

CASE REPORT

IgG4-related systemic sclerosing disease: a diagnosis to be considered

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SUMMARY

IgG4-related systemic sclerosing disease is a chronic autoimmune disorder with diverse clinical presentation. We report a 56-year-old patient who has presented with obstructive jaundice, bulky pancreas and mesenteric lymph node mass. He was later diagnosed to have IgG4-sclerosing disease involving pancreas, small bowel mesentery, common bile duct, liver, gallbladder and submandibular salivary glands and has required multiple surgical interventions. IgG4-related systemic sclerosing disease appears to be more commonly encountered than it was once thought and needs considered in patients presenting with pancreatitis of no obvious underlying cause. Although the disease is primarily managed by medical therapy, there is a role for surgical intervention in order to obtain tissue for diagnosis, exclude other possible neoplastic aetiology and to manage disease-related complications.

BACKGROUND

IgG4-related sclerosing disease is an autoimmune clinical syndrome characterised by extensive IgG4-positive plasma cells and T-cell lymphocyte infiltration resulting in inflammation and fibrosis of the affected organs.¹ The pancreas is the most commonly affected organ. The biliary tract, liver and renal tracts are the other frequently involved organ systems but it can also involve salivary glands, lungs, thyroid and retroperitoneal tissue. Possession of the HLA DRB1* 0405-DQB1*0401 genotype confers an increased risk of disease development.²

Diagnosis and treatment of the condition are often delayed due to the non-specific nature of the disease. It is important to consider this uncommon condition in patients presenting with common conditions such as pancreatitis.

CASE PRESENTATION

A 56-year-old man presented with a 3-week history of painless jaundice. His medical history included hypercholesterolaemia, hypertension and ischaemic heart disease. Physical examination revealed jaundice but there was no palpable abdominal mass.

INVESTIGATIONS

His liver function tests were deranged: total bilirubin 111 µmol/l (normal range 3–18 µmol/l), alkaline phosphatase 421 U/l (normal range 35–120 U/l), aspartate aminotransferase 256 U/l (normal range 10–40 U/l), alanine aminotransferase 378 U/l (normal range: 10–56 U/l) and γ glutamyl transferase 610 U/l (normal range 12–58 U/l). Carbohydrate

antigen 19–9 was mildly elevated at 80 U/ml (normal range 0–37 U/ml).

Ultrasound scan of the abdomen revealed a dilated common bile duct (CBD) measuring 15 mm in diameter with intrahepatic duct dilation and a bulky pancreas. CT scan of the chest, abdomen and pelvis demonstrated biliary dilation with a diffusely swollen pancreas (figure 1). There was no focal mass lesion or calcification of the pancreas. A 6.4×3.5 cm hypervascular nodal mass was identified adjacent to the superior mesenteric vessels (figure 2). There was no evidence of metastatic disease or mediastinal lymphadenopathy.

MR cholangiopancreatography (MRCP) revealed the pancreas to be diffusely swollen with evidence of peripancreatic inflammation. A short stricture of the distal third of the CBD was demonstrated. This was stented via endoscopic retrograde cholangiopancreatography (ERCP). Biliary brushings were negative for atypia and malignancy. Autoimmune profiling showed mild elevation of IgG: 18 g/l (normal range 6–14 g/l). An autoimmune aetiology was thus considered and oral corticosteroid therapy started (oral prednisolone 40 mg daily).

DIFFERENTIAL DIAGNOSIS

Chronic pancreatitis

- ▶ Radiological features of chronic pancreatitis such as calcification, pseudocyst formation, fat necrosis are usually absent in autoimmune pancreatitis (AIP).
- ▶ On histological examination, inflammatory changes are usually mild and plasma cells are typically absent in chronic pancreatitis.

