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**Long-term outcomes of autoimmune pancreatitis**

Ikeura T *et al.* Long-term outcome of AIP

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**Abstract**

Autoimmune pancreatitis (AIP) has been considered a favorable-prognosis disease; however, currently, there is limited information on natural course of AIP during long-term follow-up. Recently published studies regarding the long-term outcomes of AIP has demonstrated the developments of pancreatic stone formation, exocrine insufficiency, and endocrine insufficiency are observed in 5%-41%, 34%-82%, and 38%-57% of patients having the disease. Furthermore, the incidence rate of developing pancreatic cancer ranges from 0% to 4.8% during the long-term follow-up. The event of death from AIP-related complications other than accompanying cancer is likely to be rare. During follow-up of AIP patients, careful surveillance for not only relapse of the disease but also development of complications at regular intervals is needed.

**Key words:** Autoimmune pancreatitis; Prognosis; Outcome; Cancer

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**Core tip:** There is limited information on long-term outcomes of patients with autoimmune pancreatitis (AIP). This review provides a current overview of AIP regarding long-term outcomes such as pancreatic stone formation, pancreatic exocrine or endocrine dysfunction, associated malignancy, and mortality.

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**Introduction**

Autoimmune pancreatitis (AIP), which was first proposed as a novel clinical entity by Yoshida *et al*[1,2] in 1995, is a unique chronic inflammation of the pancreas. The disease is radiologically characterized by focal or diffuse pancreatic enlargement and irregular narrowing of the main pancreatic duct[3]. The main clinical finding is a dramatic response to steroids. Two histological subtypes of AIP have been recognized, namely types 1 and 2[3-6]. Type 1 AIP is histologically characterized by periductal abundant infiltration of lymphocytes with IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis. Patients with type 1 AIP are often elderly men, with elevated serum IgG4 levels and extrapancreatic lesions (*e.g.*, sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis). Recently, type 1 AIP is considered as a pancreatic manifestation of IgG4-related disease (IgG4-RD)[7,8]. By contrast, the histological findings of type 2 AIP are characterized by the presence of granulocytic epithelial lesions (GEL), but not IgG4-positive plasma cells around the large or medium sized pancreatic duct. Patients with type 2 AIP are often younger, have normal serum IgG4 levels, and frequently develop inflammatory bowel diseases, particularly ulcerative colitis[9].

Generally, the short-term prognosis of AIP is considered favorable based on the remarkable improvement of clinical and radiological findings after steroid therapy. By contrast, information on the long-term prognosis of AIP is limited because it is approximately 15 years after discovery of high serum IgG4 concentrations in patients with AIP[10]. This review provides a current overview of AIP regarding long-term outcomes such as pancreatic stone formation, pancreatic exocrine or endocrine dysfunction, associated malignancy, and mortality.

**OCCURRENCE OF PANCREATIC STONE AND DYSFUNCTION DURING LONG-TERM FOLLOW-UP IN PATIENTS WITH AIP**

***Development of pancreatic stone***

In ordinary chronic pancreatitis (CP), especially alcohol-induced pancreatitis, pancreatic stone is the most common complication. Pancreatic stone formation results from the hypersecretion of protein from acinar cells and stasis of pancreatic juice[11]. In type 1 AIP, newly formed pancreatic stones or increased formation of pancreatic stones during follow-up is observed in 5%–41% of cases, whereas no patient with type 2 AIP develop pancreatic stone formation (Table 1)[12-15]. In a multinational study, pancreatic duct stones are regarded as a relatively uncommon complication, occurring only in 7% of type 1 AIP patients with follow-up, and pancreatic stone formation occurs more frequently in patients with relapse of the disease at least once than in patients without relapse[12]. A multivariate analysis by Hirano *et al*[13] demonstrated that ethanol consumption of > 50 g/d was a significant risk factor of pancreatic stone formation during the clinical course of type 1 AIP [odd ratio (OR) = 7.47; 95% confidence interval (CI), 1.093–51.1; *P* = 0.040], indicating that similar to ordinary CP, changes in the pancreatic juice component due to high alcohol consumption may in part contribute to stone formation. By contrast, Maruyama *et al*[14] reported that the independent risk factor of pancreatic stone formation is not alcohol intake but narrowed Wirsung’s and Santorini’s ducts at diagnosis of AIP (OR = 4.4; 95%CI: 1.3–15.5, *P* = 0.019). Moreover, residual pancreatic head swelling and/or narrowing of Wirsung’s and Santorini’s ducts after corticosteroid therapy were more frequently found in patients with newly formed pancreatic stone than in patients without stone. These results indicate that the stone formation in AIP results from stasis of pancreatic juice due to the narrowing of the pancreatic head[14].

