

Case Report

Chronic sclerosing sialadenitis as the initial manifestation of the IgG4-related sclerosing disease

Ke Sun¹, Bo Wang¹, Jianfeng Wei², Hongtian Yao¹

Departments of ¹Pathology, ²Hepatobiliary Surgery, The First Affiliated Hospital, College of Medicine, Zhejiang University, Qingchun Road 79#, Hangzhou, Zhejiang, China

Received October 25, 2015; Accepted December 23, 2015; Epub February 1, 2016; Published February 15, 2016

Abstract: Three Chinese patients, one female aged 63 years, two males aged 52 and 54 years, respectively, all presented with chronic sclerosing sialadenitis (CSS) as the initial clinical manifestation, followed by IgG4-related sclerosing pancreatitis. The kidneys and lungs were involved in case 1. Moreover, enlargement of hilar lymph nodes was also noted in this patient. After steroid therapy, the clinical symptoms alleviated in all three patients.

Keywords: IgG4-related sclerosing disease, IgG4-related sclerosing pancreatitis, chronic sclerosing sialadenitis, Kuttner tumor

Introduction

Chronic sclerosing sialadenitis (CSS), also known as “Kuttner tumor”, has recently been considered as a part of the spectrum of immunoglobulin G4 (IgG4)-related sclerosing diseases [1], which includes sclerosing pancreatitis, sclerosing cholangitis, mediastinal fibrosis, interstitial pneumonia, tubulointerstitial nephritis and chronic sclerosing sialadenitis. IgG4-related sclerosing disease is characterized by elevation of serum IgG4 level and extensive infiltration of IgG4-positive plasma cells in various organs accompanied by corresponding clinical manifestations. These patients usually show good response to steroid therapy. Herein, we analyzed three Chinese cases of IgG4-related sclerosing disease which initially presented with chronic sclerosing sialadenitis and subsequently developed IgG4-related sclerosing pancreatitis. The kidneys and lungs were involved in case 1. Moreover, enlargement of hilar lymph nodes were also noted in this patient. After steroid therapy, the clinical symptoms alleviated in all the three patients.

Case report

Case 1

The first patient was a 63-year-old Chinese female who presented with gradually enlarged

painless mass in bilateral submandibular region for 6 months. She denied a history of diabetes mellitus. A physical examination showed the presence of firm, non-fixed and boundary masses involving the bilateral submandibular region. The bilateral enlarged submandibular lymph nodes were also palpable. Among the laboratory findings, liver function tests were normal. The value of fasting blood glucose was 6.96 (3.92-6.16 mmol/L). Chest X-ray revealed no special signs. Submandibular gland excision was carried out. Histological sections showed preservation of lobular architecture. Between the atrophic acini and the ducts, infiltration of diffuse lymphoplasmacytic cells was found (**Figure 1A**), associated with many follicular hyperplasia. Prominent cellular interlobular fibrosis was noted. The nerves were invaded by extensive lymphoplasmacytic cells and several eosinophils (**Figure 1B**). Periphlebitis and obliterating phlebitis (**Figure 1C**) were also seen. Immunohistochemically, a high content of IgG4-positive plasma cells (**Figure 1D**) was identified. The mean number of IgG4-positive and IgG-positive plasma cells per high-power field (HPF) was 100 and 137, respectively. Mean value of the IgG4: IgG ratio was 0.73. The pathological diagnosis was chronic sclerosing sialadenitis. The patient received no other treatment.

One year later, the patient was referred to our hospital again because of abdominal discom-

