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REVIEW

Autoimmune Pancreatitis

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Abstract Autoimmune pancreatitis (AIP) is a chronic fibroinflammatory disease of the pancreas that belongs to the spectrum of immunoglobulin G-subclass4-related diseases (IgG4-RD) and typically presents with obstructive jaundice. Idiopathic duct-centric pancreatitis (IDCP) is a closely related but distinct disease that mimics AIP radiologically but manifests clinically most commonly as recurrent acute pancreatitis in young individuals with concurrent inflammatory bowel disease. IgG4 levels are often elevated in AIP and normal in IDCP. Histologically, lymphoplasmacytic acinar inflammation and storiform fibrosis are seen in both. In addition, the histologic hallmark of IDCP is the granulocyte epithelial lesion: intraluminal and intraepithelial neutrophils in medium-sized and small ducts with or without granulocytic acinar inflammation often associated with destruction of ductal architecture. Initial treatment of both AIP and IDCP is with oral corticosteroids for duration of 4 weeks followed by a gradual taper. Relapses are common in AIP and relatively uncommon in IDCP, a relatively rare disease for which the natural history is not well understood. For patients with relapsing AIP, treatment with immunomodulators and more recently rituximab has been recommended. Although rare instances of pancreaticobiliary malignancy has been reported in patients with AIP, overall the lifetime risk of developing pancreatic cancer does not appear to be elevated.

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Introduction

Autoimmune pancreatitis (AIP) is a chronic fibroinflammatory steroid-responsive disease of the pancreas. Yoshida et al. [1] introduced the term autoimmune pancreatitis (AIP) in 1995 to describe a inflammatory pancreatic disease reminiscent of autoimmune hepatitis. Earlier, Kawaguchi had studied histopathologic features of this disease and described it as lymphoplasmacytic sclerosing pancreatitis (LPSP) [2]. Subsequently, based on observations by Kamisawa who noted tissue infiltration with IgG4-positive plasma cells in extrapancreatic organs, AIP is now considered to be part of multiorgan disorder called IgG4-related disease (IgG4-RD) [3].

Meanwhile, another group of investigators from Europe described an entity they called "nonalcoholic duct destructive pancreatitis" [4]. This was named idiopathic duct-centric chronic pancreatitis (IDCP) [5] because of a peculiar neutrophilic infiltration in ducts, subsequently described as the "granulocytic epithelial lesion" (GEL) which was associated with duct destruction, a histologic feature not seen in LPSP. LPSP and IDCP share histopathologic and clinical features and the term AIP came to be used for both diseases with LPSP called type 1 AIP and IDCP as type 2 AIP [6]. Although the use of the term AIP to describe both conditions highlights the overlapping clinical and histologic features of the two diseases, it also results in significant confusion since the natural history; diagnostic criteria and treatment approach of the two conditions differ significantly. Therefore, it has recently been proposed that the term AIP be

restricted in its use to describe the clinical phenotype represented by LPSP (currently called type 1 AIP) and IDCP be used for the clinical phenotype represented by IDCP (currently called type 2 AIP). For the purpose of this review, we will follow this recommendation and will use the terms AIP and IDCP, to describe the two entities.

Clinical Presentation

AIP

The most common clinical presentation of AIP is painless obstructive jaundice. This disease typically affects elderly men with a mean age of diagnosis above 60 years and a 3:1 male preponderance. However, all ages may be affected and other less common clinical presentations include focal pancreatic mass, diffuse pancreatic enlargement, pancreatic duct stricture, and rarely acute pancreatitis. Since AIP belongs to the spectrum of IgG4-RD, other organ involvement such bile duct stricture, renal involvement, orbital pseudotumor and extensive lymphadenopathy, are often important supportive diagnostic clues. Interestingly despite this being an intensely inflammatory condition the disease is largely painless, an observation which may have significant implications in understanding the mechanism of pain of pancreatic origin.

