

IgG₄-Related Sclerosing Disease: A Novel Mimic of Inflammatory Bowel Disease

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Abstract High levels of IgG₄-positive plasma cells are commonly seen in autoimmune pancreatitis. It has recently become evident that autoimmune pancreatitis is one component of a larger multi-system disease. IgG₄-positive plasma cells have been identified in many extrapancreatic tissues, including the colon, biliary tract, liver, and lungs, and thus the term “IgG₄-related sclerosing disease” has been proposed. Awareness of IgG₄-related sclerosing disease is important, as it has been shown to mimic other conditions like malignancy. This review discusses IgG₄-related colitis and its potential for mimicking inflammatory bowel disease.

Keywords Crohn’s disease · Ulcerative colitis · Inflammatory bowel disease · IgG₄ colitis · Autoimmune pancreatitis · IgG₄-related sclerosing disease

Introduction

The term “autoimmune pancreatitis” (AIP) was first proposed by Yoshida et al. in 1995 [1]. Eleven patients with a diagnosis of AIP were reviewed and found to have common features including diffuse pancreatic enlargement and irregular narrowing of the main pancreatic duct on

endoscopic retrograde cholangiopancreatography (ERCP). Serum gamma-immunoglobulins (IgG) were also found to be elevated in these patients. After numerous similar patients were described in case reports, diagnostic criteria were proposed, which included histological, radiological, serological, and clinical features of the disease, including favorable response to corticosteroids [2].

Autoimmune Pancreatitis

The prevalence of AIP is unclear. Current estimates are derived from retrospective case series analyses from various populations using different diagnostic criteria. Most cases of AIP have been reported from Japan, where a nationwide survey estimated its prevalence to be 0.82 per 100,000 [3]. An Italian multicenter study that enrolled 383 patients with chronic pancreatitis classified 23 patients (6%) as having “autoimmunity-associated” pancreatitis [4]. The Mayo Clinic found that seven of 178 (3.9%) patients who presented to their pancreas clinic between 2005 and 2006 met the HISORT criteria for the diagnosis of AIP [5]. The age of patients with AIP is reported to range from 14 to 85, but the mean age is likely between 40 and 60 [6–8]. Males are predominantly affected, with male-to-female ratios reported from 1.7 to 2.85 [3, 6].

AIP may be confused with pancreatic cancer because their presentations are similar. Patients with AIP often do not experience the severe abdominal pain that is classically associated with pancreatitis. Up to 80% experience obstructive jaundice and one-third experience weight loss [9]. New-onset diabetes mellitus has been reported in 42–76% of patients [10].

Non-specific IgG production from polyclonal B cell activation is a common feature of all chronic inflammatory

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disorders, including autoimmune disease. While hypergammaglobulinemia is noted in 37–76% of individuals with AIP, an increase in serum IgG4 is more sensitive and specific for its diagnosis [10]. The IgG4 subclass is a rare gamma globulin subtype, and accounts for only 3–6% of total serum IgG [11]. One series found the sensitivity of elevated serum IgG4 (≥ 135 mg/dl) for diagnosis of AIP to be between 67 and 94% [11]. Another series of 45 patients with AIP found serum IgG4 levels greater than 140 mg/dl to be 76% sensitive and 93% specific for diagnosis of AIP [12]. However, it has also been shown that some patients with pancreatic cancer may have elevated serum IgG4 levels. Ghazale et al. found elevated serum IgG4 levels greater than 140 mg/dl in 13/135 (10%) patients with pancreatic cancer [12]. In contrast, serum CA 19-9 was elevated in 71% of pancreatic cancer patients compared to 9% of AIP patients.

Specific IgG directed against the plasminogen-binding protein (PBP) of *Helicobacter pylori* was reported in 33/35 (94%) patients with AIP versus 5/110 (5%) with pancreatic cancer [13]. In this cohort, only 19/35 (54%) patients with AIP had IgG4 levels greater than 135 mg/dl, which is slightly lower than previously published series. Both patients who were anti-PBP negative had detectable IgG4 levels, whereas all 16 IgG4-negative patients were anti-PBP positive. Thus, measuring serum IgG4, IgG anti-PBP and serum CA 19-9 may help distinguish AIP from pancreatic cancer. It is unclear whether these autoimmune antibodies represent epiphenomena or play a role in pathogenesis of disease.

A “sausage-like” enlargement of the pancreas is often seen in patients with AIP on ultrasonography (US), computed tomography (CT), or magnetic resonance imaging (MRI) [14]. Focal pancreatic enlargement is sometimes seen in AIP, and can be difficult to distinguish from pancreatic cancer. Ultrasound usually demonstrates a diffusely hypoechoic pancreas, but sometimes reveals scattered hyperechoic areas [14]. Dynamic CT may reveal delayed enhancement of the enlarged pancreatic parenchyma [15] or inflammation extending to adjacent adipose tissue with a low-density capsule-like peripancreatic rim [14]. Careful imaging of the pancreatic duct by ERCP or magnetic resonance cholangiopancreatography (MRCP) helps to distinguish AIP from pancreatic cancer. Segmental narrowing without proximal dilatation of the pancreatic duct is often seen in AIP, and is included in most diagnostic criteria [15].

