

The Great Pretender: Autoimmune Pancreatitis

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Abstract

Autoimmune pancreatitis is a benign disorder which frequently presents with symptoms and imaging suggestive of pancreatic malignancy. Up to 21% of pancreatoduodenectomies performed for suspected pancreatic cancer are found to have benign disease. Autoimmune pancreatitis responds rapidly to corticosteroids and may be associated with extra-pancreatic manifestations. Type 1 forms part of the IgG4-related disease while type 2 autoimmune pancreatitis is less likely to have elevated levels of IgG4. This review discusses the characteristics of the two types of autoimmune pancreatitis and highlights the management and prognosis of this condition.

Keywords

Autoimmune pancreatitis; IgG4-related disease; pancreatoduodenectomy; lymphoplasmacytic sclerosing pancreatitis, idiopathic duct centric pancreatitis.

Autoimmune pancreatitis (AIP) is a benign, infrequently recognised disorder which typically presents with symptoms and imaging suggestive of pancreatic cancer. It was first classified as a disease entity in 1995 and accounts for approximately 2% of cases of chronic pancreatitis. AIP is a great “pretender” of pancreatic carcinoma, being found in 2.4% of pancreas resection specimens.¹ Peak age of onset is in the seventh decade with the vast majority of patients being older than 45 years.²

AIP is divided into two types: type 1 or lymphoplasmacytic sclerosing pancreatitis and type 2 or idiopathic duct centric pancreatitis. AIP type 1 typically affects older patients, is characterised by positivity to IgG4 and forms part of the IgG4-related diseases.¹ IgG4-related disease is a rare systemic fibro-inflammatory disorder which may involve various abdominal organs and can lead to autoimmune pancreatitis, retroperitoneal fibrosis, sclerosing cholangitis, gallbladder pseudotumors, multifocal renal abnormalities and sclerosing mesenteritis. It is characterised by abundant infiltration of IgG4+ plasmacytes and lymphocytes.³ Extra-pancreatic manifestations of IgG4-related disease are common in AIP type 1, with 68% of patients having extra-pancreatic (usually biliary) involvement.⁴

An IgG4 level >210 mg/dl has been shown to have the greatest sensitivity (83.8%) and specificity (89.5%) for AIP though up to 35.5% of patients with pancreatic adenocarcinoma and 25.4% of patients with chronic pancreatitis have values >140 mg/dl. Therefore, elevated IgG4 levels alone are not enough to differentiate between pancreatic cancer and AIP.⁵ Serum IgG4 levels also have a poor positive predictive value in the diagnosis of IgG4-related disease with only 15% of patients with IgG4 levels >130 mg/dl having IgG4-related disease.⁶ A number of cases of type 1 AIP without IgG4 tissue infiltration or serum IgG4 elevation have also been described, suggesting that AIP should also be suspected in patients with normal IgG4 levels.⁷

Type 2 AIP typically affects younger patients, is confined only to the pancreas and is not associated with elevated levels of IgG4.⁸ Pancreatic histology is characterised by granulocytic epithelial infiltration.³ Patients with type 2 AIP typically present with abdominal pain and a tumor-like mass in the pancreas. Serum levels of IgG4 are less frequently elevated than in type 1 AIP (12% in type 2 versus 55% in type 1), so distinguishing from pancreatic cancer is even more difficult.⁹

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AIP typically presents with clinical features which are very suspicious for pancreatic malignancy, including obstructive jaundice (50%), abdominal pain (44%), fatigue and weight loss (13%). These symptoms frequently prompt surgical intervention.¹⁰ Benign lesions are found in 5-21% of pancreatoduodenectomies performed for suspected neoplasms.¹¹ A study on pathological samples in Mainz, Germany showed that 8.8% of patients (33 patients from a total of 373 patients) undergoing pancreatoduodenectomy had benign disease and 11 patients (33%) with benign disease were found to have AIP.¹¹

