World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v22.i34.7760

World J Gastroenterol 2016 September 14; 22(34): 7760-7766
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

Long-term outcomes of autoimmune pancreatitis

Tsukasa Ikeura, Hideaki Miyoshi, Masaaki Shimatani, Kazushige Uchida, Makoto Takaoka, Kazuichi Okazaki

Tsukasa Ikeura, Hideaki Miyoshi, Masaaki Shimatani, Kazushige Uchida, Makoto Takaoka, Kazuichi Okazaki, Department of Gastroenterology and Hepatology, Kansai Medical University, Hirakata, Osaka 573-1010, Japan

Author contributions: Ikeura T, Miyoshi H and Shimatani M wrote the manuscript; Uchida K and Takaoka M made revision of the manuscript; Okazaki K made final approval of the manuscript to be published.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

Manuscript source: Invited manuscript

Correspondence to: Tsukasa Ikeura, MD, PhD, Department of Gastroenterology and Hepatology, Kansai Medical University, 2-3-1, Shinmachi, Hirakata, Osaka 573-1010, Japan. ikeurat@hirakata.kmu.ac.jp
Telephone: +81-72-8040101
Fax: +81-72-8042534

Received: March 28, 2016
Peer-review started: March 31, 2016
First decision: May 12, 2016
Revised: June 4, 2016
Accepted: June 28, 2016
Article in press: June 29, 2016
Published online: September 14, 2016

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; Outcome; Cancer; Prognosis

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.

Ikeura T, Miyoshi H, Shimatani M, Uchida K, Takaoka M, Okazaki K. Long-term outcomes of autoimmune pancreatitis. *World J Gastroenterol* 2016; 22(34): 7760-7766 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i34/7760.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i34.7760

INTRODUCTION

Autoimmune pancreatitis (AIP), which was first proposed as a novel clinical entity by Yoshida *et al*[1] in 1995, is a unique chronic inflammation of the pancreas[2]. The disease is radiologically characterized by focal or diffuse pancreatic enlargement and irregular narrowing of

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

Ref.	Year	Follow-up period (mo)	Incident rate		
			Pancreatic stone	Endocrine dysfunction	Endocrine dysfunction
Uchida *et al*[15]	2006	41	4.8% (1/21)	60.0% (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	7.0% (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.

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 (OR = 7.47; 95%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%

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

Case	Ref.	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.

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

Table 3 Development of cancer at or after autoimmune pancreatitis diagnosis

Ref.	Year	Follow-up period (mo)	Incident rate of PC	Incident rate of extrapancreatic cancer
Nishino *et al*[27]	2006	41	0.0% (0/12)	16.7% (2/12)
Takuma *et al*[50]	2011	40	0.0% (0/50)	NA
Yamamoto *et al*[51]	2012	37	0.0% (0/106)[1]	10.1% (11/106)[1]
Shiokawa *et al*[52]	2012	40	0.0% (0/108)	13.9% (15/108)
Hart *et al*[12]	2013	NA	0.7% (5/659)	7.0% (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]	7.0% (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% (0/68)	11.8% (8/68)

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

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 for cancers in IgG4-related diseases or AIP ranged from 2.7 to 3.8[51,52]. In a United Kingdom 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 and endoscopic retrograde cholangiopancreatography 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.

REFERENCES

1 **Yoshida K**, Toki F, Takeuchi T, Watanabe S, Shiratori K, Hayashi N. Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. *Dig Dis Sci* 1995; **40**: 1561-1568 [PMID: 7628283]

2 **Okazaki K**, Uchida K. Autoimmune Pancreatitis: The Past, Present, and Future. *Pancreas* 2015; **44**: 1006-1016 [PMID: 26355544 DOI: 10.1097/MPA.0000000000000382]

3 **Shimosegawa T**, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, Kim MH, Klöppel G, Lerch MM, Löhr M, Notohara K, Okazaki K, Schneider A, Zhang L. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas* 2011; **40**: 352-358 [PMID: 21412117 DOI: 10.1097/MPA.0b013e3182142fd2]

