SHORT REPORT

IgG4-associated ampullitis and cholangiopathy in Crohn's disease

Udayakumar Navaneethan a, Xiuli Liu b, Ana E. Bennett b, R. Matthew Walsh c, Preethi G.K. Venkatesha a, Bo Shen a,*

a Department of Gastroenterology/Hepatology, Digestive Disease Institute, the Cleveland Clinic Foundation, Cleveland, OH 44195, United States
b Department of Anatomic Pathology, the Cleveland Clinic Foundation, Cleveland, OH 44195, United States
c Department of General Surgery, Digestive Disease Institute, the Cleveland Clinic Foundation, Cleveland, OH 44195, United States

Received 16 February 2011; received in revised form 12 March 2011; accepted 12 March 2011

KEYWORDS
Autoimmune; Ampullitis; IgG4; Cholangitis; Primary sclerosing cholangitis

Abstract

Inflammatory bowel disease (IBD) is reported to be associated with autoimmune pancreatitis and IgG4-related sclerosing disease. We report a case of a 28 year old African American male with a long history of upper gastrointestinal tract Crohn's disease (CD) with multiple surgeries who developed medically refractory disease with small bowel obstruction. He had abnormal liver function tests with imaging evidence of chronic pancreatitis and ampullary inflammatory process. He underwent Whipple's procedure. Histopathological evaluation of surgical specimens of the ampulla and distal common bile duct showed accumulation of IgG4-positive plasma cells in the lamina propria. Preoperative endoscopic biopsies also showed chronic active enteritis involving the duodenum and jejunum with increased IgG4-expressing plasma cell infiltration. His serum IgG4 was 164 mg/dL. The association of IgG4-expressing plasma cell accumulation in the gastrointestinal tract with IBD in patients with hepatobiliary manifestation may have pathogenetic, diagnostic and therapeutic implications.

© 2011 European Crohn's and Colitis Organisation. Published by Elsevier B.V. All rights reserved.

Abbreviations: AID, autoimmune disorders; AIP, autoimmune pancreatitis; CD, Crohn's disease; CBD, the common bile duct; CARP, chronic antibiotic refractory pouchitis; HPF, high-power field; IBD, inflammatory bowel disease; IAC, IgG4 associated cholangitis; IPAA, ileal pouch-anal anastomosis; MRCP, magnetic resonance cholangiopancreatography; PSC, primary sclerosing cholangitis; TNF, tumor-necrosis factor; UC, ulcerative colitis.

* Corresponding author at: Department of Gastroenterology/Hepatology-A31, The Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44195, United States. Tel.: +1 216 444 9252; fax: +1 216 444 6305.
E-mail address: shenb@ccf.org (B. Shen).

1873-9946/S - see front matter © 2011 European Crohn's and Colitis Organisation. Published by Elsevier B.V. All rights reserved.
doi:10.1016/j.crohns.2011.03.007
1. Introduction

Elevation of serum IgG4 is considered to be one of the hallmarks for autoimmune pancreatitis (AIP). At tissue level, pancreas along with other involved organs have characteristic infiltration with abundant IgG4-positive plasma cells.1–3 AIP may represent a spectrum of autoimmune disorders (AID), which may also involve extrapancreatic organs, including the bile duct, gallbladder, salivary glands, retroperitoneum, lymph node, pleura, lung, kidney, duodenum, and colon. The cluster of disease process has been termed as IgG4-related sclerosing disease.4–6 Periarteritis and interstitial lung disease due to infiltrating IgG4-positive plasma cells in the absence of AIP have been described recently.7,8 Gastrointestinal (GI) tract involvement in AIP may show IgG4-positive plasma cells in endoscopically normal-appearing mucosa.9

