Clinical Features

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Introduction

Autoimmune pancreatitis (AIP) is a unique type of chronic pancreatitis that has distinct pathological, histological, and clinical characteristics [1, 2]. In 1961, Sarles et al. first described a pancreatitis associated with hypergammaglobulinemia, suggesting autoimmunity as the etiology of pancreatitis [3]. The concept of autoimmune pancreatitis (AIP) was proposed by Yoshida et al. in 1995 [4]. Since then it has become recognized as a distinct entity, and many cases have been reported in Eastern countries, as well as in Western countries [5, 6].

The clinical manifestations of AIP are variable except a few common presentations. Identifying and categorizing of clinical manifestations of AIP is quite difficult because little is known about the natural history and clinical spectrum of the disease. Most reports of the clinical symptoms on AIP are based on small retrospective cohorts, case series, and case reports including the highly selected patients with advanced or unusual clinical presentations. Also, the absence of a single diagnostic test makes it difficult to assess the full spectrum of clinical symptoms associated with AIP. Recently, many AIP literatures had suggested that the entity of AIP consisted of two distinct histopathological and clinical forms of pancreatitis. Type 1 AIP refers to the subtype called lymphoplasmacytic sclerosing pancreatitis (LPSP) or granulocytic epithelial lesion (GEL)-negative AIP, whereas type 2 AIP refers to the subtype called idiopathic duct-centric pancreatitis (IDCP) or GEL-positive AIP [7–9]. This chapter will discuss about the clinical features of AIP as well as the differences and similarities between the two subtypes. The most crucial issue in clinical situation caring for patients with suspected AIP is to differentiate AIP from pancreatic cancer, because pancreatic cancer requires surgery and AIP responds dramatically to steroid treatment. So the different points in the clinical manifestation of AIP and pancreatic cancer will be reviewed.

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Clinical Features

AIP is a heterogeneous disease with diverse clinical symptoms due to two distinct subtypes: type 1 and type 2. The two subtypes have numerous differences along with a few similarities (Table 8.1).

The relative prevalence of type 1 and type 2 AIP is different for Asia and the West. The proportion of patients with type 2 AIP is lower in Asia (3.7 %) than in both Europe (12.9 %) and North America (13.7 %) in a recent international multicenter survey [10]. Despite increasing reports on AIP, the true prevalence of AIP is unknown due to the absence of a reliable diagnostic test, the relative rarity, the under-recognition, and the underreporting. AIP prevalence was estimated to be 0.82 per 100,000 in the nationwide survey based on the diagnostic criteria of the Japanese Pancreas Society [11]. Other authors report prevalence rates of 5–6 % of all patients with a diagnosis of chronic pancreatitis in Japan and Korea [12, 13]. In North America, about 2.4 % of patients who were performed with pancreatic resection under a misdiagnosis of pancreatic cancer were found to have type 1 AIP on surgical specimens [14], and AIP resulted in 21–23 % of patients who were performed with pancreatic resection for benign conditions [15, 16].

Type 1 AIP mainly occurs in elderly males, as most patients (up to 85 %) with it are older than 50 years [2, 17, 18]. The male to female predominance is approximately 2:1 [11]. Type 2 AIP appears to affect younger patients (less than 40 years old) and may have the male predominance [7, 8].

Type 1 AIP is the pancreatic manifestation of IgG4-related disease (IgG4-RD), a multisystem disease. The variable clinical presentations can be divided into pancreatic and extrapancreatic manifestations. In addition, the pancreatic

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Table 8.1 Clinical profile of 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
Most common presenting complaint	Obstructive jaundice (80–90 %)	Obstructive jaundice (50–60 %)
Presenting with acute pancreatitis	(10–15 %)	(30–40 %)
Serum IgG4 level	Often elevated	Normal
Histology hallmark	Lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis	Granulocytic epithelial lesion
Tissue IgG4 stain	Present	Rare
Other organ involvement	Bile duct, salivary gland, kidney, retroperitoneum	Inflammatory bowel disease
Associated with ulcerative colitis	Occasionally	Common
Steroid response	Excellent	Excellent
Recurrence	Common	Rare