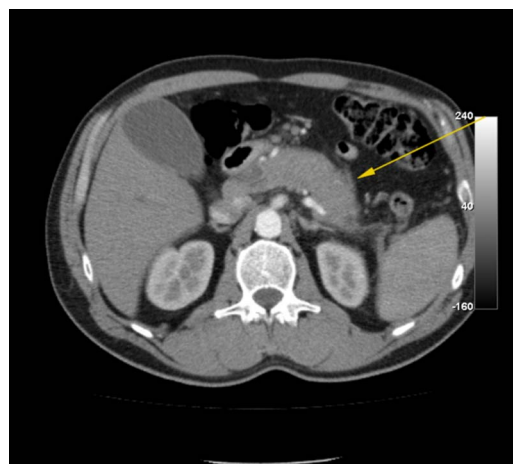


Figure 1 CT scan of the chest, abdomen and pelvis demonstrating the diffusely enlarged pancreas (arrow).

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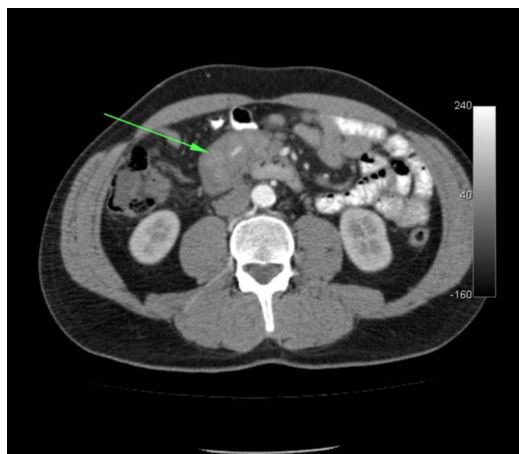


Figure 2 CT scan of the chest, abdomen and pelvis demonstrating the hyper vascular nodal mass (arrow) in the mesentery along the superior mesenteric vessels.

Pancreatic adenocarcinoma

- ▶ Adenocarcinoma of the pancreas is the most common condition that should be differentiated from AIP.
- ▶ CT findings of diffuse swollen pancreas with no focal mass lesion are suggestive of AIP. Distinguishing a localised AIP from adenocarcinoma is more challenging.
- ▶ Endoscopic ultrasound and needle aspiration cytology is most useful when histological findings confirm adenocarcinoma. Resolution of a mass lesion with steroid therapy would corroborate the diagnosis of AIP.

Primary sclerosing cholangitis (PSC)

- ▶ PSC is a chronic cholestatic liver disease characterised by diffuse inflammation and fibrosis of the biliary tree.
- ▶ It primarily affects men in their 30s and is strongly associated with ulcerative colitis.
- ▶ Cholangiographic evidence of PSC includes multifocal stricturing throughout the biliary tree, which is characteristic of alternating fibrosis and ectasia of the bile ducts.
- ▶ Most patients with autoimmune sclerosing cholangitis respond well to steroids unlike PSC.³
- ▶ Segmental strictures, dilation after confluent stricture and strictures of the lower CBD are significantly more common in sclerosing cholangitis associated with AIP than PSC. In contrast, band-like strictures, a beaded or pruned-tree appearance, and diverticulum-like out-pouching are indicative of PSC rather than sclerosing cholangitis associated with AIP.³
- ▶ Histologically, there are mucosal erosions of biliary epithelium in PSC whereas the epithelium is preserved in autoimmune sclerosing cholangitis.

Cholangiocarcinoma

- ▶ Patients with extrahepatic or hilar cholangiocarcinoma present with jaundice, pruritus, malaise and weight loss.
- ▶ A long-segmental narrowing of bile duct in sclerosing cholangitis with AIP is difficult to distinguish from that of cholangiocarcinoma.³
- ▶ ERCP and histological analysis of brush cytology and biopsy may help in the diagnosis.

TREATMENT

Exploratory laparotomy was undertaken to obtain tissue for definitive histological diagnosis. Laparoscopic biopsy was not considered due to the hypervascular nature of the nodal mass

and its proximity to the superior mesenteric vessels on pre-operative imaging. Intraoperative findings included a diffusely swollen pancreas with a nodal mass in the small bowel mesentery involving the ileocolic and right colic vessels. The ill-defined mesenteric nodal mass was resected and right hemicolectomy was performed. Histological examination of the mesenteric mass showed it to be composed of sclerosing fibrous tissue with a patchy inflammatory cell infiltrate rich in plasma cells and focal areas of fat necrosis. The lesion entrapped reactive lymph nodes (figure 3). There was no evidence of lymphoma or carcinoma. The appearances were interpreted as those of sclerosing mesenteritis.