Association between IBD and AIP has been studied recently. In a study of 71 patients with AIP, of which 3 had concurrent ulcerative colitis (UC) and 1 had Crohn’s disease (CD), immunostaining of biopsy of colon specimen from one UC patient revealed greater than 10 IgG4-positive cells per high power field (hpf), consistent with the diagnostic criteria of IgG4-related sclerosing disease.1 IgG4 may play a role in the disease process of IB in patients with or without a history of pancreatic disease. Similarly, we had recently reported a case in which a young patient with chronic antibiotic refractory pouchitis (CARP) and multiple AID who had the histologic feature of IgG4-positive plasma cell infiltration of greater than 10 cells/hpf in pouch biopsy.10 His colectomy specimen before ileal pouch anal anastomosis (IPAA) surgery did not reveal infiltration of IgG4-expressing plasma cells. A study presented as an abstract form in which IgG4 was used as a marker to differentiate UC from CD, UC patients had more IgG4-positive plasma cell accumulation than that in CD or microscopic colitis.11 To our knowledge, the role of IgG4 in CD with hepatopancreatobiliary involvement has not been reported. We report here a case of a 28 year old male with history of upper gastrointestinal CD involving the stomach, duodenum and jejunum who had underwent gastrojejunalostomy for duodenal strictures. Following surgery, he developed recurrent anastomotic strictures at gastrojejunalostomy site requiring repeat endoscopic dilations and anti-tumor necrosis factor (TNF) therapy. Biopsy at the duodenum and gastrojejunalostomy site showed infiltration of IgG4-expressing plasma cells. He also developed abnormal liver function tests and imaging evidence of chronic pancreatitis because of involvement of the ampulla by CD. He underwent Whipple’s surgery and surgical specimen showed evidence of IgG4 accumulation at the ampulla and the common bile duct (CBD). The distal stomach and duodenum showed evidence of active CD with non-caseating granulomas.

2. Case report

A 28-year-old African American male who was initially diagnosed with CD at age 17 presented to our IBD center with worsening epigastric pain, nausea and vomiting. His initial presentation was abdominal pain, nausea and vomiting and investigations then confirmed the diagnosis of CD of upper GI (stomach, duodenum, and proximal jejunum) with granulomas on biopsy specimens. He failed to respond to corticosteroid and 6-mercaptopurine therapy and required a gastro-duodenostomy at Department of Colorectal Surgery (distal duodenum-posterior wall of the stomach) for fibrostenotic CD. Subsequently he was started on infliximab. However he lost response and required a second surgery with proximal jejunal resection (~30 cm) 45 cm from the duodenojunal flexure with an end–end anastomosis for recurrent stricture disease at age 20. Three years after, he developed a recurrent stricture at the gastrojejunalostomy site and required stricturoplasty at Department of Colorectal Surgery. At age 26, he again had a recurrent stricture at the gastro-jejunalostomy site. The anastomosis was resected and a new gastrojejunalostomy performed. Since the surgery, the patient had been on adalimumab subcutaneously once every 2 weeks and also had required multiple dilations of the anastomotic stricture and needle–knife therapy. In the interim, colonoscopies, CT enterography, and histologic evaluation showed no evidence of CD at the ileum and colon. Past surgical history also included a complicated cholecystectomy for ‘gallstone attacks’ with bile leaks and abscess.

The patient presented with worsening epigastric abdominal pain,nausea and vomiting. Physical examination demonstrated mild diffuse abdominal tenderness with involuntary guarding in the epigastric region. A complete blood count and basic metabolic panel showed mild anemia. His liver function tests showed a total bilirubin 0.3 mg/dl, alkaline phosphatase 470 U/L, aspartate aminotransferase (AST) of 193 IU/L and alanine aminotransferase (ALT) of 142 IU/L, total protein of 6.7 g/dl, and serum albumin 3.8 g/dl. His serum lipase was 152 mg/dl. His serum IgG4 was also elevated at 164 mg/dl (normal<112 mg/dl). Computed tomography (CT) enterography revealed mural thickening and wall enhancement of the proximal jejunum and post-surgical changes from previous gastrojejunalostomy and jejunojejunal anastomosis. There was also a 2.5-cm anastomotic stricture at the gastrojejunalostomy (Fig. 1). Both ultrasound and magnetic resonance cholangiopancreatography (MRCP) showed mild intrahepatic biliary dilation with segmental beading in the peripheral ducts, evidence of cholecystectomy, and a dilated CBD up to 1 cm, and distal biliary stricture. Multiple attempts were made and failed to get an access to the distal CBD with endoscopic retrograde cholangiopancreatography (ERCP) due to complex surgical anatomy. MRCP showed a normally enhanced pancreas with dilation of the main pancreatic duct up to 5 mm and dilation of multiple side branches. The comment was that there may be an ampullary stricture given the dilation of the CBD and pancreatic duct. Primary sclerosing cholangitis (PSC) was listed as a differential diagnosis (Fig. 2).