Pancreatic stone is a major cause of pain in ordinary CP, and thus, some patients require pain management including medical treatment, endoscopic treatment, and surgery. By contrast, AIP patient with pancreatic stone seem not to experience chronic pain[16-18].

***Development of pancreatic functional impairment***

In the typical long-term course of ordinary CP, pancreatic exocrine and endocrine dysfunctions occur owing to the destruction of acinar and Langerhans islet cells, inducing maldigestion and diabetes mellitus as clinical presentations[19]. At the time of AIP diagnosis, exocrine and endocrine insufficiencies were observed in 66%–81% and 46%–67% of cases, respectively[20-22]. After long-term follow-up, 34%–82% and 39%–57% of AIP patients had pancreatic exocrine and endocrine dysfunctions, respectively (Table 1)[15,23,24].

The multivariate logistic regression analysis by Buijs *et al*[24] demonstrated that the risk factors of the development of endocrine insufficiency were longer follow-up period (OR = 1.36; 95%CI: 1.11–1.68) and older age at onset (OR = 1.06; 95%CI: 1.01–1.11). Aggravation of glycemic control or new onset of diabetes mellitus during the clinical course of AIP is significantly associated with pancreatic parenchymal atrophy that is observed in approximately one-third of patients after remission induced by steroid therapy[12,23,25]. High tobacco intake has been associated with the prevalence of diabetes mellitus after long-term follow-up[26].

Although the reported ameliorating effect of steroid therapy for pancreatic function varies across studies owing to differences in observation period and definition of pancreatic exocrine and endocrine dysfunctions, steroid therapy appears to induce improvement of pancreatic exocrine function, as assessed by the urine exocrine *N*-benzoyl-l-tyrosyl-*p*-aminobenzoic acid (BT-PABA) test, in 40%–73% of AIP patients and glycemic control in 15%–63% of AIP patients with preexistent diabetes mellitus[15,21,22,27,28]. Some research studies emphasize that steroid therapy should be performed to preserve insulin secretion at the early stage of AIP or to improve glucose intolerance[22,28]. However, some cases show new onset of diabetes mellitus as a side effect of steroid therapy.

***Does AIP progress to ordinary CP?***

To examine whether type 1 AIP can progress to ordinary CP over a long disease course, Maruyama *et al*[29] evaluated the data of 73 patients with type 1 AIP who underwent long-term follow-up by using the revised Japanese clinical diagnostic criteria for ordinary CP. Of the 73 patients, 16 (22%) fulfilled the diagnostic criteria for CP. Furthermore, because 7% of the patients with previously diagnosed alcoholic or idiopathic CP had elevated serum IgG4 levels, the authors were concerned about the possibility that some of the patients with advanced-stage AIP were misdiagnosed as ordinary chronic pancreatitis[30].

