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## Understanding autoimmune pancreatitis: Clinical features, management challenges, and association with malignancies

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### Abstract

In this editorial we comment on the article by Jaber *et al.* Autoimmune pancreatitis (AIP) represents a distinct form of pancreatitis, categorized into AIP-1 and AIP-2, characterized by obstructive jaundice, lymphoplasmacytic infiltrate, and fibrosis. AIP-1, associated with elevated immunoglobulin G4 (IgG4) levels, exhibits higher relapse rates, affecting older males, while AIP-2 is less common and linked to inflammatory bowel disease. AIP is considered a manifestation of IgG4-related systemic disease, sharing characteristic histological findings. Steroids are the primary treatment, with emerging biomarkers like interferon alpha and interleukin-33. AIP poses an increased risk of various malignancies, and the association with pancreatic cancer is debated. Surgery is reserved for severe cases, necessitating careful evaluation due to diagnostic challenges. AIP patients may have concurrent PanINs but display favorable long-term outcomes compared to pancreatic cancer patients. Thorough diagnostic assessment, including biopsy and steroid response, is crucial for informed surgical decisions in AIP.

**Key Words:** Autoimmune pancreatitis; Immunoglobulin G4-related disease; Pancreatic cancer; Surgery

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**Core Tip:** Autoimmune pancreatitis (AIP) is a unique form of pancreatitis, categorized into AIP-1 and AIP-2, with distinct clinical characteristics and associations. AIP-1, linked to elevated immunoglobulin G4 (IgG4) levels, exhibits higher relapse rates and predominantly affects older males, while AIP-2 is less common and associated with inflammatory bowel disease. Recognized as a manifestation of IgG4-related systemic disease, AIP poses an increased risk of malignancies, especially gastric, colorectal, and bladder cancers. Despite ongoing debates about the association with pancreatic cancer, careful diagnostic evaluation, including biopsy and response to steroids, is crucial for informed decision-making regarding surgery. AIP patients may have concurrent PanINs but generally experience better long-term outcomes compared to pancreatic cancer patients. Steroids remain the primary treatment, and emerging biomarkers like interferon alpha and interleukin-33 offer promising avenues for monitoring and managing AIP.

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## INTRODUCTION

A unique kind of pancreatitis known as autoimmune pancreatitis (AIP) is typified by fibrosis and lymphoplasmacytic infiltration, obstructive jaundice, and a noticeable reaction to steroids. AIP can be classified into two types, AIP-1 and AIP-2. AIP-1 is associated with elevated levels of immunoglobulin G4 (IgG4) and it is prevalent in the seventh decade. It has a greater male-to-female ratio, particular histological findings, a higher relapse rate, and a propensity to manifest as painless jaundice. The prevalence of type 1 AIP in Japan has increased significantly, with an incidence of 3.1 per 100000 people, a sex ratio of 2.94 (males to females), and a mean age at diagnosis of 64.8 years[1-3]. On the other hand, AIP-2 is less common, it is more prevalent in the 4<sup>th</sup>-5<sup>th</sup> decade and is characterized by specific histological findings. It is often presented with acute pancreatitis, obstructive jaundice, and is less associated with IgG4 but more with inflammatory bowel disease (IBD).

Yoshida first proposed the idea of AIP in 1995. Clinical manifestations of the condition frequently include obstructive jaundice, emaciation, exhaustion, and stomach discomfort. Serum IgG4 levels are raised, and imaging examinations show irregular stricture of the pancreatic duct and widespread or segmental enlargement of the pancreas[2]. According to histological study, AIP is typified by lymphocytic sclerosing pancreatitis, which is characterised by a substantial infiltration of IgG4-positive plasma cells and CD4-positive T cells around the pancreatic duct, resulting in occlusive fibrosis and stenosis[4].

