

Recent advances in autoimmune pancreatitis: type 1 and type 2

Terumi Kamisawa,¹ Suresh T Chari,² Markus M Lerch,³ Myung-Hwan Kim,⁴ Thomas M Gress,⁵ Tooru Shimosegawa⁶

¹Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan

²Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA

³Department of Medicine A, University Medicine Greifswald, Greifswald, Germany

⁴Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea

⁵Department of Gastroenterology, Endocrinology, Metabolism and Infectiology, Philipps-Universität Marburg, Marburg, Germany

⁶Division of Gastroenterology, Tohoku University Graduate School of Medicine, Sendai, Japan

Correspondence to

Dr Terumi Kamisawa, Department of Internal Medicine, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan; kamisawa@cick.jp

Received 24 April 2013

Revised 20 May 2013

Accepted 21 May 2013

ABSTRACT

Autoimmune pancreatitis (AIP) is a form of chronic pancreatitis characterised clinically by frequent presentation with obstructive jaundice, histologically by a lymphoplasmacytic infiltrate with fibrosis, and therapeutically by a dramatic response to steroids. When so defined, AIP can be sub-classified into two subtypes, 1 and 2. Recent international consensus diagnostic criteria for AIP have been developed for diagnosis of both forms of AIP. Type 1 AIP is the pancreatic manifestation of a multiorgan disease, recently named IgG4-related disease. Little is known about the pathogenesis of either form of AIP. Despite frequent association of type 1 AIP with elevated serum IgG4 levels and infiltration with IgG4-positive plasma cells, it is unlikely that IgG4 plays a pathogenic role in AIP. Type 1 AIP responds to steroids, but there needs to be consensus on treatment regimens for induction and therapeutic end points. Relapses are common, but can be reduced by long-term use of low-dose steroids. Recent reports suggest that immunomodulators (azathioprine, 6-mercaptopurine and mycophenolate mofetil), as well biological agents (the antibody to CD20, rituximab) may have a role in maintaining remission in relapsing type 1 AIP. Future studies should clarify the best management options for treatment of relapses and maintenance of remission. Type 2 AIP is a pancreas-specific disorder not associated with IgG4. It presents in younger individuals equally with obstructive jaundice and pancreatitis. The inflammatory process responds to steroid therapy; relapses are uncommon. The clinical spectrum and long-term outcomes of medically treated type 2 AIP are still being evaluated.

INTRODUCTION

Autoimmune pancreatitis (AIP) is a benign fibroinflammatory disease of the pancreas that has recently attracted worldwide attention.^{1–2} The term AIP was first proposed in 1995³ for a steroid-responsive pancreatic inflammatory disease; since then it has become recognised as a distinct clinicopathological entity. Patients with AIP often present with painless obstructive jaundice mimicking pancreatic cancer, which is far more common and has a dismal prognosis. As AIP dramatically responds to steroids, a correct and timely diagnosis of AIP saves unnecessary surgery. However, AIP sometimes relapses^{4–5} and its long-term prognosis is unknown. Review of worldwide data indicates that AIP comprises two subtypes, presently termed types 1 and 2.^{6–9} Here we review the pathology, pathogenesis, clinical features, diagnosis, treatment and natural history of types 1 and 2 AIP.

EVOLUTION OF THE CONCEPT OF AIP AND ITS SUBTYPES

As with many diseases, hints at recognition of a distinct entity were made several decades before the formal recognition of AIP and it took even longer for their worldwide acceptance. Even though both type 1 and type 2 are called 'autoimmune' pancreatitis, historically they followed different paths to that designation (tables 1 and 2).^{3–8–26} The concept of the entity that was later called type 1 AIP was proposed and developed predominantly in Japan with the diagnostic emphasis being on the clinical phenotype.^{3–11–14} Importantly, however, the histopathological features of this entity had previously been reported from Japan even before the concept of AIP was known.

On the other hand, the concept of what was later termed type 2 was first mooted in Europe on the basis of its unique histopathological features.²⁵ The American contribution to the field of AIP nomenclature was to recognise that the entity of 'AIP' consisted of two distinct histopathological and clinical forms of pancreatitis; the one reported from Japan was termed type 1 and the one reported from Europe was termed type 2.^{8–9} The latest development in the field is the recognition of type 1 AIP as the pancreatic manifestation of a multiorgan disorder named IgG4-related disease (IgG4-RD).^{27–28}

Diagnostic criteria for these entities, including multiple iterations of them from the same groups, had been proposed from Japan,^{13–29} Korea,¹⁸ USA,^{17–22} Germany³⁰ and Italy.³¹ The original Japanese criteria relied heavily on imaging and mandated a typical appearance on cross-sectional imaging and an endoscopic pancreatogram for diagnosis.¹³ With understanding of the full spectrum of clinical presentations of AIP, the American^{17–22} and Korean¹⁸ criteria incorporated additional diagnostic features, including varied appearance on CT, other organ involvement (OOI) and response to steroids. International consensus diagnostic criteria (ICDC) were developed to incorporate the diagnostic strategies used in the different criteria, keeping in mind differences in clinical practice throughout the world.²³

As far as treatment is concerned, there has been a natural experiment as different therapeutic strategies have been adopted by different groups for initial management of disease and prevention of disease relapse.^{4–5} Although head-to-head comparisons of these strategies in a randomised controlled trial have not been performed, one can obtain a fair idea of the efficacy of the different strategies from the published literature.

To cite: Kamisawa T, Chari ST, Lerch MM, *et al.* Gut Published Online First: [please include Day Month Year] doi:10.1136/gutjnl-2012-304224

Recent advances in clinical practice

Table 1 Type 1 AIP: timeline of most important clinical observations in the field

Year	Reference	Reported findings
1961	Sarles <i>et al</i> ¹⁰	Reported a form of idiopathic chronic pancreatitis associated with hypergammaglobulinaemia; suspected an autoimmune mechanism
1991	Kawaguchi <i>et al</i> ¹¹	Described the histopathological pattern of what was later called type 1 AIP ('lymphoplasmacytic sclerosing pancreatitis (LPSP)')
1995	Yoshida <i>et al</i> ³	Coined the term 'autoimmune pancreatitis'. Described all the major clinical features of what was later called type 1 AIP
2001	Hamano <i>et al</i> ¹²	Reported that elevated serum IgG4 levels were highly specific and sensitive for the diagnosis of AIP
2002	Japan Pancreas Society (JPS) ¹³	First JPS diagnostic criteria for AIP
2003	Kamisawa <i>et al</i> ¹⁴	Proposed that AIP was a systemic disease based on the findings that the pancreas and other involved organs have abundant infiltration with IgG4+ve plasma cells
2003	Notohara <i>et al</i> ¹⁵	Reported two histological patterns in patients with 'idiopathic chronic pancreatitis with lymphoplasmacytic infiltration sometimes called autoimmune pancreatitis' (a) LPSP and (b) idiopathic duct centric pancreatitis (IDCP)
2004	Kamisawa <i>et al</i> ¹⁶	Japanese experience of steroid therapy in AIP
2006	Chari <i>et al</i> ¹⁷	HISORt criteria for AIP published
2006	Kim <i>et al</i> ¹⁸	Korean criteria for AIP published
2008	Ghazale <i>et al</i> ¹⁹	First report of use of azathioprine in AIP
2008	Topazian <i>et al</i> ²⁰	First report of use of rituximab in AIP
2008	Moon <i>et al</i> ²¹	Steroid trial to distinguish AIP from pancreatic cancer
2009	Chari <i>et al</i> ²²	Revised HISORt criteria
2010	Chari <i>et al</i> ⁹	International consensus on classification of AIP into type 1 and type 2
2011	Shimosegawa <i>et al</i> ²³	International consensus diagnostic criteria
2012	Hart <i>et al</i> ²⁴	Proposed an algorithm for managing AIP using steroids, immunomodulators and rituximab

AIP, autoimmune pancreatitis.

