Autoimmune Pancreatitis

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Over the course of the last 2 decades our knowledge of autoimmune pancreatitis has increased exponentially. In this review, we summarize the clinical presentation, diagnosis and treatment of AIP, to better allow general gastroenterologists and primary care providers to consider AIP as a as a rare but important cause of painless obstructive jaundice and recurrent acute pancreatitis. While steroids remain the mainstay of first line therapy, a number of patients with type 1 AIP require immunomodulators or rituximab to maintain remission; recommendations on the management of relapses continue to evolve.

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INTRODUCTION

While Sarles et al. [1] first reported pancreatitis associated with increased immunoglobulin levels, the first reports of two patients with coexistent Reidel thyroiditis and retroperitoneal fibrosis respectively were published in 1963 by Bartholomew et al. [2]. Both these patients had undergone abdominal exploration for suspected pancreatic malignancy with obstructive jaundice, but biopsies did not reveal malignancy and instead showed inflammatory fibrosis and eosinophilia. A few years later, a similar patient was reported by Comings et al., who had retroperitoneal and mediastinal fibrosis, sclerosing cholangitis, and orbital pseudotumor. They proposed that these physically distinct and apparently unrelated manifestations may actually be due to a single underlying process [3]. Patients thought to have primary sclerosing cholangitis (PSC) with concurrent pancreatic involvement and associated with other autoimmune disorders such as inflammatory bowel disease, Sjogren syndrome, systemic lupus erythematosus in various combinations were reported [4–16]. A number of these patients had complete gross and histologic reversal with steroid therapy. Kawaguchi et al. [17] described 'a variant of primary sclerosing cholangitis extensively involving pancreas', a finding they termed lymphoplasmacytic sclerosing pancreatitis (LPSP). About two years later, Chari et al. [18] described the association of certain subsets of chronic pancreatitis with autoimmune diseases and proposed that these be classified separately as 'chronic autoimmune pancreatitis'. Shortly after that, Yoshida et al. [19] established the concept of autoimmune pancreatitis (AIP) by demonstrating a prompt response to steroids in a case of chronic pancreatitis with elevated gammaglobulin levels. In a landmark study, elevated IgG4 antibodies were found to be elevated in patients with AIP [20] and Kamisawa et al. [21] described that similar histologic changes i.e., infiltration of tissues with IgG4 positive plasma cells along with storiform fibrosis and obliterative phlebitis occurred in multiple sites e.g., bile ducts (now known as IgG4-associated cholangitis or IAC), salivary glands (chronic sclerosing sialadenitis), kidney (tubulointerstitial nephritis), retroperitoneal fibrosis and concluded that AIP is indeed a multisystem IgG4-related disease (IgG4 RD) [21–23]. This systemic form of AIP, characterized by involvement of multiple organs is now known as Type 1 AIP. Type 1 AIP is associated with elevated IgG4 levels in a majority of patients, and the presence of LPSP histologically.

Meanwhile, investigators from Europe described a subset of patients with non-alcoholic duct destructive chronic pancreatitis. These patients had features very distinct from alcoholic chronic pancreatitis. Whereas some of the described features overlapped with LPSP i.e., lymphoplasmacytic infiltration and fibrosis, the presence of a duct-centric neutrophilic infiltrate, along with duct destruction were characteristically different. The authors proposed the term 'chronic duct destructive pancreatitis' to describe their findings. Only 4 out of the 12 patients reported had a clear association with other extrapancreatic autoimmune diseases [24]. In a later series from Mayo Clinic, we described 35 patients with idiopathic chronic pancreatitis who had periductal lymphoplasmacytic infiltration. twenty two out of these had features similar to LPSP. The remaining 13 were younger, had an almost similar male to female distribution and were histologically characterized by a neutrophilic infiltrate associated with duct destruction and obliteration [25], similar to those described from Europe [24, 26]. This form of inflammation was termed idiopathic duct-centric pancreatitis (IDCP); the neutrophilic lesion was eventually termed granulocyte epithelial lesion (GEL) and is now well described as the histologic hallmark of IDCP [27]. Over the coming few years, as characteristics of patients with IDCP got better defined, it was established as a distinct type of autoimmune pancreatitis (Type 2 AIP), characterized mainly by a younger age at presentation, the absence of extrapancreatic involvement, lack of association with elevated IgG4 elevation and its association with inflammatory

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bowel disease [28]. International consensus diagnostic criteria (ICDC) for AIP were established in 2011 to achieve consistency in the definition and terminology, and to formally define criteria for the diagnosis of type 1 and type 2 AIP [29]. Even though the terms Type 1 and Type 2 AIP have been commonly used in literature, for the purpose of this review and to avoid confusion between the distinctive subtypes, we will refer to type 1 AIP as LPSP and Type 2 AIP as IDCP in subsequent sections of this review. We will use the term AIP as an inclusive term to describe features applicable to both LPSP and IDCP.

