Curr Gastroenterol Rep (2012) 14:95–105
DOI 10.1007/s11894-012-0246-8

PANCREAS (CE FORSMARK, SECTION EDITOR)

# Autoimmune Pancreatitis: An Update on Classification, Diagnosis, Natural History and Management

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Published online: 18 February 2012


**Abstract** Autoimmune Pancreatitis (AIP) is a recently recognized chronic fibro-inflammatory disease of the pancreas. Although rare, its recognition continues to increase worldwide. Patients often present with painless obstructive jaundice mimicking pancreatic cancer. Two subtypes of AIP are known-type 1 is a multi-organ disease associated with IgG4; type 2 appears to be a pancreas-specific disorder. Dramatic response to steroid treatment is characteristic of both forms. A non-invasive diagnosis of type 1 AIP may be possible using diagnostic criteria (in ~70% cases) while diagnosis of type 2 requires histology. These subtypes differ in natural history- type 1 often relapses while initial reports suggest that type 2 does not. Long term complications include endocrine and exocrine insufficiency and in case of type 1, disease relapses and complications from extra-pancreatic involvement. Neither form affects long term survival. The treatment and follow-up guidelines continue to evolve with our increasing experience in AIP.

**Keywords** Autoimmune pancreatitis · Chronic pancreatitis · IgG4-related systemic disease · Lymphoplasmacytic sclerosing pancreatitis · Idiopathic duct centric pancreatitis

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## Introduction

Autoimmune pancreatitis (AIP) was reported as early as 1960s [1] but it was established as a distinct entity only recently [2, 3]. Since then, recognition of AIP worldwide has continued to increase [4–16]. It is a rare disease although currently there is no population-based epidemiologic data on its prevalence. AIP mimics pancreatic cancer in presentation [17••, 18, 19]. While pancreatic cancer is much more common and has altogether different prognosis, AIP is a benign disease with dramatic steroid responsiveness. A correct and timely recognition of AIP saves unnecessary surgery and patient anxiety. However, a misdiagnosis of AIP can be a nightmare in case of a missed diagnosis of pancreatic cancer. Here we review classification, diagnosis, management and natural history of AIP.

## Classification

### The Need for Sub-classification

A landmark study in 2001 identified association of AIP with serum IgG4 elevations [20] and in 2004 with tissue infiltration with IgG4 positive cells [21]. It was then apparent that AIP patients frequently had involvement of several extra-pancreatic organs [22]. Histology in these patients revealed a distinct pattern of lymphoplasmacytic infiltrate with fibrosis in most affected organs [23]. Abundant IgG4-positive cells were noted in all affected sites including pancreas and extra-pancreatic organs [21, 24].

However, some of the pancreas specimens were observed to have a different histological pattern characterized by neutrophilic infiltrate in ductal epithelium with duct destruction

[25]. These patients had disease confined only to the pancreas and IgG4 association was not seen [25]. On follow-up, it was found that the former group had frequent relapses while the latter group of patient did not have relapses [26••]. These two groups have now been termed type 1 and type 2 AIP, respectively [27••, 28••]. Distinct histological and clinical profiles with different outcomes make such a sub-classification extremely important [26••, 29•, 30].

## Geographical Distribution

Type 1 AIP is the more common form worldwide [5••, 31]. This form appears to be the exclusive subtype in Japan and Korea [5••]. In the US, it is the predominant subtype accounting for more than 80% cases [31]. Type 2 AIP seems to be relatively common in Europe though type 1 is still the more prevalent subtype [31, 32•].

## Type 1 AIP

Type 1 AIP is associated with characteristic histological pattern known as lymphoplasmacytic sclerosing pancreatitis (LPSP) (Table 1). Extra-pancreatic involvement is frequently seen [33, 34•]. In our series, 60% of type 1 AIP patients had other organ involvement [26••]. With increasing awareness of the disease as well as ever-expanding spectrum of recognized extra-pancreatic manifestations in AIP, the reported prevalence of other organ involvement is increasing [34•]. IgG4-rich lymphoplasmacytic infiltrate is seen on histology in all affected organs [21, 24]. The inflammatory process in all affected organs responds characteristically to steroid treatment though disease relapse in the pancreas or other affected organs is common [26••]. Serum IgG4 elevation is seen in about 80% of type 1 AIP [26••]. The association with IgG4 and multiple extra-pancreatic organ involvement has led to the concept of a multi-organ disease associated with IgG4, now known as IgG4-related Disease (IgG4-RD) [22, 35]. Type 1 AIP is the pancreatic manifestation of IgG4-RD [35] and has also been called as IgG4-related pancreatitis.