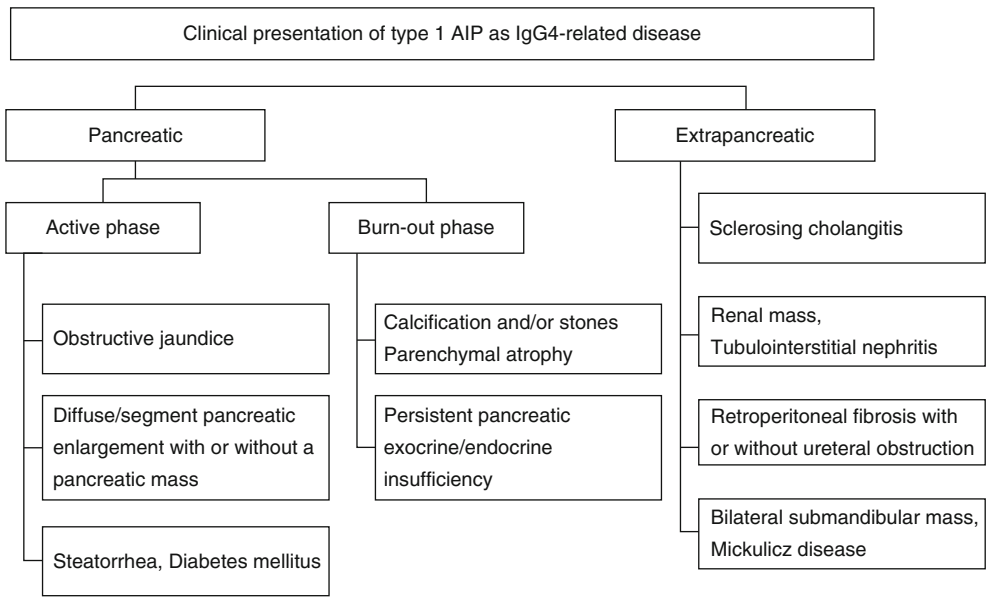

Fig. 8.1 Clinical presentation of type 1 AIP as IgG4-related disease (Adapted from Kamisawa et al. [45])

manifestation of type 1 AIP can be divided into active and late phase because of its clinical and image profile change for long times (Fig. 8.2). In the active phase of type 1 AIP, the major presentation is painless obstructive jaundice, occurring in up to 88 % of patients with a new presentation of type 1 [19, 20]. The manifestations of acute pancreatitis (abdominal pain and elevation of serum pancreatic enzymes) are more often observed in type 2 rather than type 1 [7, 21, 9]. Patients with AIP often present with mild pancreatitis that is easily cured by conservative management. It is likely to be under-recognized unless further workup is done with suspicion. According to the degree of pancreatic inflammation, it can present with a diffuse or focal pancreatic enlargement with or without a mass. The diffuse type was more common than the focal type in both groups (62.2 % in type 1 AIP and 73.3 % in type 2 AIP) [9]. In case with focal pancreatic mass, it can be clinically challenging to distinguish AIP form pancreatic cancer. Diabetes mellitus develops in up to 50 % of patients concurrently with AIP, and 8.8 % of patients developed diabetes after steroid administration as the therapy for AIP [22, 23]. Untreated or multiple-relapsed AIP may show pancreatic parenchymal atrophy and fibrosis, which in its late stages can be indistinguishable from advanced ordinary chronic pancreatitis [24]. In the late stages of disease, diabetes and steatorrhea can be caused by the failure of endocrine and exocrine function. These are discussed in more detail in subsequent chapters. In addition to the pancreatic manifestations, a characteristic feature of type 1 AIP is the extrapancreatic other organ involvement (OOI) characterized by an IgG4-positive lymphoplasmacytic infiltrate in various organs. The common involvement of other organs includes the bile duct, salivary glands, retroperitoneum, kidneys, lung, lymph nodes, and orbits. Less commonly, gallbladder and gastric involvements have been described [25–28]. OOI