Case reports have noted a number of potential extra-pancreatic manifestations in patients with AIP including: sclerosing cholangitis [16], sialadenitis [17], pulmonary hilar lymph node swelling [18], retroperitoneal fibrosis [19], tubulointerstitial nephritis [20], interstitial pneumonitis [21], thyroiditis [22], prostatitis [23], colitis [24], Schönlein-Henoch purpura and autoimmune

thrombocytopenia [25]. Biopsies from other affected organs can show histological abnormalities similar to those reported in AIP, including heavy lymphoplasmacytic infiltration, fibrosis, and the presence of prominent IgG4-positive plasma cells [26]. The presence of numerous IgG4-positive plasma cells in various organs, in addition to elevated serum IgG4 levels, led Kamisawa et al. to propose the concept of “IgG4-related sclerosing disease,” wherein pancreatitis is one manifestation of a systemic process [27, 28]. Subsequently, periarteritis and interstitial lung disease due to infiltrating IgG4-positive plasma cells in the absence of pancreatitis have been described [29, 30]. Thus IgG4-related sclerosing disease is a systemic disorder in which the pancreas may or may not be involved.

Histological analyses have revealed two subtypes of AIP. The first subtype is characterized by dense lymphocytic infiltration of the parenchyma by predominantly IgG4-positive plasma cells along with storiform fibrosis and obliterative phlebitis [6]. Between 28 and 63% of autoimmune pancreatitis cases have histology consistent with this prominently IgG4-positive plasma cell subtype [8, 31–33]. This variant has been described as “lymphoplasmacytic sclerosing pancreatitis” [34], or “lobulocentric AIP” [31]. The second subtype features destruction and infiltration of the ducts by neutrophilic granulocytes (referred to as granulocytic epithelial lesions), with diffuse lymphoplasmacytic infiltrate, but fibrosis, obliterative phlebitis and IgG4 immunopositivity are not prominent [6]. This subgroup has been referred to as “ductocentric AIP” [31] or “idiopathic duct-destructive pancreatitis” [8]. Histopathology suggestive of this subtype has been reported in 37–71% of cases [8, 31–33]. It is currently unclear whether one subtype can progress or change to the other. It is possible that the first subtype is the pancreatic manifestation of IgG4-related sclerosing disease. This histological subtype has also been demonstrated in concurrence with sclerosing cholangitis, retroperitoneal fibrosis and sialadenitis [27].

Comings et al. proposed the concept of multifocal fibrosclerosis, a rare fibroproliferative systemic disorder with a variety of manifestations including sclerosing cholangitis, retroperitoneal fibrosis, Riedel’s thyroiditis, fibrotic pseudotumour of the orbit, and mediastinal fibrosis [35]. The histopathological changes of this disorder are similar to those seen in IgG4-related sclerosing disease, including fibrotic changes with lymphoplasmacytic infiltration and occasional phlebitis. Further, several cases of chronic pancreatitis or pancreatic pseudotumour associated with multifocal fibrosclerosis have been reported in the literature [36–40]. It has been suggested that multifocal fibrosclerosis and IgG4-related sclerosing disease are likely different manifestations of a common disorder of fibroblastic proliferation [17].

Most patients with AIP respond well to treatment with corticosteroids, with improvement in pancreatic edema,

pancreatic duct patency, and extrapancreatic lesions [41–43]. Although an optimal steroid dosing schedule has not been established, the Mayo Clinic advocates a 4-week induction with prednisone 30–40 mg daily [44]. Response is assessed clinically, radiologically, and serologically before the dose is tapered by 5 mg per week. In patients with obstructive jaundice, a biliary stent is frequently placed and usually removed after 6–8 weeks of steroid therapy [44]. Between 30 and 40% of patients require re-induction with steroids for clinical or radiological relapse [44]. Relapse after a second prolonged course is uncommon, but patients with multiple relapses may require long-term immunosuppression with azathioprine. In Japan, patients are often continued indefinitely on low doses of prednisone [45].

The Japan Pancreas Society proposed three diagnostic criteria for AIP in 2002: (1) radiologic imaging showing diffuse enlargement of the pancreas and diffuse irregular narrowing of the main pancreatic duct (more than one-third the length of the entire pancreas); (2) laboratory data demonstrating abnormally elevated levels of serum gamma globulins or IgG or the presence of autoantibodies; and (3) histologic examination of the pancreas showing lymphoplasmacytic infiltration and fibrosis [46]. The diagnosis of AIP is made when criterion 1 and either criterion 2 or criterion 3 are fulfilled. The Mayo Clinic subsequently proposed the HISOR-t criteria, which recognize additional features of AIP. By these criteria, AIP is diagnosed by any of the following: (1) histological pattern of high IgG4 cell infiltration (≥ 10 IgG4-positive cells per high-power field) on immunostain of pancreatic lymphoplasmacytic infiltrate; (2) characteristic radiological findings on CT and pancreatography with elevated serum IgG4 level ≥ 140 mg/dl; or (3) unexplained pancreatic disease with negative workup for other pancreatic diseases including malignancy, elevated serum IgG4 level ≥ 140 mg/dl or other organs involved with IgG4-positive cells identified, and response of pancreatic and/or extrapancreatic lesions to steroid therapy [47].

