

## Evolution of the concept of autoimmune pancreatitis and its subtypes

*Daniel Longnecker, MD*

*Department of Pathology, Geisel School of Medicine at Dartmouth, Lebanon, NH*

*e-mail: daniel.s.longnecker@dartmouth.edu*

**Version 1.0, October 18, 2013 [DOI: 10.3998/panc.2013.11]**

The concept, recognition, and characterization of autoimmune pancreatitis (AIP) have evolved over the course of more than fifty years in multiple countries and centers. The possibility that pancreatitis was sometimes caused by autoimmune mechanisms was considered as early as 1959, but the characteristic clinical, imaging, and histopathologic features for such patients were not recorded until the 1990's. Yoshida is credited with introducing the term "autoimmune pancreatitis" into the English literature in 1995 although "autoimmunpankreatitis" was mentioned in a German review by Putzke in 1979 (25,35). Acceptance of the term (AIP) and an increasing focus on diagnosis, description, and treatment of the disease is evident in Ovid searches for "autoimmune pancreatitis" in sequential intervals. There were 192 papers listed during 1996-2005 with the majority initially coming from Japan, and 888 papers with worldwide origin during 2006-June 2013. Putzke suggested AIP as a possible cause of chronic sclerosing pancreatitis noting the prominence of interstitial lymphoplasmacytic infiltrates and perilobular, intralobular and periductal fibrosis in some pancreases consistent with current histopathologic criteria for the diagnosis of AIP (25). Yoshida mentioned 11 cases including one of their own and 10 others reported during 1961-1991 (35).

Thal et al. made an early reference to the possible autoimmune etiology of pancreatitis in 1959 when they reported antipancreatic antibodies in patients with chronic pancreatitis (32) and subsequently

commented that "the finding of true auto-antibodies in this case raised the interesting possibility that his disease was either precipitated by or aggravated by an auto-immunizing mechanism" (20).

In 1961, Sarles reported a group of patients having "primary inflammatory sclerosis" of the pancreas (27). The authors mention a lymphoplasmacytic infiltrate, perilobular fibrosis, and lobular sclerosis in one pancreas, and hypergammaglobulinemia in two patients. These findings are supportive of a diagnosis of AIP although the clinical and pathologic data are not adequate to allow a firm retrospective diagnosis of AIP for all patients in the group. The authors speculated, "It is thus possible to put forward the hypothesis that this type of pancreatitis is an inflammatory, noninfectious disease that is caused by phenomena of self-immunization" (27).

The dominant view regarding the pathogenesis of immune-mediated pancreatitis initially centered on humoral immunity. This view was based in part on studies in which animals were immunized with and developed antibodies against pancreas-derived fractions and subsequently developed pancreatic fibrosis (31). Thal stated, "It is not yet clear whether these circulating antibodies are merely a side result of a more important reaction of the delayed hypersensitivity type occurring at the cellular level" (31). A central role for antibody-mediated injury was supported by a later study in which diffuse interstitial pancreatitis developed in mice treated with antiserum from guinea pigs

immunized with pancreatic fractions (6). More recently we find the statement that it is unclear whether autoantibodies that yield elevations of IgG and IgG4 in AIP patients represent an epiphenomenon or play a role in the pathogenesis of disease (21).

The central role of cell-mediated immunity in the pathogenesis of autoimmune diseases was recognized later, beginning in 1974 (9), and was specifically supported as a possible mechanism in AIP by the demonstration of high numbers of T lymphocytes in pancreatic infiltrates in AIP (5, 23) and experimentally by the induction of pancreatitis in rats by adoptive transfer of CD4(+) T cells sensitized to a pancreatic epitope (4).

AIP is a rare disease with an estimated annual incidence in the range of 0.82 per 100,000 in Japan (22). The incidence in western nations is probably similarly low (24, 30) and most clinicians, radiologists, and pathologists are likely to see only occasional cases, slowing the recognition of AIP. There is evidence that the incidence of AIP has risen dramatically during the past two decades providing a basis for the recent wider recognition of the disease (18).