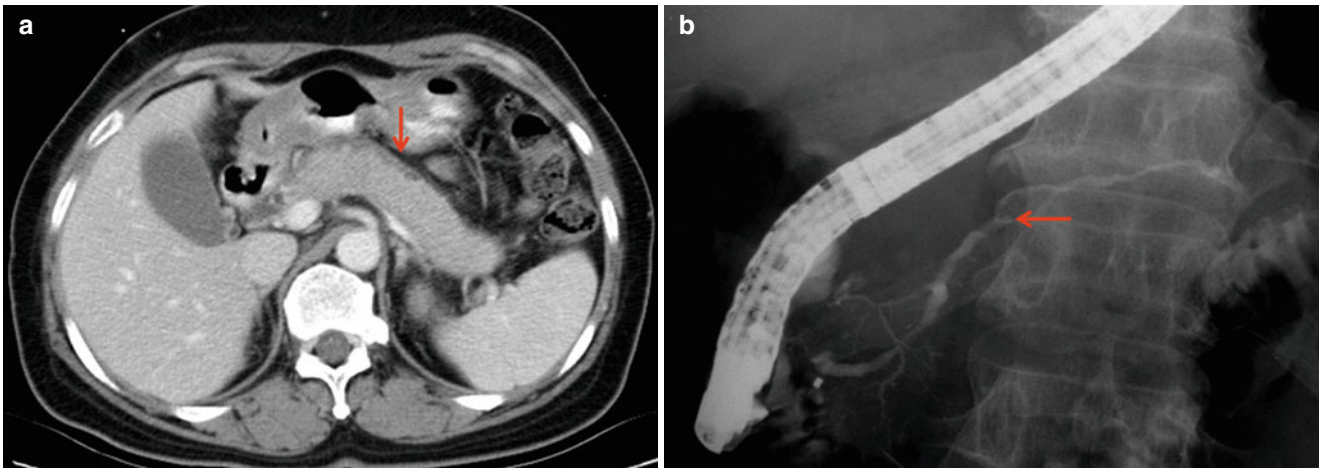

Fig. 8.2 Radiologic finding of a patient with AIP. (**a**) CT image shows diffuse enlargement with delayed enhancement and capsule-like rim (*arrow*). (**b**) ERCP shows irregular narrowing of main pancreatic duct and absence of marked upstream dilatation

may precede the diagnosis of AIP, be present concurrently, or develop metachronously over months to years after the diagnosis of AIP [25]. These extrapancreatic manifestations often provide an important clue to diagnosis.

Recent studies suggest that type 2 AIP has a clinical and histological difference from type 1 AIP and it is a distinct clinical entity. The similarities between both types are the obstructive jaundice, the diffuse pancreatic enlargement on imaging studies, and the good response to steroid therapy. However, patients with type 2 tend to be younger and are more likely to present with abdominal pain and pancreatitis than those with type 1 [8, 9]. There is an absence of elevated serum IgG4 and extrapancreatic manifestations, which are a collateral evidence of AIP to provide great clues in diagnosing AIP [8, 9, 29]. Inflammatory bowel disease is more common in type 2 than type 1 [8, 9]. Type 2 AIP has no specific serologic marker and shows minimal IgG4 immunostaining from tissues. The identifying GEL in the pancreatic tissue is the main difference from type 1 AIP and is needed for a definitive diagnosis of type 2 AIP [30]. Since occurrence is at a relatively young age and a pancreatic histology is needed for a definitive diagnosis, type 2 AIP is likely to be underrecognized. Further clinical investigation is needed to better understand the clinical profile of type 2 AIP because its clinical feature has not been defined well.

