerosing cholangitis, bile duct carcinoma, and cholangiocarcinoma.

Clinical and Imaging Features of IgG4-Related Sclerosing Cholangitis

The presenting symptoms vary, although the most-common presenting signs are obstructive jaundice and abnormal liver function test results. Some of these patients are also asymptomatic. On imaging 3 patterns of disease emerge: (1) multiple strictures, as well as dilation of the intrahepatic and extrahepatic biliary system, and an appearance that typically mimics primary sclerosing cholangitis; (2) an intrahepatic or hilar mass-forming lesion that may or may not be accompanied by biliary strictures, and an appearance that mimics cholangiocarcinoma or bile duct carcinoma; and (3) isolated stricture of the bile duct, and, in this scenario, the leading diagnosis is bile duct carcinoma.

Fortunately, 90% of the cases of IgG4-related sclerosing cholangitis are accompanied by autoimmune pancreatitis, the latter disease generally showing characteristic clinical and imaging features. The presence of either synchronous or metachronous involvement of the pancreas and biliary system, particularly if the radiologic features are compatible, argues strongly in favor of a diagnosis of IgG4-related sclerosing cholangitis. In this clinical context, an increase in serum IgG4 is usually diagnostic of IgG4-related sclerosing cholangitis, and histologic confirmation is often considered redundant. In cases unaccompanied by autoimmune pancreatitis or other manifestations of IgG4-related disease, the diagnosis of IgG4-related sclerosing cholangitis in the absence of autoimmune pancreatitis can be particularly challenging.

#### Comparison of the 2 Variants of Autoimmune Pancreatitis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Seventh decade</td>
<td>Fifth decade</td>
</tr>
<tr>
<td>Sex</td>
<td>Predominantly male</td>
<td>Equal M:F</td>
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<tr>
<td>Presentation</td>
<td>Jaundice ~75%, acute pancreatitis ~15%</td>
<td>Acute pancreatitis ~33%, jaundice ~50%</td>
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<tr>
<td>Extrapancreatic manifestations</td>
<td>Frequent</td>
<td>None</td>
</tr>
<tr>
<td>Serum immunoglobulin G4</td>
<td>Increased in 80% of cases</td>
<td>Seldom increased</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Periductal inflammation with 1 or more of the following features: 1. Storiform fibrosis 2. Obliterative phlebitis</td>
<td>~15%–30%</td>
</tr>
<tr>
<td>History</td>
<td>chedules could involve the pancreas, liver, and other systemic sites</td>
<td>Periductal inflammation with 1 or more of the following features: 1. Ductal/lobular abscesses 2. Ductal ulceration with neutrophils</td>
</tr>
<tr>
<td>Long-term outcome</td>
<td>Frequent relapses</td>
<td>Relapses are rare</td>
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Figure 7. Type-2 autoimmune pancreatitis. A dense, periductal infiltrate is present. In addition, numerous intraductal abscesses are also present—the so-called granulocytic epithelial lesions (hematoxylin-eosin, original magnification ×200).

Figure 8. Type-2 autoimmune pancreatitis. The photomicrograph demonstrates the destructive nature of the infiltrate. Note the multinucleated giant cell, likely representing a reaction to the ruptured duct (hematoxylin-eosin, original magnification ×200).

Figure 9. Intrapancreatic portion of the bile duct involved by immunoglobulin G4–related sclerosing cholangitis. The ductal epithelium is eroded, likely a consequence of an indwelling bile duct stent. A dense, inflammatory infiltrate is seen to extend through the entire thickness of the bile duct, a feature that distinguishes this disease from primary sclerosing cholangitis (hematoxylin-eosin, original magnification ×40).

Figure 10. Low-power view of a biopsy from an individual with immunoglobulin G4–related sclerosing cholangitis. Note the fibroinflammatory infiltrate effacing a portion of the liver (hematoxylin-eosin, original magnification ×100).
Histologic Features of IgG4-Related Sclerosing Cholangitis

Histology remains the gold standard for the diagnosis of IgG4-related sclerosing cholangitis. As with other manifestations of IgG4-related disease, the diagnosis rests on a triumvirate of histologic features: (1) a dense, lymphoplasmacytic infiltrate with storiform-type fibrosis; (2) obliterator phlebitis; and (3) elevated numbers of IgG4+ plasma cells, as well as an elevated IgG4 to IgG ratio. On a surgical resection, the full histologic spectrum is identified in almost all cases. However, biopsy samples represent a significant challenge, even to an experienced pathologist.