Chronic sclerosing sialadenitis

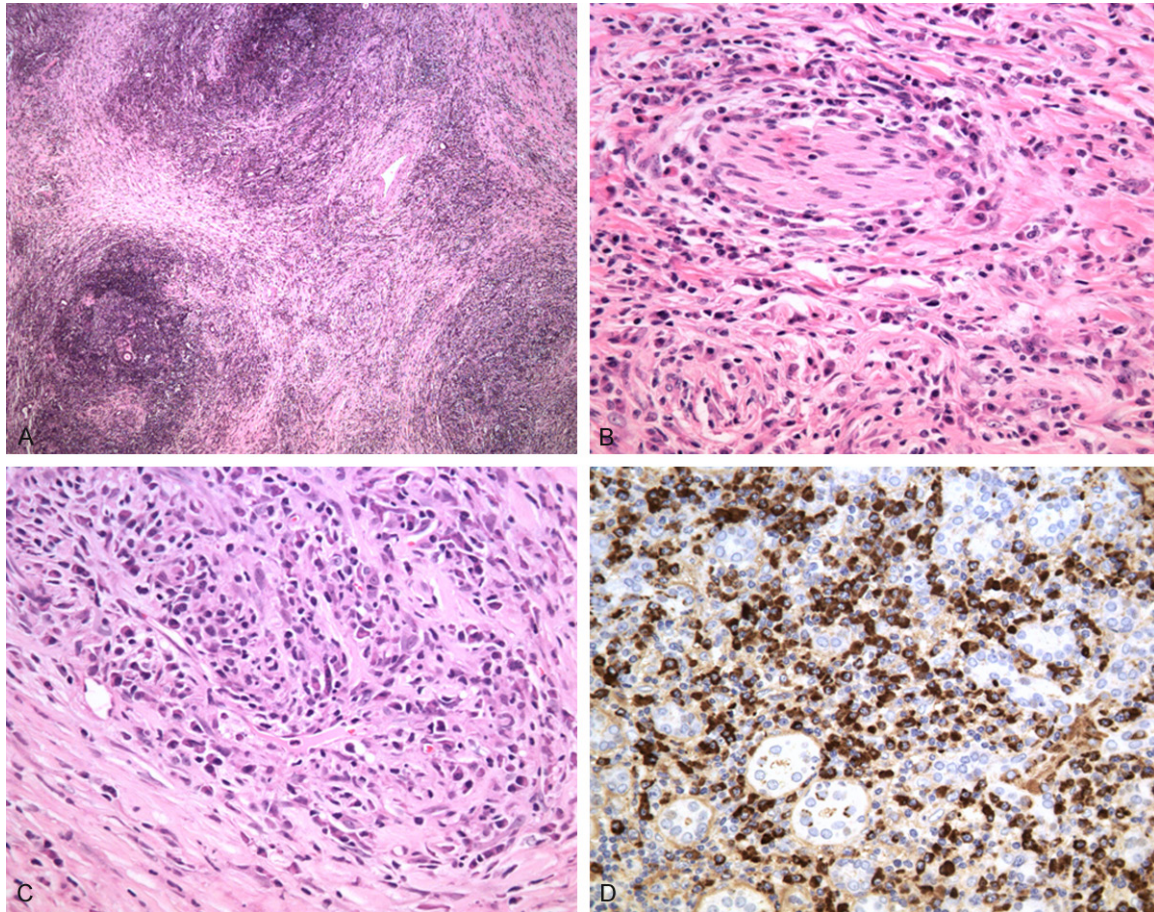


Figure 1. A. Lobular inflammation with lymphoplasmacytic infiltration. Note that the lobular architecture is vaguely preserved (original magnification $\times 50$). B. Severe lymphoplasmacytic infiltration with several eosinophils and fibrosis around the nerve are observed (original magnification $\times 400$). C. Obliterative phlebitis (original magnification $\times 400$). D. Numerous IgG4-positive plasma cells in chronic sialadenitis (original magnification $\times 400$).

fort, poor appetite, cutaneous pruritus and weight loss. Laboratory tests showed elevation of gamma glutamyltransferase, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and IgG (1800.0 mg/dL; normal range: 700.0-1600.0 mg/dL). The value of fasting blood glucose was 16.75 (3.92-6.16 mmol/L). Abdominal contrast-enhanced CT scan (**Figure 2A**) revealed diffuse enlargement of the pancreas, dilatation of gallbladder and intrahepatic bile ducts. Moreover, stenosis of splenic and left gastric artery was noted. The CT scan also demonstrated multiple masses in the bilateral kidneys. Lung contrast-enhanced CT showed a mass in the left hilum of the lung and multiple enlarged lymph nodes in the bilateral hilum of the lungs. An exploratory biopsy of the pancreas was performed. The specimen showed remarkable lymphoplasmacytic cell infiltration and fibrosis (**Figure 2B**). Immuno-

histochemical staining showed large numbers of IgG4-positive plasma cells infiltration (**Figure 2C**). According to the consensus of the Japan-Korea symposium on autoimmune pancreatitis (IgG4-related sclerosing pancreatitis), the patient was diagnosed as autoimmune pancreatitis (IgG4-related sclerosing pancreatitis) involving the kidneys and lungs with enlargement of hilar lymph nodes.