Because AIP may cause pancreatic enlargement that is often localized in the head or present with obstructive jaundice, many patients with these inflammatory masses have undergone pancreatectomy with a preoperative clinical diagnosis of a pancreatic neoplasm and were diagnosed after resection as having pancreatitis by the surgical pathologist. Experience with such cases is the basis for the histopathologic diagnosis of AIP. Retrospective studies indicate that 2.2-2.6% of pancreatectomies were done because of mass forming AIP (1, 11, 33, 34). Most of these data reflect a period before there was emphasis on the clinical diagnosis of AIP and this rate is expected to drop with improved recognition (12).

Heterogeneity in the pathology of AIP resection specimens has now resolved into the recognition of at least two subtypes of AIP. Early descriptions focused on the prominence of mixed infiltrates of lymphocytes and plasma cells in some cases of chronic pancreatitis and led to the descriptive diagnosis "lymphoplasmacytic sclerosing pancreatitis" (LPSP), now often referred to as type 1 AIP (16).

The 1997 paper by Ectors et al. is of importance because a pattern of chronic pancreatitis was identified in a group of resected pancreases from non-alcoholic patients that was clearly different than that seen in alcoholics (5). The name "chronic non-alcoholic duct destructive pancreatitis" was suggested for this type of pancreatitis. Some (4/12) of these patients had autoimmune disease manifest in other organs. An autoimmune etiology was carefully considered although the pancreatitis was ultimately classified as idiopathic. Ectors noted that intraductal aggregates of neutrophilic granulocytes were commonly associated with duct destructive lesions (5). Later, the neutrophilic aggregates were called "granulocytic epithelial lesions (GEL) and GEL are now recognized as a characteristic of type 2 AIP (17, 36). This pattern is also referred to as IDCP. The basis for this acronym is ambiguous, being defined variously as "idiopathic duct centric pancreatitis" and alternately as "idiopathic duct-centric chronic pancreatitis" (3, 23, 28, 30).

Suda described early and late stage AIP, the latter based on prominent loss of acinar cells (29). All specimens were from pancreatic resection or biopsy and all contained inflamed ducts. Although the late stage patients (n=11) were about 2.5 years older than the early stage group (n=20) at disease onset, the age difference was not significant. The degree of lymphoplasmacytic infiltration was more variable and venulitis was less frequent in the late stage pancreases, but it is not obvious that the late stage group should be regarded as end stage. It is not known if the end

stage of AIP could be distinguished from the late state of chronic pancreatitis of other etiologies.

The possible role of IgG4 in the pathogenesis of AIP and subsequent recognition of IgG4-associated systemic autoimmune disease evolved as follows (13). As was noted above, AIP is often associated with concordant involvement of other organs (5, 35). Overall, it appears that there is evidence of involvement of other organs by autoimmune processes in a quarter to more than half of AIP patients in various series.

A variety of autoantibodies were detected in patients with AIP, and hypergammaglobulinemia was documented in some patients (27, 35). This led to the examination of immunoglobulin subclasses and recognition in 2001 that IgG4 was elevated in the serum of most Japanese patients with AIP (10). Later, increased numbers of IgG4-positive plasma cells were demonstrated in a high fraction of pancreases with AIP, and finally similar elevations of IgG4-positive cells were identified in other involved organs (13). This led to the proposal that AIP was part of an IgG4-associated systemic autoimmune disease (13, 15). In a 2008 review, Kamisawa states, "This disease includes AIP, sclerosing cholangitis, cholecystitis, sialadenitis, retroperitoneal fibrosis, tubulointerstitial nephritis, interstitial pneumonia, prostatitis, inflammatory pseudotumor and lymphadenopathy, all IgG4-related" (14). Almost all "autoimmune" disorders associated with AIP have now been proven to be manifestations of IgG4-related disease.