Percutaneous transhepatic cholangiogram and liver biopsy were performed for persistent abnormal LFTs and distal CBD stricture. Cholangiogram confirmed the smooth stricture of the distal CBD with proximal dilation. The liver biopsy revealed normal hepatic parenchyma with no histologic evidence of PSC and IgG4 immunostaining was negative. An upper endoscopy again showed strictured gastrojejunalostomy (Fig. 3). The biopsies from the duodenum and strictured gastrojejunalostomy site where there was a focal stricture showed focal active enteritis with ulceration and pyloric gland metaplasia (Fig. 4) and diffuse infiltration of IgG4-expressing plasma cells (Fig. 5). Given his presentation with complex CD, ampullary stricture and CBD dilation and stricturing gastrojejunalostomy, the case
was presented at a multi-disciplinary medical and surgical conference and a consensus was made to proceed with Whipple's surgery. Adalimumab was held for 4 weeks before the surgery. Whipple's procedure was successfully performed with resections of the distal stomach, duodenum, head of pancreas, and common bile duct. Histopathological evaluation showed chronic active duodenitis, patchy chronic gastritis with non-caseating granulomas (Fig. 6A and B), and mild chronic pancreatitis with periductal scarring and mild periductal inflammation and acinar atrophy. There was no histologic evidence of storiform fibrosis or obliteration phlebitis suggestive of AIP. The resected gastrojejunoscopy showed ulceration and scarring. Sections of the ampulla and CBD show marked chronic active inflammation and fibrosis (Fig. 7A and B). Immunostaining showed the presence of up to 80 IgG4-expressing plasma cells in the lamina propria in the ampullary and CBD specimens (Fig. 7C and D).

The patient recovered from the surgery and is being followed up. He has been doing well after a follow-up of 2 months and has been started on post-operative prophylactic treatment with adalimumab. Review of his prior surgical specimens and his ileal and colonic biopsy reports did not reveal any evidence of infiltration of IgG4-expressing plasma cells.

3. Discussion

This report describes a patient with upper GI CD with hepatopancreaticbiliary involvement which may attribute to IgG4-mediated process. The patient had elevated serum IgG4 and evidence of IgG4-expressing plasma cell infiltration at the gastrojejunal anastomosis as well as distal CBD and
ampulla with active inflammation. All of these were found in a patient on treatment with adalimumab and corticosteroids intermittently. The patient had no AIP. We postulated that IgG4 may provide a common link between his complicated disease processes of CD and hepatopancreatobiliary disorders. The other possibility is that the infiltration of IgG4-expressing cells in the CBD and ampulla may be secondary to IgG4-associated cholangitis co-existing with CD. Further studies are needed to illustrate the role of plasma cells and their IgG4 production in IBD patients, particularly in those with hepatopancreatobiliary complications.

IgG4-associated cholangitis (IAC) has been described in patients with AIP as a part of a systemic autoimmune process with an increased serum IgG4 (termed IgG4-related systemic disease) or as a separate disease entity. Although an increased serum IgG4 level was observed in 9% of patients with PSC, IAC appears to be a histologically and pathogenetically distinct entity with response to corticosteroid therapy in contrast to the progressive and refractory nature in PSC. Increased numbers of IgG4-expressing plasma cells were found in 23% of explanted liver specimens from 99 patients with orthotopic liver transplantation for PSC. IAC has also been described in two patients with concurrent IBD. The two patients were HLA-identical siblings and both had UC with co-existing IAC responsive to low-dose corticosteroid therapy. Although clinical presentation of IAC may be similar to that of autoimmune hepatitis (AIH) or AIH/PSC overlap, the involvement of large extra-hepatic bile duct is not seen with AIH. The favorable response to corticosteroids and the lesser-progressive nature of the disease also suggest that the disease process of IAC be distinct from that of PSC. Our patient had evidence of IgG4-positive plasma cell infiltration in the CBD, consistent with the diagnosis of IAC. In addition, our patient had concurrent IgG4-expressing plasma cell infiltration in the gastrojejunostomy site and duodenal/ampulla, suggesting that this patient's IAC may be a part of systemic disease process. However, the patient was on steroids for almost 3 months with no response to treatment, unlike those with IgG4-mediated AIP.

