

Current Management of Type 1 Autoimmune Pancreatitis: From the Viewpoint of Pancreatic Endocrine and Exocrine Function

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Abstract

Autoimmune Pancreatitis (AIP) is a pancreatic inflammatory disease caused by an autoimmune mechanism. Histologically, two subtypes exist: type 1 characterized by lymphoplasmacytic sclerosing pancreatitis and type 2 characterized by idiopathic duct-centric chronic pancreatitis. Type 1 AIP often involves extra pancreatic lesion, and also known as a pancreatic lesion of systemic “immunoglobulin G4 (IgG4)-related disease”. In addition, pancreatic endocrine dysfunction induced diabetes mellitus and exocrine dysfunction is common complications. While steroid therapy improves the outcome of the disease in some patients including pancreatic endocrine/exocrine function, others do not respond to steroids that results in the eventual progression to pancreatic endocrine/exocrine dysfunction, such as chronic pancreatitis. In the management of type 1 AIP, presence of pancreatic endocrine/exocrine function should always be considered, in addition to the regular steroid therapy.

Keywords: Autoimmune pancreatitis; Diabetes mellitus; Endocrine dysfunction; Exocrine dysfunction; Immunoglobulin G4 (IgG4); Steroid therapy

Abbreviations: AIP: Autoimmune Pancreatitis; AQP-1: aquaporine-1; CP: Chronic Pancreatitis; CFTR: Cystic Fibrosis Transmembrane Conductance Regulator; DM: Diabetes Mellitus; GEL: Granulocyte Epithelial Lesions; IDCP: Idiopathic Duct-centric Chronic Pancreatitis; IgG4: Immunoglobulin G4; LPSP: LymphoPlasmacytic Sclerosing Pancreatitis

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Introduction

In 1961, Sarles et al. [1] reported the first cases of chronic inflammatory sclerosis of the pancreas that was diagnosed in 10 patients with hypergammaglobulinemia or jaundice, possibly involving an autoimmune mechanism. In 1991, Kawaguchi et al. [2] presented LymphoPlasmacytic Sclerosing Pancreatitis (LPSP) on the basis of pathological findings. Yoshida et al. [3]

proposed the concept of autoimmune pancreatitis (AIP) in 1995, and was clearly characterized by Ito et al. [4] in 1997.

AIP is known to have two clinical and histological subtypes; type 1 and type 2 [5-7] [Table 1]. Type 1 AIP is prevalent in Asia and occurs mostly in elderly men [8-12], which typical pathological finding is defined as LPSP characterized by IgG4-positive plasmacyte infiltration [Figure 1 A, B]. In contrast, type

2 AIP is prevalent in western countries and occurs mostly in young people, which is characteristically complicated with inflammatory bowel disease [5, 6, 11, 13]. Pathologically, type 2 AIP is defined as Idiopathic Duct-centric Chronic Pancreatitis (IDCP) characterized mainly by neutrophilic infiltration [5] or Granulocyte Epithelial Lesions (GEL) [14] [Figure 1 C].