As the literature for AIP is reviewed it is necessary to consider what is included in each report. It is typical for series from Japan to be composed entirely or predominantly of type 1 AIP patients; the type of AIP that is seen in the multi-organ IgG4-related disease. Accordingly, we find that as many as 95% of the patients have elevated serum IgG4 in series from Japan (10). In

contrast, in series from the USA and Europe, the fraction of patients with elevation of IgG4 is reported as 50-76% in various series, depending in part on the cut-off level (7, 8). The lower frequency of serum IgG4 elevation may be due to the inclusion of type 2 AIP patients who typically do not have elevation of serum IgG4 (26). However, true seronegative (i.e, with normal serum IgG4) type 1 AIP is also well described; such patients do show abundant infiltration with IgG4+ plasma cells despite normal serum IgG4 levels (2).

Although most AIP can be classified by expert pathologists as type 1 or type 2 on the basis of histopathology when a resection specimen is available, a few cases are difficult to classify by the current criteria (3, 37). We do not know if these are simply examples of type 1 or type 2 AIP that are atypical, perhaps due to differences in stage or degree of involvement, or whether they might represent rarer subtypes of the disease. Recognition of rare subtypes of a rare disease will be difficult and may require new genetic or immunologic markers.

The concept of AIP and its subtypes has evolved as understanding of this unique form of pancreatitis has improved. The following chapters further expand this discussion and focus on a variety of aspects of AIP including the key diagnostic features, treatment, and long-term outcomes.

### **Acknowledgement**

This introduction is excerpted in part from a previously published chapter on a similar topic (19).

The author thanks the current editors for substantive input during preparation of this updated overview.

