Autoimmune pancreatitis

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Introduction. Autoimmune pancreatitis (AIP) is the specific type of chronic pancreatitis due to autoimmune background and mechanism.

Characteristics. The main clinical symptoms of AIP are obstructive jaundice and abdominal discomfort. The typical histological findings are lymphocytes and IgG4 plasma cells infiltration, fibrosis and venulitis within pancreatic gland. Plasma level of IgG4 is usually extremely high.

Objectives. Diagnosis: High level IgG4 positive plasma cells in serum, lymphoplasmatic infiltration found on histological staining of pancreatic tissue, "sausage-like" pancreas in ultrasound and CT scans, and response to steroid therapy are crucial for making of diagnosis.

Classification of AIP: AIP can be classified into two subtypes. Type 1 was recognized as the pancreatic manifestation of multiorgan disorder, called IgG4 related disease. Type 2 is a pancreas-specific disorder not associated with IgG4, with similar histological signs as type 1, but also with the positivity of GEL (granulocytic epithelial lesion).

Results. Therapy: Due to its high effectivity in AIP treatment, steroid therapy is the first-line option. The alternative therapy is using immunosuppressants (azathioprine). Recently, there are also first experience in biological therapy already published.

Conclusion. Before the start of AIP therapy - the differential diagnosis between pancreatic cancer and AIP is essential.

Key words: chronic pancreatitis, autoimmune pancreatitis, immunoglobulines, IgG4, steroids, extrapancreatic lesions, pancreatic biopsy

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INTRODUCTION

Chronic pancreatitis is an inflammatory process, during which the pancreatic parenchyma is replaced with fibrotic tissue. This morphological change leads to irreversible destruction of both the exocrine and the endocrine glandular pancreatic parenchyma. The terminal point of these changes is exocrine and endocrine pancreatic insufficiency. The literature on the incidence and prevalence of chronic pancreatitis is not voluminous and time trends in incidence rates are lacking. The study in Copenhagen area in the 1970's reported an incidence of 6.9 - 10.0 new cases per 100 000 inhabitants per year¹. In the Cantabria region of Spain between 1981 and 1991 the incidence was found to be 14 per 100000 per year, of which 80% were alcohol induced². In 2002, Lankisch and co-workers published their results of chronic pancreatitis incidence in the region of Northern Germany. The incidence in the period 1988 to 1995 was 6.4 per 100000 per year^{3,4}. In 2001, Dite and co-workers reported an incidence of 7.9/100000/year in the Czech Republic and the incidence was similar to that of other European countries /France, Denmark Germany, Hungary/. The highest

incidence of chronic pancreatitis, 23/100000/year, was found in Finland⁵. Some studies have found a serious increase in the number of patients admitted to hospital with chronic pancreatitis, e.g. in the UK an increase of 100% from 1989/90 to 1999/2000 was documented⁶ (Table 1). Japan also registered an increase in prevalence from 28.5 to 32.9/100000 and from 5.4 to 5.7/100000/year during the period 1994 to 1999 (ref.⁶).

In 2001, the TIGAR-O classification system of etiological factors for chronic pancreatitis was published⁷. This system is based on the mechanism of injury of pancreatic tissue, and it addresses the risk, etiology, and complexity of the disease. Chronic pancreatitis is a complex disorder that may involve the interaction of two or more environmental or genetic factors. The TIGAR-O model addresses this potential synergistic role of multiple risk factors in a single individual with chronic pancreatitis and allows assessment of the contributory level of each of the interacting risk factors. Although the critical information about different forms of chronic pancreatitis is not fully available, the TIGAR-O system lays the foundation for further advancement in the field. The major categories include toxic-metabolic (T), idiopathic (I), genetic (G),

autoimmune (A), recurrent severe acute pancreatitis (R), and obstructive (O) mechanisms.