Two months after discharge, he developed recurrent jaundice requiring biliary stent replacement. Further episodes of jaundice and cholangitis necessitated Roux-en-Y choledochojejunostomy and cholecystectomy. Histological examination of the gallbladder wall showed an inflammatory infiltrate consisting predominantly of plasma cells and marked sclerosis, similar to the features within the previous mesenteric resection, consistent with IgG4-related sclerosing disease involving the gall bladder. Oral steroid therapy was gradually stopped because of wound infection and superficial wound dehiscence. Nine months later he developed bilateral swollen submandibular glands—sclerosing sialadenitis—that again responded to oral steroid therapy.

One year after the initial presentation, he developed recurrent upper abdominal pain, anaemia and insulin-dependent diabetes. CTAP revealed a shrunken, fibrotic pancreas, a large splenic infarct and splenic vein thrombosis with perigastric varices consistent with left-sided (sinistral) portal hypertension. Gastroscopy did not reveal any varices. He then developed a large central splenic abscess and adhesive small bowel obstruction requiring laparotomy, splenectomy and adhesiolysis.

He again developed jaundice 5 months later and IgG4 was elevated at 32 g/l. MRCP showed stenoses of the right and left hepatic ducts at the hilum with mild intrahepatic duct dilation. Similar findings at ERCP performed through the duodenum suggested sclerosing cholangitis and a liver biopsy was performed. This demonstrated bridging fibrosis with features of chronic cholangiopathy and infiltration of IgG4-positive plasma cells consistent with IgG4-related sclerosing cholangitis.

OUTCOME AND FOLLOW-UP

The patient is asymptomatic at 2 years follow-up and remains on maintenance dose of oral steroids.

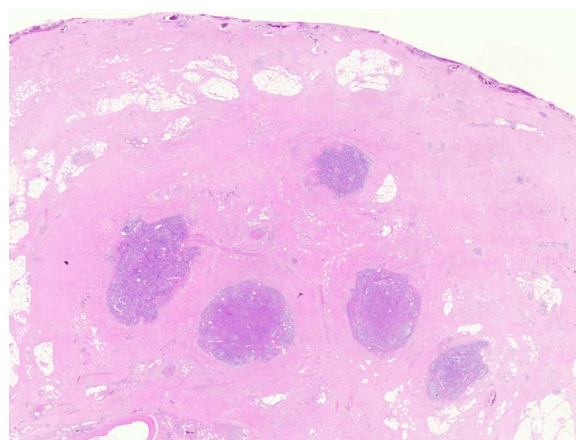


Figure 3 Histological section from the ill-defined mesenteric mass demonstrating dense fibrous tissue entrapping lymph nodes (H&E, ×40 magnification).

DISCUSSION

Discussion

Kamisawa and Okamoto proposed the concept of IgG4-related sclerosing disease as a separate clinicopathological entity⁴ to include the various IgG4-related autoimmune disorders of pancreas, biliary tract, liver, renal tracts, salivary glands, lungs, lymph nodes, thyroid and retroperitoneal tissue. It is characterised by the presence of elevated serum IgG4 levels, prominent lymphoplasmacytic infiltrates with increased IgG4-positive plasma cells and dense sclerosis of the affected organs.⁵ However, serum IgG4 levels are elevated in only 75% of the patients.⁶ In the absence of immunological evidence, clinical, histological and imaging features should help in the diagnosis. The reported patient had extensive progressive systemic IgG4-related sclerosing disease requiring surgical intervention for the management of disease-related complications.

Autoimmune pancreatitis

Idiopathic chronic pancreatitis, described by Sarles *et al*⁷ in 1960, was later recognised as AIP in the 1990s. AIP is currently considered as the pancreatic manifestation of IgG4-related sclerosing disease. The pancreas is the most commonly involved organ of this syndrome complex but AIP accounts for only 2–6% of all cases of chronic pancreatitis. One-third of patients with pancreatic disease have extrapancreatic manifestations, the most common of which are sclerosing cholangitis and hepatic inflammatory pseudotumour.