While IgG4 rich cellular infiltrate is seen in the affected organs including the pancreas in type 1 AIP, a subset of patients do not have elevated IgG4 levels in the serum. In our series, about 20% patients were seronegative at the time of diagnosis [26••]. The significance of seronegativity is unknown [36] though serum IgG4 levels are known to fluctuate [37•, 38]. It is important to recognize that a subset of type 1 patients may be seronegative and that seronegativity in itself should not be used to reclassify patients as type 2 AIP.

## Type 2 AIP

Presence of neutrophils in the pancreas with characteristic granulocyte-epithelial lesions (GELS) on histology defines type 2 AIP [32•, 39] (Table 1). Currently, a definitive diagnosis of type 2 AIP requires histology [17••]. Based on clinical presentation, imaging features, serology and other organ involvement alone, a definitive diagnosis of type 2 AIP cannot be made though these can be suggestive of the diagnosis [17••, 28••]. Type 2 patients present at a younger age compared to type 1 [5••] (Table 1). About a third of these patients present with acute pancreatitis [5••, 26••]. However, obstructive jaundice is still the most common presentation as in type 1 AIP [26••, 27••]. Imaging alone cannot differentiate between the subtypes but type 2 patients are more likely to have focal findings [28••]. These patients do not have involvement of other extra-pancreatic organs [32•, 39]. There is no associated IgG4 rich infiltrate on histology and serum IgG4 elevation is unlikely. Inflammatory bowel disease is seen more commonly, in about 16–30% of patients [5, 26••] (Table 1). Response to steroids is

**Table 1** Profile of Type 1 and Type 2 AIP

| | Type 1 AIP | Type 2 AIP |
|---|---|---|
| Defining histopathologic pattern | Lymphoplasmacytic sclerosing pancreatitis | IDCP (idiopathic duct centric pancreatitis or GEL + ve pancreatitis) |
| Non-invasive diagnosis | Possible in >70% of cases using diagnostic criteria | Currently, definitive diagnosis cannot be made without histology |
| Mean age at presentation | Seventh decade | Fifth decade |
| Presentation | Obstructive jaundice 75% | Obstructive jaundice 50% |
| | Acute pancreatitis 15% | Acute pancreatitis ~33% |
| Imaging | Diffuse swelling 40%<br>Focal features 60% | Focal features ~85% |
| IgG4 Association | IgG4 elevations in serum<br>Positive IgG4 staining in tissues | Not associated with IgG4 |
| Other organ involvement | Multiple | None |
| Associated IBD | 2% to 6% | 16% |
| Long term outcome | Frequent Relapses | No relapse |

characteristic and, at least in initial reports of histologically confirmed type 2 AIP, relapses do not occur in type 2 AIP [26••].

## Diagnosis

The diagnosis of AIP is challenging even at the expert centers [40]. This is partly because AIP is a new entity that is known to be rare whereas its close differential, pancreatic cancer, is relatively more common. Misdiagnosis of AIP in the setting of pancreatic cancer is to be avoided.

In the last decade, many diagnostic criteria for AIP have been put forth [4, 12•, 41–43]. The differences in diagnostic criteria reflect regional differences in practice as well as possible differences in clinical profile and epidemiology. For example, most Asian criteria require pancreatic duct imaging by ERP/MRP [41, 42]. While the Mayo Clinic HISORt criteria [17••] does not require for ERP/MRP as current practice in the US does not include routine ERP/MRP for evaluation of obstructive jaundice. Recently international consensus diagnostic criteria (ICDC) have been developed which unify these diagnostic criteria while accommodating regional differences in practice and strategy [28••]. The ICDC [28••] incorporates most of the features of the revised HISORt criteria and combines the salient features of Asian/Japanese criteria that include ductal imaging (ERP/MRP) as well as ampullary biopsies with IgG4 staining. The ICDC provides a unified framework that allows for regional flexibility in establishing an institutional approach for diagnosing AIP based on available expertise and local practice pattern.

In this brief review we discuss clinical presentation of AIP and focus on the diagnosis of type 1 and type 2 AIP with emphasis on a practical approach to distinguish AIP from pancreatic cancer.