In 1961, Sarles and co-workers described the idiopathic form of pancreatitis with minimal subjective symptoms, obstructive jaundice and hypergammaglobulinemia and they were the first to suspect an autoimmune process as an etiological factor⁸. In 1995, Yoshida and co-workers described a patient with obstructive jaundice, with diffusely enlarged pancreas, irregular pancreatic duct and hypergammaglobulinemia. The pancreatic biopsy revealed pancreatic fibrosis. The symptoms resolved after steroid therapy. The term "AUTOIMMUNE PANCREATITIS" was used for the first time⁹. Recent knowledge supports the concept of autoimmune pancreatitis (AIP) as a unique clinical entity within putative IgG4 systemic diseases. The pathogenetic mechanisms remain unclear¹⁰, but autoimmune etiology is presumed.

EPIDEMIOLOGY

Epidemiological data on AIP is still very poor. A nationwide study in Japan estimated the prevalence of AIP to be 0.82 per 100 000 habitants¹¹, when diagnostic criteria for AIP proposed by the Japanese Pancreas Society in 2002 were used¹². AIP is at least twice as common in men as in women. The onset of the disease is typical in patients over 55 years of age^{11,13,14}. The incidence of AIP appears to have risen in last few years - from 2.0 to 4.0 in our series.

Clinical feature

- mild abdominal symptoms
- occasional presence of obstructive jaundice
- high level of serum gammaglobulin IgG and IgG4
- presence of non-specific antibodies
- diffuse enlargement of the pancreas ("sausage-like"), in CT scan with capsule-like low density rim
- diffuse irregular of pancreatic duct on ERCP
- histomorphologically lymphocyte and IgG4-positive plasmacyte infiltration and fibrosis, obliterative phlebitis
- association with extrapancreatic lesions
- responsibility to steroid therapy

HISTOLOGY

Histopathological features support the hypothesis of two histological and clinical subtypes of AIP (ref. ^{14,15}).

The histological pattern in type 1 is identical to the classic description of the disease and is associated with the histological pattern known as lymphoplasmatic sclerosing pancreatitis - LPSP. Typical histological signs are dense periductal lymphoplasmacytic infiltrates, swirling fibrosis, obliterative venulitis and IgG4 tissue positivity. The main serological marker is elevation of serum immunoglobulin IgG4. Type-1 AIP is considered to be a part of IgG4-associated systemic disease for which extrapancreatic involvement is typical. The bile ducts, kidneys, salivary glands, retroperitoneum and mediastinum

Table 1. Incidence of Chronic Pancreatitis.

Country	Incidence
Switzerland	1.2/100 000/year
Poland	4.0/100 000/year
Germany	7.4/100 000/year
Czech Rep.	7.9/100 000/year
Hungary	8.0/100 000/year
Denmark	10.0/100 000/year
Sweden	10.0/100 000/year
Finland	23.0/100 000/year
United States	5.7-7.6/100 000/year

Table 2. Autoimmune pancreatitis – subtypes.

Type 1	
Lymphoplasmatic sclerosing pancreatitis (LPSP)	- periductal lymphoplasmatic infiltrates - high amount IgG4 - positive plasma cells - swirling fibrosis - obliterative venulitis
Type 2	
Idiopathic duct-centric pancreatitis (IDCP)	- ductal epithelial granulocytic infiltration - ductal damage
„non-alcoholic duct destructive pancreatitis“	- obliteration

are among the most commonly affected extrapancreatic organs¹⁶⁻²⁰ (Table 2).

The most frequent clinical symptom in type 1 AIP is obstructive jaundice. In patients with AIP type 2 features typical for acute or chronic pancreatitis can be occasionally seen. IgG4 elevation is very rare in type 2 AIP, but very frequent (about 80%) in patients with type 1 AIP. Association between inflammatory bowel disease, primary biliary cirrhosis and AIP is connected with type 2 AIP. In contrast, type 1 AIP is combined with extrapancreatic manifestations, as are IgG4 sclerosing cholangitis, sialoadenitis, retroperitoneal fibrosis, etc.²¹ (Table 3). According to the TIGAR-O classification system⁷ AIP can be subdivided into isolated and syndromic subgroups with syndromic AIP being associated with inflammatory bowel disease and primary biliary cirrhosis²¹. In our sample of patients with AIP, we also identified IgG4 mastitis and Mikulicz syndrome (Table 4).