IgG4-related systemic disease (IgG4-RD) is a fibroinflammatory disease involving multiple organs. IgG4-RD is a chronic, inflammatory disease with increased serum IgG4 concentrations and fibrosis as well as enlarged organs infiltrated with IgG4+ plasmacytes. Type 1 AIP is now considered a pancreatic manifestation of systemic IgG4-RD, with characteristic histological findings including lymphocyte and IgG4-positive plasma cell infiltration, fibrosis, and obliterative phlebitis[3,5,6]. Approximately 60% to 80% of AIP patients demonstrate obstructive jaundice with sclerosing cholangitis, resembling primary sclerosing cholangitis, pancreatic cancer, or cholangiocarcinoma.

AIP 1 has a difficult to predict recurrence risk. However, some factors, including diffuse pancreas enlargement, persistently high IgG4 levels, slow IgG4 level decrease, increased IgG4 level following glucocorticoid treatment, and proximal IgG4-associated sclerosing cholangitis, may be suggestive of recurrence[1,4]. According to recent research, interleukin-33 (IL-33) and interferon alpha (IFN- $\alpha$ ) may function as biomarkers for IgG4-RD and AIP. The first-line recommended treatment for AIP is steroids, which over 90% of individuals with type 1 AIP have remission from[2,4].

The pathogenesis of type 1 AIP has yet to be deciphered. Toll-like receptors (TLRs) play a role in the development of AIP-1, with overexpression observed in the pancreas and salivary glands of AIP and IgG4-RD patients. TLR-7 upregulation is documented in IgG4-RD, and plasmacytoid dendritic cells (pDCs) may contribute to the pathogenesis of AIP/IgG4-RD. Unregulated production of IFN- $\alpha$  by pDCs is associated with AIP. Apoptosis inhibitor of macrophages may serve as a potential biomarker for autoimmune and inflammatory diseases with tissue fibrosis, including IgG4-RD and AIP[3,5].

Pancreatic parenchymal and ductal imaging, serology, pancreatic histology, involvement of other organs, and response to steroid therapy are among the diagnostic criteria for AIP[7]. Serum IgG4 concentration, though not ideal, is a commonly used biomarker, and other serological markers, such as hypocomplementemia, antinuclear antibodies, rheumatoid factor positivity, and specific autoantibodies, have been investigated. The cutoff value for serum IgG4 is confirmed at 140 mg/dL[7]. Histopathological evaluation involves assessing IgG4 immunostaining of the duodenal papilla, neutrophil infiltration and molecular markers like IFN- $\alpha$  and IL-33, which are considered valuable for diagnosis and monitoring. Radiological imaging reveals diffuse pancreatic swelling, irregular narrowing of the main pancreatic duct, and characteristic patterns on dynamic computed tomography and contrast-enhanced magnetic resonance imaging. Endoscopic retrograde cholangiopancreatography typically shows narrowing of the main pancreatic duct, and magnetic resonance cholangiopancreatography may display multiple intermittent absences[7]. Endoscopic ultrasound (EUS) fine-needle aspiration is a useful technique for tissue sampling, especially in cases of focal AIP or when serum IgG4 levels are within normal limits[7].

## AFTEREFFECTS OF IGG4 RELATED PANCREATITIS

AIP is correlated with an increased incidence of various diseases. Haghbin *et al*[2], over a follow-up period ranging from 6 months to 22 years observed in their systematic review and metanalysis, that among 2746 AIP patients, 9.6% were found to have malignancies. Notably, 3.7% of these malignancies were diagnosed before or concurrently with AIP, while 4.6% were diagnosed after AIP. This emphasizes the importance of early and comprehensive cancer surveillance in AIP patients, as malignancies can manifest at any stage. Huggett *et al*[8] discovered that 13 of 115 patients with type 1 AIP (11.3%) had a malignancy, indicating a statistically significant risk of malignancy in individuals with type 1 AIP. However, the incidence of pancreatic cancer was low[2,8]. The most prevalent cancers in the AIP population were stomach, colorectal, and bladder cancer. These findings indicate the possibility that AIP is linked to malignancies outside of the affected organ[2,8].