LYMPHOPLASMACYTIC SCLEROSING PANCREATITIS (LPSP)

Clinical presentation

Patients with LPSP most commonly present with painless obstructive jaundice. Despite the intense underlying inflammation in the pancreata of these patients, LPSP tends to be relatively painless and the presence of narcotic requiring abdominal pain suggests an alternative diagnosis. The typical patient with LPSP is over 60–70 years of age, and males are affected three times more often as females. Other clinical presentations include a pancreatic mass on imaging, focal or diffuse pancreatic enlargement, pancreatic ductal strictures and rarely, acute pancreatitis [28, 30]. As LPSP is the pancreatic manifestation of a systemic IgG4- related disorder (IgG4-RD), extrapancreatic involvement is often seen in these patients. This most commonly manifests in the form IgG4-associated cholangitis (IAC), seen in up to 80% patients with LPSP [30, 31]. A number of other organs can also be involved in LPSP. These include orbital pseudotumor (IgG4- associated pseudolymphoma), IgG4-related plasmacytic exocrinopathy of the salivary gland, pulmonary interstitial fibrosis and nodules, mediastinal or retroperitoneal fibrosis and tubulointerstitial nephritis [32–35]. Interestingly, intraabdominal involvement is not very common in patients with IgG4-RD above the diaphragm (e.g., such as those with IgG4 related orbital pseudotumor) [36]. It should be noted that while the involvement of other organs is supportive, the absence of other organ involvement does not rule out LPSP, and isolated pancreatic involvement can be seen in about 50% of the patients [28]. Also, LPSP may coexist with underlying pancreatic adenocarcinoma, and steroids should only be initiated after underlying malignancy has been completely ruled out. We use the modified HISORt (Histology, Imaging, Serology, Other organ involvement, and Response to therapy) criteria for diagnosis of AIP, a schematic of which is shown below in Fig. 1 and discussed in further detail in our previous publications [37, 38]. Besides serological criteria which are detailed below in laboratory findings, the characteristic features of the criteria that comprise Histological, Imaging, Other organ involvement, and Response to therapy components of HISORt are also shown below in Figs. 2–5 respectively. The ICDC criteria, which were developed after review of the existing criteria, including the Japanese Pancreatic Society, HISORt, Korean, Asian, Mannheim and Italian criteria, can also be used [29, 38–43]. However, in their current form, the ICDC criteria suggest the use of endoscopic retrograde pancreatography (ERP) for ductal imaging, which is not routinely performed to diagnose AIP in the West [29]. Therefore, we suggest using non-invasive modalities such as computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) if using the ICDC criteria in the Western setting.

Laboratory findings

Patients with LPSP most commonly present with a cholestatic pattern of liver enzyme elevation. Besides this, elevated IgG4 levels ($>2\times$ the upper limit of normal) are a 'Level 1' criterion for the diagnosis of LPSP according to the and are seen in about 2/3rd of patients with LPSP, consistent with the thought that LPSP is the pancreatic manifestation of an IgG4 criteria [29, 37]. Using the higher threshold (i.e., $>2\times$ times the normal IgG4) leads to a lower sensitivity in differentiating LPSP from pancreatic cancer but increases the specificity to 99% [44]. However, in combination with other features of AIP as shown in Fig. 1, an IgG4 elevation $<2\times$ the upper limit of normal may also be diagnostic. It should be noted that about 10% of patients with pancreatic cancer may have elevated serum IgG4 values, and 1% have elevation $>2\times$ the upper limit of normal [44]. Other antibodies that have been reported to be associated with autoimmune pancreatitis include antibodies to carbonic anhydrase, Lactoferrin, antimitochondrial antibodies (AMA), antismooth muscle antibodies (ASMA) and antithyroglobulin [19, 45–48]. Recently, antibodies against a peptide homologous to an amino-acid sequence of plasminogen-binding protein (PBP) of Helicobacter pylori was reported to be positive patients with AIP but was also found to be positive in 5% patients with pancreatic cancer [49].