PATHOGENESIS

Although there is now a consensus that two entities, namely type 1 and type 2, are to be distinguished within the disease designator AIP⁷⁻⁹ and that both subtypes undergo remission when treated with corticosteroids,^{5 32 33} there is little agreement about their pathogenesis. The categorisation of AIP as an autoimmune disorder is based on the observations that the disease is associated with infiltration of immune cells into pancreatic tissue and that the disease dramatically responds to steroid therapy; type 1 AIP is also associated with hypergammaglobulinaemia and autoantibodies, albeit non-specific.

The pancreas of patients with AIP is often infiltrated by various types of immune cells, including CD4-positive T-cells, IgG4-producing plasma cells (in type 1 AIP), and granulocytes (in type 2 AIP), among others. Moreover, a variety of circulating autoantibodies including those directed against lactoferrin, carbonic anhydrase, ubiquitin ligase, trypsin and pancreatic secretory trypsin inhibitor (PSTI), nuclear antigen and helicobacter pylori antigens, most of which are IgG1-class antibodies, have been reported from different populations of patients with AIP.^{34 35} It remains unclear whether the formation of these antibodies constitutes a pathogenetic event or whether they merely represent an epiphenomenon of AIP.³⁶⁻³⁸ What seems clear is

that treatment directed against B-cells (eg, with the CD20 antibody, rituximab), a mature form of which, so called plasma cells, are responsible for antibody production, is effective in patients with AIP who have disease recurrence after corticosteroid treatment.²⁴

None of the serum antibody markers described so far has a high enough specificity to be of much use for diagnostic discrimination between AIP and other pancreatic disorders, with the notable exception of increased IgG4 levels in type 1 AIP. Could this observation be a clue to the pathogenesis of the disease? It accounts for less than 5% of the total IgG circulating in a healthy person³⁶⁻³⁸ and its levels vary widely between individuals. The way it is composed via a complex 'Fab-arm exchange' make it, at least in theory, unable to crosslink antigens or to form immune complexes. It also does not activate the classical complement cascade. Therefore, it would be an unusual immunoglobulin to be playing a pathogenic role in AIP. Not surprisingly, no IgG4 antibodies against specific antigens (rather than antibodies from other IgG subclasses) have been detected in patients with AIP or other varieties of IgG4-RDs. Physiological IgG4 responses are induced by prolonged antigen exposure and controlled by type 2 helper T-cells.³⁸ Most likely, the increased IgG4 levels are therefore an epiphenomenon

Table 2 Type 2 AIP: timeline of most important observations in the field

Year	Reference	Reported findings
1997	Ectors <i>et al</i> ²⁵	Provided first description of the histological pattern of what was later termed type 2 AIP ('nonalcoholic duct destructive pancreatitis')
2003	Notohara <i>et al</i> ¹⁵	Reported two histological patterns in patients with 'idiopathic chronic pancreatitis with lymphoplasmacytic infiltration, sometimes called autoimmune pancreatitis' (a) lymphoplasmacytic sclerosing pancreatitis (LPSP) and (b) idiopathic duct centric pancreatitis (IDCP)
2004	Zamboni <i>et al</i> ²⁶	Described the 'granulocytic epithelial lesion (GEL)', the pathognomonic lesion of type 2 AIP
2010	Sah <i>et al</i> ⁸	Described a series of type 2 and compared with type 1

AIP, autoimmune pancreatitis.

rather than the cause of AIP, but the mechanism that induces them—related to T-cells—may play a role in pathogenesis.

In addition to the T-cell infiltrates in the pancreas of patients with AIP, some genetic studies also point to an involvement of T-cells. Polymorphisms in the gene for the cytotoxic T-lymphocyte antigen-4 (CTLA-4, CD152) have been reported to be a susceptibility factor in Chinese³⁹ and Japanese⁴⁰ patients. Animal experiments confirm that the inhibition of CTLA-4, which reduces regulatory T-cells, increases the severity of experimental AIP.⁴¹

Polymorphisms that are known to impair innate immunity, such as those in Toll-like receptor 4, could be linked with neither autoimmune⁴² nor other varieties of pancreatitis.⁴³ For HLA class II subtypes, the evidence is more equivocal and inconclusive. While in Japanese patients the HLA class II haplotype DRB1*0405-DQB1*0401 conferred susceptibility to AIP,⁴⁴ this was not confirmed in a Korean cohort where DQB1 was found to be a predictor of relapse.⁴⁵

While these studies have not solved the ultimate question of pathogenesis of AIP, they point to an involvement of T-cells. Further evidence comes from genetically modified animals that were generated to mimic AIP. The most recent example is the lymphotoxin α/β model in which a cytokine from the tumour necrosis factor (TNF) superfamily was first found to be overexpressed in the pancreatic tissue of patients with AIP and then, when overexpressed in the acinar cells of the mouse pancreas, resulted in a disease phenotype that closely mimics AIP.⁴⁶ The disease severity further depended on the presence of lymphocytes, and steroid treatment could reduce pancreatitis but not the associated production of antibodies. This study was therefore one of the first to experimentally discriminate between bona fide T-cell and B-cell effects in AIP. Lymphotoxins are interesting cytokines because they are physiologically secreted by activated immune cells but can, under pathological conditions, be expressed by epithelial cells as well. Other members of the TNF superfamily, such as TNF α , have recently been found to have a role in pancreatitis that goes far beyond the induction of apoptosis and implicates immune cells in the premature and intrapancreatic activation of digestive proteases,⁴⁷ a process that has previously been implicated in other varieties of pancreatitis,^{48, 49} specifically in hereditary pancreatitis,⁵⁰ but not necessarily in AIP. In the pancreas of patients with AIP, the critical protease, trypsin (which includes cationic as well as anionic trypsin), is greatly downregulated, whereas, in parallel, the patients carry high serum antibody titres against trypsin (PRSS1) as well as PSTI.³⁵ Whether this finding indicates that pancreatic proteases represent a disease-specific target in AIP, as could be the case for ubiquitin ligases of the N-end rule pathway with their known role in pancreatic inflammation,^{34, 51} or are merely indicative of pancreatic damage and subsequent antibody formation against circulating pancreatic proteins, remains at present unknown.