Distinguish AIP from Malignancy

The patient with AIP often presents with painless obstructive jaundice or pancreatic mass mimicking the presentation of pancreatic cancer. It is important to differentiate between these two entities due to a dismal prognosis and a narrow therapeutic window for surgical resection in pancreatic cancer. Many diagnostic criteria for AIP, such as Japanese criteria, Korean criteria, HISORt criteria, and international consensus diagnostic criteria (ICDC), have been proposed. Each of the criteria does not provide a strategy to distinguish AIP from pancreatic cancer and has strengths and weaknesses in distinguishing AIP from pancreatic cancer [31]. However, clinical feature, serology, pancreatic imaging, and steroid response may be helpful in distinguishing AIP from malignancy [32]. The jaundice in AIP sometimes fluctuates more frequently than in pancreatic cancer, whereas obstructive jaundice in pancreatic cancer typically progresses steadily. Serum IgG4 levels are frequently and significantly elevated in type 1 AIP, although it is an uncommon finding in type 2 AIP. Hamano et al. reported in 2001 that using the serum IgG4 level enabled distinguishing AIP from other pancreatic disorders with high sensitivity (95 %) and specificity (97 %) [33]. In one study, an elevation of serum IgG4 levels (>135 mg/dL) was detected in 71 % of AIP patients and 6 % of PC patients [34]. In another study, about 10 % of pancreatic cancers have elevated IgG4 levels, most being less than twice the upper limit of normal [35]. Therefore, an elevated serum IgG4 level alone cannot rule out pancreatic cancer, while this finding may be a diagnostic clue. The differential diagnosis for AIP and pancreatic malignancy usually begins with cross-sectional images. Previous studies show that diffuse enlargement with delayed enhancement, capsule-like rim, long (>1/3 the length of the main pancreatic duct) or multiple stricture, and absence of marked upstream dilatation have high specificity for AIP (Fig. 8.2) [19, 34, 36]. Furthermore, "ICDC" guidelines suggest that these findings indicate a high level of suspicion of AIP [37]. On the other hand, non-enhanced mass, upstream dilatation of the main pancreatic duct, and proximal parenchymal atrophy are highly suggestive findings for pancreatic cancer (Fig. 8.3) [19, 34, 36]. However, some AIP cases are not compatible with the typical findings of AIP. Among these

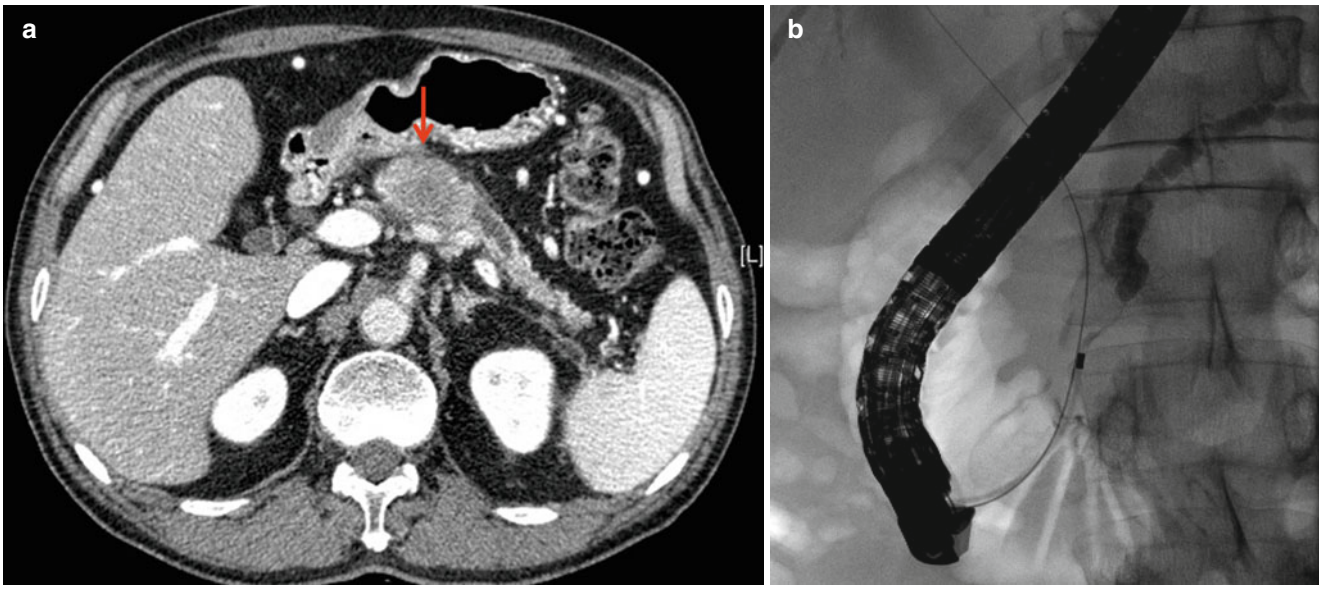

Fig. 8.3 Radiologic finding of a patient with pancreatic cancer. (**a**) CT image shows no enhancement mass (*arrow*) with upstream PD dilatation and parenchymal atrophy. (**b**) ERCP shows pancreatic duct cutoff and upstream main pancreatic duct dilatation (>5 mm)

atypical cases of AIP, focal type AIP can be difficult to differentiate from pancreatic cancer. In our series of 23 patients [38], 85.7 % (6/7) of focal-type AIP patients showed homogeneous enhancement, whereas only 3 chronic pancreatitis patients (25 %) and none of the pancreatic cancer patients showed homogeneous enhancement. None of the focal type AIP patients showed upstream duct dilatation (>5 mm) or proximal pancreatic atrophy. If a pancreatic mass has homogeneous enhancement, absence of significant upstream MPD dilatation (>5 mm), and absence of proximal pancreatic atrophy, further evaluation for AIP should be considered to avoid unnecessary surgery.