Radiology and endoscopy

Pancreatic findings on abdominal CT or magnetic resonance imaging (MRI) are often the initial findings that raise the suspicion of underlying pancreatic cancer. It should be kept in mind that AIP (LPSP and IDCP) are overall uncommon as compared to pancreatic cancer; therefore, the diagnosis of AIP should be considered once a thorough workup for underlying pancreatic cancer is negative. Diffuse enlargement of the pancreas (also referred to as sausage-shaped pancreas) with delayed enhancement on CT suggests possible LPSP and is a Level 1 diagnostic criterion for the same [29, 50–52]. A low-attenuating rim-like capsule may be seen in only about 30–40% patients but is very specific for AIP [52]. Findings on MRI include diffuse hypointensity on T1-weighted images, and slightly hyperintensity on T2-weighted images, along with heterogeneously diminished enhancement during the early phase and delayed enhancement during the late phase of contrast enhancement [53, 54]. Positron emission tomography (PET) is not required for diagnosis. When performed due to suspicion for underlying pancreatic cancer and staging, it may show intense, diffuse or focal fluorine-18 fluorodeoxyglucose (FDG) uptake in the inflamed areas of the pancreas, which resolves with steroid treatment. Therefore, a single PET scan may not allow for a distinction to be made between pancreatic cancer and AIP [55].

MRCP and Endoscopic retrograde cholangiopancreatography (ERCP) may reveal diffuse narrowing of the pancreatic duct with long (>1/3rd of the pancreatic duct) or multifocal strictures, with

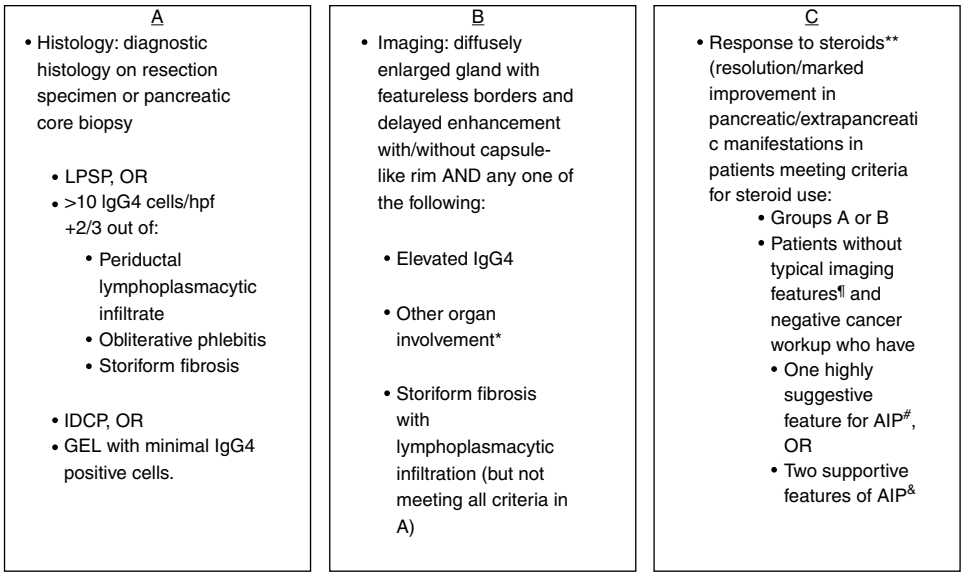

Fig. 1 Diagnosis of autoimmune pancreatitis. Patients meeting criteria as listed in any of the boxes **a–c** can be diagnosed as having AIP. Modified and adapted from Chari et al., 2009 [38]. **The authors strongly discourage using a trial of steroids in the absence of collateral evidence and definitive histology, solely to distinguish between AIP and PDAC. ∗Typical histology in affected organ OR typical radiologic features + positive IgG4 immunostain in affected organ OR radiologic evidence of hilar/intrahepatic biliary strictures, renal involvement, retroperitoneal fibrosis, parotid/lacrimal gland enlargement, positive IgG4 immunostaining in other organs (gallbladder, ampulla), inflammatory bowel disease (seen in 30% patients with IDCP; Only 6% with LPSP so not considered other organ involvement for LPSP). ¶Focally enlarged gland without features highly suggestive of cancer (low density mass, pancreatic ductal dilatation/cutoff, upstream pancreatic atrophy or liver lesions suggestive of, or biopsy proven metastases). #Serum IgG4 >2 times upper limit of normal or definitive other organ involvement & Supportive features of AIP: <2-fold elevation of IgG4, clinical/radiologic, evidence of other organ involvement (radiologic evidence of hilar/intrahepatic biliary strictures, renal involvement, retroperitoneal fibrosis, parotid/lacrimal gland enlargement, positive IgG4 immunostaining in other organs, inflammatory bowel disease, compatible histology as listed in Box B. LPSP lymphoplasmacytic sclerosing pancreatitis, IDCP idiopathic duct centric pancreatitis, GEL granulocyte epithelial lesion, AIP autoimmune pancreatitis, hpf high-power field