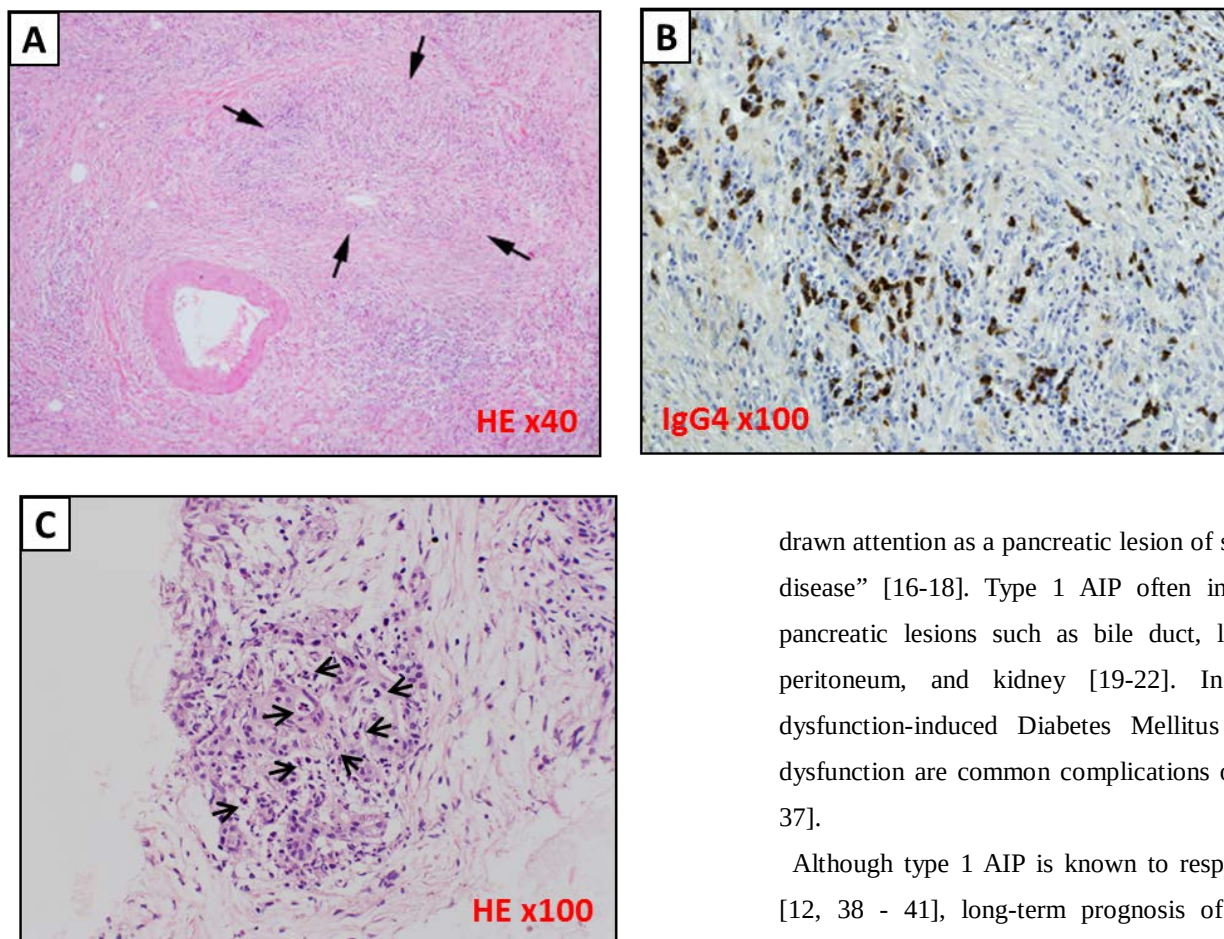


Figure 1: Typical histopathological features of type 1 and type 2 AIP

Hematoxylin-Eosin (HE) staining (A, C) and IgG4 immunostaining (B) for pancreatic lesion.

(A) Arrow indicates LPSP. (B) Plasma cells are stained with IgG4. (C) Arrow indicates GEL.

Type 1 AIP is also characterized by elevated serum levels of immunoglobulin G4 (IgG4) [15]. Recently, type 1 AIP has

drawn attention as a pancreatic lesion of systemic “IgG4-related disease” [16-18]. Type 1 AIP often involves multiple extra pancreatic lesions such as bile duct, lachrymal gland, retro peritoneum, and kidney [19-22]. In addition, endocrine dysfunction-induced Diabetes Mellitus (DM) and exocrine dysfunction are common complications of type 1 AIP [10, 23-37].

Although type 1 AIP is known to respond to steroid therapy [12, 38 - 41], long-term prognosis of type 1 AIP remains unclear. It is reported that some patients develop disease relapse over time [6, 38, 42-44], and others may show pancreatic calcification associated with Chronic Pancreatitis (CP) [25, 26, 45-47] or complications associated with malignant tumors [38, 48]. Therefore, for AIP management, it is important to plan a therapeutic strategy in view of the projected long-term prognosis including protection of pancreatic endocrine/exocrine function. In this review, the management of type 1 AIP is discussed, focusing on pancreatic endocrine/exocrine function, and we describe type 1 AIP as AIP.

Table 1: Differences of clinicopathological features between type 1 and type 2 autoimmune pancreatitis (AIP)

	Type 1	Type 2
Age	Elderly	Young, Middle-aged
Gender	Male > Female	Equal
Epidemiology	Asia > Europe, USA	Europe, USA > Asia
Clinical presentation		
Obstructive jaundice	Frequent	Frequent
Abdominal pain (Acute pancreatitis)	Rare	Occasional
Serum IgG4 levels	Elevated	Normal
Histological pattern	LPSP	IDCP / with GEL
Infiltration cells	Plasmacyte (IgG4 positive)	Neutrophil
Pancreatic enlargement	Diffuse 40%, Focal 60%	Focal 85%
Extrapancreatic lesions	Multiple	Inflammatory bowel disease
(Other organ involvement)	Sialadenitis, Cholangitis, Retroperitoneal fibrosis, Nephritis, dacryoadenitis	
Steroid response	Good	Good
Relapse	Frequent	Rare