**DEVELOPMENT OF PANCREATIC AND EXTRAPANCREATIC CANCERS IN AIP**

Chronic inflammatory processes play a role in carcinogenesis in various organs, such as liver cancer in chronic hepatitis B and C infections[31], gastric cancer in *Helicobacter pylori*-induced gastritis[32], colon cancer in inflammatory bowel disease[33], cholangiocarcinoma in primary sclerosing cholangitis[34], and pancreatic cancer (PC) in ordinary CP[35]. In type 1 AIP, persistently high IgG4 serum concentrations were observed in 60% of patients even after steroid therapy[36], and the relapse rate of type 1 AIP is relatively high, reaching up to 31%–57%[12,37,38]. This suggests the existence of persisting pancreatic inflammation during an apparent clinical remission. Therefore, it is reasonable to assume that type 1 AIP also carries the risk for pancreatic carcinogenesis. Indeed, several case reports[39-44] and cohort studies[12,37,45-49] reported that AIP cases synchronously or metachronously develop PC. Of the AIP patients who developed PC, 12 had partly or fully available clinical information, and their characteristics are shown in Table 2. The mean age of the 12 patients was 65.7 years (range, 39–80 years). Five (63%) of 8 patients had diabetes mellitus before the diagnosis of PC. PC was found simultaneously with AIP in 4 patients and developed in 8 patients during the mean follow-up period of 100.6 mo (range, 31–186 mo).

Although the accurate prevalence of the development of PC in AIP is currently unclear because the clinical profile of patients and surveillance strategy of AIP during follow-up differ depending on published studies, the incidence rate of developing PC ranges from 0% to 4.8% during the follow-up period of 33–75 mo[12,24,27,37,45-52] (Table 3). In an international multicenter analysis, 5 (0.8%) of 659 patients with type 1 AIP were reported to develop PC more than 3 years after the diagnosis of AIP, with the exception of one patient[12]. Whether the risk of pancreatic and extrapancreatic cancer is increased in patients with AIP compared with the general population is controversial. Japanese studies have demonstrated that the standardized incidence rate (SIR) for cancers in IgG4-related diseases or AIP ranged from 2.7 to 3.8[51,52]. In a UK cohort, the odds ratio of developing cancer at diagnosis or during follow-up was identified to be 2.25 times greater among patients with AIP/IgG4-related sclerosing cholangitis than among patients with age- and sex-matched national statistical data (95%CI: 1.12–3.94; *P* = 0.02)[37]. By contrast, some studies reported that the risk of developing cancer during follow-up in patients with AIP is comparable with that in patients without AIP[24,47]. To clarify whether AIP patients are more susceptible to pancreatic or extrapancreatic cancer, a well-designed multicenter study is needed to eliminate various biases.

# Few studies provide histological and biological evidence to support the likelihood of developing PC in type 1 AIP. Gupta *et al*[48] focused on pancreatic intraepithelial neoplasia (PanIN), widely recognized as the precursor lesion of invasive ductal carcinoma, arising within the pancreases resected from AIP patients. They demonstrated that the prevalence rates of PanIN-1, PanIN-2, and PanIN-3 in AIP patients were 82%, 25%, and 4%, respectively. These rates are comparable with those in ordinary CP, which is a well-established risk factor of PC. In our previous study[46], 2 patients with type 1 AIP who developed accompanying PC had no PanIN lesion in the non-cancerous region. However, one patient histologically exhibited marked lymphoplasmacytic infiltration with severe fibrosis around the PC, suggesting that carcinogenesis can result from LPSP, as addressed by Motonaga *et al*. Meanwhile, in a genetic research by Kamisawa *et al*[53], K-*ras* mutation, an essential factor in the development of pancreatic ductal adenocarcinoma[54,55], was identified in the pancreases of all patients with AIP, whereas 40% of patients with chronic alcoholic pancreatitis showed a K-*ras* mutation. These results provide the possibility that AIP is a risk factor of pancreatic carcinogenesis.