4 **Notohara K**, Burgart LJ, Yadav D, Chari S, Smyrk TC. Idiopathic chronic pancreatitis with periductal lymphoplasmacytic infiltration: clinicopathologic features of 35 cases. *Am J Surg Pathol* 2003; **27**: 1119-1127 [PMID: 12883244]

5 **Zamboni G**, Lüttges J, Capelli P, Frulloni L, Cavallini G, Pederzoli P, Leins A, Longnecker D, Klöppel G. Histopathological features of diagnostic and clinical relevance in autoimmune pancreatitis: a study on 53 resection specimens and 9 biopsy specimens. *Virchows Arch* 2004; **445**: 552-563 [PMID: 15517359 DOI: 10.1007/s00428-004-1140-z]

6 **Ikeura T**, Manfredi R, Zamboni G, Negrelli R, Capelli P, Amodio A, Caliò A, Colletta G, Gabbrielli A, Benini L, Okazaki K, Vantini I, Frulloni L. Application of international consensus diagnostic criteria to an Italian series of autoimmune pancreatitis. *United European Gastroenterol J* 2013; **1**: 276-284 [PMID: 24917972 DOI: 10.1177/2050640613495196]

7 **Kamisawa T**, Okamoto A. Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. *J Gastroenterol* 2006; **41**: 613-625 [PMID: 16932997 DOI: 10.1007/s00535-006-1862-6]

8 **Okazaki K**, Uchida K, Miyoshi H, Ikeura T, Takaoka M, Nishio A. Recent concepts of autoimmune pancreatitis and IgG4-related disease. *Clin Rev Allergy Immunol* 2011; **41**: 126-138 [PMID: 21170607 DOI: 10.1007/s12016-010-8214-2]

9 **Kawa S**, Okazaki K, Notohara K, Watanabe M, Shimosegawa T. Autoimmune pancreatitis complicated with inflammatory bowel disease and comparative study of type 1 and type 2 autoimmune pancreatitis. *J Gastroenterol* 2015; **50**: 805-815 [PMID: 25399203 DOI: 10.1007/s00535-014-1012-5]

10 **Hamano H**, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N, Kiyosawa K. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001; **344**: 732-738 [PMID: 11236777 DOI: 10.1056/NEJM200103083441005]

11 **Steer ML**, Waxman I, Freedman S. Chronic pancreatitis. *N Engl J Med* 1995; **332**: 1482-1490 [PMID: 7739686 DOI: 10.1056/NEJM199506013322206]

12 **Hart PA**, Kamisawa T, Brugge WR, Chung JB, Culver EL, Czakó L, Frulloni L, Go VL, Gress TM, Kim MH, Kawa S, Lee KT, Lerch MM, Liao WC, Löhr M, Okazaki K, Ryu JK, Schleinitz N, Shimizu K, Shimosegawa T, Soetikno R, Webster G, Yadav D, Zen Y, Chari ST. Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis. *Gut* 2013; **62**: 1771-1776 [PMID: 23232048 DOI: 10.1136/gutjnl-2012-303617]

13 **Hirano K**, Tada M, Isayama H, Watanabe T, Saito T, Uchino R, Hamada T, Miyabayashi K, Mizuno S, Mohri D, Sasaki T, Kogure H, Yamamoto N, Sasahira N, Toda N, Takahara N, Yagioka H, Akiyama D, Ito Y, Koike K. High alcohol consumption increases the risk of pancreatic stone formation and pancreatic atrophy in autoimmune pancreatitis. *Pancreas* 2013; **42**: 502-505 [PMID: 23146923 DOI: 10.1097/MPA.0b013e31826b3984]

14 **Maruyama M**, Arakura N, Ozaki Y, Watanabe T, Ito T, Yoneda S, Maruyama M, Muraki T, Hamano H, Matsumoto A, Kawa S. Risk factors for pancreatic stone formation in autoimmune pancreatitis over a long-term course. *J Gastroenterol* 2012; **47**: 553-560 [PMID: 22183858 DOI: 10.1007/s00535-011-0510-y]

15 **Uchida K**, Yazumi S, Nishio A, Kusuda T, Koyabu M, Fukata M, Miyoshi H, Sakaguchi Y, Fukui T, Matsushita M, Takaoka M, Okazaki K. Long-term outcome of autoimmune pancreatitis. *J Gastroenterol* 2009; **44**: 726-732 [PMID: 19396390 DOI: 10.1007/s00535-009-0049-3]