Experimental models of AIP have provided further evidence for the assumption that the disease is most likely T-cell-mediated. Agents that increase the number or activity of regulatory T-cells, such as the mammalian target of rapamycin (mTOR) inhibitor, sirolimus, or which decrease the number or activity of effector T-cells, such as the calcineurin inhibitor cyclosporin A, have highly beneficial effects on the course of experimental AIP.⁴¹ Successful treatment in this model was not paralleled by a reduction in either the level of serum autoantibodies or in the concentrations of mouse IgG1, IgG2 or IgG3.

Future perspectives

As noted above, the pathogenesis and pathophysiology of human AIP remain largely unknown. Research studies have so

far mainly addressed immunological aspects of IgG4-related type 1 AIP, and have delivered inconclusive results, which have recently been summarised by Okazaki and coworkers³⁶ and elsewhere in this review. This lack of knowledge on pathogenesis and pathophysiology contributes to the relatively slow progress in the development of novel treatment approaches—for example, a maintenance therapy for relapsing AIP.

Future studies will have to address several related issues such as relative roles of B-cells, T-cells and other immune cells⁵² in the initiation, progression or relapse of AIP. Answering this question is critical for targeting appropriate therapies during the respective phase of the disease and includes the question of whether a Th1 or a Th2 response predominates.³⁸ Mouse models, precisely mirroring the human disease, could help us understand the pathogenesis of AIP and thereby develop and preclinically test novel treatment approaches. The MRL/Mp mouse model mentioned above has strong resemblance to type 1 AIP,^{53, 54} and has recently been used for the first time to test the efficacy of various immunosuppressant treatments.⁴¹ Although not a perfect model for human AIP, it has provided interesting clues on the mechanism of action of immunosuppressants. Interestingly, azathioprine, which has been used for maintenance therapy in relapsing AIP, was shown not to have a meaningful beneficial effect in this model. This corroborates the recent report by Hart *et al*²⁴ on human AIP of the equivocal benefit of this agent. The reported mouse data suggest that mTOR inhibitors may be more suitable immunosuppressants than azathioprine for long-term administration in patients.

The genetic basis of AIP is unknown at present and only a few studies report association of individual selected candidate genes or selected single-nucleotide polymorphisms with the disease.^{39, 40, 42, 55} So far no genome-wide searches for genetic risk factors—for example, by use of genome-wide association studies or the novel next-generation sequencing approaches—have been carried out for AIP, but may contribute to our understanding of the pathogenesis, or deliver novel disease-susceptibility genes and treatment targets.

Another open issue is the pathogenesis of the enigmatic type 2 AIP, whether it differs from that of type 1 AIP, whether type 2 AIP requires different treatment regimens beyond corticosteroids, and whether it is characterised by different biological or imaging⁵⁶ markers other than granulocytic epithelial lesion on histology and the absence of IgG4 elevations. This leaves much room for basic and clinical research on this fascinating disorder.

TYPE 1 AIP

Clinical features

Since type 1 AIP is the pancreatic manifestation of IgG4-RD, a multiorgan disorder, it has a variety of clinical presentations which can be divided into pancreatic and extrapancreatic manifestations (figure 1). Since AIP has been followed long term, it has become clear that its clinical and imaging profile changes over time. Therefore, pancreatic manifestation of type 1 AIP can be further divided into active and late phase presentations. The most common clinical presentation in the active phase of type 1 AIP is painless obstructive jaundice, whereas features suggestive of acute pancreatitis (abdominal pain and elevation of serum pancreatic enzymes greater than three times upper limit of normal) are more often observed in type 2 AIP.^{32, 57, 58} It may also present as a pancreatic mass or less commonly with steatorrhoea. Patients who present late in the course of the disease after multiple relapses or those in whom the initial presentation was undiagnosed or misdiagnosed may show pancreatic parenchymal atrophy associated with stones/calcifications, similar to

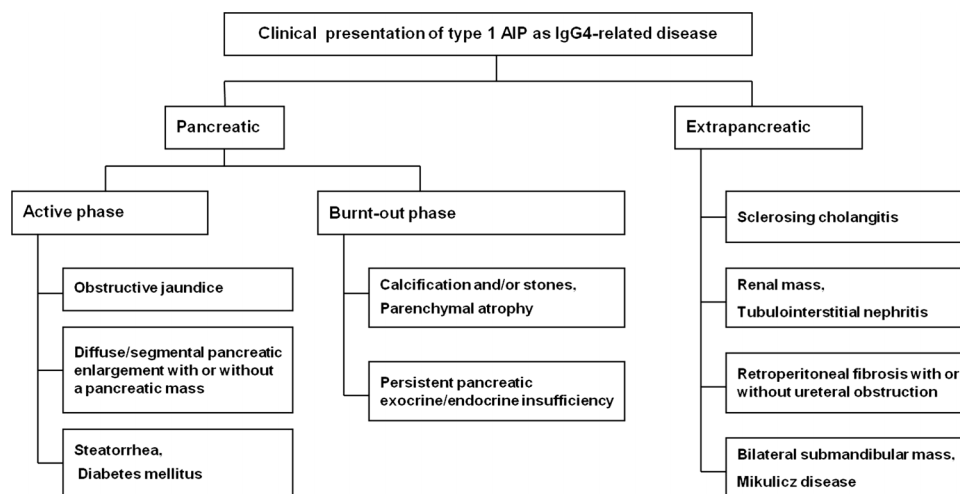


Figure 1 Clinical presentation of type 1 autoimmune pancreatitis (AIP) as IgG4-related disease.

features of advanced ordinary chronic pancreatitis.⁵⁹ Functional impairment with endocrine and exocrine failure leading to diabetes and steatorrhoea, respectively, is also common in late stages of disease.

A characteristic feature of type 1 AIP is extrapancreatic OOI, a reflection of it being the pancreatic manifestation of IgG4-RD. IgG4-RD is characterised by an IgG4-rich lymphoplasmacytic infiltrate in the affected organs including the biliary tree, salivary/lacrimal glands, retroperitoneum, kidney, lung, lymph nodes, prostate, aorta, pericardium and pituitary gland (figures 1 and 2).^{28–38} OOI in type 1 AIP may precede the diagnosis of AIP, be present concurrently, or develop metachronously over months to years after diagnosis of AIP.³⁸

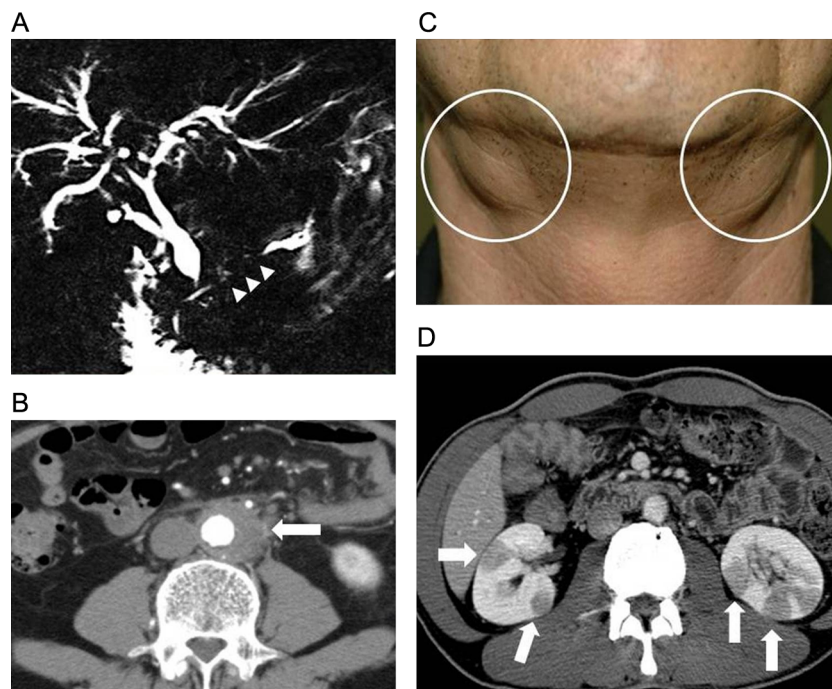
Diagnosis and differential diagnosis: international consensus diagnostic criteria