The patient was treated with prednisone at 40 mg/day for one month, with reduction to 35 mg/day a week later. Thereafter, she continued the treatment at the frequency of a reduction of 5 mg/day. Finally, the clinical symptoms alleviated. She denied abdominal pain, fever, headache or dizziness. The value of fasting blood glucose and postprandial blood sugar was within normal range. She underwent surgical resection of colon cancer and received chemothera-

Chronic sclerosing sialadenitis

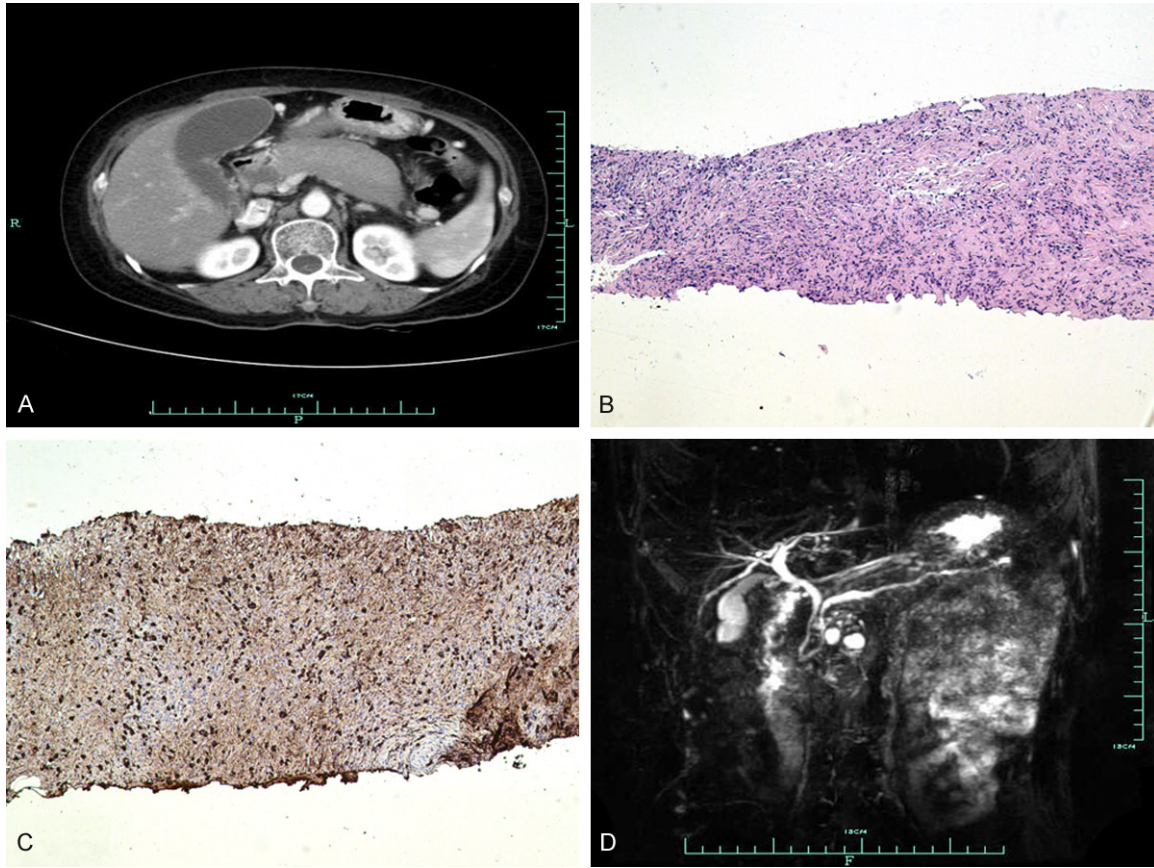


Figure 2. A. Abdominal contrast-enhanced CT image showing diffuse enlargement of pancreas and dilatation of the gallbladder. B. Plasma cell-rich infiltrate with fibrosis (original magnification $\times 100$). C. Numerous IgG4-positive cells (original magnification $\times 100$). D. MRCP indicates diffuse beading and stricturing of lower common bile duct and pancreatic duct, with dilation in intrahepatic bile duct, common hepatic duct and upper common bile duct.