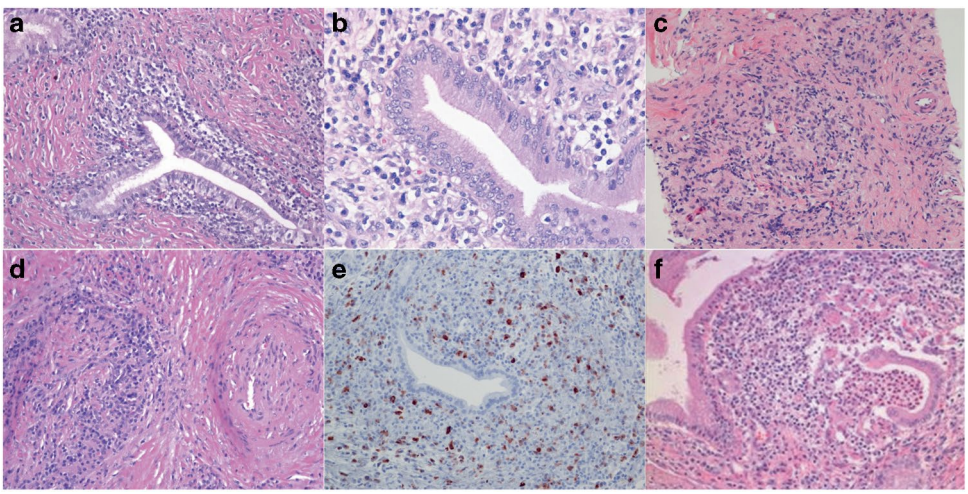

Fig. 2 Characteristic features of LPSP and IDCP. Histological features of LPSP (Images **a**–**e**) and IDCP (Image **f**). **a** Low power and **b** High power view of lymphoplasmacytic infiltration surrounding the duct, **c** Storiform fibrosis, **d** Obliterative phlebitis, **e** IgG4 infiltration (>10/ hpf) and **f** GEL (granulocyte epithelial lesion) showing neutrophilic infiltration with duct epithelial destruction

lack of upstream dilatation and side branches originating from a strictured segment [56]. However, it should be noted that ERCP alone is not a reliable modality to diagnose AIP. ERCP is also not reliably able to distinguish IAC, which is the most common extrapancreatic manifestation of AIP, from primary sclerosing cholangitis or cholangiocarcinoma [57].

Histology

Because ruling out malignancy is of paramount importance, obtaining pancreatic tissue is critical to definitively distinguish AIP from pancreatic cancer. While fine needle aspiration (FNA) usually suffices for the diagnosis of adenocarcinoma, the diagnosis of AIP can be difficult and often requires a larger sample than can

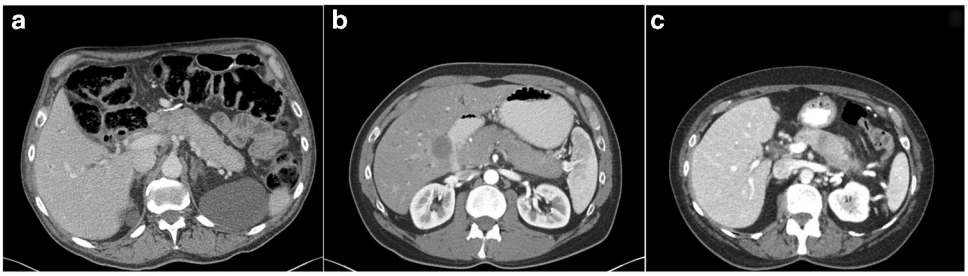

Fig. 3 Pancreatic Imaging findings of AIP. **a** Diffuse enlargement of the pancreas with peripheral rim-like hypoenhancement; **b** diffuse enlargement without peripheral hypoenhancement and **c** mass-like presentation