Many diagnostic criteria for AIP have been published (table 1).^{13–17, 18, 22, 29–31} The diversity of diagnostic criteria for

AIP from individual countries may reflect differences in practice patterns in the use of various tests and local expertise. Whereas Asian diagnostic criteria have focused on type 1 AIP, American and Italian diagnostic criteria may pertain to both subtypes.⁸ Recently, the ICDC for AIP have been proposed because of the need to diagnose AIP regardless of practice patterns in the use of various tests and to incorporate differentiation of the two subtypes of AIP.²³

The ICDC use the combination of five cardinal features of AIP: pancreatic imaging (parenchyma and duct), serology, OOI, histology and immunostaining, and steroid responsiveness.²³ The first four features are graded into levels 1 and 2 depending on their strength of association with type 1 AIP—for example, serology level 1, IgG4 level >2 times upper limit of normal; serology level 2, ≤2-fold elevation of serum IgG4. Different diagnostic criteria are used for the two AIP subtypes, and even in type 1 AIP the diagnostic criteria differ based on CT features (typical vs indeterminate).²³ In patients with typical CT imaging

Figure 2 Spectrum of other organ involvement of type 1 autoimmune pancreatitis. (A) Magnetic resonance cholangiopancreatography shows a long-segment stricture (arrowheads) of the main pancreatic duct associated with hilar bile duct strictures. (B) Retroperitoneal fibrosis (arrow). (C) Physical examination reveals bilateral enlargement (circles) of the submandibular salivary glands. (D) Multiple round or wedge-shaped renal mass (arrows).



for AIP, if there is supporting evidence from serology (elevation of serum IgG4 level) or OOI, definitive diagnosis of type 1 AIP can be made without the need for endoscopic retrograde pancreatography (ERP).

In the ICDC, total serum IgG level or autoantibodies such as antinuclear antibody or rheumatoid factor are not included as serological criteria because of their low specificities. Because pancreatic cancer is far more common than AIP, maintaining high specificity of diagnostic criteria is more important than increasing sensitivity. In the ICDC, the performance of diagnostic ERP is not mandatory, and pancreatographic findings assume the role of collateral evidence when CT features are not typical or in seronegative patients without OOI.^{23 60} It is clear that ~30% of patients with AIP cannot be diagnosed simply on the basis of CT features, serology and OOI, and will require a pancreatic core biopsy to look for unique histological and immunohistological characteristics.^{22 61} In this setting, diagnostic ERP is reserved for patients who have inconclusive results on core biopsy or in whom core biopsy is not feasible. The key ERP findings highly suggestive of AIP include (i) a long stricture involving more than one-third of the duct length, (ii) lack of upstream duct dilatation from the stricture, and (iii) multifocal strictures.^{62 63} In the ICDC, endoscopic retrograde cholangiopancreatography has multiple roles in the diagnosis of AIP, such as providing a direct pancreatogram and guiding bile duct/ampulla biopsy with IgG4 immunostaining, in addition to relieving biliary obstruction.

Although type 1 AIP, as a pancreatic manifestation of IgG4-RD, can involve virtually any organ in the body, the ICDC restrict the radiological/physical evidence of OOI only to proximal bile duct stricture (figure 2A), retroperitoneal fibrosis (figure 2B), symmetrically enlarged salivary glands (figure 2C) and renal involvement (figure 2D). This is because the imaging features of extrapancreatic organ involvement (eg, lymph node, lung) may be non-specific and do not permit reliable distinction between AIP and pancreatic cancer.

The use of a steroid trial to 'diagnose' AIP is included in the ICDC. A steroid trial to diagnose AIP involves use of prednisolone with reassessment of imaging after 2 weeks of steroid trial.²¹ Subjects with indeterminate CT features should first be investigated for pancreatic cancer, and a steroid trial should be considered only if work-up for cancer including endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is negative.

In patients without collateral evidence, the diagnosis of AIP can be challenging, and pancreatic histology is required for definitive diagnosis. However, histopathology is often not available in the diagnostic workup of a patient with suspected AIP. Transcutaneous core biopsies should be avoided if malignancy cannot be excluded. EUS-guided biopsy is an option, but the more widely available EUS-FNA is usually not suitable for histological diagnosis. EUS-guided core biopsy would be a solution, allowing tissue specimens to be obtained for histological and immunohistochemical analysis of stromal, inflammatory and parenchymal tissue components, but it is not yet widely available, and it may not be feasible to access all areas in the pancreas requiring histological verification.^{64 65} Furthermore, even if EUS-guided core biopsy samples of adequate size were available, a full histopathological evaluation may still not be possible because of the limitations in quantity and quality of biopsy samples. Criteria for diagnosing AIP in core biopsy specimens have been proposed,^{66 67} but need to be validated in larger series. Establishing histopathological diagnosis on minute biopsy specimens such as micro-tissue core fragments aspirated in EUS-FNA, as previously suggested for pancreatic cancer,⁶⁸ may

be a clue to optimising the diagnosis of AIP. The fact that, after a complete diagnostic workup, a few cases still require a diagnostic steroid trial and the risk of misdiagnosing or delaying the diagnosis of even a single case of the far more common pancreatic cancer underscore the necessity for novel diagnostic approaches.

Future perspectives

To improve conventional EUS imaging of the pancreas, several techniques of image enhancement such as contrast-enhanced EUS to evaluate vascularisation patterns and EUS plus elastography to estimate the elasticity of hypoechoic masses in the pancreas have been used.^{64 69} It has been suggested that contrast-enhanced EUS shows hypervascularisation of AIP lesions, whereas pancreatic cancer lesions appear to be more hypovascular masses.⁷⁰ With elastography, masses caused by AIP in contrast with pancreatic cancer show loss of tissue elasticity not only in the mass but also in the surrounding pancreatic parenchyma.⁷¹ Furthermore, preliminary data from small numbers of patients suggest that AIP lesions show reduced 'apparent diffusion coefficient' values in diffusion-weighted MRI⁷² and reduced maximal 'standardised uptake values' (SUVmax) in [¹⁸F]fluorodeoxyglucose positron emission tomography CT.⁷³

In addition, novel serum markers for initial diagnosis, in particular for type 2 AIP and for monitoring of treatment response, are urgently needed. Some efforts have been made in this field and include antibodies in the serum of patients with AIP detecting a peptide with homology to the amino acid sequence shared by the *Helicobacter pylori* plasminogen-binding protein and ubiquitin protein ligase E3 component n-recogin 2 highly expressed in pancreatic acinar cells,³⁴ autoantibodies against the trypsinogens, PRSS1, PRSS2 and PSTI,³⁵ or an autoantibody against amylase α -2A.⁷⁴

However, none of the novel imaging modalities and serum markers has so far been validated in larger independent series or been established in clinical routine.