### Clinical Presentation and Clues to Diagnosis

The most common presentation of AIP is with obstructive jaundice. About 75% of type 1 and about 50% of type 2 patients have obstructive jaundice at presentation [5••, 26••]. Thus, AIP closely mimics pancreatic cancer in its acute presentation. AIP can also present with acute pancreatitis [44]. In fact, our experience at a tertiary referral center indicates that about 4% of patients evaluated for pancreatitis (both acute and chronic) may have AIP as the etiology [44]. In our series, 15% of type 1 and 32% of type 2 patient presented with acute pancreatitis; however, most also had biliary involvement leading to obstructive jaundice and/or elevated liver enzymes [44]. Recurrent acute pancreatitis without biliary involvement is a rare presentation of AIP. A large proportion of patients experience abdominal pain which is mild (40% type 1 and about 70% of type 2 AIP) [5••]. In fact narcotic requiring chronic pain is not a feature of AIP. A proportion of patients may present late with features of painless chronic pancreatitis (11% in our series) [44].

Similarly the other organ systems involved in type 1 AIP/IgG4-RD frequently mimic organ specific diseases with similar presentation. For example, the clinical and radiological picture in IgG4-associated cholangitis (IAC) may resemble primary sclerosing cholangitis or cholangiocarcinoma [45, 46•], and salivary and lacrimal gland involvement mimics Sjogren's syndrome [47]. However, the response to steroids in AIP is dramatic which is typically not seen in the corresponding organ-specific counterparts.

### International Consensus Diagnostic Criteria for AIP

The clinical profile of AIP has five components- Histology (H), Imaging (I), Serology (S), Other organ involvement (OOI) and Response to steroid treatment (Rt). These form the basis of ICDC [28••] (as well as the revised HISORt criteria [17••]). Unlike older criteria which required both pancreatic parenchymal imaging by CT/MRI (P) [17••] and pancreatic ductal imaging by endoscopic retrograde pancreatogram (ERP) (D) [41, 42], the ICDC allows for either feature to be used (Table 2).

Each of these components may provide level 1 (highly suggestive) or level 2 (supportive) evidence. For example, Serum IgG4 elevation $\geq$ 2X upper limit of normal is highly suggestive of AIP (denoted as level 1 S), <2X upper limit of normal is supportive of AIP (denoted as level 2 S). The ICDC details and definitions are provided in table 2 [28••]. Different combinations of these features are considered diagnostic.

### Diagnostic Groups Based on ICDC

Type 1 AIP may be diagnosed non-invasively, using pancreatic histology or, in select cases, using steroid trial (28) (Table 2)-

A. Non-Invasive Diagnosis: AIP can be diagnosed in patients with
   1) highly suggestive parenchymal imaging (level 1 P) if there is any additional collateral evidence of AIP- one of elevated Serology or presence of Other organ involvement (one of S, OOI (level 1 or 2))
   2) only supportive parenchymal imaging (level 2 P) with a negative cancer work-up if there are at least two pieces of collateral evidence (two or more level 1 S/OOI) + ductal imaging (level 1 or 2 D))
B. Invasive Diagnosis:

Patients can be diagnosed with AIP if there are features of LPSP on resection specimens or core biopsy (Level 1 H) regardless of presence or absence of collateral evidence