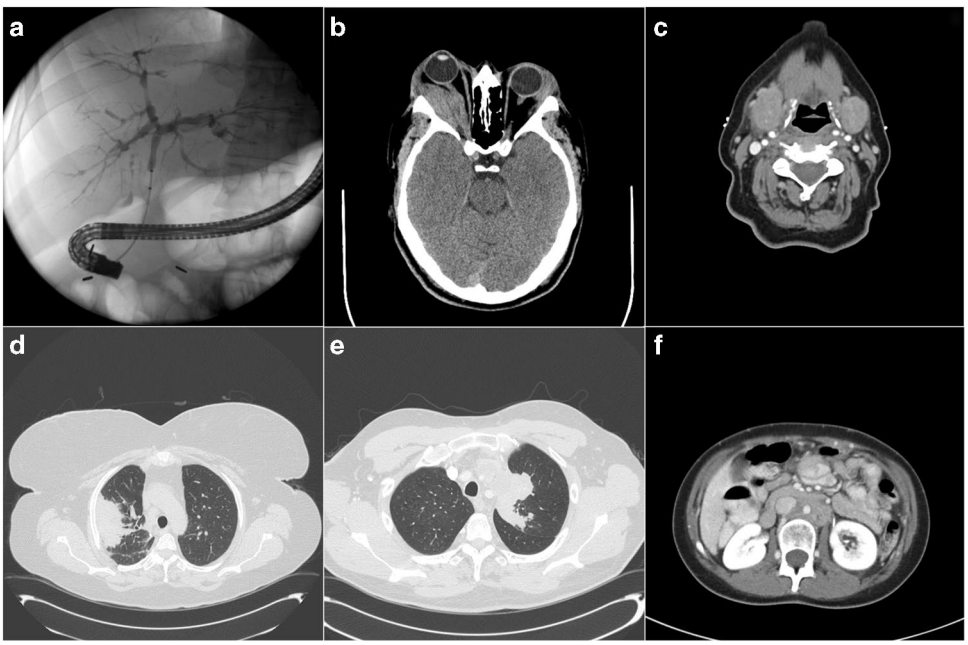

Fig. 4 Other organ involvement in LPSP. **a** Cholangiogram revealing extensive biliary stricturing from IgG4-associated cholangitis; **b** orbital pseudolymphoma; **c** submandibular gland involvement; **d** interstitial lung disease; **e** mediastinal involvement, and **f** retroperitoneal involvement

be provided by FNA. Endoscopic ultrasound (EUS) guided trucut biopsy has been proposed as a means to overcome this difficulty and allows for a larger tissue sample with preserved architecture to be collected [58]. The use of trucut biopsy is also endorsed by the ICDC [29]. However, when needles for EUS-trucut biopsy sampling are not commercially available, the use of 22 G and 19 G needles has been reported [59, 60]. Besides definitive histology, no other feature is pathognomonic for AIP.

Patients with LPSP have characteristic histologic features comprising of lymphoplasmacytic infiltration, usually in a single file between thick, swirling collagen fibers (storiform fibrosis), along with obliterative phlebitis [17] (Fig. 2). The presence of positive immunostaining for IgG4 in plasma cell infiltrates (>10 cells per high power field) provides support for LPSP [61]. Lymphoid follicles may be seen at the periphery of the interlobular pancreatic ducts and in adipose tissue. Fat necrosis and pseudocyst formation and calcification are not observed [26, 28, 62, 63]. Similar histological changes can be appreciated on biopsies from extrapancreatic sites [36, 64–74].

Treatment and long-term outcomes

While steroids are considered the mainstay of initial treatment, there is emerging evidence on the use of other immunomodulators and rituximab. Most patients with LPSP have remarkable initial improvement with the use of prednisone, as evidenced by a rapid decrease in liver enzymes. We recommend using high dose prednisone at 40 mg/day for 4 weeks, although some have suggested that a lower dose (20 mg/day) may be used [75]. After 4 weeks, response can be assessed with clinical evaluation, radiology, and serology (IgG4 levels) [31]. If clinical, serologic and radiologic response is documented at 4 weeks, the dose of prednisone can be tapered by 5 mg/week. We have demonstrated excellent response to steroids in patients with LPSP limited to the pancreas as well as those with extrapancreatic disease [31, 76]. A lower dose (30 mg/day) can be considered in patients with pre-existing diabetes. In a select group of patients who have had a negative evaluation for malignancy, a therapeutic trial of steroids may be undertaken for 2 weeks with reassessment at the end of the trial period [77]. Alternatively, rituximab can be used for induction of