Another mechanism was proposed regarding the accompanying cancer in AIP. In a multicenter cohort study by Shiokawa *et al*[52], 14% of AIP patients developed several extrapancreatic cancers, including gastric cancer, lung cancer, lymphoma, prostatic cancer, colon cancer, bile duct cancer, and thyroid cancer, during the follow-up period, whereas none of the patients developed PC. Approximately half of these cancers were diagnosed simultaneously with AIP. The detection rate of concurrent cancers at the diagnosis of AIP was significantly higher than those of any cancers in the control population consisting of individuals who underwent for the first time a medical checkup with full examinations. In this cohort, the relative risk of cancer at AIP diagnosis was 4.9 (95%CI: 1.7–14.9). Moreover, most of the patients with cancer diagnosed prior to the diagnosis of AIP did not experience AIP relapse after successful treatment of their cancers. Based on these results, they proposed that AIP may be a manifestation of paraneoplastic syndrome, which is a rare condition triggered by an altered immune system response to a neoplasm[56]. To clarify the question, “Which comes first, AIP or cancer,” further epidemiological data are needed.

In the patients with AIP accompanied by PC, tumors are incidentally discovered as new findings such as mass formation and stricture of the lower bile duct on imaging examination performed as surveillance for AIP relapse. These findings may lead to misdiagnosis as AIP relapse because of the resemblance of the two diseases. In case the development of cancer is suspected in the followed-up patients with AIP, in addition to the assessment of serum CA19-9 level, pathological examination using endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) and endoscopic retrograde cholangiopancreatography (ERCP) should be performed.

**OUTCOMES OF LONG-TERM MAINTENANCE STEROID THERAPY**

Relapses of type 1 AIP more frequently occur during follow-up, compared to type 2 AIP. An international analysis demonstrated relapse rate in type 1 AIP was significantly higher than that in type 2 AIP (31% *vs* 9%; *P* < 0.001)[12]. The Japanese consensus guidelines for AIP proposed steroid maintenance therapy (2.5–5 mg/d) within 3 years to prevent relapse of the disease, whereas steroid therapy protocol without maintenance therapy is common in Western countries[57]. Most recently, Hirano *et al*[58] prospectively investigated outcomes after long-term maintenance steroid therapy in 21 patients with AIP. In the study, clinical relapse rate after the cessation of maintenance steroid therapy was unexpectedly high (48%, 11/21). Base on the results, authors concluded it was desirable to continue maintenance steroid therapy for over 3 years to prevent relapse. However, it is still unknown whether maintenance steroid therapy leads to favorable long-term outcomes not only in terms of prevention of relapse and progression of AIP but also in terms of steroid-related side effects.

**AIP-RELATED MORTALITY**

Patients with AIP are less likely to die from AIP-related complications other than accompanying cancer, although mortality due to complications of IgG4-related diseases, such as liver and renal failure, has been reported in rare cases[15,50]. No significant difference in survival was observed between patients with AIP and age- and sex-matched controls from the national population[24]. When the event of death during follow-up was compared between type 1 and type 2 AIP, the mortality rate in type 1 AIP was significantly higher than that in type 2 AIP[59]. The explanation for the higher mortality in the patients with type 1 AIP could be partly attributed to their higher age.

Long-term use of maintenance steroid therapy to prevent relapse of the disease can cause serious side effects, which can be fatal and therefore requires considerable attention[45].

**CONCLUSION**

Although the characteristics, magnitude, and sequelae of complications that occur during a long-term course of AIP are still poorly understood, careful surveillance for not only relapse of the disease but also development of complications at regular intervals during follow-up of AIP patients is important.

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**Table 1 Development of pancreatic stone formation and functional impairment in autoimmune pancreatitis patients during long-term follow-up**

|  |  |  |  |
| --- | --- | --- | --- |
| **Authors** | **Year** | **Follow-up period (mo)** | **Incident rate** |
| **Pancreatic stone** | **Endocrine dysfunction** | **Endocrine dysfunction** |
| Uchida *et al*[15] | 2006 | 41 | 4.8% (1/21) | 60% (6/10) | 46.2% (6/13) |
| Maire *et al*[23] | 2011 | 50 | NA | 34.1% (15/44) | 38.6% (17/44) |
| Maruyama *et al*[14] | 2012 | 91 | 40.6% (28/69) | NA | NA |
| Hart *et al*[12] | 2013 | NA | 7% (46/659) | NA | NA |
| Hirano *et al*[13] | 2013 | 76 | 11.3% (8/71) | NA | NA |
| Buijs *et al*[24] | 2015 | 75 | NA | 82.4% (56/68) | 56.1% (37/66) |

NA: Not available.