Treatment

Induction of remission

The first goal of therapy in type 1 AIP is to induce remission. Response to steroid therapy in patients with AIP is dramatic and consistently leads to clinical improvement regardless of the subtypes.⁵ As a result, steroids have become the standard therapy for inducing remission in AIP.^{4 75} In the ICDC the starting dose of steroid for remission induction is defined as 0.6–1 mg/kg per day.²³

Issues to be solved in the induction of remission

Many issues need to be agreed upon in the initial management of AIP. For example, there is still no consensus on the details of the steroid regimen to be used to induce remission, including the duration of induction therapy and tapering schedule. Also, there is as yet no consensus on the definition of 'clinical remission', how much radiological improvement should be seen before steroid tapering is initiated,⁷⁶ or what constitutes 'radiological remission'. Clearly defining remission would be a very important issue in the treatment of AIP because patients who experience relapse during the course of steroid taper or while on steroid maintenance might represent a recrudescence of residual disease which is not yet in remission.⁷⁶

There are some patients, especially those with severe diabetes, who tolerate steroids poorly or have serious adverse effects during steroid therapy (eg, psychosis, infection or avascular necrosis of the hip). In such patients the only drug that has been

Recent advances in clinical practice

reported to induce remission is the CD20 antibody, rituximab.²⁴ On the basis of initial reports of efficacy of this drug in AIP and IgG4-related sclerosing cholangitis, an open label trial is underway in the USA to determine its role in the management of IgG4-RD.

Maintenance of remission

Disease relapse is common in type 1 AIP, ranging from 30% to 50%.⁴⁻⁸ Relapse rates reported in different publications vary and may be caused by inconsistent definitions of disease relapse, study design (retrospective trials, short follow-up, small patient populations), inconsistent separation of subtypes and, most likely, ethnic variability. The issue of whether maintenance therapy should be used on all patients with AIP or restricted to patients who relapse at least once also remains to be resolved.

The primary purpose of maintenance therapy is prevention of relapse; however, the choice of medication (ie, steroid or immunomodulator) and the optimal duration of maintenance therapy have not yet been standardised. Currently there are three options for managing patients with a relapse of type 1 AIP (figure 3).²⁴ To prevent relapses in type 1 AIP, Japanese groups advocate maintenance therapy with a low dose of prednisone for an extended time period after induction of remission.⁴⁻⁷⁵ In contrast, the Mayo group suggests that not all patients receive maintenance therapy since, in their experience, nearly half of patients have not relapsed 3 years after the induction therapy with steroids.¹⁹

In a recent study by the Mayo group in patients with relapsing AIP, immunomodulators such as azathioprine were not shown to be better than an additional course of steroids alone.²⁴ In the same study, a small case series (n=12) with a high clinical response to rituximab treatment and low risk of disease relapse and treatment-related side effects was reported.²⁴ Unfortunately, it is at present difficult to set a standard for maintenance treatment since the different studies are usually based on small numbers of patients and use different regimens, different criteria for patient selection and different study designs.

Issues to be resolved in the maintenance of remission

Overall, what is needed most in the field of AIP are prospective studies of novel diagnostic and treatment approaches, since what is known so far is mostly based on uncontrolled and retrospective data. Thus, the degree of evidence is low for virtually all aspects of diagnosis and treatment of AIP. In view of the rareness of the disease, multicentric and multinational concerted actions are needed to create a critical mass of patients to allow performance of clinical trials with sufficient statistical power to

develop internationally accepted treatment regimes. Approaches such as the recently published international survey of long-term outcomes of AIP patients²⁴ point in the right direction and should be the basis for designing and conducting prospective trials.

Natural history

According to a recent international multicentre study, 31% of patients with type 1 AIP experienced at least one disease relapse.⁵ More than half of patients who experienced multiple relapses had pancreatic calcifications or stones. With multiple relapses, type 1 AIP may result in irreversible damage with intense fibrosis, and these patients do not show steroid responsiveness.³⁸⁻⁵⁹ However, the long-term survival of patients with type 1 AIP has been reported to be similar to age- and gender-matched subjects from the general population.⁸

Several cases of pancreatic cancer have been reported in patients with AIP, where most were suspected to have type 1 AIP.⁷⁵⁻⁷⁷ Pancreatic cancers were diagnosed synchronously with AIP or detected during the follow-up after the remission of AIP. The lessons learned from these cases are that diagnosis of AIP using pancreatic biopsy alone should be performed carefully and close follow-up examinations are mandatory for AIP even after remission.

Future perspectives

While sporadic cases of cancer complicating AIP have been reported, no systematic case-control studies have been performed to evaluate the risk of cancer in AIP. Since type 1 AIP is a disease of the elderly, the risk of cancer may be underestimated. It would require long-term follow-up of a relatively young cohort of patients to determine if AIP truly increases the risk of cancer in affected organs.

TYPE 2 AIP

The evolution of the concept of two subtypes of AIP started with the identification of two distinct histopathological patterns in subjects undergoing pancreatic resection for suspicion of cancer who proved not to have cancer. When the clinical profiles of patients with these two histological entities were compared, they were distinctly different (table 3).^{5-9 24 32 57 78} There is also a difference in the prevalence of the two subtypes. Type 2 AIP appears to be relatively common in the USA and Europe but rare in East Asia; nevertheless, patients with type 1 AIP outnumber those with type 2 AIP even in Western countries.^{5 8 32 78} However, since definitive diagnosis of type 2 AIP requires pancreatic histology, under-recognition of type 2 AIP is

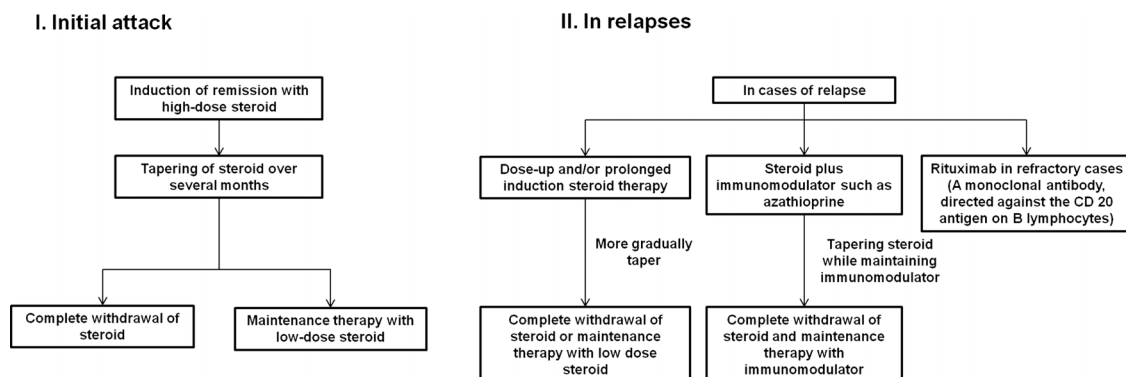


Figure 3 Current practice in the treatment of type 1 autoimmune pancreatitis.