DIAGNOSIS

Asian consensus criteria (Table 5) and/or HISORT criteria of AIP (table 6) are generally accepted²²⁻²⁴. The problem with the Japanese Diagnostic Criteria is a lower sensitivity (80%) and specificity (87%) than HISORT criteria (92% sensitivity and 97% specificity) (ref.²⁵).

Five cardinal feature of AIP are as follows:

- pancreatic histology
- serology
- imaging of pancreatic parenchyma and duct

Table 3. Comparison of type 1 and type 2 AIP.

	Type 1 AIP	Type 2 AIP
Mean Age	Sixth decade	Fourth decade
Gender	Predominantly male	Equal
Histological pattern	Lymphoplasmacytic sclerosing pancreatitis	Duct-destructive pancreatitis
Histological signs	Periductal lymphoplasmacytic infiltrates Swirling fibrosis Obliterative venulitis	Lymphoplasmacytic infiltrates Granulocyte epithelial lesions with partial/ complete duct obstruction (GEL)
IgG4 cells on immunostaining	Moderate-severe (98%)	Moderate (40%) in one study
Serum IgG4 levels	Elevated	Normal
Other organ involvement	Sclerosing sialadenitis, IgG4-associated cholangitis, retroperitoneal fibrosis, IgG4- associated tubulointerstitial nephritis, pneu- monitis, prostatitis, IgG4 mastitis	Inflammatory bowel disease Primary biliary cirrhosis

Table 4. AIP with extrapancreatic lesions (n=13).

Gender	Age	Concomitant autoimmune disease
Male	36	IgG4 sclerosing cholangitis
Male	43	Sialadenitis
Male	53	Sjögren sy
Female	54	Sjögren sy, autoimmune hepatitis
Male	56	autoimmune hepatitis
Male	32	autoimmune hepatitis
Female	55	primary biliary cirrhosis
Male	51	IBD
Male	46	Xxx
Female	33	Xxx
Female	58	IgG4 positive mastitis, sialadenitis
Female	55	IgG4 sclerosing cholangitis
Male	49	IgG4 sclerosing cholangitis

- other organ involvement
- response to steroid therapy

Diagnostic biopsy with histological examination is usually sufficient for the diagnosis of type 1 of AIP and is a mandatory procedure in the differential diagnosis between AIP and pancreatic cancer²⁶⁻²⁸. Sausage-like enlargement of the gland in CT imaging and/or endosonography is present in more than 50% of patients with AIP. Dynamic CT and MRI show delayed enhancement of the swollen pancreas, in some patients forming a "capsule-like rim" surrounding the pancreas. ERCP, better than MRCP, shows diffuse narrowing of the pancreatic duct with some irregularities. Positron emission tomography /PET/ does not play any role in diagnostic work-up²⁵. In the case

Table 5. Clinical diagnostic criteria for AIP 2006.

1. Diffuse or segmental narrowing of the MPD with irregular wall and diffuse or localized enlargement of the pancreas by imaging studies, such as abdominal US, CT, and magnetic resonance.
2. High serum γ -globulin, IgG, or IgG4, or the presence of autoantibodies such as antinuclear antibodies and rheumatoid factor.
3. Marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells in the periductal area, occasionally with lymphoid follicles in the pancreas.

Diagnosis of AIP is established when criterion 1 and criterion 2 and/or 3 are fulfilled. However, it is necessary to exclude malignant diseases.

of typical histology, serological positivity of IgG4, other organ involvement and typical imaging in CT or EUS, the diagnosis of autoimmune pancreatitis is most certain. Narrowed pancreatic duct, enlarged gland with sausage-like shape, elevation of serum IgG4 and/or compatible histology are typical for AIP type 1. Other serological markers are less specific but rheumatoid factor or high titres of ANA may also be present^{11,29}. In AIP-type 2, IgG4 cells on immunostaining are usually absent and IgG4 serum level is usually normal. Histological hallmarks are lymphoplasmatic infiltration and granulocyte epithelial lesions with partial or complete duct obstruction - duct-centric destructive pancreatitis /IDCP/. The wall of the duct is usually infiltrated with neutrophils, lymphocytes and plasma cells with involvement of the duct epithelium and lumen. The ductal lesions are called GEL - granulocyte epithelial lesion^{13,14}.