## **References**

1. **Abraham SC, Wilentz RE, Yeo CJ, Sohn TA, Cameron JL, Boitnott JK and Hruban RH.** Pancreaticoduodenectomy (Whipple resections) in patients without malignancy: are they all 'chronic pancreatitis'? *Am J Surg Pathol.* 27: 1: 110-120, 2003. [PMID: 12502933](#)
2. **Balashramanian G, Sugumar A, Smyrk TC, Takahashi N, Clain JE, Gleeson FC, Hart PA, Levy MJ, Pearson RK, Petersen BT, Topazian MD, Vege SS, and Chari, ST.** Demystifying seronegative autoimmune pancreatitis. *Pancreatology* 12: 4: 289-294, 2012. [PMID: 22898628](#)
3. **Chari ST, Kloppel G, Zhang L, Notohara K, Lerch MM, Shimosegawa T.** Autoimmune Pancreatitis International Cooperative Study Group (APICS). Histopathologic and clinical subtypes of autoimmune pancreatitis: the Honolulu consensus document. *Pancreas* 39: 5: 549-554, 2010. [PMID: 20562576](#)
4. **Davidson TS, Longnecker DS and Hickey WF.** An experimental model of autoimmune pancreatitis in the rat. *Am J Pathol* 166: 3: 729-736, 2005. [PMID: 15743785](#)
5. **Ectors N, Maillet B, Aerts R, Geboes K, Donner A, Borchard F, Lankisch P, Stolte M, Luttges J, Kremer B and Kloppel G.** Non-alcoholic duct destructive chronic pancreatitis. *Gut* 41: 2: 263-268, 1997. [PMID: 9301509](#)
6. **Freytag G and Kloppel G.** Experimental pancreatitis and inflammation of the islets after treatment with immune sera against extract of pancreas of varying degrees of purity. *Beitr Pathol Anat.* 139: 2: 138-160, 1969. [PMID: 4897405](#)
7. **Frulloni L, Scattolini C, Falconi M, Zamboni G, Capelli P, Manfredi R, Graziani R, D'Onofrio M, Katsotourchi AM, Amodio A, Benini L and Vantini I.** Autoimmune pancreatitis: differences between the focal and diffuse forms in 87 patients. *Am J Gastroenterol.* 104: 9: 2288-2294, 2009. [PMID: 19568232](#)
8. **Ghazale A, Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Clain JE, Pearson RK, Pelaez-Luna M, Petersen BT, Vege SS and Farnell MB.** Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. *Am J Gastroenterol* 102: 8: 1646-1653, 2007. [PMID: 17555461](#)
9. **Gonatas NK and Howard JC.** Inhibition of experimental allergic encephalomyelitis in rats severely depleted of T cells. *Science* 186: 4166: 839-841, 1974. [PMID: 4143378](#)
10. **Hamano H.** High Serum IgG4 Concentrations in Patients with Sclerosing Pancreatitis. *N Engl J Med.* 344: 10: 732-738, 2001. [PMID: 11236777](#)
11. **Hardacre JM, Iacobuzio-Donahue CA, Sohn TA, Abraham SC, Yeo CJ, Lillemoe KD, Choti MA, Campbell KA, Schulick RD, Hruban RH, Cameron JL and Leach SD.** Results of pancreaticoduodenectomy for lymphoplasmacytic sclerosing pancreatitis. *Ann Surg.* 237: 6: 853-858, 2003. [PMID: 12796582](#)
12. **Hughes DB, Grobmyer SR and Brennan MF.** Preventing pancreaticoduodenectomy for lymphoplasmacytic sclerosing pancreatitis: cost effectiveness of IgG4. *Pancreas* 29: 2: 167, 2004. [PMID: 15257110](#)
13. **Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, Okamoto A, Egawa N and Nakajima H.** A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol.* 38: 10: 982-984, 2003. [PMID: 14614606](#)
14. **Kamisawa T and Okamoto A.** IgG4-related sclerosing disease. *World J.Gastroenterol.* 14: 25: 3948-3955, 2008. [PMID: 18609677](#)
15. **Kamisawa T and Okamoto A.** Autoimmune pancreatitis: proposal of IgG4-related sclerosing disease. *J Gastroenterol.* 41: 7: 613-625, 2006. [PMID: 16932997](#)
16. **Kawaguchi K, Koike M, Tsuruta K, Okamoto A, Tabata I and Fujita N.** Lymphoplasmacytic sclerosing pancreatitis with cholangitis: a variant of primary sclerosing cholangitis extensively involving pancreas. *Hum Pathol.* 22: 4: 387-395, 1991. [PMID: 2050373](#)
17. **Kloppel G, Detlefsen S, Chari ST, Longnecker DS and Zamboni G.** Autoimmune pancreatitis: the clinicopathological characteristics of the subtype with granulocytic epithelial lesions. *J Gastroenterol.* 45: 8: 787-793, 2010. [PMID: 20549251](#)
18. **Kojima M, Sipos B, Klapper W, Frahm O, Knuth HC, Yanagisawa A, Zamboni G, Morohoshi T and Klöppel G.** Autoimmune pancreatitis: frequency, IgG4 expression, and clonality of T and B cells. *Am J Surg Pathol.* 31: 4: 521-528, 2007. [PMID: 17414098](#)
19. **Longnecker DS.** Background and Perspectives. Chapter 1. In: Autoimmune (IgG4-related) Pancreatitis and Cholangitis, edited by Levy MJ and Chari ST. *Springer, New York*, pp. 1-6, 2013.
20. **Murray MJ and Thal AP.** The clinical significance of circulating pancreatic antibodies. *Ann Intern Med.* 53: 548-555, 1960. [PMID: 13727030](#)
21. **Narula N, Vasudev M and Marshall JK.** IgG4-related sclerosing disease: a novel mimic of inflammatory bowel disease. *Dig Dis Sci.* 55: 11: 3047-3051, 2010. [PMID: 20521111](#)