Up to 70% of patients with AIP can be diagnosed by cross-sectional imaging, serology, and clinical presentation [48]. The remainder may require pancreatic core needle biopsy via computed tomography or endoscopic ultrasound guidance. For patients in whom the diagnosis remains unclear, assessing response to an empiric trial of steroids may avoid unnecessary pancreatic surgery but could delay diagnosis of resectable pancreatic carcinoma [48].

Pancreatitis in IBD

A relationship between pancreatitis and inflammatory bowel disease (IBD) was first proposed over five decades ago. In a postmortem study of patients with ulcerative

colitis (UC), Ball et al. found that 46/86 (53%) patients had chronic interstitial pancreatitis [49]. Another autopsy study in patients with Crohn's disease (CD) revealed evidence of pancreatic fibrosis in 15/39 (38%) patients. These studies predate use of immunosuppressive therapies that now are often implicated in episodes of IBD-associated acute pancreatitis. In CD patients with duodenal involvement, pancreatitis has been attributed to duodenal reflux or papillary obstruction [50, 51]. However, other mechanisms must be responsible for the high incidence of chronic pancreatitis reported in these autopsy studies.

Barthet et al. have proposed that pancreatitis is an extraintestinal manifestation of IBD [52]. Their case series found 11 of 427 IBD patients in southern France had been diagnosed clinically with pancreatitis. In three patients, medications were identified as the cause of acute pancreatitis. The remaining eight patients had unexplained chronic pancreatitis, based on pancreatic symptoms and a pancreatogram or biopsy consistent with chronic pancreatitis. From this cohort and a review of the published literature, the incidence of chronic pancreatitis in patients with IBD was estimated to be 1.2%, which was 250-fold higher than that in the general population [52]. Another case series reported the prevalence of "idiopathic" pancreatitis associated with IBD to be 1.5% [53].

Chronic pancreatitis in patients with IBD is often subclinical and causes symptoms that mimic the IBD itself. For instance, Barthet et al. found that only 16% of UC and 48% of CD patients with chronic pancreatitis experienced pain, versus over 80% of patients with chronic calcifying pancreatitis (mostly alcohol-induced) [52]. Weight loss is seen in 12% of CD patients and 41% of UC patients and hyperamylasemia was present in only 64 and 44% respectively [52]. Since IBD-associated chronic pancreatitis may not be recognized clinically, some investigators have estimated its incidence using pancreatic function tests. Hegnohj et al. found reduced activity of amylase ($p < 0.02$) and lipase ($p < 0.001$) in duodenal aspirates from 143 patients with CD compared to 115 controls and noted that exocrine pancreatic insufficiency correlated with the extent of ileal disease [54]. Heikius et al. found pancreatic insufficiency in 71/237 (30%) IBD patients, as defined by a two-fold increase in serum amylase or lipase levels or urinary para-aminobenzoic acid (PABA) excretion less than 40% [55]. Unequivocal pancreatic duct abnormalities were seen in 8.4% of these patients [55]. Katz et al. found that eight of 97 (8%) patients had hyperamylasemia, of which 50% was confirmed to be of pancreatic origin [56]. Thus, although clinical pancreatitis affects just over 1% of IBD patients, the prevalence of subclinical pancreatic disorders is much higher and could be of autoimmune origin.

A Novel Mimic of IBD

From case reports and case-control studies, it has been estimated that the incidence of IBD among patients with a prior diagnosis of AIP is approximately 7.6% [25]. However, the incidence of IgG4-positive plasma cell-mediated colitis in the absence of AIP is unclear. As noted above, IgG4-related sclerosing disease is a systemic disease that can occur without pancreatic involvement [29, 30]. Ravi et al. studied 71 patients with AIP and found that four had concurrent IBD (three UC and one CD) [24]. All UC patients had pancolitis and two required total colectomy for refractory disease [24]. Immunostaining of biopsies from one of the patients with refractory UC revealed more than ten IgG4-positive cells per HPF, which is considered consistent with IgG4-related sclerosing disease [27, 28]. This suggests that additional patients with a clinical diagnosis of IBD, with or without a history of pancreatic disease, may have an IgG4-related colitis. Enhanced vigilance for non-IBD colitis may improve clinical phenotyping, direct discovery of additional autoimmune antibodies, and lead to novel therapies.

Conclusions

IgG4-related sclerosing disease manifests most commonly as autoimmune pancreatitis, but can affect other organ systems in the absence of pancreatitis. Diagnosis can be confirmed by histology of affected organs, which reveals increased numbers of IgG4-positive plasma cells, but requires a high index of suspicion and specific IgG4 immunostaining. Treatment with steroids and immunosuppressive agents is effective in most cases, but further study of this under-recognized disorder is needed. IgG4-related sclerosing disease should be considered in the differential diagnosis of all immune-mediated presentations including colitis.

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