Accurate diagnosis of the AIP-type 2 requires core biopsy of the gland. Patients with type 1 are typically males with a mean age in the sixth decade. Patients with

AIP type 2 tend to be younger with a mean age in the fourth decade and with equal gender distribution¹⁴. From a practical point of view, the distinction between the AIP subtypes will help in clarifying the clinical features, pathogenesis and natural history of disease.

THERAPY

Most patients with AIP respond well to steroid therapy^{29,30}. Corticosteroids reduce inflammation and restore both digestive enzymes and HCO₃ secretion in patients with AIP by regenerating acinar cells and correcting CFTR localization in pancreatic duct cells, mislocalized to the cytoplasm of duct cells^{31,32}. For the induction of remission in type 1 AIP, a dose of 30-40 mg for 2 weeks is generally recommended^{11,30}. The dose of steroids is tapered by 5 mg per two weeks. The total time of therapy is usually 6-12 months. The monitoring of clinical and biochemical status is essential. Only in a few patients with obstructive jaundice, short-term biliary stent insertion is indicated¹¹. The relapse of AIP can be seen in about approximately 30% of the patients with AIP. In AIP relapse (after the steroid therapy), a combination of steroids (1 mg/kg) with azathioprine (2 mg/kg) for 12 weeks is recommended³³. A new drug, which was reported to induce remission is the CD20 antipody, ritiximab. Preliminary results with this drug are promising³⁴.

Reliable data on treating AIP type 2 are scarce but steroid use appears to be preferred and is effective. Whether AIP predisposes to pancreatic cancer is not known but case-report studies of pancreatic cancer complicating AIP have been published^{27,28}.

DISCUSSION

Current research on AIP focuses on the pathogenesis of the disease. Genetic factors of AIP, humoral immunity and target antigens of cellular immunity and effector cells and the role of microbial infection (*H. pylori* infection and molecular mimicry) are being intensively studied³⁵. Okazaki and co-workers¹¹ hypothesised that the pathogenesis of AIP involves a biphasic mechanism consisting of "induction" and "progression". In the early stage, the initial response to self-antigens (antilactoferrin, carbonic anhydrase II, pancreatic secretory trypsin inhibitor and alfa-fodrin) and molecular mimicry are induced by a decrease in naïve regulatory T-cells (Tregs) and T-helper (Th1) cells mediated release of proinflammatory cytokines. In the chronic stage, progression is supported by increase in memory Tregs (regulatory T cells) and Th2 immune responses. The complement system pathway may be activated by the IgG1 complex. A model published by Chari's group from Rochester, USA is similar and considers IgG4 to be related to the differentiation phase of Treg function. During the evolution of AIP, Treg activity may be related to specific amino acid substitution of HLA class II. IgG1 immune complex may be related to IgG4-negative and granulocyte epithelial lesion (GEL)-positive

Table 6. HISORt criteria of AIP.