IDCP

The most common clinical presentation of IDCP is acute pancreatitis, occurring in nearly 50% of patients. Alternative presentations include painless obstructive jaundice, focal pancreatic mass and symptomatic pancreatic duct stricture. Compared to AIP, IDCP typically affects younger individuals without a gender predilection. In a series of 43 patients from Mayo Clinic the median age of diagnosis was 31 years and approximately half the patients were women [7]. The co-occurrence of inflammatory bowel disease is a supportive diagnostic criterion. In the series mentioned previously, concurrent IBD was present in 44% (19/43) of patients and in majority (15/19) of those patients the diagnosis of IBD preceded or was simultaneously established at the time of diagnosis of IDCP. Interestingly presentation with acute pancreatitis was significantly more common in patients with concurrent IBD.

Serology

AIP

Immunoglobulin subclass 4 (IgG4) is a serologic marker for AIP. Although elevated levels of IgG4 support the diagnosis, normal levels cannot be used to exclude the diagnosis. Also, the utility of trending IgG4 levels to monitor disease response is fairly limited. Recent studies have shown that high pre-treatment IgE levels may identify patients at a higher risk of relapse. This observation was made in a cohort of patients with IgG4-RD treated with rituximab and not specifically in patients with AIP.

IDCP

There is currently no serologic marker available for IDCP and elevated IgG4 levels are not a feature of this disease.

Radiology

AIP

Diffuse parenchymal enlargement is a characteristic radiologic feature of AIP. Enlargement accompanied by effacement of the lobular contour of the pancreas gives the gland a ‘featureless’ or ‘sausage-shaped’ appearance. A low-attenuating capsule-like ‘rim’ around the enlarged pancreas is also a relatively specific finding for AIP. Other less common parenchymal changes include focal mass-like enlargement, segmental low-density area without mass and diffuse pancreatic atrophy. A normal appearing pancreas does not rule out the diagnosis of AIP. Cases with a focal mass can sometimes be radiologically indistinguishable from pancreatic malignancy. The presence of a sharp demarcation between the mass and surrounding normal pancreas, an iso-attenuating mass and the lack of downstream parenchymal atrophy favor a diagnosis of AIP in these cases. Perfusion abnormalities are a useful adjunct to morphologic features and the involved areas of the pancreas typically demonstrate decreased enhancement in the pancreatic phase with gradually increased enhancement in the delayed phase. The most commonly observed ductal change is the presence of diffuse or segmental, often multifocal narrowing of the main pancreatic duct. The presence of a dilated main pancreatic duct is distinctly uncommon at initial presentation and should raise suspicion of an alternative diagnosis. The presence of extrapancreatic involvement in the form of biliary strictures, renal lesions, and retroperitoneal fibrosis if present provide critically important diagnostic clues.

IDCP

In a recently published series the presence of focal mass was the most common radiologic feature of IDCP, noted in about one-third of patients. The next most common was diffuse pancreatic enlargement (28%) and other less

common findings included presence of a low-density segment without mass (13%), interstitial pancreatitis and a normal or atrophic appearing pancreas. In those with diffuse enlargement, the absence of peripancreatic fat stranding favors a diagnosis of IDCP compared to other etiologies of acute pancreatitis. Abnormalities of perfusion and pancreatic ductal changes in IDCP are less well studied due to the relative rarity of this condition (Fig. 1).

Histology

AIP

The histopathologic hallmark of AIP is a triad of, lobular lymphoplasmacytic infiltrate obliterative phlebitis and storiform fibrosis (Fig. 2a) [2]. Although IgG4 immunostaining of the lobular infiltrate provides supportive evidence for the diagnosis, it is non-specific and can be seen both in pancreatitis from other causes and pancreaticobiliary malignancies. A tissue IgG4/IgG ratio >0.4 favors a diagnosis of AIP. Tissue acquisition for histologic diagnosis in AIP is not straightforward, and a surgical biopsy or core biopsy is often necessary for diagnosis. FNA has limited diagnostic role and cytology does not feature in the international consensus diagnostic criteria (ICDC) diagnostic criteria. EUS-guided core biopsy requires technical expertise and tissue yield can be variable. EUS-FNA using a standard 22-gauge FNA needle has poor sensitivity and hence is ineffective as a diagnostic tool for majority of patients with AIP [8]. Using a larger needle does not improve diagnostic yield [9]. Unlike FNA samples, EUS-guided core biopsy and/or surgical biopsy provides tissue specimens with preservation of gland architecture that allows for a histologic diagnosis of AIP. Although core biopsy requires considerable expertise, it appears to be safe and effective [10, 11]. Based on available evidence it can be concluded that EUS-FNA does not enhance existing consensus diagnostic criteria and core biopsy either endoscopic or surgical is the preferred modality of diagnostic tissue acquisition when necessary [12].