Bile Duct Biopsy in IgG4-Related Sclerosing Cholangitis

The disease can involve the entire length of the bile duct, including the intrapancreatic portion, which is involved in almost all cases of type-1 autoimmune pancreatitis. Histologically, the disease involves the entire thickness of the bile duct, a characteristic histologic finding (Figure 9). Obliterator phlebitis typically involves veins within the outer portion of the bile duct. This pattern of involvement differs from primary sclerosing cholangitis in which the inflammation is centered immediately beneath the lining epithelium with loss of the surface columnar epithelial cells. In contrast, the lining epithelium in cases of IgG4-related sclerosing cholangitis is preserved, with the exception of the lining epithelium in patients with indwelling biliary stents.

Because the characteristic changes of IgG4-related sclerosing cholangitis are generally confined to the outer half of the bile duct, those features are seldom captured on a biopsy. Biopsies from the biliary system are typically tiny, and the crush artifacts associated with those biopsies further compound the difficulties associated with their interpretation. Therefore, the diagnosis rests on the presence of a dense, lymphoplasmacytic infiltrate and more IgG4+ plasma cells—both relatively nonspecific findings. Both primary sclerosing cholangitis and bile duct carcinomas can be associated with a dense, chronic, inflammatory infiltrate and more IgG4+ plasma cells. In fact, approximately 43% of bile duct carcinomas are associated with more than 10 IgG4+ plasma cells, the threshold commonly used to diagnose IgG4-related sclerosing cholangitis. An IgG4 to IgG ratio of more than 40% provides an additional level of security. Unfortunately, immunoperoxidase preparations performed on biopsy samples are often associated with significant background staining, a statement that particularly applies to the IgG stain. Furthermore, because only a tiny portion of the bile duct is sampled on biopsy, the potential threat of undersampling a malignant process is fairly high. Thus, when dealing with bile duct and ampullary biopsies, the histology report should include a strong note of caution and highlight the not-so-uncommon association between IgG4+ plasma cells and malignancy.

Hepatic Manifestations of IgG4-Related Disease

The histologic alterations in the liver are similar to those seen in the bile duct. The differential diagnoses are also similar, although the interpretation of a hepatic core biopsy comes with its own set of unique challenges. On imaging, IgG4-related sclerosing cholangitis can present as a mass lesion, mimicking intrahepatic cholangiocarcinoma; alternatively, diffuse sclerosis of the biliary system can mimic primary sclerosing cholangitis.

Distinguishing Primary Sclerosing Cholangitis From IgG4-Related Sclerosing Cholangitis—Some cases that were classified in the past as primary sclerosing cholangitis are now thought to be better-characterized as IgG4-related sclerosing cholangitis. Although some cases are associated with autoimmune pancreatitis, in other patients, the disease is isolated to the biliary tract or may be associated with other forms of IgG4-related disease. Clinically, this is an important distinction: IgG4-related sclerosing cholangitis is associated with a swift and complete response to immunosuppressive therapy—the strictures melt with therapy. Additionally, preliminary evidence suggests that the risk of malignancy in IgG4-related sclerosing cholangitis is less than that seen in primary sclerosing cholangitis.

The unequivocal distinction of these 2 types of sclerosing cholangitis is seldom possible based on imaging alone. Although the serum IgG4 levels in cases of IgG4-related sclerosing cholangitis are significantly greater, there is considerable overlap between the 2 entities—approximately 10% of cases of primary sclerosing cholangitis are associated with increased serum levels of IgG4. A serum IgG4 level more than twice that of reference range is, however, considered highly suggestive of IgG4-related sclerosing cholangitis. Interestingly, it appears that individuals with primary sclerosing cholangitis and increased serum IgG4 levels may also respond to steroids, although independent validation of that observation is awaited.