**Table 2** International Consensus Diagnostic Criteria for Type 1 AIP

| | Level 1 | Level 2 |
|---|---|---|
| Pancreatic Imaging-parenchyma (P) | Typical: | Indeterminate/suggestive: |
| | Diffuse enlargement with delayed enhancement (sometimes associated with rim like enhancement) without low-density mass, ductal dilatation or duct cutoff | Segmental/focal enlargement with delayed enhancement (Atypical*: apparently normal pancreas, low-density mass, pancreatic ductal dilatation or distal atrophy) |
| Pancreatic Imaging-duct (D) | ERP: Long (>1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation | ERP: Segmental/focal narrowing without marked upstream dilatation (duct size <5 mm) |
| Serology (S) | IgG4 >2 X upper limit of normal value | IgG4 1–2 X upper limit of normal value |
| Other organ involvement (OOI) | Any one of a or b: | Any one of a or b: |
| | a) Histology of extrapancreatic organs: showing any three of the following | a) Histology of extrapancreatic organs including endoscopic biopsies of bile duct showing both of the following** |
| | i. Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration | i. Marked lymphoplasmacytic infiltration without granulo-cytic infiltration and |
| | ii. Storiform fibrosis | ii. Abundant (>10 cells/hpf) IgG4 positive cells |
| | iii. Obliterative phlebitis | b) Physical or radiological evidence of at least one of the following |
| | iv. Abundant (>10 cells/hpf) IgG4 positive cells | i. Symmetrically enlarged salivary/lacrimal glands on physical examination |
| | b) Typical radiological evidence of at least one of the following)<br>i. Segmental/multiple proximal (hilar/intra hepatic) or proximal and distal bile duct stricture | ii. Radiologic evidence of renal involvement described in association with AIP |
| | ii. Retroperitoneal fibrosis | |
| Histology(H) of pancreas | LPSP (Core biopsy/resection): | LPSP (Core biopsy): |
| | at least 3 features | any 2 features |
| | i. Periductal lymphoplasmacytic infiltrate without granulocytic infiltration | i. Periductal lymphoplasmacytic infiltrate without granulocytic infiltration |
| | ii. Obliterative phlebitis | ii. Obliterative phlebitis |
| | iii. Storiform fibrosis | iii. Storiform fibrosis |
| | iv. Abundant (>10 cells/hpf) IgG4 positive cells | iv. Abundant (>10 cells/hpf) IgG4 positive cells |
| Diagnostic steroid response | | |
| Response to steroid therapy (Rt) # | Rapid (<2 wk) radiologically demonstrable resolution or marked improvement in pancreatic or extra-pancreatic manifestations | |

# Rt should be used with these caveats

a) This option should be exercised only after negative work-up for cancer including EUS-FNA

b) General feeling of well being, resolution of mild symptoms (e.g., arthralgia, dyspepsia) and reduction in serum IgG4 levels are not included in "response" as they can all occur non-specifically with high dose steroid therapy even in patients without AIP

c) In patients with clinical pancreatitis at presentation, spontaneous improvement in pancreatic swelling may occur with resolution of pancreatitis and "response" to steroids should be interpreted with caution

d) Currently recognized spectrum of presentation of type 1 AIP does not include idiopathic recurrent pancreatitis or typical painful chronic pancreatitis. Diagnosis of AIP in this setting is to be made by definitive histology rather than by response to steroid therapy

* Atypical: Some AIP cases may show low-density mass, pancreatic ductal dilatation or distal atrophy. Such atypical imaging findings in patients with obstructive jaundice and/or pancreatic mass are highly suggestive of pancreatic cancer. Such patients should be managed as pancreatic cancer unless there is strong collateral evidence for AIP and a thorough work-up for cancer is negative (see algorithm)

** Endoscopic biopsy of duodenal papilla is a useful adjunctive method because ampulla is often involved pathologically in AIP

C. Steroid trial in a select group:

This approach should be used sparingly. Type 1 AIP can be diagnosed in patients with characteristic response to steroids who have all the following criteria

a) supportive parenchymal imaging (level 2 P)
b) negative cancer work-up and
c) one of the following-
   i) one level 1 S/OOI

ii) two level 2 S/OOI
iii) one level 2 S/OOI with ductal imaging (level 1 or 2 D)

In a validation study, about 70% of suspected patients could be diagnosed with type 1 AIP by highly suggestive imaging plus one collateral evidence in the form of other organ involvement or serum IgG4 elevations (group 1 above) [17••]. This has great practical utility and forms the basis of the approach described here (Fig. 1). The remaining 30% suspected patients require either histology or a steroid trial [17••]. This is the difficult area requiring meticulous patient selection.

## A Practical Approach to Differential Diagnosis of AIP Vs Cancer

### Initial Parenchymal Imaging- CT Scan/MRI

This approach revolves around initial imaging in the form of a CT scan with contrast or MRI in patients with obstructive jaundice. This is consistent with the usual practice for initial work-up of a patient with painless obstructive jaundice in the US [17••]. Based on imaging features, patients can be stratified into three groups – suggestive of cancer, highly suggestive of AIP, or supportive for AIP.