Table 3 Differences in clinical profiles between type 1 and type 2 AIP

	Type 1 AIP	Type 2 AIP
Synonym	Lymphoplasmacytic sclerosing pancreatitis AIP without GEL	Idiopathic duct-centric chronic pancreatitis AIP with GEL
Epidemiology	Asia>USA, Europe	Europe>USA>Asia
Age at diagnosis	Old	Young
Gender distribution	Striking male predominance	Equal or small difference
Clinical presentation	Obstructive jaundice (painless)	Obstructive jaundice (painless) Abdominal pain/acute pancreatitis
Serum IgG4 level	Often elevated	Normal
Other organ involvement	Proximal bile duct, salivary gland, kidney, retroperitoneum	Not seen
Association with ulcerative colitis	Occasionally	Common
Steroid responsiveness	Excellent	Excellent
Recurrence	Common	Rare

AIP, autoimmune pancreatitis; GEL, granulocytic epithelial lesion.

far more likely than that of type 1 AIP. For example, there are numerous case reports and case series of 'idiopathic fibrosing pancreatitis' in children. The profile of this entity is suspiciously similar to that of type 2 AIP; it occurs in young patients, often presents with painless obstructive jaundice, is sometimes associated with inflammatory bowel disease, and can resolve spontaneously. A review of the pancreatic histopathology of these patients by a pathologist familiar with AIP will help resolve the issue of whether this entity is the same as type 2 AIP.

Clinical presentation

Our understanding of the clinical spectrum of type 2 AIP continues to evolve. From published studies it is clear that the clinical profile of type 2 AIP is sufficiently different from that of type 1 AIP to suggest that it is an entirely different disease entity. The similarities to type 1 AIP are that type 2 can also present with obstructive jaundice and have diffuse pancreatic enlargement on imaging studies and the inflammatory process responds to steroid therapy. However, patients with type 2 are significantly younger than those with type 1, and, as noted above, it may be missed in the really young, as the pancreas is rarely biopsied in that age group. While the majority of patients with type 1 AIP present with obstructive jaundice, those with type 2 are as likely to present with abdominal pain and pancreatitis as with obstructive jaundice. There is an absence of any collateral evidence of AIP, such as elevated serum IgG4 and OOI, evidence that is of great help in non-invasively diagnosing type 1 AIP. Inflammatory bowel disease is more common in type 2 than type 1 AIP, although even type 1 has a higher prevalence of it compared with the general population. Among those not intimately familiar with the literature, the term 'AIP' evokes the profile of an IgG4-associated disease typical of type 1. The indiscriminate use of the same term without subtype specification to describe the two diseases may hamper progress in understanding this uncommon disorder.

Treatment and follow-up

Initial reports of type 2 AIP included only patients who had undergone surgical resection. In such patients no further treatment was required and no relapses were reported. In the limited

experience with histologically confirmed and medically treated type 2 AIP, it appears to either spontaneously resolve or respond promptly to steroid therapy (STC, personal experience). When treated with a 3-month tapering course of steroids, relapses are still uncommon.

CONCLUSION

The field of AIP is rapidly evolving. In the past few years the following facts have been recognised. (i) AIP has at least two distinct subtypes, type 1 and 2. (ii) Type 1 AIP is the pancreatic manifestation of a multiorgan syndrome called IgG4-RD. (iii) Relapses in type 1 AIP can be prevented using immunomodulators or biological agents. There is a growing suspicion that, while IgG4 is a useful biomarker for diagnosis of type 1 AIP, it is unlikely that it plays a pathogenetic role in type 1 AIP. (iv) Type 2 AIP is a distinct disease entity that shares some common features with type 1 AIP. While it responds to steroid therapy, relapses are uncommon. (v) The continued use of the term 'AIP' to describe both entities without subtype specification does cause confusion, as the term often evokes a profile of type 1 AIP, which is so deeply entrenched in the literature.

Contributors All authors drafted the manuscript.

Competing interests None.

Ethics approval This is retrospective review paper, and ethics approval was therefore not required.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES

- Okazaki K, Kawa S, Kamisawa T, *et al.* Japanese clinical guidelines for autoimmune pancreatitis. *Pancreas* 2009;38:849–66.
- Kamisawa T, Takuma K, Egawa N, *et al.* Autoimmune pancreatitis and IgG4-related sclerosing disease. *Nat Rev Gastroenterol Hepatol* 2010;7:401–9.
- Yoshida K, Toki F, Takeuchi T, *et al.* Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. *Dig Dis Sci* 1995;40:1561–8.
- Kamisawa T, Shimosogawa T, Okazaki K, *et al.* Standard steroid treatment for autoimmune pancreatitis. *Gut* 2009;58:1504–7.
- Hart PA, Kamisawa T, Brugger WR, *et al.* Long-term outcomes of autoimmune pancreatitis: a multicentre international analysis. *Gut* Published Online First: 11 Dec 2012. doi:10.1136/gutjnl-2012-30361
- Kamisawa T, Notohara K, Shimosogawa T. Two clinicopathologic subtypes of autoimmune pancreatitis: LPSP and IDCP. *Gastroenterology* 2010;139:22–5.
- Park DH, Kim MH, Chari ST. Recent advances in autoimmune pancreatitis. *Gut* 2009;58:1680–9.
- Sah RP, Chari ST, Pannala R, *et al.* Differences in clinical profile and relapse rate of type 1 versus type 2 autoimmune pancreatitis. *Gastroenterology* 2010;139:140–8.
- Chari ST, Kloppel G, Zhang L, *et al.* Histologic and clinical subtypes of autoimmune pancreatitis: The Honolulu Consensus Document. *Pancreas* 2010;39:549–54.
- Salles H, Salles JC, Muratore R, *et al.* Chronic inflammatory sclerosing of the pancreas—An autonomous pancreatic disease? *Am J Dig Dis* 1961;6:688–98.
- Kawaguchi K, Koike M, Tsuruta K, *et al.* Lymphoplasmacytic sclerosing pancreatitis with cholangitis: a variant of primary sclerosing cholangitis extensively involving pancreas. *Hum Pathol* 1991;22:387–95.
- Hamano H, Kawa S, Horiuchi A, *et al.* High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001;344:732–8.
- Members of the Criteria Committee for Autoimmune Pancreatitis of the Japan Pancreas Society. Diagnostic criteria for autoimmune pancreatitis by the Japan Pancreas Society (2002). *Suizo* 2002;17:585–7. (in Japanese with English abstract)
- Kamisawa T, Funata N, Hayashi Y, *et al.* A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003;38:982–4.
- Notohara K, Burgart LJ, Yadav D, *et al.* Idiopathic chronic pancreatitis with periductal lymphoplasmacytic infiltration. Clinicopathologic features of 35 cases. *Am J Surg Pathol* 2003;27:1119–27.
- Kamisawa T, Egawa N, Nakajima H, *et al.* Morphological changes after steroid therapy in autoimmune pancreatitis. *Scand J Gastroenterol* 2004;39:1154–8.
- Chari ST, Smyrk TC, Levy MJ, *et al.* Autoimmune pancreatitis: diagnosis using histology, imaging, serology, other organ involvement and response to steroids. *Clin Gastroenterol Hepatol* 2006;4:1010–16.
- Kim KP, Kim MH, Kim JC, *et al.* Diagnostic criteria for autoimmune chronic pancreatitis revised. *World J Gastroenterol* 2006;12:2487–96.