The potential association between pancreatic cancer and AIP is a subject of ongoing debate. While AIP is a rare form of chronic pancreatitis, concerns have been raised, particularly in type 1 AIP, characterized by a higher incidence of disease relapse after steroid therapy. Existing studies, present conflicting evidence on the link between AIP and pancreatic cancer. Hart *et al*[9] observed an incidence of pancreatic cancer in type 1 AIP Patients of 0.51% with 5 diagnoses out of 978 type 1 AIP patients. Xiang *et al*[10] report an incidence of pancreatic cancer up to 6.7% and Macinga *et al*[11], in their review, observed that out of the 33 cases of patients with pancreatic cancer and AIP, 67% of those had their diagnosis at median period of 66.5 months (2-186 m), explaining the need for more systematic research in this area and a long term cancer surveillance[10,11].

Investigating the link between AIP-2 and IBD, particularly the increased rates of CRC in IBD, revealed no significant difference in CRC prevalence between the two types of AIP. This suggests a need for further exploration of the relationship between AIP-2, IBD, and CRC[2]. Non-malignant manifestations of AIP included sclerosing cholangitis, sialadenitis, and retroperitoneal fibrosis. Sclerosing cholangitis was observed up to 80% of AIP patients, emphasizing the diverse systemic impact of AIP[4]. About 60% to 80% of AIP patients presented with obstructive jaundice, often associated with sclerosing cholangitis. Additionally, AIP has been linked to IgG4-associated sclerosing cholangitis, resembling primary sclerosing cholangitis, pancreatic cancer, or cholangiocarcinoma in cholangiography features. It is known that various cancers have been reported in association with AIP or IgG4-RD, suggesting a complex interplay. However, there is a lack of prospective studies supporting the notion that AIP or IgG4-RD may develop as paraneoplastic syndromes.

Long-term chronic inflammation, a hallmark of AIP, is recognized for its role in carcinogenesis. Contrary to expectations, some studies showed no occurrence of pancreatic cancer in AIP and/or IgG4-RD patients during follow-up periods. The risk of malignancies in AIP patients appears higher within the first year after diagnosis, and treating coexisting cancers has been associated with preventing AIP relapse. Miyagawa *et al*[5] suggest that in some cases AIP as well as IgG4 related disease may be a paraneoplastic syndrome for other cancers, activating an IgG4 immune response.

## ROLE OF SURGERY IN AIP

Typically, surgery is not the primary option for AIP. Nevertheless, it should be contemplated when suspicions of malignant or premalignant lesions persist following a comprehensive diagnostic evaluation. The International Consensus Diagnostic Criteria (ICDC) advocates nonoperative approaches for managing AIP patients, with surgical intervention reserved for those experiencing severe symptoms, or to resolve associated biliary strictures[12].

Ensuring a thorough evaluation before surgery is crucial to optimize patient selection and avoid unnecessary procedures. A heightened clinical suspicion for AIP plays a crucial role in refining the decision-making process for surgical interventions. Early consideration of the potential for AIP is vital to prevent unnecessary surgeries or diagnostic procedures[12]. In cases where AIP is strongly suspected, it is recommended to measure serum IgG4 levels and perform a biopsy, with EUS-guided trucut biopsy being the preferred modality. When the biopsy fails to provide a clear diagnosis or raises suspicions of malignancy, a brief 2-wk steroid treatment may serve as an alternative to surgery. A swift resolution of imaging abnormalities, typically within two weeks, is observed in cases of AIP. In contrast, if a malignant lesion is present, no change in operability is anticipated during this brief period[13]. If the diagnosis of AIP is confirmed, and malignancy is ruled out, opting for rituximab treatment may prove to be a more effective alternative, resolving biliary manifestations without the need for surgery[12]. Moreover, in cases where AIP is strongly suspected, it is advisable to undergo a biopsy. If the biopsy results do not indicate features suggestive of malignancy, a brief course of steroid treatment should be contemplated. Corticosteroid therapy is the primary treatment for AIP, achieving remission in over 90% of cases. In cases involving a solid mass suggestive of malignancy, there is a consensus that obtaining biopsy proof is not obligatory before proceeding with resection[14]. However, patients with borderline resectable disease should confirm malignancy before undergoing neoadjuvant therapy and exploration for resection. The International Study Group of Pancreatic Surgery recommends surgical resection of a pancreatic solid mass without the need for histopathological confirmation of malignancy[15].