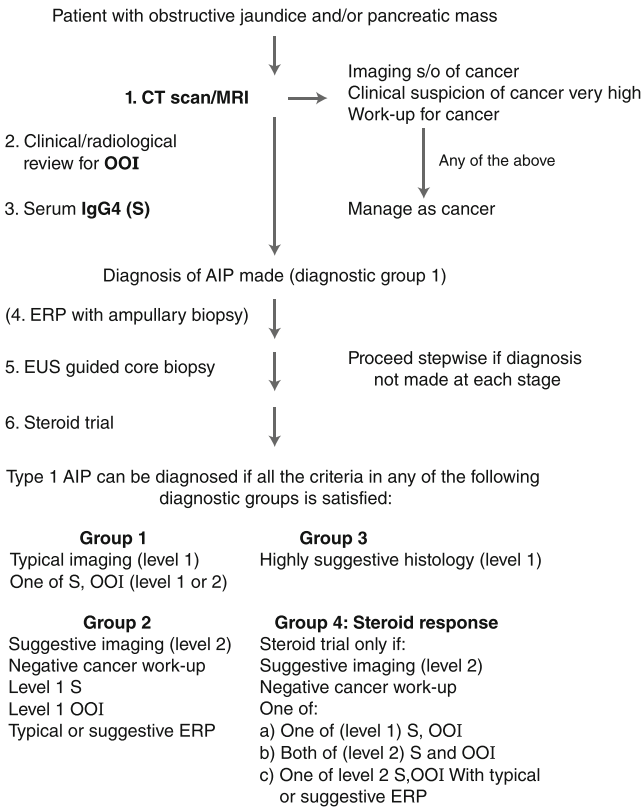


**Fig. 1** A practical approach to differential diagnosis of AIP Vs Cancer. Initial step in the work-up of a patient with obstructive jaundice and/or pancreatic mass is obtaining parenchymal imaging (CT/MRI). This is followed by clinical and radiologic review for evidence of other organ involvement (OOI), and obtaining serum IgG4 levels (S). At this stage, about 70% of type 1 AIP can be diagnosed. Further stepwise diagnostic approach includes: +/− ERP followed by EUS guided pancreatic core biopsy or steroid trial if all the criteria are met. Based on ICDC, type 1 AIP can be diagnosed when all the criteria listed in any of the diagnostic groups are satisfied. See text for details

This is followed by search for the evidence of other organ involvement (clinical review and review of CT scan/MRI) and evaluation of serum IgG4. About 70% patients can be diagnosed as type 1 AIP at this stage [17••].

This may be followed by ERP with ampullary biopsies (for possibility of diagnostic group #2 above) though the diagnostic utility of ERP in the American context [48•] and of ampullary biopsies for IgG4 stain [49–51] are still controversial.

### Pancreatic Core Biopsy

FNA is routinely done for evaluation of pancreatic cancer but is not useful for histological evaluation of AIP [4]. We recognize recognized that EUS is available only at expert centers. However, only a handful of suspected patients with AIP require histological evidence [17••]. EUS guided pancreatic biopsies are relatively new in practice. It is believed that as experience with the technique of pancreatic core biopsies and its interpretation increases, it will be accepted as an invaluable tool [52, 53].

### Diagnostic Steroid Trial

Use of steroid trial may result in delay in diagnosing cancer and is strongly discouraged except in expert setting in the selected patient group meeting the criteria noted above (Fig. 1, group 4).

## Type 2 AIP

Type 2 AIP can be suspected in relatively younger patients with obstructive jaundice who are seronegative and have no other organ involvement typical of type 1 AIP with or without IBD. In all suspected cases after a thorough negative cancer work-up, pancreatic core biopsy is recommended. Currently, the definitive diagnosis of type 2 AIP requires histology [26••, 28••, 32•, 39]. Due to difficulty in diagnosis, it is possible that type 2 AIP is frequently under-recognized and under-reported. Hopefully in future, with greater awareness and recognition of the condition, biomarkers can be identified that can help diagnose type 2 AIP without need for histology.

Diagnostic histology (level 1 H) for type 2 AIP which is called IDCP requires both (28) -

1) GEL with or without granulocytic and lymphoplasmacytic acinar infiltrate

2) absent/scant IgG4 positive cells.

Absence of GELs but presence of rest of the above features constitutes supportive histology (level 2) which may indicate probable type 2 AIP.

## AIP-NOS

Some patients may not meet any diagnostic groups. Although possible, these would be rare if the diagnostic steps are carefully carried out. One example would be a patient with obstructive jaundice with negative workup for malignancy, has typical parenchymal imaging features who is seronegative and has no evidence of other organ involvement and histology shows lymphoplasmacytic infiltrate with storiform fibrosis (which is common supportive feature of both type 1 and type 2) [17••] but no IgG4 staining and no GELs. The diagnostic challenge is Type 2 AIP Vs seronegative Type 1 AIP (36). The patients may be classified as AIP-NOS and managed with steroid treatment.