Category	Criteria
A. Histology	<ol style="list-style-type: none"> Diagnostic (any one): <ol style="list-style-type: none"> Pancreatic histology showing periductal lymphoplasmacytic infiltrate with obliterative hlebitis (LPSP) Lymphoplasmacytic infiltrate with abundant (>10 cells/hpf) IgG4 positive cells in the pancreas Supportive (any one) <ol style="list-style-type: none"> Lymphoplasmacytic infiltrate with abundant (>10 cells/hpf) IgG4 positive cells in involved extra-pancreatic organ Lymphoplasmacytic infiltrate with fibrosis in the pancreas
B. Imaging	<p>Typical imaging features:</p> <ol style="list-style-type: none"> CT/MR: diffusely enlarged gland with delayed (rim) enhancement ERCP: Diffusely irregular, attenuated main pancreatic duct <p>Atypical Imaging Features: Pancreatitis, focal pancreatic mass, focal pancreatic duct stricture, pancreatic atrophy, pancreatic calcification</p>
C. Serology	Elevated serum IgG4 level (normal 8-140 mg/dL)
D. Other Organ involvement	Hilar/intrahepatic biliary strictures, persistent distal biliary stricture, Parotid/lacrimal gland involvement, Mediastinal lymphadenopathy, Retroperitoneal fibrosis
E. Response to steroid therapy	Resolution/marked improvement of pancreatic/extrapancreatic manifestation with steroid therapy

AIP/idiopathic duct-centric pancreatitis IDCP. The IgG4 immune complex may correlate with IgG4-positive and GEL-negative AIP. Further research is necessary to confirm the cellular model of AIP. In 2008, Kamisawa et al.³⁶ proposed a new clinicopathological entity – IgG4 related sclerosing disease (IgG4-RSC) (ref.³⁵). The clinical manifestation of this systemic disease is different and related to the fragmentary involvement of the pancreas, liver, bile duct, salivary gland, kidney and lung³⁷. Typical for this disease is abundant IgG4 positive plasma cells and T-lymphocyte organ infiltration^{38,39}. Masaoki et al. extended the IgG-RSC complex into an even more extensive clinical entity – IgG4-positive multiorgan lymphoproliferative syndrome (IgG4-MOLPS). This syndrome includes inflammatory pseudotumors (liver, breast, lung, Mikulicz's syndrome, intestinal fibrosis and autoimmune hypophysitis). Sjögren syndrome is not considered a part of IgG4-MOLPS (ref.⁴⁰).

In 2009 experts from Europe, Japan, Korea and USA met in Honolulu to describe the entity of AIP (ref.⁴¹). The

Honolulu Consensus Document characterized AIP as a pancreatitis, which has unique histopathologic features allowing it to be distinguished from other forms of chronic pancreatitis, and with histopathological correlates of 2 distinct forms of AIP. The last international consensus - diagnostic criteria consensus, published in 2011 (ref.⁴²) recognizes the spectrum of AIP as we know it today. In 2011 the criteria of the Japan Pancreas Society (HISORTs criteria) together with Korean, Asian, Italian and Mannheim criteria, led to the International Consensus Diagnostic Criteria for autoimmune pancreatitis.

The diagnostic criteria were separated into two levels. In level 1, the typical criterion is a diffuse enlargement of the pancreas with delayed enhancement. In the pancreatic duct, there is a typical sign- in more than 1/3 the length of the main pancreatic duct, there are multiple strictures without marked upstream dilatation.

Elevation of IgG4 >2x upper normal value

The diagnosis of AIP typically includes involvement of other organs with histological changes-lymphoplasmatic infiltration with fibrosis and without granulocytic infiltration with storiform fibrosis, obliterative flebitis and an abundance of IgG4 positive cells-more than 10 cells / HPF. At least 3 of the pancreatic histological signs are typical for the diagnosis. An alternative to histological changes is the presence of typical radiological markers which are a segmental proximal or multiple proximal or proximal and distal bile duct stricture and retroperitoneal fibrosis.

In the histology of pancreas at least 3 of the following markers are relevant:

- periductal lymphoplasmatic infiltrate without GEL
- obliterative flebitis
- storiform fibrosis
- abundant IgG4 positive cells

The important diagnostic criterion is the response to steroid therapy, when radiologically it is possible to demonstrate the resolution or improvement in pancreatic and extrapancreatic manifestation.