**Table 2 Characteristics of the autoimmune pancreatitis patients with pancreatic cancer whose clinical data were available**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Case** | **Authors** | **Year** | **Age** | **Sex** | **Smoking** | **Alcohol** | **Diabetes** | **Location of the PC** | **Period onset of AIP to PC** |
| 1 | Inoue *et al*[39] | 2006 | 62 | M | Yes | No | Yes | Body | 0 (Synchronous) |
| 2 | Ghazale *et al*[40] | 2007 | 72 | M | NA | NA | NA | Body | 60 |
| 3 | Witkiewicz *et al*[41] | 2008 | 80 | M | NA | NA | NA | Head | 0 (Synchronous) |
| 4 | Motosugi *et al*[42] | 2009 | 59 | M | NA | NA | Yes | Body and tail | 0 (Synchronous) |
| 5 | Matsubayashi *et al*[43] | 2009 | 65 | M | No | No | No | NA | 0 (Synchronous) |
| 6 | Gupta *et al*[48] | 2012 | 73 | M | NA | NA | NA | Tail | 120 |
| 7 | Gupta *et al*[48] | 2012 | 69 | M | NA | NA | NA | Head | 60 |
| 8 | Hirano *et al*[47] | 2014 | 58 | M | No | NA | Yes | NA | 119 |
| 9 | Hirano *et al*[47] | 2014 | 70 | M | No | NA | Yes | NA | 162 |
| 10 | Ikeura *et al*[46] | 2014 | 61 | F | Yes | No | No | Head | 31 |
| 11 | Ikeura *et al*[46] | 2014 | 39 | F | No | No | No | Body | 186 |
| 12 | Ikeura *et al*[46] | 2014 | 80 | M | No | No | Yes | Head | 67 |

NA: Not available; AIP: Autoimmune pancreatitis; PC: Pancreatic cancer.

**Table 3 Development of cancer at or after autoimmune pancreatitis diagnosis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Authors** | **Year** | **Follow-up period (mo)** | **Incident rate of PC** | **Incident rate of extrapancreatic cancer** |
| Nishino *et al*[27] | 2006 | 41 | 0% (0/12) | 16.7% (2/12) |
| Takuma *et al*[50] | 2011 | 40 | 0% (0/50) | NA |
| Yamamoto *et al*[51] | 2012 | 37 | 0% (0/106) 1 | 10.1% (11/106)1 |
| Shiokawa *et al*[52] | 2012 | 40 | 0% (0/108) | 13.9% (15/108) |
| Hart *et al*[12] | 2013 | NA | 0.7% (5/659) | 7% (46/659) |
| Gupta *et al*[48] | 2013 | 49 | 2.4% (2/84) | NA |
| Hart *et al*[49] | 2014 | 43 | 0.9% (1/116) | 9.5% (11/116) |
| Huggett *et al*[37] | 2014 | 33 | 0.9% (1/115)2 | 7% (8/115)2 |
| Hirano *et al*[47] | 2014 | 73 | 2.1% (2/95) | 11.5% (13/113)1 |
| Ikeura *et al*[46] | 2014 | 62 | 4.8% (3/63) | 3.2% (2/63) |
| Shimizu *et al*[45] | 2015 | 54 | 1.2% (1/84) | 11.9% (8/84) |
| Buijs *et al*[24] | 2015 | 75 | 0% (0/68) | 11.8% (8/68) |

1Includes patients with systemic IgG4-related disease without autoimmune pancreatitis; 2Includes patients with IgG4-related sclerosing cholangitis. NA: Not available; PC: Pancreatic cancer.