IDCP

Histologic features of AIP and IDCP have some features in common and some distinct differences. The presence of a lymphoplasmacytic acinar inflammation and storiform fibrosis are seen in both. The histologic hallmark of IDCP

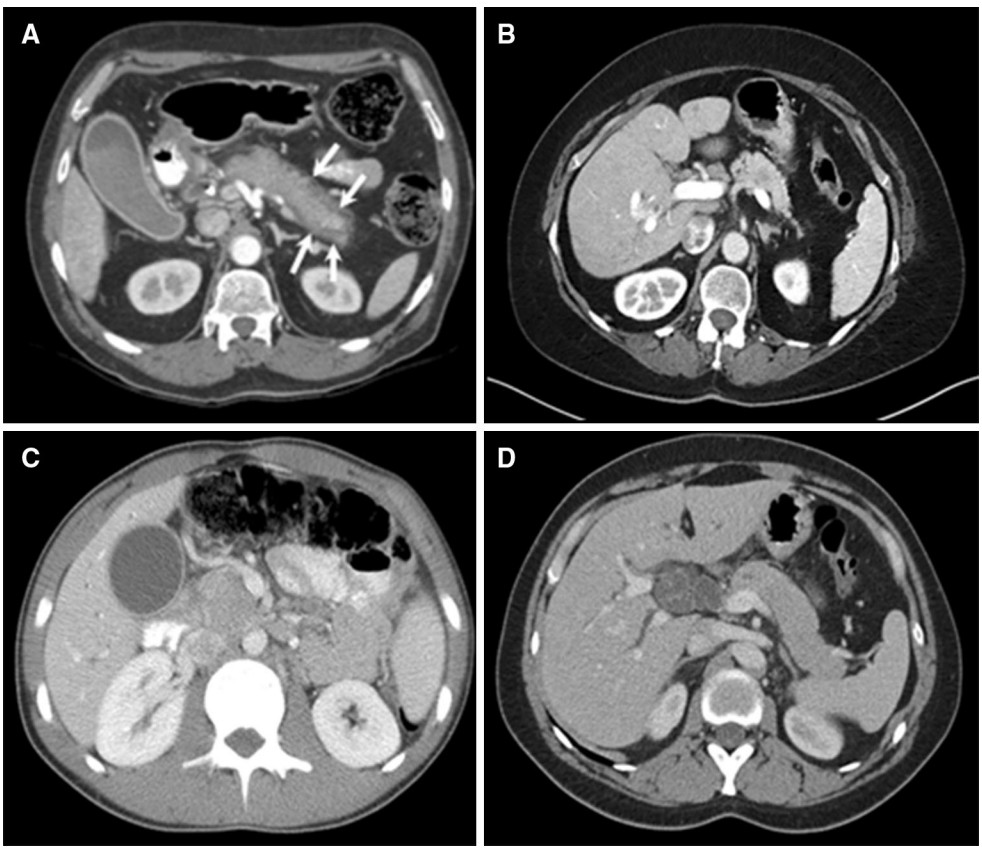

Fig. 1 CT scan demonstrating. **a** Diffuse pancreatic enlargement with enhancing 'rim' characteristic of AIP. **b** AIP presenting as pancreatic mass without pancreatic duct dilation **c** IDCP presenting with focal pancreatic mass **d** Diffuse pancreatic enlargement in IDCP