IgG4 is the rarest of the IgG subclasses and normally accounts for only 3% to 6% of total IgG in the serum. Though elevation of serum IgG4 is characteristic of AIP and several reports confirm increased numbers of IgG4-positive plasma cells in the pancreatic tissue of AIP, the role of IgG4 in AIP is unknown at present. A recent study suggested that IgG4 may contribute the disease process of IBD in patients with or without a history of pancreatic disease. IBD has been associated with both type 1 and 2 AIP, although it is more common with type 2 AIP. Similarly, we have observed a series of patients with IgG4 deposition in the pouch mucosa of patients with UC who had undergone IPAA with subsequent pouch dysfunction. The presence of PSC and/or autoimmune factors correlated with the presence of IgG4-associated pouchitis. (Authors unpublished data) Prior to this, we had reported a young patient with IgG4-associated pouchitis in a patient with CARP. Immunostaining of the mucosa of the pouch body and the afferent limb revealed greater than 10 cells/hpf consistent with a diagnosis of IgG4-associated disease.

The pathogenesis of IBD is traditionally thought to be T cell mediated process. The expression of Th2 (IL-4, IL-5, and IL-13) and regulatory cytokines (IL-10) have been shown to be up-regulated in the affected tissues of patients with IgG4 associated disease. IL-10 has been shown to direct B cells to switch from IgE to IgG4 antibody production at the tissue. Thus infiltration of IgG4-expressing plasma cells in the tissue may be indicative of a Th2-mediated process. However CD is mediated predominantly by Th1 and Th 17 response. However infiltration of IgG4-expressing plasma cells is indicative of Th 2 cell activity. Thus the deposition of infiltration of IgG4-expressing plasma cells in the gastrointestinal tract in CD is interesting. In fact in a recent study, IgG4 was suggested as a marker to differentiate UC and CD based on predominant Th 2 expression and IgG4 positive plasma cell accumulation in UC.
CD patients had a mean of 2.1 IgG4 positive cells/hpf similar to patients with microscopic colitis, while UC patients had a mean of 10.6 IgG4-positive plasma cell infiltration. The authors suggested that patients with UC are more likely to have more IgG4-positive plasma cells. Given all these data, it was very surprising to see IgG4-positive plasma cell infiltration in CD. Whether the use of biological agents in our patient altered the immune response resulting in predominant Th 2 mediated response needs to be explored. The other possibility is that the consistently high number of IgG4-positive plasma cells may merely represent a secondary response to an as yet unidentified primary trigger of the inflammatory process. Rituximab, a monoclonal antibody against CD20 has been used in the management of IgG4-related sclerosing disease. Similarly in patients with IgG4-mediated disease process, treatment with other options including anti-B cell therapies can be explored.

There are unexplored questions. We do not know whether infiltration of IgG4-expressing plasma cells is a result or cause of inflammation and disease process. We know that in patients with IgG4-associated sclerosing disease, a high level of serum IgG4 is not directly pathogenic as patients may have increase in IgG4 on treatment with clinical improvement. Also the natural course of IBD patients with infiltration of IgG4-plasma cells.

4. Conclusion

Our current case of CD clearly has an IgG4-associated process involving the proximal small bowel and ampullary region. IgG4 may provide a common like between upper GI CD and concurrent hepatopancreatobiliary disorders.

Conflict of interest

The authors declared no conflict of interest.

References