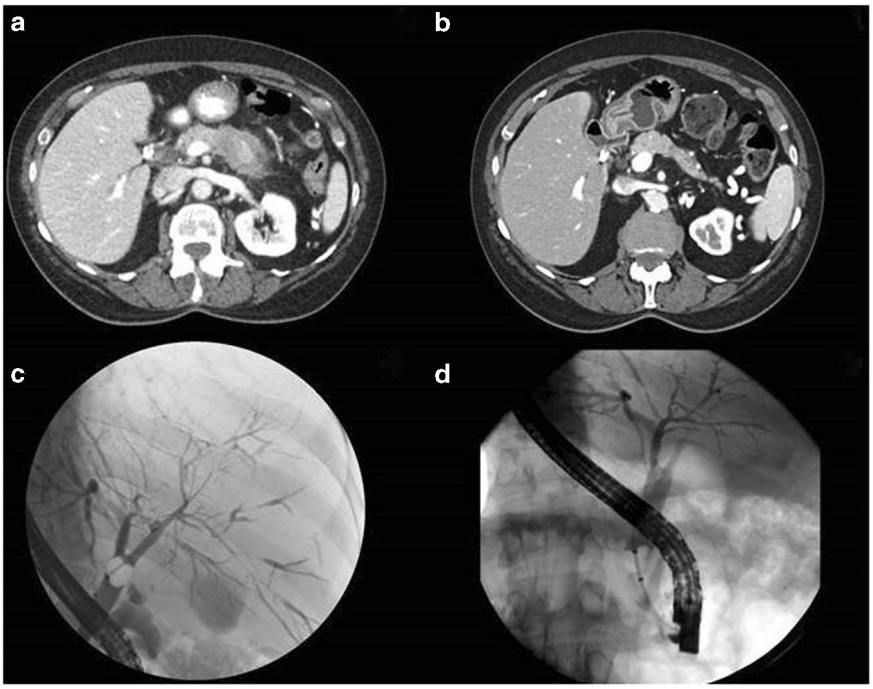

Fig. 5 Response to therapy in patients with AIP. Images **a** and **b** show a computed tomography (CT) scan of a patient with LPSP and images **c**, **d** show the cholangiogram of a patient with IgG4-associated cholangitis (IAC) demonstrating response to treatment

remission as a first line agent if steroids are absolutely contraindicated [76]. Rituximab can also be considered as initial treatment for patients at a high risk of relapse, such as those with proximal biliary involvement, younger age and high alkaline phosphatase levels at initial presentation [78]. To date, there have been no randomized clinical trials among patients with AIP assessing or comparing the efficacy of steroids or other therapies for the induction of remission in these patients.

A timely diagnosis of LPSP can help avoid a delay in treatment and prevent resultant complications. Pancreatic atrophy can be seen in up to 25% of patients and this may manifest as exocrine pancreatic insufficiency or pancreatogenic (Type 3c) diabetes mellitus. Patients with extrapancreatic involvement (e.g., IAC) with concurrent LPSP may also have accelerated progression to secondary biliary cirrhosis if untreated. In our previous study on patients with IAC, 4 out 53 patients developed portal hypertension due to cirrhosis. Three out of these were treatment-naive and the fourth patient was a non-responder to treatment [31]. There are conflicting data on whether LPSP (or IDCP) increase the risk of pancreatic malignancy, although overall it does not appear to be the case [79]. On the contrary, in a subset of patients, a high incidence of extrapancreatic cancers was reported within the first year of diagnosis of AIP, suggesting that in these patients AIP may be a paraneoplastic phenomenon secondary to the underlying malignancy [80]. Other reports have also suggested this association [81].