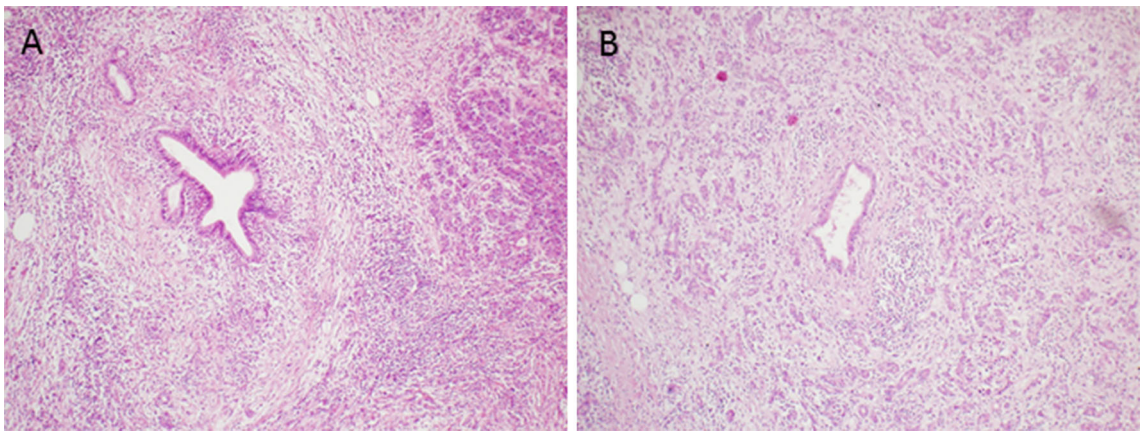

Fig. 2 **a** Histologic features of AIP characterized by periductal dense lymphoplasmacytic infiltrate and storiform fibrosis and **b** IDCP characterized by periductal lymphoplasmacytic infiltrate with edematous stroma and neutrophils in the ductal epithelium-granulocytic epithelial lesion (GEL)

is the granulocyte epithelial lesion (GEL): intraluminal and intraepithelial neutrophils in medium-sized and small ducts as with or without granulocytic acinar inflammation often associated with destruction of ductal architecture (Fig. 2b). Paucity of IgG4-positive plasma cells (<10/HPF) is also characteristically seen in IDCP, although not considered as reliable as the presence of GEL for distinguishing AIP from IDCP. According to the ICDC, a definitive diagnosis of IDCP can be established in the absence of GEL if there is supportive radiologic and histologic evidence and the presence of concurrent IBD [13]. However, in the absence of IBD, a definitive diagnosis of IDCP can only be made if a GEL is identified on histology [13].

Management of AIP

The management of AIP is primarily medical (Fig. 3) with occasional need for endoscopic intervention. Recently, a panel of international experts has published an international consensus on the treatment of AIP [14]. Surgical intervention is not needed and sometimes occurs inadvertently in the setting of diagnostic confusion regarding pancreaticobiliary malignancy. The aim of managing AIP is to control pancreatic inflammation. Although, this often provides dramatic symptom relief, which can be helpful for confirming the diagnosis, whether the early use of corticosteroids delays parenchymal atrophy and fibrosis is unclear and the fibroatrophic changes that accompany the initial presentation of the disease are typically permanent.

The gastroenterologist managing AIP needs to have a clear understanding of the terms used to describe treatment goals and outcomes in the management algorithm of AIP. 'Remission' is a term used to describe complete resolution of the inflammatory component of the disease with or without restitution of normal structure and function. This is clinically manifest by symptom resolution, along with evidence of radiologic and biochemical improvement. In AIP, the rapid and complete resolution of clinical symptoms such as abdominal pain or jaundice after initiation of corticosteroids is the norm; persistent symptoms in patients on high-dose steroids indicate an alternate diagnosis and needs a careful evaluation to rule out underlying malignancy or usual chronic pancreatitis. It is important to understand that normal pancreatic morphology and function may not be restored with steroid therapy, and sometimes the fibroatrophic component of the disease becomes radiologically more overt after the inflammatory component has been treated. Confirmation of histologic remission after treatment, although ideal, is rarely feasible and is best avoided in a patient with symptomatic and radiologic improvement. Using normalization of serum IgG4 level as a treatment endpoint is not a reliable strategy as serologic activity correlates poorly with clinical or radiologic remission. "Recrudescence" refers to the worsening of disease or "flare" during treatment before the disease is in remission. This typically happens during corticosteroid dose reduction or withdrawal. "Relapse" refers to recurrent clinical, radiologic or biochemical evidence of disease activity that occurs any time after achieving complete remission. Relapse may occur in the pancreas or present as signs and symptoms compatible with IgG4-RD in another, previously unaffected, organ. Abdominal pain as a standalone symptom in the absence of pancreatic inflammation, and elevation of IgG4 without concomitant biochemical or radiologic change does not represent relapse and does not necessitate retreatment.