## Management

AIP is exquisitely responsive to steroid treatment [10••, 54••, 55]. In fact, response to steroids is so consistent and characteristic that lack of response should prompt consideration of alternate diagnosis [17••, 56]. Multiple case series have studied steroid treatment with improvement in both pancreatic and in case of type 1 AIP, affected extra-pancreatic organs [10••, 54••, 57]. The treatment protocols vary among different centers [54••]. We use a protocol starting with 40 mg/day for 4 weeks and tapering off by 5 mg/week to complete a course of 11 weeks [54••, 55]. Treatment response is objectively monitored by clinical follow-up, follow-up imaging and biochemical tests (LFT) [54••, 55]. Steroid taper is started once response to treatment is confirmed objectively [54••, 55].

## Additional Initial Management: Biliary Decompression

Most AIP patients present with obstructive jaundice. The Japanese and Asian guidelines, which require ERP for diagnosis, recommend routine biliary decompression in all patients with obstructive jaundice prior to starting surgery [41, 42, 58]. These guidelines also recommend treatment of diabetes prior to starting steroids [58]. In our experience, if diagnosis of AIP is definitive, routine ERP for drainage is not required as steroid treatment generally improves jaundice quickly without need for drainage in AIP [46•]. However, when diagnosis of AIP is uncertain, biliary drainage could be considered prior to treatment [46•, 54••, 55]. In such cases ERP may aid in diagnosis as in the Asian diagnostic criteria.

## Disease Relapse in Type 1 AIP

Disease relapse is common in type 1 AIP while patients with type 2 AIP do not relapse [26••, 59]. Most series estimate the frequency of relapse in type 1 AIP in the range from 30% to 50% [5••, 6–8, 10••, 11, 12•, 13–16, 34•, 54••, 57, 60, 61]. In our series of 78 type 1 AIP patients with a median follow-up of 42 months, symptomatic disease relapse was seen in 47% patients with a 3-year cumulative relapse rate of 59% in type 1 AIP patients who were medically managed [26••]. Lack of a uniform definition of disease relapse, short follow-up, small patient population, lack of identification of subtypes and possible ethnic variability contributes to the wide range of reported relapse rates from across the world [5••, 6–8, 10••, 11–15, 57, 60–62]. In our series, we considered only clinically symptomatic relapse excluding asymptomatic serologic and biochemical recurrence alone as relapse [26••, 46•].

It is also unclear as to what happens to relapse rates as AIP progresses. Some autoimmune diseases are characterized by an active phase and then a burnt-out phase with no recurrences, for example, Hashimoto's thyroiditis [63]. On the other hand, autoimmune hepatitis is characterized by recurrent relapses and life-long immunosuppressive therapy is indicated [64]. Most relapses (~90%) seem to occur within the first 3 years in type 1 AIP [10••, 26••]. However, to conclude that relapses in the later stage of disease are uncommon will need longer follow-up of patients.

Relapses appear to be common in the proximal bile duct (presenting as biliary stricture with jaundice with or without cholangitis) and in the pancreas (presenting as diffuse swelling, pancreatitis, steatorrhea) [5••, 10••, 26••, 46•, 62]. In our series, 54% patients with relapses had recurrence in proximal bile duct and 27% patients had relapse in the pancreas [26••]. Extra-pancreatic disease relapse are also observed although with much less frequency, the common sites being- RPF, kidney, lungs, lymph nodes and liver [5••, 10••, 26••, 34•, 60].

## Predictors of Relapse

In our series, proximal bile duct involvement and diffuse swelling of the pancreas were factors predictive of disease relapse in type 1 AIP in a multivariate analysis with hazard ratios of 2.12 and 2.00 ($p$=0.03 and 0.04) respectively for proximal bile duct involvement and diffuse pancreatic swelling [26••]. Similar results have been noted in most other case series [6, 10••, 11, 12•, 16, 34•, 57, 61, 62].