Work-up for patients with suspected AIP

Laboratory investigations frequently show deranged liver function tests (with a typical obstructive picture). Serum immunoglobulin and IgG4 levels are typically increased. Initial imaging (CT scan) and ultrasound abdomen will reveal a focally enlarged pancreas (in 38% - this increases the suspicion of pancreatic adenocarcinoma) or a diffusely enlarged pancreas (in 62%). Unfortunately, a good number of these patients undergo surgical resection for a condition which can be managed medically. Histological analysis typically reveals pancreatic interstitial fibrosis with infiltration of lymphocytes and plasma cells.¹⁰ Pancreatic parenchyma is usually infiltrated by immune cells, particularly CD4 or CD8 T lymphocytes and IgG4-bearing plasma cells.¹² While radiological and clinical findings frequently raise the suspicion of pancreatic cancer in patients with AIP, specific findings on CT and MRI may help distinguish between the two. Diffuse pancreatic enlargement, capsule-like rim and delayed homogenous enhancement are more suggestive of AIP. Main pancreatic duct narrowing by >1/3 of the pancreatic length, skipped narrowing in the main pancreatic duct and smooth and straight intra-pancreatic common bile duct stenosis on MRCP are more in keeping with AIP.¹³ Another common finding at MRCP is the presence of multiple, long stenoses of the main pancreatic duct without dilatation in the remaining portions of the pancreatic duct.¹⁴

There is typically a rapid clinical and radiological response to treatment with corticosteroids in patients with AIP. Pancreatic swelling improves in 83% while pancreatic duct irregularities improve in 75% within 2 weeks of starting corticosteroid therapy.¹⁵

Endoscopic tools in the diagnosis of AIP include endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS). Endoscopic ultrasound images the main pancreatic and common bile ducts and also allows sampling of pancreatic tissue for histological analysis. Diffuse, irregular narrowing of the main pancreatic duct in the absence of upstream dilatation from the stricture (<5mm) is a typical finding at ERCP, though localized narrowing may be difficult to

differentiate from stenosis secondary to pancreatic cancer. The main pancreatic duct and common bile duct immediately adjacent to the papilla (up to 1.5cms from the ampullary orifice) are frequently maintained with no narrowing seen in the initial portion of these two ducts.¹⁶ Transpapillary biopsy with IgG4 immunostaining of biliary strictures may be necessary to rule out cholangiocarcinoma and to reach a diagnosis of IgG4-sclerosing cholangitis. IgG4 immunostaining of histological specimens from the major papilla may also be helpful in diagnosing AIP.¹⁷ Biliary stent placement during ERCP is important in the initial management of AIP with biliary stenting being useful in relieving jaundice in 71% of type 1 and 77% of type 2 AIP.¹⁸

EUS allows operators to obtain cytological and histological samples by fine needle aspiration. EUS typically shows diffuse hypoechoic pancreatic enlargement. Novel EUS techniques including EUS-elastography and contrast-enhanced harmonic EUS are also able to differentiate between AIP and pancreatic cancer, though histological sampling of the pancreas is by far considered the gold standard diagnostic technique.¹⁹

Classification

Several different classification criteria have been devised to diagnose AIP. The most recent classification system (the International Consensus Diagnostic Criteria - ICDC) has been shown to have higher sensitivity, specificity and accuracy than the older HISORt and Asian criteria.²⁰ The ICDC criteria include:

1. imaging of the pancreatic duct and parenchyma
2. serology
3. other organ involvement
4. pancreatic histology
5. the optional criterion of response to steroid therapy

Diagnosis of type 1 or type 2 AIP may be definitive or probable depending on the strength of the findings and in some cases, one may not be able to distinguish between the subtypes (AIP *not otherwise specified*). Imaging and response to steroids is not able to distinguish between type 1 and type 2 AIP. Typical serological abnormalities as well as other organ involvement are seen only in type 1; however inflammatory bowel disease seems to be associated with both types. Absence of serological abnormalities and other organ involvement does not necessarily imply a diagnosis of type 2 AIP since type 1 may also be seronegative and without other organ involvement.²¹ Therefore, even with the use of the ICDC criteria, it is not always possible to confirm AIP subtype without histological analysis of pancreatic tissue.²²

These diagnostic criteria are bound to change further. A recent international symposium on the diagnosis of AIP held in Seoul has concluded that there is room for improvement in the ICDC and that further

modifications might be required in the future.²³

Management and Prognosis

Treatment for AIP should be considered if patients develop jaundice, systemic manifestations or persistent pain. Initial treatment is with corticosteroids though azathioprine may be necessary if patients relapse on tailing down steroids.¹ Clinical remission is achieved in 99% of type 1 and 92% of type 2 AIP with corticosteroid therapy.¹⁸ The recommended dose of prednisolone for induction of remission is 30-40 mg/day tailing down over 2-3 months to a maintenance dose of 5-7.5 mg/day for a period of 3 years.²⁴