Medical management of AIP can be divided into three phases: induction of remission, treatment of relapse, and

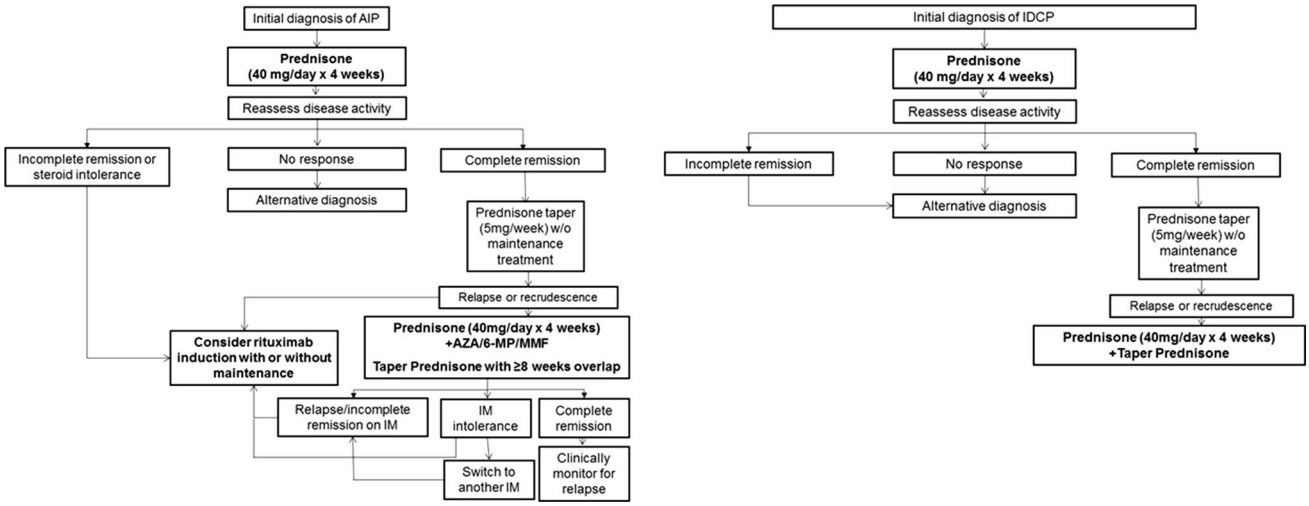

Fig. 3 Mayo Clinic treatment algorithm for management of initial presentation and subsequent disease relapses for patients with established autoimmune pancreatitis

maintenance of remission. Corticosteroids are the preferred agent for induction of remission. Steroid-sparing agents are reserved for long-term maintenance of remission in patients with relapse or recrudescence and occasionally for induction of remission in patients who are steroid-intolerant.

Management of Initial Presentation

Induction of Remission

High-dose corticosteroids, prednisolone 0.6 mg/kg/day or prednisone 40 mg once daily are the most common treatment regimens in treatment naïve patients. This high-dose induction therapy is typically administered for 4 weeks. In patients demonstrating remission or at least significant radiologic and biochemical improvement in target organ inflammation; this is followed by a gradual corticosteroid taper using a dose decrement of 5 mg per week. Rituximab (RTX), a chimeric monoclonal antibody against CD20 antigen on B cells can induce remission in AIP. Although typically used in patients with relapsing disease, it can be considered as first-line therapy when steroids are contraindicated or poorly tolerated. The two most commonly used induction regimens for RTX are 375 mg/m^2 once weekly for 4 weeks or 1000 mg, 2 doses 2 weeks apart. There is currently insufficient data to recommend the use of RTX as first-line treatment for AIP. However, based on previously published treatment outcomes in three patients, knowledge gained from treating other organ involvement by IgG4-RD at our center and additional unpublished experience ($n = 7$) it does appear that RTX can be considered for use as first-line and sole agent for induction of remission, if necessary [15] [16].