IgG4: immunoglobulin G4; **LPSP:** Lymphoplasmacytic Sclerosing Pancreatitis; **IDCP:** Idiopathic duct-Centric Chronic Pancreatitis; **GEL:** Granulocyte Epithelial Lesions

Endocrine dysfunction in AIP

(1) Onset mechanism

In AIP-associated endocrine dysfunction, the secretional capacity for both insulin and glucagon are impaired. The onset mechanism may involve the effect to the Langerhans

due to impaired blood flow caused by lymphoplasmatic cell infiltration and fibrosis in the exptpancreatic secretor gland [28, 49] [Figure 2 A, B]. However, further studies are required to clarify this process.

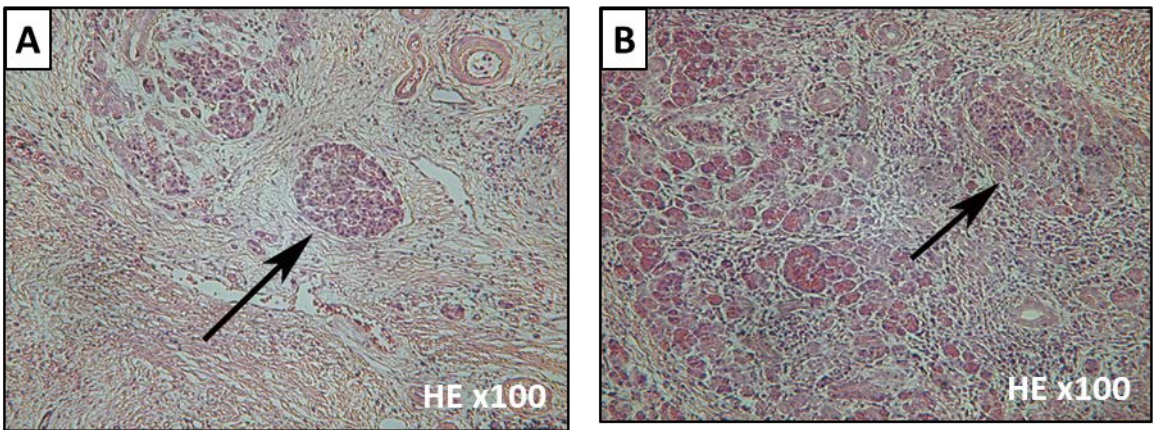


Figure 2: Histological findings around islet cell in AIP

Representative photomicrographs of the pancreas in AIP

(A) Arrow indicates intact islet cell surrounded by marked fibrosis. (B) Arrow indicates islet cell damaged by lymphoplasmatic cell infiltration and fibrosis. Source: Ito T, et al. *Pancreas* 2007; 34: 254-259 [28]. Reprinted with permission from Lippincott Williams & Wilkins

(2) Incidence and onset timing of DM in AIP

DM is known to develop in 24–83% of AIP patients due to endocrine dysfunction [10, 24, 26, 27, 30-33, 36].

According to the 2006 national survey in Japan [30], DM develops before the AIP onset in 33.3% of patients, and at the same time as the AIP onset in 51.6% of patients. According to the study by Ito et al. [34] on 102 AIP patients with DM, more patients in the group with DM before AIP onset had poor nutritional state, poor blood glucose control, insulin dependence, and diabetic complications, than the patients that developed DM at the time of AIP onset. In addition, patients with alcohol consumption or with no enzyme supplementation experienced hypoglycemic attacks at least once a month. Therefore, according to the report, alcohol abstinence and enzyme supplementation are necessary.

(3) Steroid therapy and endocrine function

Steroid therapy is reported to improve endocrine function in 13–100% of patients [25, 31-33, 35, 36]. AIP-associated endocrine dysfunction is considered to be reversible to a certain extent. The possible mechanism of reversibility involves the following: improvement of impaired blood flow and inflammation of Langerhans owing to the disappearance of inflammatory cell infiltration and fibroblasts; moreover, the regeneration mechanism of the Langerhans cells is strengthened owing to the suppression of localized cytokine production in the pancreas [49]. According to the examination of the pancreatic tissue before and after steroid therapy [37], the pancreatic acinar cells that had disappeared were partially regenerated by steroid therapy, with possible involvement of CD133-

positive progenitor cells. However, the details of the mechanism are still unknown.