AIP commonly presents in elderly male patients as painless obstructive jaundice due to a distal CBD stricture. Exocrine and endocrine functions of the pancreas are usually preserved in patients with AIP. It is important to differentiate AIP from pancreatic cancer. In a retrospective study from the Johns Hopkins Institute, it was noted that 2.5% of patients who underwent pancreatoduodenectomy for possible pancreatic cancer were histologically diagnosed to have AIP.⁸

The diagnosis of AIP is based on five cardinal features: histology, radiological imaging, serology, other organ involvement and response to steroids. Histological findings include dense lymphoplasmacytic infiltration and dense fibrosis in a periductal and interlobular distribution. The acinar cells are replaced by inflammatory cells and fibrosis, with loss of lobular architecture of the pancreas. Periductal fibrosis often results in a narrowed pancreatic duct. Immunohistochemistry shows infiltration of the pancreas by CD4 or CD8 T-lymphocytes and IgG4-positive plasma cells.

CT scan usually shows diffuse sausage-shaped enlargement of the pancreas with no focal abnormality. Inflammatory and fibrous changes in the peripancreatic adipose tissue result in a low-density capsule-like rim around the pancreas. Pancreatic calcification or pseudocyst is uncommon. ERCP can show an irregular, narrow main pancreatic duct without upstream dilation at the narrowed ductal segments. Stenosis of the extrahepatic or intrahepatic bile duct is frequently observed.⁹

Hamano *et al*¹⁰ reported a high sensitivity (95%), and specificity (97%), when a cut-off value of 135 mg/dl for the serum IgG4 level was used in AIP patients. Tissue immunoreactivity for IgG4 plasma cells has been reported to be a reliable marker of AIP.

Sclerosing mesenteritis

A small subset of sclerosing mesenteritis cases are most likely related to IgG4-related systemic sclerosing disease^{11 12} and show

significant infiltration by IgG4-positive plasma cells, or increased IgG4: total IgG immunostaining ratio.

Sclerosing mesenteritis most commonly involves the small bowel mesentery, with involvement of the mesocolon in 20% of cases. Affected individuals are typically in the fifth and sixth decades, and the condition is encountered twice as frequently in males. The disease can present clinically as single mass or multiple masses, or as a diffuse thickening of the mesentery. Patients with sclerosing mesenteritis present with symptoms of abdominal pain (70% of patients), bloating, distension, diarrhoea and weight loss. Approximately 50% of patients present with an abdominal mass, tenderness and chylous ascites. Sclerosing mesenteritis was previously categorised based on its pathological characteristics: if fat necrosis and inflammation dominated, the term mesenteric panniculitis was used; if fibrosis and retraction were predominant, the term retractile mesenteritis was applied. Sclerosing mesenteritis encompasses both of these conditions and is the current preferred diagnostic term.

The CT appearances of sclerosing mesenteritis need distinguished from those of lymphoma, carcinoid tumour or carcinomatosis. Sclerosing mesenteritis appears as a soft-tissue mass in the small bowel mesentery. Mesenteric vessels and lymph nodes are often enveloped by the mass with preservation of the fat plane around the vessels (fat ring sign). A pseudocapsule and/or calcification may be present in the mass with or without mesenteric or retroperitoneal lymphadenopathy.¹³

Sclerosing cholangitis

IgG4-related sclerosing cholangitis is frequently associated with AIP. Stenosis is most often in the distal CBD (70%).³ Intrahepatic (5%) and hilar ductal (8%) involvement can be radiologically indistinguishable from PSC. Most patients present with obstructive jaundice and respond well to steroids (unlike PSC). Histologically, there is dense lymphoplasmacytic infiltration of the bile duct wall with preservation of biliary epithelium, in contrast to PSC where mucosal erosions are often present.¹

Hepatitis

Liver dysfunction is frequently observed in patients with autoimmune pancreatitis—either due to obstruction of the biliary tract or inflammatory hepatitis. IgG4-hepatopathy includes portal inflammation and sclerosis, lobular hepatitis and canalicular cholestasis. IgG4-positive plasma cells are more numerous and serum IgG4 levels are higher than in other autoimmune liver conditions.¹⁴ Hepatic inflammatory pseudotumour is another manifestation of IgG4-related sclerosis. These mass lesions can be either fibrohistiocytic or lymphoplasmacytic type.¹⁴