Despite remarkable improvement seen after initial treatment with steroids, patients with LPSP have a high likelihood of having subsequent relapses, which can be seen in up to 60% of patients [26, 51, 82–84]. This is similar to what we had reported in our previous study where relapse rates of 25%, 44% and 59% were seen at 1,2 and 3 years respectively [28]. Relapses can be managed with a repeat course of prednisone or rituximab. Considering the high likelihood of relapsing disease, consideration of a regimen to maintain remission should be a priority, even on the initial presentation of LPSP. This is especially true for patients deemed to be at a higher risk for relapse (such as those with intrahepatic and suprapancreatic portion of the common bile duct, those with diffuse pancreatic enlargement, younger age, higher IgG4-Responder Index (IgG4-RI) score after induction therapy, and elevated serum alkaline phosphatase levels either at baseline or after RTX induction) [78]. Studies from Japan suggest the use of a prolonged taper followed by a low dose of steroids (2.5–10 mg/day) for 1–3 years and sometimes even indefinitely [85]. In our experience, azathioprine (2 mg/kg daily) or mycophenolate mofetil (750 mg twice daily) also appear to be effective in maintaining remission and allow for a steroid-free regimen to be used for these patients (REF). Alternatively, rituximab may be used to maintain remission [76]. Our suggested approach to relapses is detailed in Fig. 6.

IDIOPATHIC DUCT-CENTRIC PANCREATITIS (IDCP)

Clinical presentation

In contrast to LPSP, patients with IDCP tend to be younger, with a mean age of about 40–50 years. IDCP affects males and females in 1:1 ratio. Patients with IDCP tend to present mostly with recurrent acute pancreatitis, which affects nearly 50% of these patients. Similar to LPSP, others might present as painless obstructive jaundice, focal pancreatic mass and pancreatic ductal strictures. Although IDCP is confined to the pancreas, and extrapancreatic involvement is characteristically absent, it is more strongly associated

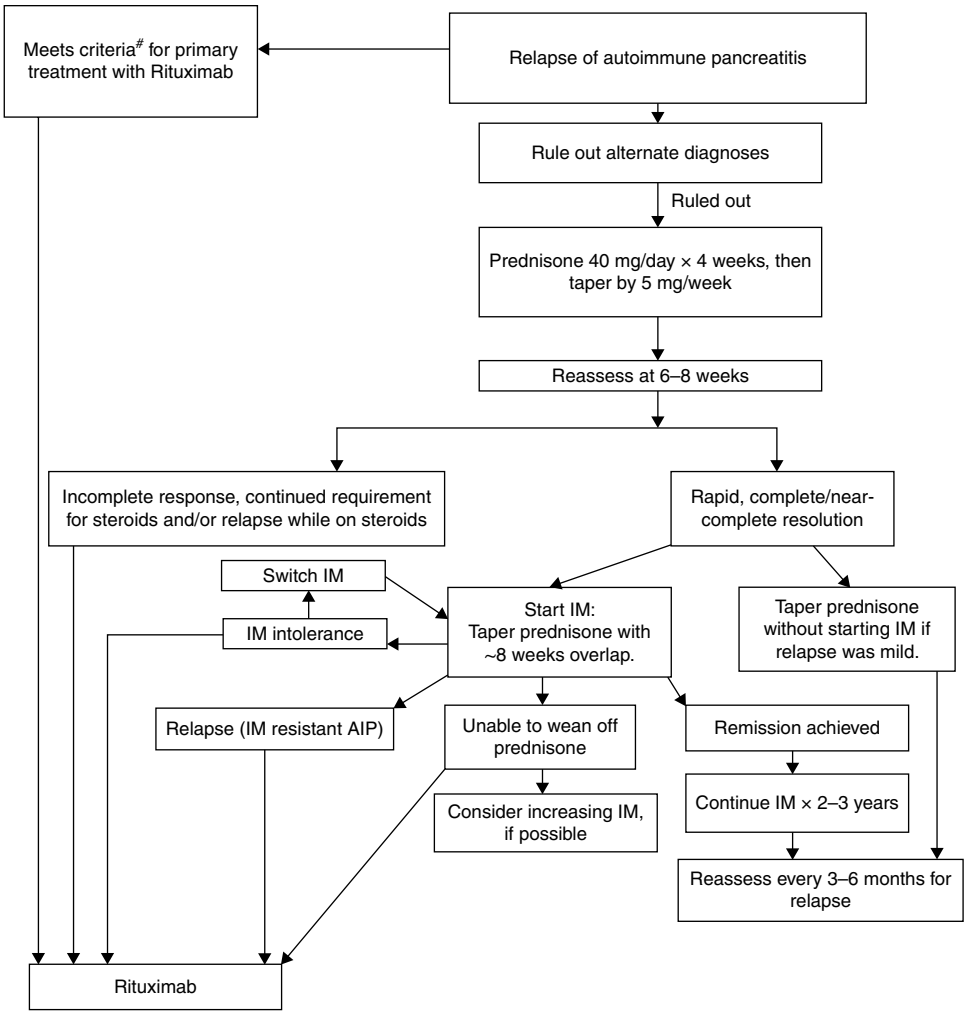

Fig. 6 Suggested algorithm for management of relapses of AIP (LPSP»IDCP). # see text for indications for use of rituximab

with concurrent IBD (predominantly ulcerative colitis) as compared to LPSP [28]. In fact, in a patient suspected to have IDCP, the presence of IBD is a supportive (Level 2) diagnostic criterion [29]. The presence of concurrent IBD may also make it more likely for patients with IDCP to present with acute pancreatitis.