Meanwhile, blood glucose control worsened by steroid therapy in 75% of the patients who had developed DM before AIP [33]. The finding suggests that steroid therapy might not improve endocrine dysfunction in patients with a history of DM, or in those with severely damaged glucose tolerance [35]. According to some reports [32, 33], long-term steroid therapy induced DM in about 10% of patients, and its onset was 1.8 years after steroid induction [34]. Therefore, even in patients with no DM at the time of AIP diagnosis, the possibility of DM development should always be considered when steroid therapy is continued.

Exocrine dysfunction in AIP

(1) Onset mechanism

The possible onset mechanism of exocrine dysfunction in AIP may involve the following: reduction of pancreatic enzyme secretion due to loss of acinar cells caused by substantial plasmacytic infiltration and fibrosis, and impairment in the pancreatic juice flow induced by inflammatory cell infiltration around the pancreatic duct and by a narrowed pancreatic duct [28, 32, 33]. Ito et al [28] examined the exocrine function by the secretin test in 12 AIP patients and 25 CP patients, and found significant correlations between AIP and a reduction in volume, and between CP and a reduction in the maximum bicarbonate concentration [Table 2]. Histologically, the morphology of the pancreatic ductal basement membranes were intact in AIP [Figure 3A], whereas basement membranes of the duct were injured in CP [Figure 3B]. In AIP, the secretion of pancreatic juice and amylase may have reduced because of the narrowed pancreatic duct, whereas bicarbonate may have decreased in CP owing to the injured basement membrane.

Table 2: Difference of Exocrine functional behavior between autoimmune pancreatitis (AIP) and Chronic Pancreatitis (CP)

	AIP (n=12)		CP (n=25)		
Abnormal factor					
Volume (mL/kg)					
< 2.8	11	(92%)	7	(28%)	P < 0.001
2.8≤	1	(8%)	18	(72%)	
Amylase Output (SU/mL)					
< 1349	11	(92%)	15	(60%)	P = 0.064
1349≤	1	(8%)	10	(40%)	
HCO ₃ ⁻ (mE/L)					
< 78	5	(42%)	25	(100%)	P < 0.001
78≤	7	(58%)	0	(0%)	
Number of abnormal factor					
One factor	2	(17 %)	11	(44%)	
(1) / (2) / (3)	1 / 1 / 0		0 / 0 / 11		
Two factors	5	(42%)	7	(28%)	
(1)+(2) / (1)+(3) / (2)+(3)	5 / 0 / 0		0 / 0 / 7		
Three factors	5	(42%)	7	(28%)	

Modified from reference [28].
AIP: autoimmune pancreatitis; **CP:** chronic pancreatitis; **HCO₃⁻:** max bicarbonate concentration