Maintenance of Remission

There is considerable debate on the need for continuing long-term low-dose corticosteroids in patients who achieve remission with initial therapy. In regimens favoring long-term prednisone maintenance, a low dose (2.5–10 mg/day) is continued for 1–3 years. Most centers in Europe and North America however recommend weaning prednisone to discontinuation over 8–10 weeks after the initial 4 weeks of high-dose treatment. In a large Japanese study patients who received maintenance corticosteroid treatment had a lower relapse rate (23 vs. 34%; $p = 0.048$) [17]. However, even in patients treated for 3 years without relapse, there is significant risk of relapse after steroid discontinuation. In a study that followed 21 AIP patients for a median duration of 43 months after steroid discontinuation, about half (10/21) of the patients relapsed off steroids and the authors concluded that low-dose steroids may need to be continued indefinitely to prevent disease relapse [18]. A recent multicenter trial randomized patients after the induction of remission with initial high-dose prednisolone treatment, to either maintenance therapy at 5–7.5 mg/day for 3 years or steroid withdrawal. The primary endpoint which was relapse-free survival over 3 years was significantly lower in the maintenance therapy group than that in the steroid cessation group ($p = 0.011$) [19]. Although the study was underpowered to assess the primary outcome, it is the first randomized controlled trial for treatment of AIP and provides clinically relevant preliminary results that could inform future studies in this field.

In view of the high rate of relapse in AIP (30–50%), and the potential risks of long-term steroid therapy, an alternative approach involves the use of immunomodulators as steroid-sparing agents. Although azathioprine is the most commonly used agent for this purpose, the choice of immunomodulator does not impact treatment outcomes with 6-mercaptopurine and mycophenolate mofetil having similar results. Comparative effectiveness has not been studied, and the optimal dose and duration of treatment are not well defined. Azathioprine at higher doses similar to those used in the management of inflammatory bowel disease (2.0–2.5 mg/kg) is more effective than lower doses (1 mg/kg) [15].

Patients at the highest risk of relapse are likely to be the ones to benefit most from maintenance therapy. Predictors of relapse include proximal biliary strictures, diffuse pancreatic enlargement, elevated baseline IgG4, IgE, peripheral eosinophilia, and possibly those with persistent elevation of IgG4 at the end of induction therapy [20]. Patients with a partial response to induction steroids, or in those with recrudescence during steroid withdrawal early use of immunomodulators or RTX needs to be considered to avoid long-term high-dose corticosteroid use.

Management of Relapse

Although steroid response is the norm in AIP, relapses are common, with up to 60% of patients experiencing a disease flare either during taper or after discontinuation [17, 21, 22]. Therapeutic options in these cases are limited and the following have been variably implemented, (1) high-dose corticosteroid for 4–6 weeks followed by gradual taper and either maintenance on low-dose steroids (2.5–10 mg daily) or discontinuation, (2) high-dose corticosteroids for 4–6 weeks along with co-administration of immunomodulator followed by steroid taper and discontinuation, (3) RTX induction therapy alone with either 4 weekly doses (375 mg/m^2 BSA) or 2 doses (1000 mg each) administered 2 weeks apart and (4) RTX induction therapy followed by maintenance RTX infusions (375 mg/m^2 BSA) every 2–3 months for a 2-year period (8 doses).