Recently, some case-series have suggested that IgG4 elevations and evidence of other organ involvement may be predictive of relapse [6, 11, 34•, 61, 62]. These appear to be a confounding factors as these series are mixtures of type 1 and type 2 AIP, with type 1 AIP more likely to relapse and also more likely to have IgG4 elevations and other organ involvement. When we analyzed our data after separating AIP subtypes, initial IgG4 elevation as well as other organ involvement other than proximal bile duct did not predict relapses in type 1 AIP [26••]. Further, association of substitution of aspartic acid at position 57 of DQβ1 with increased relapse was described by Park et al. [65] while another study failed to see this association [66].

## Management of Relapse and Maintenance Therapy

Corticosteroids are effective in treating relapses as well and long term maintenance therapy may be necessary in patients who relapse [54••]. The role of maintenance corticosteroid therapy for primary prevention of relapses and utility of immunosuppressive drugs like azathioprine in refractory cases remain to be studied in controlled studies, though there is some experience with successful use of immunosuppressive drugs in refractory cases with frequent relapses [6, 16, 46•, 67].

The major point of contention is the need for maintenance steroid therapy. Centers in Japan routinely use a prolonged maintenance therapy for up to 3 years with the logic that most patients relapse within 3 years [10••, 58]. The benefit of universal and prolonged maintenance therapy has not been established. In a multicenter study from Japan, it was shown that maintenance therapy reduced the relapse rate to 23% from 34% in those who weaned off steroids [10••]. In our experience, universal use of maintenance steroid therapy is not recommended because the risks of long term steroid use outweigh the benefits in AIP [54••]. Unlike Autoimmune Hepatitis where relapse is universal on withdrawal of immunosuppressive therapy [64], about half of type 1 AIP patients do not relapse after short-course of steroid treatment [5••, 26••, 54••, 60]. Monitoring of liver enzymes to detect early biliary relapse and prompt steroid treatment of any relapse is beneficial in our experience [26••, 54••, 60]. We start maintenance therapy with azathioprine (2–2.5 mg/kg) after the first or second relapse [54••, 68]. Following this approach, we have observed that 30% to 40% AIP patients will eventually require maintenance therapy to prevent frequent relapses [54••, 68].

## Utility of IgG4 in Monitoring Treatment and Relapse

Monitoring serum IgG4 levels could be potentially relevant in two settings-1) monitoring of therapy, and 2) monitoring for disease relapse. However, currently there is no convincing evidence that monitoring of serum IgG4 is helpful in either of these two proposed settings [37•]. A large proportion of treated patients did not normalize IgG4 levels after treatment (115/182 (63%) in the largest multicenter cohort from Japan [10••]). Further, only 30% of these patients with persistent IgG4 elevations relapse (Vs 10% in patients with normalization of IgG4 levels) [10••]. In our cohort, among the 47 patients who had elevated serum IgG4 at presentation, 37 received steroids. Among these 37, we have follow-up IgG4 data on 19 patients. It is interesting to note that only 11/19 (57.9%) patients had normalization of IgG4 levels while in the remaining 8/19 (42.1%), IgG4 levels remained persistently elevated [37•]. Further, we noted that the proportion of patients who normalized serum IgG4 did not differ between patients with and without relapse [46•]. Therefore, it appears that a significant proportion of patients will fail to normalize IgG4 levels upon treatment and only a minority of them may relapse.

## Long Term Outcomes

### Long Term Survival

We compared long term survival in AIP patients, both type 1 and type 2 to age- and gender-matched population and found that these were similar [26••]. Therefore, despite long term outcomes including pancreatic insufficiency, diabetes, extra-pancreatic involvement, and complication related to therapy that could contribute to morbidity, neither type 1 nor type 2 AIP affects long term survival [26••].

### Risk of Malignancy

Several case reports of pancreatic cancer have been described in patients with AIP [10••, 12•, 61, 62, 69–75]. Interestingly one case was noted at the time of presentation of AIP which poses an interesting diagnostic scenario [76]. Whether these malignancies can be attributed to older age is unknown. However, AIP being a rare disease and pancreatic cancer also a relatively uncommon disease, simultaneous occurrence of both in several patients does suggest a cause-effect relationship. Interestingly, Kamisawa et al. [77] observed high frequency of KRAS mutation in the pancreatobiliary region of AIP patients. It is very likely that the process of chronic inflammation and fibrosis in AIP may increase the risk of cancer. Careful long term follow-up of patients for development of malignancies is therefore recommended.