16 American Gastroenterological Association Medical Position Statement: treatment of pain in chronic pancreatitis. *Gastroenterology* 1998; **115**: 763-764 [PMID: 9721174]

17 **Di Sebastiano P**, di Mola FF, Bockman DE, Friess H, Büchler MW. Chronic pancreatitis: the perspective of pain generation by neuroimmune interaction. *Gut* 2003; **52**: 907-911 [PMID: 12740353]

18 **Maruyama M**, Watanabe T, Kanai K, Oguchi T, Asano J, Ito T, Muraki T, Hamano H, Arakura N, Uehara T, Kawa S. Extracorporeal shock wave lithotripsy treatment of pancreatic stones complicated with advanced stage autoimmune pancreatitis. *BMC Gastroenterol* 2015; **15**: 28 [PMID: 25887404 DOI: 10.1186/s12876-015-0255-9]

19 **Hayakawa T**, Naruse S, Kitagawa M, Ishiguro H, Jin CX, Kondo T. Clinical evidence of pathogenesis in chronic pancreatitis. *J Hepatobiliary Pancreat Surg* 2002; **9**: 669-674 [PMID: 12658399 DOI: 10.1007/s005340200092]

20 **Kawa S**, Hamano H. Clinical features of autoimmune pancreatitis.

J Gastroenterol 2007; **42** Suppl 18: 9-14 [PMID: 17520217 DOI: 10.1007/s00535-007-2044-x]
21 **Ito T**, Nishimori I, Inoue N, Kawabe K, Gibo J, Arita Y, Okazaki K, Takayanagi R, Otsuki M. Treatment for autoimmune pancreatitis: consensus on the treatment for patients with autoimmune pancreatitis in Japan. *J Gastroenterol* 2007; **42** Suppl 18: 50-58 [PMID: 17520224 DOI: 10.1007/s00535-007-2051-y]
22 **Miyamoto Y**, Kamisawa T, Tabata T, Hara S, Kuruma S, Chiba K, Inaba Y, Kuwata G, Fujiwara T, Egashira H, Koizumi K, Sekiya R, Fujiwara J, Arakawa T, Momma K, Asano T. Short and long-term outcomes of diabetes mellitus in patients with autoimmune pancreatitis after steroid therapy. *Gut Liver* 2012; **6**: 501-504 [PMID: 23170157 DOI: 10.5009/gnl.2012.6.4.501]
23 **Maire F**, Le Baleur Y, Rebours V, Vullierme MP, Couvelard A, Voitot H, Sauvanet A, Hentic O, Lévy P, Ruszniewski P, Hammel P. Outcome of patients with type 1 or 2 autoimmune pancreatitis. *Am J Gastroenterol* 2011; **106**: 151-156 [PMID: 20736934 DOI: 10.1038/ajg.2010.314]
24 **Buijs J**, Cahen DL, van Heerde MJ, Rauws EA, de Buy Wenniger LJ, Hansen BE, Biermann K, Verheij J, Vleggaar FP, Brink MA, Beuers UH, van Buuren HR, Bruno MJ. The Long-Term Impact of Autoimmune Pancreatitis on Pancreatic Function, Quality of Life, and Life Expectancy. *Pancreas* 2015; **44**: 1065-1071 [PMID: 26355549 DOI: 10.1097/MPA.0000000000000451]
25 **Masuda A**, Shiomi H, Matsuda T, Takenaka M, Arisaka Y, Azuma T, Kutsumi H. The relationship between pancreatic atrophy after steroid therapy and diabetes mellitus in patients with autoimmune pancreatitis. *Pancreatology* 2014; **14**: 361-365 [PMID: 25278305 DOI: 10.1016/j.pan.2014.07.005]
26 **Maire F**, Rebours V, Vullierme MP, Couvelard A, Lévy P, Hentic O, Palazzo M, Hammel P, Ruszniewski P. Does tobacco influence the natural history of autoimmune pancreatitis? *Pancreatology* 2014; **14**: 284-288 [PMID: 25062878 DOI: 10.1016/j.pan.2014.05.793]