py in August 2014. So far, she was in a good condition.

Case 2

The patient was a 52-year-old Chinese male, who hospitalized because of the rapid enlargement of a soybean-like mass in the right submandibular region two years ago. He had a history of noninsulin-dependent diabetes mellitus for eight years. Physical examination showed a painless, non-fixed and well-defined boundary mass in the right submandibular region. Enlarged lymph nodes could also be palpable beside the mass. Serological examination revealed a slight elevation of globulin and gamma glutamyltransferase. The right submandibular gland excision was carried out. Microscopic evaluation revealed a diffuse lymphoplasmacytic inflammatory infiltrate with the formation of focal lymphoid follicles. Immuno-

histochemical staining showed the mean number of IgG4-positive and IgG-positive plasma cells per HPF was 395 and 430, respectively. Mean value of the IgG4: IgG ratio was 0.92. The findings were consistent with the clinicalpathologic features of CSS. The patient underwent no other treatment after excision.

Four months later, the patient was referred to our hospital again because of weight loss. Laboratory tests showed elevation of IgG (4540.0 mg/dL; normal range: 700.0-1600.0 mg/dL), gamma glutamyltransferase, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase. Abdominal contrast-enhanced CT scan revealed diffuse enlargement of the pancreas and a slight peripancreatic infiltration. Magnetic resonance cholangiopancreatography (MRCP) (**Figure 2D**) suggested diffuse beading and stricturing of lower common bile duct and pancreatic duct,

with dilation in intrahepatic bile duct, common hepatic duct and upper common bile duct. Endoscopic ultrasound revealed a significant enlargement of the head of the pancreatic with internal heterogeneous echo. The main pancreatic duct dilated, with a diameter of about 0.7 cm, and the boundary was not well-defined. The body and tail of the pancreas also enlarged, with heterogeneously decreased echo. Multiple foci of erosions and small ulcerations were found at gastric antrum. The wall of gallbladder became thicker. The patient was diagnosed as autoimmune pancreatitis (IgG4-related sclerosing pancreatitis) and treated with methylprednisolone tablets 4 pills/day after discharge. The dose was reduced to 2 pills/day gradually. During this period the patient suffered from fatigue and weight loss. He was referred to our hospital again one year later for the bad control of blood glucose. He continued to take methylprednisolone for 1 pill/day for three years. Till now the patient was in a good condition.

Case 3

The patient was a 54-year-old Chinese male. He found a mass in the right submandibular region in 2006 and a mass in the left submandibular region in 2010. He paid no attention to it because it was asymptomatic. He presented with painless obstructive jaundice in January 2011. Serum tests showed elevation of IgG (2510 mg/dL; normal range: 700.0-1600.0 mg/dL), kappa light chain (3840 mg/dL; normal range: 574-1280 mg/dL), lambda light chain (2000 mg/dL; normal range: 269-638 mg/dL). Abdomen CT revealed a diffusely enlarged pancreas. The wall of the bile duct became thicker. Stenosis was observed in the head of pancreas part of the bile duct. The wall of gallbladder became thicker. Multiple enlarged lymph nodes were present. He was diagnosed as autoimmune pancreatitis. He was treated with prednisolone at 40 mg/day for two months. Thereafter, the dose was reduced by 10 mg/month. Three months later, the dose maintained at 5 mg/day for another six months. The bilateral submandibular masses decreased during the prednisolone therapy. But the masses quickly enlarged after the drug discontinuance. Physical examination revealed firm and fixed masses involving the bilateral submandibular region. The left mass was 5 cm in maximum dimension, while the right mass was 4 cm