Recent advances in clinical practice

- 19 Ghazale A, Chari ST, Zhang L, *et al.* Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. *Gastroenterology* 2008;134:706–15.
- 20 Topazian M, Witzig TE, Smyrk TC, *et al.* Rituximab therapy for refractory biliary strictures in immunoglobulin G4-associated cholangitis. *Clin Gastroenterol Hepatol* 2008;6:364–6.
- 21 Moon SH, Kim MH, Park DH, *et al.* Is a 2-week steroid trial after initial negative investigation for malignancy useful in differentiating autoimmune pancreatitis from pancreatic cancer? A prospective outcome study. *Gut* 2008;57:1704–12.
- 22 Chari ST, Takahashi N, Levy MJ, *et al.* A diagnostic strategy to distinguish autoimmune pancreatitis from pancreatic cancer. *Clin Gastroenterol Hepatol* 2009;10:1097–103.
- 23 Shimosegawa T, Chari ST, Frulloni L, *et al.* International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas* 2011;40:352–8.
- 24 Hart PA, Topazian MD, Witzig TE, *et al.* Treatment of relapsing autoimmune pancreatitis with immunomodulators and rituximab: the Mayo Clinic experience. *Gut* Published Online First: 30 Aug 2012. doi:10.1136/gutjnl-2012-302886
- 25 Ectors N, Maillet B, Aerts R, *et al.* Non-alcoholic duct destructive chronic pancreatitis. *Gut* 1997;41:263–8.
- 26 Zamboni G, Luttges J, Capelli P, *et al.* Histopathological features of diagnostic and clinical relevance in autoimmune pancreatitis: a study on 53 resection specimens and 9 biopsy specimens. *Virch Arch* 2004;445:552–63.
- 27 Stone JH, Khosroshahi A, Deshpande V, *et al.* Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. *Arthritis Rheum* 2012;64:3061–7.
- 28 Umehara H, Okazaki K, Masaki Y, *et al.* Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 2012;22:21–30.
- 29 Shimosegawa T; Working group members of the Japan Pancreas Society; Research Committee for Intractable Pancreatic Disease by the Ministry of Labor, Health and Welfare of Japan. The amendment of the Clinical Diagnostic Criteria in Japan (JPS2011) in response to the proposal of the International Consensus of Diagnostic criteria (ICDC) for autoimmune pancreatitis. *Pancreas* 2012;41:1341–2.
- 30 Schneider A, Lohr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classification of the disease. *J Gastroenterol* 2007;42:101–19.
- 31 Frulloni L, Scattolini C, Falconi M, *et al.* Autoimmune pancreatitis: differences between the focal and diffuse forms in 87 patients. *Am J Gastroenterol* 2009;104:2288–94.
- 32 Kamisawa T, Chari ST, Giday SA, *et al.* Clinical profile of autoimmune pancreatitis and its histological subtypes: an international multicenter survey. *Pancreas* 2011;40:352–8.
- 33 Pickartz T, Mayerle J, Lerch MM. Autoimmune pancreatitis. *Nat Clin Pract Gastroenterol Hepatol* 2007;4:314–23.
- 34 Frulloni L, Lunardi C, Simone R, *et al.* Identification of a novel antibody associated with autoimmune pancreatitis. *N Engl J Med* 2009;361:2135–42.
- 35 Löhr JM, Faissner R, Koczan D, *et al.* Autoantibodies against the exocrine pancreas in autoimmune pancreatitis: gene and protein expression profiling, and immunoassays identify pancreatic enzymes as a major target of the inflammatory process. *Am J Gastroenterol* 2010;105:2060–71.
- 36 Okazaki K, Uchida K, Miyoshi H, *et al.* Recent concepts of autoimmune pancreatitis and IgG4-related disease. *Clin Rev Allergy Immunol* 2011;41:126–38.
- 37 Okazaki K, Uchida K, Koyabu M, *et al.* Recent advances in the concept and diagnosis of autoimmune pancreatitis and IgG4-related disease. *J Gastroenterol* 2011;46:277–88.
- 38 Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med* 2012;366:539–51.
- 39 Chang MC, Chang YT, Tien YW, *et al.* T-cell regulatory gene CTLA-4 polymorphism/haplotype association with autoimmune pancreatitis. *Clin Chem* 2007;53:1700–5.
- 40 Umemura T, Ota M, Hamano H, *et al.* Association of autoimmune pancreatitis with cytotoxic T-lymphocyte antigen 4 gene polymorphisms in Japanese patients. *Am J Gastroenterol* 2008;103:588–94.
- 41 Schwaiger T, van den Brandt C, Fitzner B, *et al.* Autoimmune pancreatitis in MRL/Mp mice is a T-cell mediated disease responsive to cyclosporine A and rapamycin treatment. *Gut* Published Online First: 5 Apr 2013. doi:10.1136/gutjnl-2012-303635
- 42 Umemura T, Katsuyama Y, Hamano H, *et al.* Association analysis of Toll-like receptor 4 polymorphisms with autoimmune pancreatitis. *Hum Immunol* 2009;70:742–6.
- 43 Guenther A, Aghdassi A, Muddana V, *et al.* Toll-like receptor 4 polymorphisms in German and US patients are associated with occurrence or severity of acute pancreatitis. *Gut* 2010;59:1154–5.
- 44 Kawa S, Ota M, Yoshizawa K, *et al.* HLA DRB10405-DQB10401 haplotype is associated with autoimmune pancreatitis in the Japanese population. *Gastroenterology* 2002;122:1264–9.
- 45 Park DH, Kim MH, Oh HB, *et al.* Substitution of aspartic acid at position 57 of the DQB1 affects relapse of autoimmune pancreatitis. *Gastroenterology* 2008;134:440–6.
- 46 Seleznik GM, Reding T, Romrig F, *et al.* Lymphotoxin β receptor signalling promotes development of autoimmune pancreatitis. *Gastroenterology* 2012;143:1361–74.
- 47 Sendler M, Dummer A, Weiss FU, *et al.* Tumor necrosis factor α secretion induces protease activation and acinar cell necrosis in acute experimental pancreatitis in mice. *Gut* 2013;62:430–9.
- 48 Krüger B, Lerch MM, Tessenow W. Direct detection of premature protease activation in living pancreatic acinar cells. *Lab Invest* 1998;78:763–4.
- 49 Halangk W, Krüger B, Ruthenbürger M, *et al.* Trypsin activity is not involved in premature, intrapancreatic trypsinogen activation. *Am J Physiol Gastrointest Liver Physiol* 2002;282:G367–74.
- 50 Ellis I, Lerch MM, Whitcomb DC. Genetic testing for hereditary pancreatitis: guidelines for indications, counselling, consent and privacy issues. *Pancreatology* 2001;1:405–15.