Further, there are some reports of other solid organ malignancies [61, 78, 79] including biliary intra-epithelial neoplasia [75] as well as lymphomas [80] and lymphoproliferative

disorders [81]. The exact association of these with AIP is currently unknown

## Pancreatic Insufficiency: Exocrine and Endocrine

The pancreatic exocrine and endocrine function of many AIP patients is impaired by extensive destruction of the acini and islets by the inflammatory process [71]. The prevalence of exocrine insufficiency was estimated to be well in the order of 90% if subclinical insufficiency is included as well [82, 83]. Diabetes mellitus was reported in 26% to 78% patients [12•, 84–86]. Though there is no conclusive evidence, some studies indicate improvement of pancreatic function after steroid treatment [71, 84, 87, 88] while one study [85] noted negative effect on glucose tolerance in some older AIP patients treated with steroids. It appears that diabetes in the initial acute phase may improve with steroid treatment or even spontaneously. In the late phase, glycemic control may worsen with steroids and glycemic control may be more difficult to achieve in patients with diabetes while on treatment [54••].

### Other Manifestations Affecting Prognosis

Inflammatory bowel disease (IBD) is seen in about 2% to 6% patients with type 1 AIP and 16% to 18% of patients with type 2 AIP [5••, 26••]. Patients with both AIP and IBD may have increased severity of IBD [89]. Similarly, hypothyroidism occurs in a significant proportion of patients requiring thyroxine supplementation [90]. Recently, increased prevalence of asthma and allergic disorders has been described in AIP [91].

### Long Term Outcomes of Extrapancreatic Involvement in Type 1 AIP

Proximal bile duct involvement is the most common symptomatic extra-pancreatic manifestation of type 1 AIP/ IgG4-RD which has been given its own name- IgG4 associated Cholangitis (IAC) [46•]. Unlike biliary strictures seen in primary sclerosing cholangitis (PSC), the biliary strictures in IAC typically respond to steroid therapy [45, 46•]. However, untreated IAC may rapidly progress to end stage liver disease [46•]. Salivary gland involvement which is common in type 1 AIP is known as IgG4 related sialoadenitis (Miculicz disease) which differs from Sjogren's syndrome by lack of anti-SSA and anti-SSB antibodies, lack of association with rheumatoid arthritis, presence of elevated serum IgG4 levels and IgG4-rich infiltrate and response to steroids [47]. Kidney involvement includes tubulointerstitial nephritis (seen in 35% patients with AIP [92]), nodular lesions mimicking metastatic tumors [93], pseudotumors [94]and membranous nephropathy [95] all of which improve on steroid treatment [35, 92]. Retroperitoneal fibrosis (RPF), in which a thick mass covers abdominal aorta and compresses ureters that could lead to lower extremity edema and hydronephrosis/renal failure respectively, is seen in 8% to 16% of type 1 AIP [33, 35, 96]. IgG4 related pulmonary disease, presenting as interstitial infiltrates which could deteriorate to respiratory failure if untreated, has been recently characterized with prevalence from 3% [34•] to 13% [97] in type 1 AIP. Mediastinal or hilar lymphadenopathy is perhaps the most common extrapancreatic involvement, reported in as high as 77% [34•] to 80% [33, 35]. Recently, Chung et al. [98] reported positive IgG4 staining in 9 of 24 liver biopsies of autoimmune hepatitis (AIH) patients that correlated with more dramatic steroid response compared to IgG4-negative AIH, thus suggesting existence of IgG4-related hepatopathy [99]. Numerous other associations in IgG4-RD have been described - IgG4-assocaited prostatitis [100], pericarditis [101], inflammatory pseudotumors, gastric ulcers and gastric and colon polyps associated with IgG4 [60]. Though these are mostly case reports, most of these other IgG4-related lesions appear to be responsive to steroids [60].

## Conclusions

AIP is a recently characterized chronic disease of the pancreas. Type 1 AIP, the relatively more common form, is a multi-organ disease associated with IgG4 with characterized by relapsing natural course. Type 2 AIP is confined to pancreas and associated with granulocyte epithelial lesions (GELs) on histology. The diagnosis of type 1 AIP can be made non-invasively in a majority of patients while type 2 AIP can only be diagnosed on histology. Steroid treatment is the mainstay of management, with characteristic dramatic response. Despite long term outcomes including pancreatic insufficiency, extra-pancreatic involvement and complications related to immunosuppressive therapy, neither type 1 nor type 2 AIP affects long term survival.

**Disclosure** No potential conflicts of interest relevant to this article were reported.

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- •• Of major importance

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