Despite a comprehensive preoperative assessment, a subset of patients persists in whom malignancy cannot be ruled out without resorting to pancreatic resection. Complicating the decision to operate or not, it is crucial to recognize that AIP is a rare disease[14]. In contrast, pancreatic ductal adenocarcinoma (PDAC) ranks as the 11<sup>th</sup> most common cancer globally, accounting for 4.5% of all cancer-related deaths in 2018, while the preoperative diagnosis of AIP does not eliminate the possibility of simultaneous pancreatic cancer[12]. Retrospective analysis revealed that approximately 23% of patients had concurrent malignant or premalignant lesions with AIP[14]. National Comprehensive Cancer Network

guidelines suggest that when a high suspicion for malignancy exists, surgical intervention is considered in pancreatic resections performed for suspected malignancy and the final histological examination often reveals benign conditions in 8% to 10% of patients. AIP constitutes approximately one-third of these cases, making up 2.5% of all pancreatic resections [16].

These occurrences need to be prevented since life-threatening complications might exacerbate the postoperative course after pancreatic resections. One of the most serious complications is a pancreatic fistula, which can have septic and hemorrhagic effects[12]. Strategies such as modifying anastomotic techniques, placing pancreatic duct stents, and prophylactic use of somatostatin analogs have been employed to enhance postoperative outcomes. Despite a notable decrease in perioperative mortality with increased surgical experience and improved critical care management, morbidity rates remain elevated, particularly in high-volume centers[17]. Despite the growing understanding of AIP, the number of patients undergoing pancreatic resection and being incorrectly diagnosed with pancreatic malignancy hasn't decreased over time, as observed[14].

Ikeura *et al*[18] highlighted the challenges in diagnosing AIP. The diagnostic yield of the ICDC without histology and response to steroids was low in focal AIP, diagnosing AIP in only 20% of patients suspected of having cancer. However, a steroid trial after excluding pancreatic cancer boosted ICDC's diagnostic yield to 73%, even in the lack of histology. This highlights the significance of pancreatic core needle biopsy or surgical excision in the remaining individuals[18]. In a study involving 114 European patients with surgically treated AIP, the relapse rate was 41.2% for AIP type 1 and 15.4% for AIP type 2[19]. In AIP, concurrent PanINs are frequently identified, with approximately 25% of patients in this study having incidental PanINs[16]. This aligns with findings from other studies indicating a notable occurrence of PanINs in individuals undergoing surgery for benign pancreatic conditions. These precursor lesions likely elevate the risk of future PDAC development, suggesting that a subset of patients may benefit from surgical resection. In comparison to patients undergoing resection for confirmed malignancy, those with AIP exhibit remarkable long-term outcomes[16]. In this cohort, only 18% experienced serious sequelae ( $\geq$  Clavien-Dindo grade 3), compared to 30% in a recent multi-institutional study of PDAC. Furthermore, whereas the 5-year survival rate for pancreatic cancer is normally approximately 8%, virtually all AIP patients survive at the 5-year milestone, with a rate around 100%[16].

## CONCLUSION

In conclusion, AIP is intricately linked to malignancies, emphasizing the importance of vigilant cancer surveillance in AIP patients. The association with various cancers beyond the pancreas suggests a systemic impact, and further research is needed to elucidate the complex relationship between AIP, IgG4-RD, and cancer. Surgery is reserved for severe cases or unresolved biliary strictures, with careful consideration due to the challenges in distinguishing AIP from malignancy. While AIP patients may have concurrent PanINs, they exhibit better long-term outcomes and survival compared to pancreatic cancer patients. Thorough diagnostic evaluation, including biopsy and response to steroids, is crucial in refining the decision-making process for surgery in AIP.

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