In addition, a 2-week steroid trial has been advocated as a means of differentiating the two clinical entities [39], including Korean, HISORt criteria, and ICDC. The reasons to support a 2-week steroid trial are as follows: (1) radiological improvement of AIP can occur as early as 1–2 weeks after steroid therapy [40] and (2) concern about cancer progression during the trial of steroid therapy; one study reported that complete resection was possible in all patients after the 2-week trial [39]. Improvement of clinical symptoms can be seen in pancreatic cancer patients due to the anti-inflammatory effect of steroids. The falsely elevated IgG4 in pancreatic cancer also can decrease after steroid therapy [37]. The obstructive pancreatitis associated with ductal adenocarcinoma may be relieved with steroid therapy. Therefore, the response from the steroid trial must be interpreted with an objective measurement, such as rapid (≤2 weeks) radiological resolution or marked improvement in pancreatic or extrapancreatic manifestations (Fig. 8.4). In the assessment of steroid responsiveness, relief of pancreatic ductal narrowing and/or resolution of the pancreatic mass is critical. Additionally, a steroid trial should be restricted only to suspected AIP patients who have a negative workup for cancer including EUS-FNA [41].

It is important to remember that AIP is a rare disease and thought to be much less common than pancreatic cancer. Clinical tips to help avoid misdiagnosis of pancreatic cancer as autoimmune pancreatitis are showed in Table 8.2.

Natural History and Prognosis of AIP

The natural history and long-term prognosis of AIP is unknown despite many investigation of this disease. Although types 1 and 2 AIP showed excellent response to steroid treatment, many patients develop relapse either during steroid tapering or follow-up period and steroid discontinuation. Recent studies reported that the relapses were more common in type 1 (31–50 %) than type 2 AIP (0–15.3 %) [8–10]. The location of the recurrence is predominantly in the biliary system or pancreas [10]. In a study of biliary involvement in AIP, frequent relapses occurred in proximal biliary involvement (proximal extrahepatic and intrahepatic biliary strictures) than strictures in the intrapancreatic portion of the bile duct. Continuous incomplete remission of radiological and serological abnormalities during the maintenance period can cause relapse. Relapses were more common in AIP patients with IgG4-related sclerosing cholangitis (56 % vs. 26 %), while there is controversy about whether the diffuse or focal type is an independent predictor of relapse [8, 10, 42].