Figure: 3

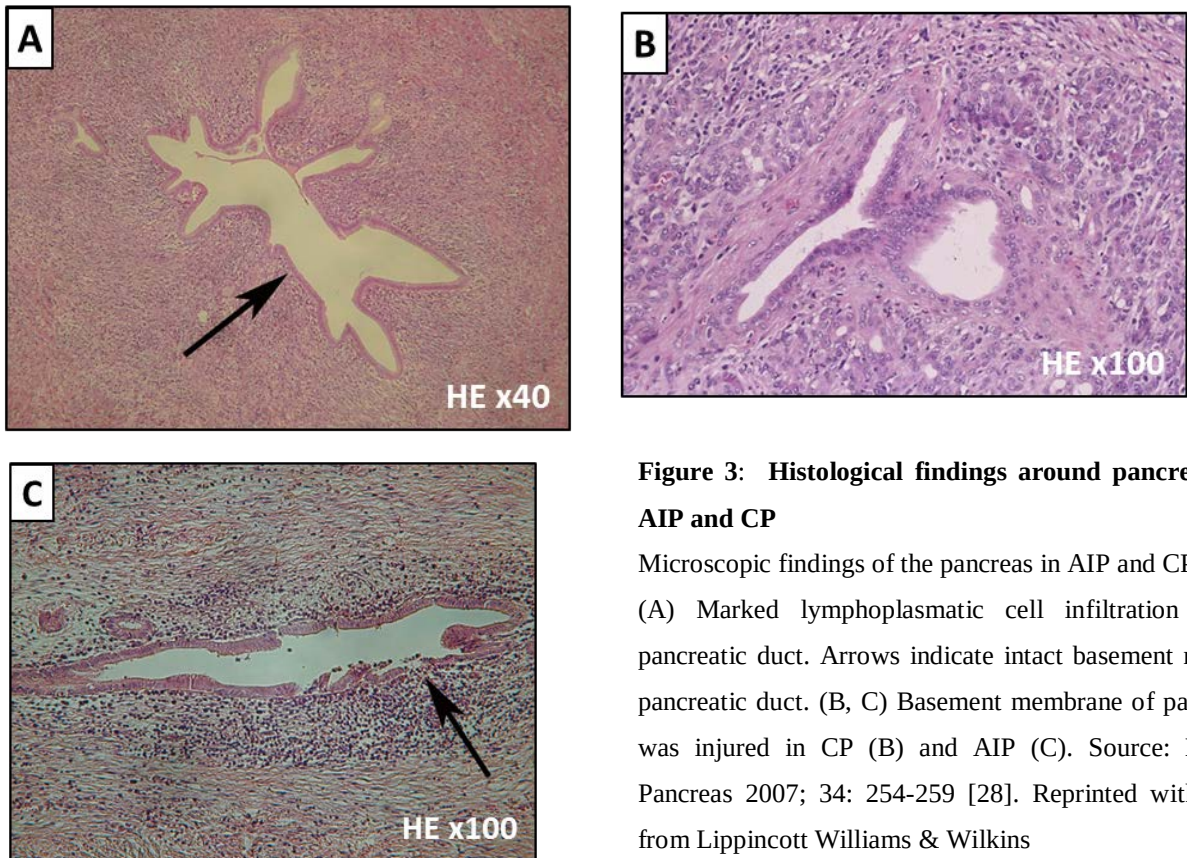


Figure 3: Histological findings around pancreatic duct in AIP and CP

Microscopic findings of the pancreas in AIP and CP
 (A) Marked lymphoplasmatic cell infiltration around the pancreatic duct. Arrows indicate intact basement membrane of pancreatic duct. (B, C) Basement membrane of pancreatic duct was injured in CP (B) and AIP (C). Source: Ito T, et al. Pancreas 2007; 34: 254-259 [28]. Reprinted with permission from Lippincott Williams & Wilkins

(2) Incidence of exocrine dysfunction in AIP

In a previous report [24, 26, 31-33, 36], exocrine dysfunction was observed in 82–91% of patients in AIP. However, Ito et al. [28] observed exocrine dysfunction in 75 (74%) of 102 AIP patients with DM, although no significant correlation was found between blood glucose control and exocrine dysfunction.

(3) Steroid therapy and exocrine function

Steroid therapy was reported to improve exocrine dysfunction in 38–100% of patients [24, 25, 29, 31-33, 36, 37]. Steroid therapy could possibly improve both exocrine and endocrine dysfunction.

There are several interesting reports about the pancreatic regeneration which can explain the mechanism of exocrine function improvement by steroid therapy in AIP. According to Yamaguchi et al. [50,51], Pdx1-positive cells (considered to be pancreatic progenitor cells) did not exist in the pancreatic duct epithelium of the irreversible pancreatitis model rat (oleic acid-induced pancreatitis) and speculated that pancreatic regeneration would be impossible when the pancreatic duct system is severely injured. Furthermore, in irreversible pancreatitis, they reported that matrix metalloproteinase-2 (MMP-2) continuously degrades type IV collagen in the basement membrane, which is important for stabilizing and regenerating the pancreatic duct epithelium, and the impaired remodeling of basement membrane of pancreatic duct and acini leads histological change in pancreas to irreversible state.

In contrast, pancreatic duct alteration in AIP is caused by the displacement/deformation due to pancreatic enlargement associated with inflammatory cell infiltration into the parenchyma; the pancreatic duct itself and the basement membrane are not injured. Therefore, when inflammatory cells infiltration is eliminated by steroid therapy, the pancreatic structure/function is possibly restored. In contrast, in cases of AIP progressing to CP, the infiltration of inflammatory cells including plasmacytes

and lymphocytes may destruct the basement membrane [Figure 3C], which results in reduced secretion of bicarbonate and irreversible damage of pancreatic duct epithelium and acinar cells.

In addition, Ko et al. [37] reported that exocrine dysfunction in AIP is induced by the abnormal localization and expression of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) and aquaporine-1 (AQP-1) in the pancreatic duct epithelium, and improvement of exocrine function by steroid therapy is attributed to the correction of CFTR localization and regeneration of pancreatic acinar cells.

Again, though exocrine dysfunction associated with AIP could improve with steroid therapy, its long-term prognosis is still unknown. Evaluation of pancreatic exocrine function and appropriate enzyme supplementation are indispensable during AIP treatment.

Conclusion

We presented a discussion on the management of AIP by focusing on endocrine/exocrine function. While treating AIP, the possible complication of pancreatic endocrine/exocrine dysfunction should always be considered in addition to regular steroid therapy. Long-term prognosis of AIP, in particular pancreatic function, is mostly unknown, and further investigation is required.

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