Laboratory findings

A cholestatic pattern of elevation might be seen in patients with IDCP, as seen in LPSP. However, only about 25% of patients with IDCP have elevated IgG4 levels [86]. There is no laboratory-based test specific to IDCP, so its diagnosis can be challenging and histopathology is the mainstay of diagnosis, which itself can be challenging to obtain.

Histopathology

IDCP is characterized by intense lymphoplasmacytic infiltration and inflammation which more prominent in the periductal regions as compared to the acini [25–27, 35]. The ductal epithelium is infiltrated by neutrophils forming what has been described as the 'GEL', a diagnostic feature of IDCP [25, 26] (Fig. 2). IgG4 + positive cells may be present but in much lower numbers as typically seen in LPSP and constitute <40% of the IgG + plasma cells. As compared to FNA, obtaining an EUS-guided trucut biopsy may provide a better tissue yield, enough to diagnose LPSP [87].

Imaging and endoscopy

The pancreatic findings on imaging and endoscopy in patients with IDCP are very similar to LPSP as detailed above. Table 1 below compares the above-mentioned features of patients with LPSP and IDCP is provided below.

Treatment

The treatment of IDCP is similar to the initial presentation of LPSP and comprises of steroids. The symptoms and inflammation associated with LPSP respond rapidly to corticosteroid therapy. We recommend using prednisone at an initial dose of 40 mg/day for 4 weeks, at which time the response can be assessed with clinical evaluation, radiology and measurement of liver biochemistries. If response is documented, a steroid taper can be initiated at 5 mg/week. As the likelihood of relapses is low (<10%), the risks of long-term immunosuppression outweigh any benefits and therefore, we do not recommend consideration

Table 1 Features of lymphoplasmacytic sclerosing pancreatitis (LPSP; Type 1 AIP) and idiopathic duct-centric pancreatitis (IDCP; Type 2 AIP)

Feature	LPSP	IDCP
Clinical		
Age	7th decade	5th decade
Gender (M:F)	3:1	1:1
Increased serum IgG (>2×)	~2/3rd	~1/4th
Extrapancreatic involvement/association with IgG4 RD	Yes	No
Association with IBD	Weak	Strong (10–20%)
Imaging	Similar imaging features in LPSP and IDCP	
Histology		
Lymphoplasmacytic infiltration	Yes	Yes
Periductal inflammation	Yes	Yes
Storiform fibrosis	More prominent	Less prominent
Obliterative phlebitis	Characteristic	Rare
Granulocyte epithelial lesion (GEL)	Absent	Characteristic
IgG4 staining	Abundant; >10/hpf	Rare; <10/hpf
Treatment		
Response to steroids	~100%	~100%
Relapse	Up to 60%	<10%

of other immunomodulators for maintenance treatment. Also, in the rare case that a relapse does occur it responds very well to steroids.

CONCLUSION

The term AIP comprises two distinct forms of steroid response chronic pancreatitis, LPSP and IDCP. Even though they are clinically and histopathologically distinct, both are characterized by a brisk initial response to steroids. However, LPSP has a relapsing-remitting course and often requires the use of maintenance immunomodulation. On the other hand, IDCP tends not to relapse after initial treatment.

Future directions

Despite significant progress in the field, key questions related to the pathophysiology, diagnosis, and treatment of AIP remain unanswered. While circumstantial evidence that suggests that AIP is indeed an autoimmune process, the precise antigen responsible for triggering the inflammation remains unknown. Also, it is not known why patients with AIP have complete absence of pain AIP despite intense inflammation in and around the pancreas, as compared to other inflammatory conditions of the pancreas such as acute and chronic pancreatitis which can be very painful. Finally, more studies are also required to better define the emerging role of rituximab treatment in terms of frequency and especially, duration and end-points of treatment.

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CONFLICT OF INTEREST

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REVIEW ARTICLE

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