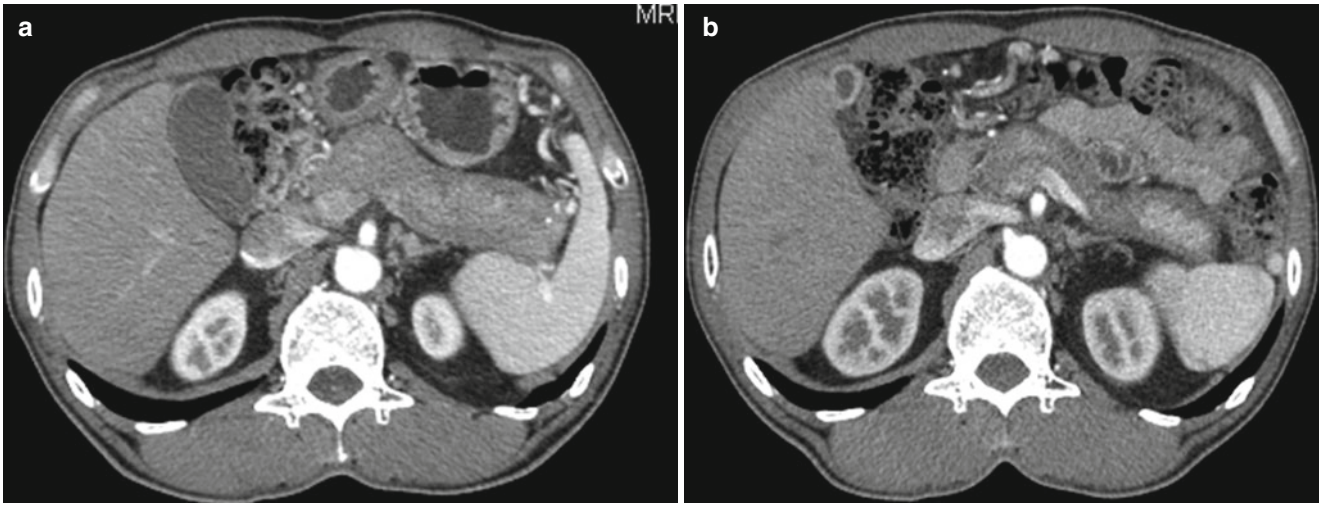

Fig. 8.4 Serial images of a patient with steroid response who was finally diagnosed with AIP. (**a**) Pretreatment: CT image shows diffuse enlargement without a discrete mass. (**b**) Posttreatment: after 2 weeks of steroid trial, the pancreatic lesion was markedly reduced

Table 8.2 Clinical tips to differentiate AIP from pancreatic cancer

1. Utilize the international consensus diagnostic criteria (ICDC) to help diagnose AIP and differentiate it from malignant disease
2. It is important to remember that AIP is a rare disease and thought to be much less common than pancreatic cancer
3. Pancreatic imaging is the basis of suspicion and diagnosis of AIP and differentiation from pancreatic cancer
4. All focal pancreatic masses should be sampled prior to initiating corticosteroids
5. An elevated serum IgG4 level alone cannot diagnose AIP or rule out pancreatic cancer. Serum IgG4 levels are elevated in 10 % of pancreatic cancer and 6 % of chronic pancreatitis
6. Elevated serum IgG4 levels can decrease in patients with pancreatic cancer who are inappropriately treated with corticosteroids
7. In the assessment of steroid responsiveness, relief of pancreatic ductal narrowing and/or resolution of the pancreatic mass is critical
8. Improvement of AIP is usually seen as early as 2 weeks after steroid therapy. If no objective response is seen within 2–4 weeks, the diagnosis is unlikely to be AIP and the resection is considered

Two major sequelae of chronic pancreatitis are pancreatic duct stone and pancreatic cancer. Patients with at least one relapse have a high prevalence of pancreatic calcification or stones. Also, multiple relapses may result in irreversible damage with fibrosis and steroid unresponsiveness [24]. For patients with AIP identified as having predictors of relapse, the treatment strategy may need to be adjusted by including higher dose or longer administration of maintenance steroid therapy or additional treatment with another immunosuppressive agent.

The life expectancy of patients with AIP has been reported to be similar to the general population. The late sequelae of AIP such as the pancreatic atrophy and pancreatic insufficiency do not seem to alter long-term survival [8].

Several cases of pancreatic cancer have been reported in patients with AIP who were suspected to have type 1. Pancreatic cancers were diagnosed synchronously with AIP or detected during the follow-up [10, 43, 44]. Because of limited date and no systematic case–control studies, further studies are needed to understand whether to increase the risk of cancer compared with the general population.

Summary

The clinical spectrum varies widely in AIP with two distinct subtypes. The AIP type 1 and type 2 have both overlapping and separate clinical features. The relative frequencies of subtypes in Asia are different from those observed in the West. The proportion of type 2 AIP is lower in East Asia than in the West. Most commonly, patients with type 1 AIP are older males presenting with painless jaundice and an elevated IgG4 level. Those with type 2 AIP tend to be younger and are likely to present with acute pancreatitis and normal IgG4 levels. Type 2 AIP is not related to the extrapancreatic disease except ulcerative colitis. Also, the differentiation of AIP from pancreatic cancer is challenging because of the presentation of AIP mimicking that of pancreatic cancer and absence of a single diagnostic test. It is important to remember several clinical tips to avoid misdiagnosis. Further clinical investigation and more experience will provide better understanding and more optimal treatment plan in AIP.

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