The principle question posed to the pathologist is the distinction of IgG4-related sclerosing cholangitis from primary sclerosing cholangitis. Unfortunately, a needle biopsy sample is unlikely to capture the characteristic morphologic changes: Storiform-type fibrosis and obliterator phlebitis are seldom seen on a nonfocal liver biopsy. The feature that may help in this context is the presence of fibroinflammatory nodules: foci of fibroinflammatory tissue with effacement of the underlying hepatic parenchyma (Figures 10 and 11). Although cases of primary sclerosing cholangitis may show more IgG4+ plasma cells, the presence of more than 10 IgG4+ plasma cells, as well as an IgG4 to IgG ratio of more than 40%, supports the diagnosis of IgG4-related sclerosing cholangitis. The changes in the small...
caliber bile ducts may also assist in that distinction: (1) the presence of periductal, onion-skin–type fibrosis would favor a diagnosis of primary sclerosing cholangitis (although this author has occasionally seen those changes in biopsies from individuals with IgG4-related sclerosing cholangitis); and (2) a paucity of bile ducts would favor primary sclerosing cholangitis.

**IgG4-Related Inflammatory Pseudotumor.**—This is a clinically distinctive lesion that on imaging mimics intrahepatic cholangiocarcinoma. This mass-forming lesion is composed of a dense, lymphoplasmacytic infiltrate with storiform-type fibrosis. Characteristically, a diffuse and dense infiltrate of IgG4+ plasma cells is observed. Not all inflammatory mass-forming lesions of the liver, however, belong to the IgG4-related disease spectrum. The differential diagnosis includes other mass-forming inflammatory diseases—some of which are generally characterized by a prominent histiocytic infiltrate and fewer IgG4+ plasma cells. An inflammatory myofibroblastic tumor is another diagnostic consideration because some of those neoplasms show more IgG4+ plasma cells. Approximately one-half of those neoplasms are positive for ALK, a finding not observed in IgG4-related disease.

**OTHER ORGAN INVOLVEMENT—A VALUABLE DIAGNOSTIC CLUE**

Involvement of other organs, particularly histologically documented disease, has an important role in the diagnostic algorithm. Individuals with IgG4-related disease invariably show involvement of other organs, some of which may be clinically unsuspected and only detectable on positron emission tomography scans. A concerted effort should be made to retrieve all prior biopsies, particularly those samples from sites that are commonly involved by IgG4-related disease. A review of those archival samples may spare such individuals an exhaustive diagnostic workup as well as the morbidity and mortality associated with major surgery: Samples from the gallbladder (Figure 12) or salivary gland may demonstrate characteristic features of IgG4-related disease, avertzing a pancreatic or hepatic resection.

**Immunohistochemistry for IgG4 on Ampullary Biopsy**

A blind ampullary biopsy may assist in distinguishing pancreatic adenocarcinoma from autoimmune pancreatitis, as well as with the diagnosis of IgG4-related sclerosing cholangitis. Using a cutoff of greater than 10 IgG4+ plasma cells per high-power field, the sensitivity and specificity in one study was 52% and 89%, respectively. Although other studies report a higher specificity and sensitivity, as with other manifestations of this disease, it is unusual to base a diagnosis of autoimmune pancreatitis solely on the presence of more IgG4+ cells; IgG4-related disease is an uncommon disease, far less common than bile duct and pancreatic carcinoma. Thus, the pretest probability of IgG4-related disease is relatively low, and that parameter should be factored into the interpretation of ampullary biopsies, as well as biopsies from other sites of disease.

**INVolvement of the Tubular Gut**

Although involvement of the liver and pancreas is common, IgG4-related disease affecting the tubular gut is distinctly uncommon, and reported cases with disease in the tubular gut are generally met with a healthy dose of skepticism. Nevertheless, some variants of the disease are well accepted, such as involvement of the stomach. Small-bowel involvement has also been reported, and the disease may also involve the serosal surface of the gastrointestinal tract.

**THERAPY**

Steroids remain the primary treatment, and this disease responds swiftly to immunosuppressive therapy. As mentioned, the lack of response to steroids should raise an alarm and prompt a thorough review of all available material to exclude malignancy. However, some forms of the disease, particularly lesions with marked fibrosis, may show only a partial response to immunosuppressive therapy. Furthermore, recurrences are common, and in an attempt to reduce those episodes, some physicians place their patients on long-term (sometimes indefinite) steroid therapy. More recently, rituximab, an anti-CD20 antibody, has had remarkable success, sparing those patients the risks associated with long-term steroid use.

**References**