However, different countries use different tailing down regimes of steroids. In the United States, the initial induction dose is of 40 mg prednisolone for 4 weeks with the steroids being tailed down by 5 mg per week until the steroids are stopped completely.²⁵ In Japan, the initial induction dose is given for 2-4 weeks, after which steroids are tailed down by 5 mg every 1-2 weeks until a prednisolone dose of 15 mg is reached. At this point, the steroid dose is reduced more slowly (by 2.5 – 5 mg every 2-8 weeks) until a maintenance dose of 2.5-5 mg per day is reached. Researchers from Holland have shown that response to low-dose (10-20mg/day), medium-dose (30 mg/day) and high-dose (40-60 mg/day) prednisolone as induction therapy for AIP was comparable.²⁶ However, while resolution of pancreatic abnormalities is relatively quick, extra-pancreatic lesions (retroperitoneal fibrosis, bile duct strictures and ductal wall thickening) take more time to resolve and tailing down of steroids should therefore be tailored to each patient according to the disease activity of all organs involved.

Risk of relapse is high in type 1 (up to 30-50% relapse within 6-12 months) while risk of relapse in type 2 AIP is much less frequent.²⁷ The largest study on AIP carried out so far (1064 patients from 23 institutions in 10 different countries) showed that relapse occurs in 31% of type 1 and 9% of type 2 AIP. Remission is rapidly achieved on re-introducing corticosteroid therapy.¹⁸

Since the sensitivity and specificity of serological tests (IgG4 and Ca19.9) and imaging (CT and MRI) in distinguishing between AIP and pancreatic cancer is low, an important tool in differentiating between the two conditions involves the empirical treatment with corticosteroids. AIP exhibits a quick and dramatic response to corticosteroids while pancreatic cancer does not exhibit such a response.²⁸

Management of AIP is important not only to manage the symptoms associated with this condition but also to avoid the development of chronic pancreatitis. While acute phase AIP responds immediately to corticosteroids, the long-term prognosis and outcome of AIP are still unknown. Up to 20% of patients progress

to chronic pancreatitis and AIP is suspected to lead to the development of pancreatic duct stones, probably secondary to narrowing of the pancreatic ducts.²⁹

Smoking appears to increase the risk of pancreatic damage and increase the risk of diabetes in AIP. Smoking cessation should be encouraged in all patients.³⁰

Initial analysis on cancer risk in patients with AIP and IgG4 related disorders has revealed no increased risk of malignancy in these patients with the cancer risk being similar to that of age-and gender-matched controls.³¹⁻³² However, prospective follow-up of 115 patients from two large tertiary referral centres in the UK showed that both type 1 AIP and IgG4-related sclerosing cholangitis are associated with significant morbidity and mortality owing to extra-pancreatic organ failure and malignancy.³³ The largest study on AIP carried out to date has shown that pancreatic calculi and cancer are rare in type 1 and absent in type 2 AIP.¹⁸

Since AIP is frequently mistaken for pancreatic malignancy, it is important to consider whether a biopsy of a pancreatic mass lesion should be carried out before undertaking major surgery. With 5-21% of resected pancreatic specimens being benign, an international panel of pancreatic surgeons working in well-known, high-volume centres reviewed the literature and worked together to establish a consensus on when to perform a pancreatoduodenectomy in the absence of positive histology. Consensus was reached that histological proof is not required before surgical resection in the presence of a solid mass suspicious for malignancy. However, malignancy should always be confirmed histologically (preferably by EUS-guided FNA or biopsy) for patients with borderline resectable disease who need treatment with neoadjuvant therapy before exploration for resection. A biopsy is also recommended when a diagnosis of AIP is highly suspected and a short course of steroids considered if the biopsy does not suggest malignancy.³⁴

Conclusion

AIP is the great “pretender” of pancreatic malignancy. Increasing awareness of the clinical, radiological, serological and extra-pancreatic involvement associated with this disorder may allow early recognition and avoid unnecessary surgery for this benign condition. Better classification criteria and a standardised therapeutic plan with corticosteroids and other immune-suppressants are needed in AIP.

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