in maximum dimension. Enlarged lymph nodes could also be palpable beside the mass. Submandibular gland excision was carried out. The final pathological diagnosis of CSS was made. Immunohistochemical staining showed the mean number of IgG4-positive and IgG-positive plasma cells per HPF was 218 and 380, respectively. Mean value of the IgG4: IgG ratio was 0.57. The patient suspended the prednisolone therapy after surgery. One month later, he received CT scan for the swelling of the upper eyelids. The CT scan revealed significant enlargement of lacrimal glands with well-defined boundary. The morphology of bilateral eyeballs was normal. There was no change of the optic nerve. CT scan also showed fluid density foci in the bilateral maxillary sinuses, ethmoidal sinuses, frontal sinuses, sphenoidal sinuses and nasal cavity. The wall of the sinuses was complete. Moreover, CT scan demonstrated no hyperplasia or destruction of the bone tissue. He resumed the prednisolone therapy. He was in a good condition so far.

Discussion

IgG4-related sclerosing disease is a novel concept which was put forward over the past decades [2]. It is a systemic disease characterized by fibrosis, lymphoplasmacytic infiltration, presences of abundant IgG4-positive plasma cells and high serum concentrations of IgG4. It mainly affects middle-aged and elderly patients, with a slight male predominance. The clinical manifestation is protean, depending on the distribution of the involved organs. These patients show good response to steroid therapy.

In 2001, Hamano et al. [3] first reported the significant elevation of serum IgG4 level and the presence of abundant IgG4-positive plasma cells in pancreas in sclerosing pancreatitis. These cases showed good response to steroid therapy. Histologically, this subtype corresponded to lymphoplasmacytic sclerosing pancreatitis, but was different from the idiopathic duct-centric chronic pancreatitis. The former type was recently proposed to be designated as "IgG4-related sclerosing pancreatitis". They found this type of pancreatitis co-existed with retroperitoneal fibrosis [4]. Despite the different locations, the histological features were similar with the infiltration of a large number of

IgG4-positive plasma cells. Since then, a series of such lesions outside the pancreas have been reported, such as sclerosing cholangitis, mediastinal fibrosis, interstitial pneumonia, tubulointerstitial nephritis and chronic sclerosing sialadenitis [1, 5]. These lesions can be alone or as a part of a systemic disease. They can occur with pancreatic lesions synchronously or metachronously, or even in the absence of pancreatic lesions [6]. The etiology and pathogenesis of IgG4-related sclerosing disease remains unclear. IgG4 is the most rare subtype of IgG, only representing about 3%~6% of the serum total IgG under normal circumstances [7]. The elevation of serum IgG4 level and the presence of abundant IgG4-positive plasma cells in the lesions indicate that IgG4 may play an important role in the pathogenesis of the disease. CSS, mostly affecting the submandibular gland, is a benign tumor-like lesion presenting with firm mass and well-defined boundary. Clinically, it can be sometimes difficult to distinguish from neoplasm. CSS can occur unilaterally or bilaterally, with a predominance in male and middle-aged to elderly patients [8]. The histological features of CSS are similar to lymphoplasmacytic sclerosing pancreatitis. Immunohistochemical staining shows diffuse infiltration of large numbers of IgG4-positive plasma cells. Recently, CSS has been proposed to be a member of the IgG4-related sclerosing disease group [1]. From three large scale of researches [9-11], a total of 29 cases of IgG4-related CSS were described. These were 16 males and 13 females, with mean age of 61 years old. Two patients presented with autoimmune disease (Graves disease and Hashimoto thyroiditis respectively). Eight patients had IgG4-related sclerosing disease outside salivary glands, 3 of whom with multiple organs involved. Morphological features of the 29 patients were similar. Of all the patients, the mean number of IgG4-positive plasma cell per HPF was 162; the ratio of the IgG4 to IgG-positive plasma cells was 0.79.