27 **Nishino T**, Toki F, Oyama H, Shimizu K, Shiratori K. Long-term outcome of autoimmune pancreatitis after oral prednisolone therapy. *Intern Med* 2006; **45**: 497-501 [PMID: 16702740]
28 **Hirano K**, Isogawa A, Tada M, Isayama H, Takahara N, Miyabayashi K, Mizuno S, Mohri D, Kawakubo K, Sasaki T, Kogure H, Yamamoto N, Sasahira N, Toda N, Nagano R, Yagioka H, Yashima Y, Hamada T, Ito Y, Koike K. Long-term prognosis of autoimmune pancreatitis in terms of glucose tolerance. *Pancreas* 2012; **41**: 691-695 [PMID: 22249131 DOI: 10.1097/MPA.0b013e31823bcdee]
29 **Maruyama M**, Arakura N, Ozaki Y, Watanabe T, Ito T, Yoneda S, Maruyama M, Muraki T, Hamano H, Matsumoto A, Kawa S. Type 1 autoimmune pancreatitis can transform into chronic pancreatitis: a long-term follow-up study of 73 Japanese patients. *Int J Rheumatol* 2013; **2013**: 272595 [PMID: 23762066 DOI: 10.1155/2013/272595]
30 **Maruyama M**, Watanabe T, Kanai K, Oguchi T, Asano J, Ito T, Ozaki Y, Muraki T, Hamano H, Arakura N, Kawa S. Autoimmune pancreatitis can develop into chronic pancreatitis. *Orphanet J Rare Dis* 2014; **9**: 77 [PMID: 24884922 DOI: 10.1186/1750-1172-9-77]
31 **Koike K**. Hepatocarcinogenesis in hepatitis viral infection: lessons from transgenic mouse studies. *J Gastroenterol* 2002; **37** Suppl 13: 55-64 [PMID: 12109667]
32 **Asaka M**, Takeda H, Sugiyama T, Kato M. What role does Helicobacter pylori play in gastric cancer? *Gastroenterology* 1997; **113**: S56-S60 [PMID: 9394761]
33 **Eaden JA**, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001; **48**: 526-535 [PMID: 11247898]
34 **Singh S**, Talwalkar JA. Primary sclerosing cholangitis: diagnosis, prognosis, and management. *Clin Gastroenterol Hepatol* 2013; **11**: 898-907 [PMID: 23454027 DOI: 10.1016/j.cgh.2013.02.016]
35 **Lowenfels AB**, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, Dimagno EP, Andrén-Sandberg A, Domellöf L. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. *N Engl J Med* 1993; **328**: 1433-1437 [PMID: 8479461 DOI: 10.1056/NEJM199305203282001]
36 **Kawa S**, Hamano H, Ozaki Y, Ito T, Kodama R, Chou Y, Takayama M, Arakura N. Long-term follow-up of autoimmune pancreatitis: characteristics of chronic disease and recurrence. *Clin Gastroenterol Hepatol* 2009; **7**: S18-S22 [PMID: 19896092 DOI: 10.1016/j.cgh.2009.07.041]
37 **Huggett MT**, Culver EL, Kumar M, Hurst JM, Rodriguez-Justo M, Chapman MH, Johnson GJ, Pereira SP, Chapman RW, Webster GJ, Barnes E. Type 1 autoimmune pancreatitis and IgG4-related sclerosing cholangitis is associated with extrapancreatic organ failure, malignancy, and mortality in a prospective UK cohort. *Am J Gastroenterol* 2014; **109**: 1675-1683 [PMID: 25155229 DOI: 10.1038/ajg.2014.223]
38 **Sah RP**, Chari ST, Pannala R, Sugumar A, Clain JE, Levy MJ, Pearson RK, Smyrk TC, Petersen BT, Topazian MD, Takahashi N, Farnell MB, Vege SS. Differences in clinical profile and relapse rate of type 1 versus type 2 autoimmune pancreatitis. *Gastroenterology* 2010; **139**: 140-148; quiz e12-e13 [PMID: 20353791 DOI: 10.1053/j.gastro.2010.03.054]