22. **Nishimori I, Tamakoshi A and Otsuki, M.** Research Committee on Intractable Diseases of the Pancreas, Ministry of Health, Labour, and Welfare of Japan. Prevalence of autoimmune pancreatitis in Japan from a nationwide survey in 2002. *J Gastroenterol* 42: Suppl. 18: 6-8, 2007. [PMID: 17520216](#)
23. **Notohara K, Burgart LJ, Yadav D, Chari S and Smyrk TC.** Idiopathic chronic pancreatitis with periductal lymphoplasmacytic infiltration: clinicopathologic features of 35 cases. *Am J Surg Pathol.* 27: 8: 1119-1127, 2003. [PMID: 12883244](#)
24. **Pannala R and Chari ST.** Autoimmune pancreatitis. *Curr Opin Gastroenterol.* 24: 5: 591-596, 2008. [PMID: 19122500](#)
25. **Putzke HP.** Morphology of acute and chronic pancreatitis. *Z Gesamte Inn Med.* 34: 10: 266-271, 1979. [PMID: 483921](#)
26. **Sah RP, Pannala R, Chari ST, Sugumar A, Clain JE, Levy MJ, Pearson RK, Smyrk TC, Petersen BT, Topazian MD, Takahashi N and Vege SS.** Prevalence, diagnosis, and profile of autoimmune pancreatitis presenting with features of acute or chronic pancreatitis. *Clin Gastroenterol Hepatol.* 8: 1: 91-96, 2010. [PMID: 19800984](#)
27. **Sarles H, Sarles JC, Muratore R and Guien C.** Chronic inflammatory sclerosis of the pancreas--an autonomous pancreatic disease?. *Am J Dig Dis.* 6: 688-698, 1961. [PMID: 13746542](#)
28. **Shimosegawa T and Kanno A.** Autoimmune pancreatitis in Japan: overview and perspective. *J Gastroenterol.* 44: 6: 503-517, 2009. [PMID: 19377842](#)
29. **Suda K, Nishimori I, Takase M, Oi I and Ogawa M.** Autoimmune pancreatitis can be classified into early and advanced stages. *Pancreas* 33: 4: 345-350, 2006. [PMID: 17079937](#)
30. **Sugumar A and Chari S.** Autoimmune pancreatitis: an update. *Expert Rev Gastroenterol Hepatol* 3: 2: 197-204, 2009. [PMID: 19351289](#)
31. **Thal AP.** The occurrence of pancreatic antibodies and the nature of the pancreatic antigen. *Surg.Forum* 11: 367-369, 1960. [PMID: 13776154](#)
32. **Thal AP, Murray MJ and Egner W.** Isoantibody formation in chronic pancreatic disease. *Lancet* 1: 7083: 1128-1129, 1959. [PMID: 13665981](#)
33. **van Heerde MJ, Biermann K, Zondervan PE, Kazemier G, van Eijck CH, Pek C, Kuipers EJ and van Buuren HR.** Prevalence of autoimmune pancreatitis and other benign disorders in pancreatoduodenectomy for presumed malignancy of the pancreatic head. *Dig Dis Sci* 57: 9: 2458-2465, 2012. [PMID: 22588243](#)
34. **Weber SM, Cubukcu-Dimopulo O, Palesty JA, Suriawinata A, Klimstra D, Brennan MF and Conlon K.** Lymphoplasmacytic sclerosing pancreatitis: inflammatory mimic of pancreatic carcinoma. *J Gastrointest Surg* 7: 1: 129-137, 2003. [PMID: 12559194](#)
35. **Yoshida K, Toki F, Takeuchi T, Watanabe S, Shiratori K and Hayashi N.** Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis. *Dig Dis Sci.* 40: 7: 1561-1568, 1995. [PMID: 7628283](#)
36. **Zamboni G, Luttges J, Capelli P, Frulloni L, Cavallini G, Pederzoli P, Leins A, Longnecker D and Kloppel G.** Histopathological features of diagnostic and clinical relevance in autoimmune pancreatitis: a study on 53 resection specimens and 9 biopsy specimens. *Virchows Arch.* 445: 6: 552-563, 2004. [PMID: 15517359](#)
37. **Zhang L, Chari S, Smyrk TC, Deshpande V, Kloppel G, Kojima M, Liu X, Longnecker DS, Mino-Kenudson M, Notohara K, Rodriguez-Justo M, Srivastava A, Zamboni G and Zen Y.** Autoimmune pancreatitis (AIP) type 1 and type 2: an international consensus study on histopathologic diagnostic criteria. *Pancreas* 40: 8: 1172-1179, 2011. [PMID: 21975436](#)