Relapse-free survival is not different among those treated with steroids versus steroids and immunomodulators for their first relapse of AIP [15]. For patients resistant or intolerant to steroids and immunomodulators, RTX is the only currently available alternative therapeutic option for inducing remission. RTX induction therapy (two infusions separated by 15 days) has been shown to be highly effective in IgG4-RD (12/60 patients had AIP), inducing clinical response in greater than 90% patients [20]. In this study, about one-third of patients relapsed following RTX induction and the median time interval between RTX treatment and relapse was 244 days [20]. In our experience, RTX induces a clinical response in majority of patients with pancreaticobiliary IgG4-RD. The subsequent relapse rate appears to be lower in patients receiving maintenance RTX therapy compared to those treated with induction therapy alone. Although RTX maintains remission, relapses are known to occur after discontinuation of the drug. Future studies aimed at identifying optimum dose and duration of maintenance treatment and predictors of relapse are necessary.

Management of IDCP

Steroids are the cornerstone of treatment. The dose and duration are similar to AIP and subsequent relapses are uncommon. In a study of 31 subjects with a definitive diagnosis (as per ICDC) of IDCP, the relapse rate was 25% at 12 months in patients treated with high-dose steroids without any maintenance therapy [7]. Since relapses are infrequent and respond to steroids, long-term maintenance therapy with low-dose steroids or immunomodulators is currently not recommended.

Long-Term Sequelae of AIP and IDCP

Exocrine and Endocrine Insufficiency

Both AIP and IDCP are associated with pancreatic parenchymal fibrosis which often becomes more apparent after the inflammatory component has been treated. Significant pancreatic atrophy is noted in up to 25% patients and this may lead to exocrine insufficiency over time [23]. Interestingly although radiologically the pancreas often appears significantly atrophic, clinically overt steatorrhea is uncommon. Using a diagnostic cut-off of FE-1 <200 μgm/gm, pancreatic exocrine insufficiency, has been reported to affect more than 80% of patients with AIP [24]. Our clinical practice has been to use of pancreatic enzyme replacement therapy only in patients with clinical evidence of fat malabsorption manifest by excess stool fat (>14 gm/day) on a 48-h stool collection or fat-soluble vitamin deficiency. Endocrine insufficiency on the other hand appears to be fairly common and risk factors for developing diabetes mellitus include advanced age and long duration of disease resulting in extensive parenchymal atrophy. Periodic monitoring of glycemic status allows early detection and timely intervention, especially in patients with risk factors.

Pancreatic Cancer

It is unclear whether AIP is associated with increased lifetime risk of developing pancreatic cancer. In a study reporting increased risk, the risk was highest in the first year after AIP diagnosis [25]. In a recently published study with 6-year median follow-up none of the 107 AIP patients studied had a new diagnosis of pancreatic cancer during the study period [26]. Although some patients developed a extrapancreatic malignancy cancer risk was found to be comparable to an age- and gender-matched reference population. More importantly, pancreatic cancer and AIP can co-exist, and thus it is important to diligently exclude underlying cancer before initiating treatment for AIP [27]. Primary non-response to steroid therapy is extremely unusual in AIP and should raise suspicion for an alternative diagnosis.

These long-term disease related sequelae of IDCP are not well defined largely because of the relative rarity of the disease. In a recently published Mayo Clinic series none of the patients with IDCP developed a pancreaticobiliary malignancy during median follow-up of 2.9 years.

Conclusion

AIP is a chronic steroid-responsive fibroinflammatory disease and a combination of radiologic and histologic features are necessary to confirm the diagnosis. Relapses are not uncommon but are also typically steroid responsive. Treatment of relapses requires a thoughtful approach with the judicious use of immunomodulators or rituximab. The optimum dosing regimen and duration of treatment for rituximab needs further study. IDCP is distinct from AIP and does not belong to the spectrum of IgG4-RD. This disease typically involves younger individuals and clinically manifests commonly as recurrent acute pancreatitis. Radiologic features may mimic AIP. The concomitant presence of IBD and characteristic histologic features serve as important diagnostic clues. Both diseases can eventually lead to pancreatic atrophy and exocrine and endocrine insufficiency. The risk of malignancy appears to be exceedingly low. In the absence of any reliable serologic marker of disease activity, post-treatment surveillance is symptom based. Novel biomarkers that correlate with disease activity are necessary and when available may be used to predict relapses and guide therapeutic decision algorithms.

Compliance with ethical standards

Conflicts of interest None of the authors have any conflicts of interest to disclose.

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