- 51 Zenker M, Mayerle J, Lerch MM, *et al.* Deficiency of UBR1, a ubiquitin ligase of the N-end rule pathway, causes pancreatic dysfunction, malformations and mental retardation (Johanson-Blizzard syndrome). *Nat Genet* 2005;37:1345–50.
- 52 Mayerle J, Dummer A, Sendler M, *et al.* Differential roles of inflammatory cells in pancreatitis. *J Gastroenterol Hepatol* 2012;27(Suppl 2):47–51.
- 53 Kanno H, Nose M, Itoh J, *et al.* Spontaneous development of pancreatitis in the MRL/Mp strain of mice in autoimmune mechanism. *Clinical and experimental immunology* 1992;89:68–73.
- 54 Qu WM, Miyazaki T, Terada M, *et al.* A novel autoimmune pancreatitis model in MRL mice treated with polyinosinic:polycytidylic acid. *Clinical and experimental immunology* 2002;129:27–34.
- 55 Ota M, Ito T, Umehara T, *et al.* Polymorphism in the KCNA3 gene is associated with susceptibility to autoimmune pancreatitis in the Japanese population. *Dis markers* 2011;31:223–9.
- 56 Lerch MM, Mayerle J. The benefits of diagnostic ERCP in autoimmune pancreatitis. *Gut* 2011;60:565–6.
- 57 Song TJ, Kim JH, Kim MH, *et al.* Comparison of clinical findings between histologically confirmed type 1 and type 2 autoimmune pancreatitis. *J Gastroenterol Hepatol* 2012;27:700–8.
- 58 Kamisawa T, Kim MH, Liao WC, *et al.* Clinical characteristics of 327 Asian patients with autoimmune pancreatitis based on Asian diagnostic criteria. *Pancreas* 2011;40:200–5.
- 59 Takayama M, Hamano H, Ochi Y, *et al.* Recurrent attacks of autoimmune pancreatitis result in pancreatic stone formation. *Am J Gastroenterol* 2004;99:932–7.
- 60 Kim JH, Kim MH, Byun JH, *et al.* Diagnostic Strategy for Differentiating Autoimmune Pancreatitis From Pancreatic Cancer: Is an Endoscopic Retrograde Pancreatography Essential? *Pancreas* 2012;41:639–47.
- 61 Sugumar A, Chari ST. Distinguishing pancreatic cancer from autoimmune pancreatitis: a comparison of two strategies. *Clin Gastroenterol Hepatol* 2009;7:559–62.
- 62 Kamisawa T, Imai M, Chen YO, *et al.* Strategy for differentiating autoimmune pancreatitis from pancreatic cancer. *Pancreas* 2008;37:e62–7.
- 63 Sugumar A, Levy MJ, Kamisawa T, *et al.* Endoscopic retrograde pancreatography criteria to diagnose autoimmune pancreatitis: an international multicentre study. *Gut* 2011;60:666–70.
- 64 Moon SH, Kim MH. The role of endoscopy in the diagnosis of autoimmune pancreatitis. *Gastrointest Endosc* 2012;76:645–56.
- 65 Kamisawa T, Shimosegawa T. Pancreas: Histological diagnostic criteria for autoimmune pancreatitis. *Nat Rev Gastroenterol Hepatol* 2012;9:8–10.
- 66 Detlefsen S, Drewes A, Mohr, Vyberg M, *et al.* Diagnosis of autoimmune pancreatitis by core needle biopsy: application of six microscopic criteria. *Virchows Arch* 2009;454:531–9.
- 67 Mizuno N, Bhatia V, Hosoda W, *et al.* Histological diagnosis of autoimmune pancreatitis using EUS-guided trucut biopsy: a comparison study with EUS-FNA. *J Gastroenterol* 2009;44:742–50.
- 68 Brais RJ, Davies SE, O'Donovan M, *et al.* Direct histological processing of EUS biopsies enables rapid molecular biomarker analysis for interventional pancreatic cancer trials. *Pancreatology* 2012;12:8–15.
- 69 Fusaroli P, Saftoiu A, Mancino MG, *et al.* Techniques of image enhancement in EUS (with videos). *Gastrointest Endosc* 2011;74:645–55.
- 70 Hocke M, Ignee A, Dietrich CF. Contrast-enhanced endoscopic ultrasound in the diagnosis of autoimmune pancreatitis. *Endoscopy* 2011;43:163–5.
- 71 Dietrich CF, Hirsch TO, Ott M, *et al.* Real-time tissue elastography in the diagnosis of autoimmune pancreatitis. *Endoscopy* 2009;41:718–20.
- 72 Kamisawa T, Takuma K, Anjiki H, *et al.* Differentiation of autoimmune pancreatitis from pancreatic cancer by diffusion-weighted MRI. *Am J Gastroenterol* 2010;105:1870–5.
- 73 Kamisawa T, Takuma K, Anjiki H, *et al.* FGD-PET/CT findings of autoimmune pancreatitis. *Hepatogastroenterology* 2010;57:447–50.
- 74 Endo T, Takizawa S, Tanaka S, *et al.* Amylase α -2A autoantibodies: novel marker of autoimmune pancreatitis and fulminant type 1 diabetes. *Diabetes* 2009;58:732–7.
- 75 Kamisawa T, Okazaki K, Kawa S, *et al.* Japanese consensus guidelines for management of autoimmune pancreatitis: III. Treatment and prognosis of AIP. *J Gastroenterol* 2010;45:471–7.
- 76 Kim MH, Moon SH. The need for a consensus on the definition of remission of autoimmune pancreatitis after steroid treatment. *Gut* 2010;59:1730.
- 77 Iida H, Kubota K, Yoneda M, *et al.* A Case of Autoimmune pancreatitis developed pancreatic tail cancer. *Pancreas* 2009;38:483–4.
- 78 Maire F, Le Baleur Y, Rebours V, *et al.* Outcome of patients with type 1 or 2 autoimmune pancreatitis. *Am J Gastroenterol* 2011;106:151–6.



Recent advances in autoimmune pancreatitis: type 1 and type 2

Terumi Kamisawa, Suresh T Chari, Markus M Lerch, et al.

Gut published online June 8, 2013
doi: 10.1136/gutjnl-2012-304224

Updated information and services can be found at:
<http://gut.bmj.com/content/early/2013/06/08/gutjnl-2012-304224.full.html>

These include:

References

This article cites 75 articles, 12 of which can be accessed free at:
<http://gut.bmj.com/content/early/2013/06/08/gutjnl-2012-304224.full.html#ref-list-1>

P<P

Published online June 8, 2013 in advance of the print journal.

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections

Articles on similar topics can be found in the following collections

[GUT Recent advances in clinical practice](#) (61 articles)
[Pancreas and biliary tract](#) (1813 articles)
[Pancreatitis](#) (490 articles)

Notes

Advance online articles have been peer reviewed, accepted for publication, edited and typeset, but have not yet appeared in the paper journal. Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>