Sclerosing cholecystitis

Twenty-five per cent of the patients with AIP have associated lymphoplasmacytic cholecystitis. This is characterised by marked mural and extramural lymphoplasmacytic inflammation, rich in IgG4-positive plasma cells and elevated serum levels of IgG4.^{4 15}

Sclerosing sialadenitis

The salivary glands are frequently involved in IgG4-related sclerosing disease. Mikulicz's disease—bilateral, painless, symmetrical swelling of the lacrimal, parotid and submandibular glands—is also considered as a part of IgG4-related syndrome complex. When the salivary glands are involved, infiltration of IgG4-positive cells and fibrosis¹ are common. Serum IgG4 and IgG4-positive plasma cell levels are elevated in these patients and are useful in distinguishing from other causes of sialadenitis.¹⁴

Other organ involvement

Less commonly, IgG4-related sclerosis can also involve other organs including the retroperitoneum, mediastinum, gastrointestinal tract, kidney, lung, prostate, thyroid gland and lymph nodes.⁹

Management

Diagnosis of IgG4-related sclerosing disease is difficult unless the disease is suspected and serum IgG4 levels are elevated. Tissue biopsy is not required in cases such as AIP when the diagnosis is supported by immunological and radiological findings. However, in patients with focal mass lesions (such as the reported case), histological evidence is sought to confirm the diagnosis and exclude neoplasia.

Treatment should be tailored on an individual basis and primarily involves medical therapy. Steroids have proven to be effective clinically and morphologically in these patients. The preferred initial dose of prednisolone is 40 mg/day and it is then reduced by 5 mg every 1–2 weeks. The role of continuous maintenance therapy is not yet clearly defined but low-dose steroids have been used in patients with AIP for up to 3 years.¹⁶ Use of azathioprine (1.5–2 mg/kg/day) has been reported for maintenance of remission.⁶ Mycophenolate mofetil,¹⁷ cyclophosphamide and colchicines are the other drugs reported in the management of the disease. High remission rates (up to 30%) have been reported in cases with autoimmune pancreatitis.⁶

The role of surgery is limited to excisional biopsy for tissue diagnosis and the management of disease-related complications. However, surgery for excision biopsy could involve a major resection, such as hemicolectomy or pancreatectomy, depending on the site of lesion. Biliary strictures are usually managed by ERCP but the reported patient required biliary bypass surgery due to recurrent blockage of the stent and cholangitis while awaiting a response to steroids. In addition, splenectomy was required for a large splenic abscess. Small bowel resection and anastomosis have been reported for bowel obstruction and bowel perforation in similar cases.¹⁸

Tabata and colleagues examined the serial changes of IgG4 levels in response to steroid therapy and concluded that serial measurements of serum IgG4 levels are useful to determine disease activity and monitor immunosuppression therapy. IgG4 levels decreased with steroid therapy but not necessarily to normal level. Persistent elevation of IgG4 levels might be a predictor for lack of response and re-elevation suggests relapse of the disease.¹⁶

Diagnosis of IgG4-related sclerosing disease is often delayed unless there is a high index of suspicion and serum IgG4 levels are found to be elevated. Not uncommonly, the condition is misdiagnosed as malignancy, especially when presenting in the pancreas. Although the disease is primarily managed by medical therapy, there is a role for surgical intervention in order to obtain tissue for confirmation of diagnosis, exclude neoplasia and to manage disease-related complications.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Learning points

- ▶ IgG4-related systemic sclerosing disease is now considered to be more common than it was once thought and should be considered as a differential diagnosis in patients with common clinical presentations such as pancreatitis, obstructive jaundice.
- ▶ Diagnosis of IgG4-related sclerosing disease is difficult unless the disease is suspected and serum IgG4 levels are elevated.
- ▶ Tissue biopsy is not required in cases such as autoimmune pancreatitis when the diagnosis is supported by immunological and radiological findings.
- ▶ Medical management includes oral corticosteroids and immunomodulators such as azathioprine.
- ▶ The role of surgery is limited to tissue biopsy for diagnosis and the management of disease-related complications.

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