39 **Inoue H**, Miyatani H, Sawada Y, Yoshida Y. A case of pancreas cancer with autoimmune pancreatitis. *Pancreas* 2006; **33**: 208-209 [PMID: 16868495 DOI: 10.1097/01.mpa.0000232329.35822.3a]
40 **Ghazale A**, Chari S. Is autoimmune pancreatitis a risk factor for pancreatic cancer? *Pancreas* 2007; **35**: 376 [PMID: 18090248 DOI: 10.1097/MPA.0b013e318073ccb8]
41 **Witkiewicz AK**, Kennedy EP, Kennyon L, Yeo CJ, Hruban RH. Synchronous autoimmune pancreatitis and infiltrating pancreatic ductal adenocarcinoma: case report and review of the literature. *Hum Pathol* 2008; **39**: 1548-1551 [PMID: 18619645 DOI: 10.1016/j.humpath.2008.01.021]
42 **Motosugi U**, Ichikawa T, Yamaguchi H, Nakazawa T, Katoh R, Itakura J, Fujii H, Sato T, Araki T, Shimizu M. Small invasive ductal adenocarcinoma of the pancreas associated with lymphoplasmacytic sclerosing pancreatitis. *Pathol Int* 2009; **59**: 744-747 [PMID: 19788620 DOI: 10.1111/j.1440-1827.2009.02437.x]
43 **Matsubayashi H**, Matsunaga K, Uesaka K, Fukutomi A, Sasaki K, Furukawa H, Ono H. A case of pancreatic carcinoma with suspected autoimmune pancreatitis. *Clin J Gastroenterol* 2009; **2**: 59-63 [PMID: 26191812 DOI: 10.1007/s12328-008-0045-9]
44 **Fukui T**, Mitsuyama T, Takaoka M, Uchida K, Matsushita M, Okazaki K. Pancreatic cancer associated with autoimmune pancreatitis in remission. *Intern Med* 2008; **47**: 151-155 [PMID: 18239323]
45 **Shimizu S**, Naitoh I, Nakazawa T, Hayashi K, Miyabe K, Kondo H, Nishi Y, Yoshida M, Umemura S, Hori Y, Kato A, Okumura F, Sano H, Hirata Y, Takada H, Ohara H, Joh T. Correlation between long-term outcome and steroid therapy in type 1 autoimmune pancreatitis: relapse, malignancy and side effect of steroid. *Scand J Gastroenterol* 2015; **50**: 1411-1418 [PMID: 26061806 DOI: 10.3109/00365521.2015.1054424]
46 **Ikeura T**, Miyoshi H, Uchida K, Fukui T, Shimatani M, Fukui Y, Sumimoto K, Matsushita M, Takaoka M, Okazaki K. Relationship between autoimmune pancreatitis and pancreatic cancer: a single-center experience. *Pancreatology* 2014; **14**: 373-379 [PMID: 25278307 DOI: 10.1016/j.pan.2014.04.029]
47 **Hirano K**, Tada M, Sasahira N, Isayama H, Mizuno S, Takagi K, Watanabe T, Saito T, Kawahata S, Uchino R, Hamada T, Miyabayashi K, Mohri D, Sasaki T, Kogure H, Yamamoto N, Nakai Y, Yoshida H, Ito Y, Akiyama D, Toda N, Arizumi T, Yagioka H, Takahara N, Matsubara S, Yashima Y, Koike K. Incidence of malignancies in patients with IgG4-related disease. *Intern Med* 2014; **53**: 171-176 [PMID: 24492683]
48 **Gupta R**, Khosroshahi A, Shinagare S, Fernandez C, Ferrone C, Lauwers GY, Stone JH, Deshpande V. Does autoimmune pancreatitis increase the risk of pancreatic carcinoma?: a retrospective analysis of pancreatic resections. *Pancreas* 2013; **42**: 506-510 [PMID: 23271394 DOI: 10.1097/MPA.0b013e31826bef91]
49 **Hart PA**, Law RJ, Dierkhising RA, Smyrk TC, Takahashi N, Chari ST. Risk of cancer in autoimmune pancreatitis: a case-control study and review of the literature. *Pancreas* 2014; **43**: 417-421 [PMID: 24622072 DOI: 10.1097/MPA.0000000000000053]