In our research, all the three patients presented with CSS as the initial clinical manifestation, followed by IgG4-related sclerosing pancreatitis. Case 1 and case 2 did not take serum IgG test before submandibular resection in our hospital, and no abdominal CT scan was carried out. Neither of them received steroid therapy after the submandibular resection. Both of the

patients suffered from weight loss and elevation of serum IgG level postoperatively. CT scan showed diffuse enlargement of pancreas. In addition, case 1 simultaneously presented with lesions in kidneys and lungs, and enlargement of hilar lymph nodes. This patient also underwent pancreas biopsy. The diagnosis of IgG4-related sclerosing pancreatitis was made in the three patients according to the Asian diagnostic criteria for autoimmune pancreatitis (IgG4-related sclerosing pancreatitis) in 2008 [12]. The occurrence of CSS also supported the diagnosis. The third patient developed the swelling of bilateral lacrimal glands, which strongly suggested the occurrence of IgG4-related dacryadenitis, though the biopsy was not available. These 3 cases can be considered as IgG4-related sclerosing disease initially presenting with CSS. CSS may be a warning sign for the development of IgG4-related sclerosing disease.

In conclusion, CSS may be a part of IgG4-related sclerosing diseases. When diagnosis is made, it is necessary to ascertain whether the lesions occur within salivary gland only or in combination with other IgG4-related sclerosing disease. The establishment of follow-up is also necessary. Some patients show good response to steroid therapy.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Bo Wang, Department of Pathology, The First Affiliated Hospital, College of Medicine, Zhejiang University, 79 Qingchun Road, Hangzhou, Zhejiang, China. Tel: +86-57187236368; Fax: +86-57187236368; E-mail: wangbo19800623@sohu.com

References

- [1] Cheuk W, Chan JK. IgG4-related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. *Adv Anat Pathol* 2010; 17: 303-332.
- [2] Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, Okamoto A, Egawa N, Nakajima H. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003; 38: 982-984.
- [3] Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N, Kiyosawa K. High serum

Chronic sclerosing sialadenitis

- IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001; 344: 732-738.
- [4] Hamano H, Kawa S, Ochi Y, Unno H, Shiba N, Wajiki M, Nakazawa K, Shimojo H, Kiyosawa K. Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. *Lancet* 2002; 359: 1403-1404.
- [5] Kamisawa T, Nakajima H, Egawa N, Funata N, Tsuruta K, Okamoto A. IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis with lymphadenopathy. *Pancreatology* 2006; 6: 132-137.
- [6] Kamisawa T, Okamoto A. IgG4-related sclerosing disease. *World J Gastroenterol* 2008; 14: 3948-3955.
- [7] Van der Zee JS, Aalberse RC. Immunochemical characteristics of IgG4 antibodies. *N Engl Reg Allergy Proc* 1988; 9: 31-33.
- [8] Chan JK. Kuttner tumor (chronic sclerosing sialadenitis) of the submandibular gland: an underrecognized entity. *Adv Anat Pathol* 1998; 5: 239-251.
- [9] Kitagawa S, Zen Y, Harada K, Sasaki M, Sato Y, Minato H, Watanabe K, Kurumaya H, Katayanagi K, Masuda S, Niwa H, Tsuneyama K, Saito K, Haratake J, Takagawa K, Nakanuma Y. Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Kuttner's tumor). *Am J Surg Pathol* 2005; 29: 783-791.
- [10] Geyer JT, Ferry JA, Harris NL, Stone JH, Zukerberg LR, Lauwers GY, Pilch BZ, Deshpande V. Chronic sclerosing sialadenitis (Kuttner tumor) is an IgG4-associated disease. *Am J Surg Pathol* 2010; 34: 202-210.
- [11] Laco J, Ryska A, Celakovsky P, Dolezalova H, Mottl R, Tucek L. Chronic sclerosing sialadenitis as one of the immunoglobulin G4-related diseases: a clinicopathological study of six cases from Central Europe. *Histopathology* 2011; 58: 1157-1163.
- [12] Otsuki M, Chung JB, Okazaki K, Kim MH, Kamisawa T, Kawa S, Park SW, Shimosegawa T, Lee K, Ito T, Nishimori I, Notohara K, Naruse S, Ko SB, Kihara Y. Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. *J Gastroenterol* 2008; 43: 403-408.