50 **Takuma K**, Kamisawa T, Tabata T, Inaba Y, Egawa N, Igarashi Y. Short-term and long-term outcomes of autoimmune pancreatitis. *Eur J Gastroenterol Hepatol* 2011; **23**: 146-152 [PMID: 21287714]

51 **Yamamoto M**, Takahashi H, Tabeya T, Suzuki C, Naishiro Y, Ishigami K, Yajima H, Shimizu Y, Obara M, Yamamoto H, Himi T, Imai K, Shinomura Y. Risk of malignancies in IgG4-related disease. *Mod Rheumatol* 2012; **22**: 414-418 [PMID: 21894525 DOI: 10.1007/s10165-011-0520-x]

52 **Shiokawa M**, Kodama Y, Yoshimura K, Kawanami C, Mimura J, Yamashita Y, Asada M, Kikuyama M, Okabe Y, Inokuma T, Ohana M, Kokuryu H, Takeda K, Tsuji Y, Minami R, Sakuma Y, Kuriyama K, Ota Y, Tanabe W, Maruno T, Kurita A, Sawai Y, Uza N, Watanabe T, Haga H, Chiba T. Risk of cancer in patients with autoimmune pancreatitis. *Am J Gastroenterol* 2013; **108**: 610-617 [PMID: 23318486 DOI: 10.1038/ajg.2012.465]

53 **Kamisawa T**, Tsuruta K, Okamoto A, Horiguchi S, Hayashi Y, Yun X, Yamaguchi T, Sasaki T. Frequent and significant K-ras mutation in the pancreas, the bile duct, and the gallbladder in autoimmune pancreatitis. *Pancreas* 2009; **38**: 890-895 [PMID: 19752775 DOI: 10.1097/MPA.0b013e3181b65a1c]

54 **Berrozpe G**, Schaeffer J, Peinado MA, Real FX, Perucho M. Comparative analysis of mutations in the p53 and K-ras genes in pancreatic cancer. *Int J Cancer* 1994; **58**: 185-191 [PMID: 8026879]

55 **Tada M**, Omata M, Ohto M. Clinical application of ras gene mutation for diagnosis of pancreatic adenocarcinoma. *Gastroenterology* 1991; **100**: 233-238 [PMID: 1983826]

56 **Tai P**, Yu E, Joseph K, Miale T. A review of autoimmune diseases associated with cancer. *Front Biosci* (Elite Ed) 2010; **2**: 122-126 [PMID: 20036861]

57 **Kamisawa T**, Okazaki K, Kawa S, Ito T, Inui K, Irie H, Nishino T, Notohara K, Nishimori I, Tanaka S, Nishiyama T, Suda K, Shiratori K, Tanaka M, Shimosegawa T. Amendment of the Japanese Consensus Guidelines for Autoimmune Pancreatitis, 2013 III. Treatment and prognosis of autoimmune pancreatitis. *J Gastroenterol* 2014; **49**: 961-970 [PMID: 24639058 DOI: 10.1007/s00535-014-0945-z]

58 **Hirano K**, Tada M, Isayama H, Sasahira N, Umefune G, Akiyama D, Watanabe T, Saito T, Takagi K, Takahara N, Hamada T, Mizuno S, Miyabayashi K, Mohri D, Kogure H, Yamamoto N, Nakai Y, Arizumi T, Toda N, Koike K. Outcome of Long-term Maintenance Steroid Therapy Cessation in Patients With Autoimmune Pancreatitis: A Prospective Study. *J Clin Gastroenterol* 2016; **50**: 331-337 [PMID: 26565969 DOI: 10.1097/MCG.0000000000000440]

59 **Detlefsen S**, Zamboni G, Frulloni L, Feyerabend B, Braun F, Gerke O, Schlitter AM, Esposito I, Klöppel G. Clinical features and relapse rates after surgery in type 1 autoimmune pancreatitis differ from type 2: a study of 114 surgically treated European patients. *Pancreatology* 2012; **12**: 276-283 [PMID: 22687385 DOI: 10.1016/j.pan.2012.03.055]

P- Reviewer: Fan RY, Sharma SS, Wilcox CM **S- Editor**: Yu J
L- Editor: A **E- Editor**: Ma S

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327