For level 2 the criteria for AIP- there are no typical markers, for example no diffuse enlargement. The sign is segmental or focal enlargement of pancreatic parenchyma. Other signs are symmetrically enlarged salivary/lacrimal glands, renal involvement described in association with AIP, segmental or focal narrowing of the pancreatic duct without marked upstream dilatation (duct size <5.0 mm). There is no doubt, that autoimmune pancreatitis is still a challenge for pancreatologists, endoscopists, surgeons, histopathologists, immunologists and radiologists and it is a "hot topic" in internal medicine. Type 1 AIP is the pancreatic manifestation of the multiorgan syndrome-IgG4 related disease (called also MOLPS - MultiOrgan Lympho Proliferative Syndrome). Relapses of AIP type 1 can be prevented using immunomodulators or biological agents. Type 2 autoimmune pancreatitis is a distinct disease entity with some markers common to type 1 AIP. AIP type 2 responds promptly to steroid therapy and subsequent relapse is uncommon^{43,44}.

CONCLUSION

1) Autoimmune pancreatitis (AIP) is a distinct form of pancreatitis. Currently, two forms of AIP have been described - Lymphoplasmatic sclerosing pancreatitis (LPSP) and Idiopathic duct-centric pancreatitis (IDCP).

2) Clinically LPSP appears to be the pancreatic manifestation of the group of systemic diseases-IgG4 related disease. IDCP does not appear to be a systemic disease.

3) The main acute clinical symptoms are obstructive jaundice and pancreatic swelling (focal or diffuse). Typical pancreatic pain is very rare.

4) Diagnostic criteria for AIP.

- changes in pancreatic parenchyma and pancreatic duct (CT/MRI,MRCP,ERCP)
- high plasma levels of IgG, IgG4 and ANA
- histopathology of the pancreas
- steroid therapy response

5) Differential diagnosis between pancreatic tumor and AIP is essential. Endosonographically guided pancreatic biopsy is recommended.

ABBREVIATIONS

AIP, Autoimmune pancreatitis; GEL, granulocyte epithelial lesions; IDCP, Idiopathic duct-centric pancreatitis; IgG4 + MOLPS, IgG4-positive multiorgan lymphoproliferative syndrome; IgG4-RSC, IgG4 related sclerosing disease; LPSP, Lymphoplasmatic sclerosing pancreatitis.

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CONFLICT OF INTEREST STATEMENT

The authors state there are no conflicts of interest regarding the publication of this article.

REFERENCES

1. Andersen BN, Pedersen NT, Scheel J, Worning H. Incidence of alcoholic chronic pancreatitis in Copenhagen. *Scand J Gastroenterol* 1982;17:247-52.
2. De las Heras G, Pns F. Epidemiologia y aspectos etiopatogénicos de la pancreatitis alcohólica crónica. *Res Esp Enferm Dig* 1993;84:253-8.
3. Lankisch PG, Assmus C, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic diseases in Luneburg Country. A study in a defined German population. *Pancreatol* 2002;2:469-77.
4. Dite P, Stary K, Novotný I, Precechtelová M, Dolina J, Lata J, Zboril V. Incidence of chronic pancreatitis in Czech Republic. *Eur J Gastroenterol* 2001;13:749-50.
5. Navarro S, Soriano A. Epidemiology of chronic pancreatitis : an infrequent disease or an infrequently diagnosed disease? In Dominguez - Munoz JE (ed.). *Clinical Pancreatolgy for Practising Gastroenterologists and Surgeons*. Blackwell, 2004,pp. 187-91.

6. Spanier BMW, Dijkgraaf MGW, Bruno MJ. Epidemiology, aetiology and outcome of acute and chronic pancreatitis. An update. *Best Practice Res Clin Gastroenterol* 2008;22,(1):45-53.
7. Etamad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology* 2001;120:682-97.
8. Sarles H, Sarles JC, Muratore R, Guien C. Chronic anflammatory sclerosis of the pancreas – an atonomous pancreatic disease? *Am J Dig Dis* 1961;6:688-98.
9. 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; 40:1561-68.
10. Okazaki K, Uchida K, Chiba T. Recent concept of autoimmune related pancreatitis. *J Gastroenterol* 2001;36:293-302.
11. Okazaki O, Uchida K, Fukui T. Recent advances in autoimmune pancreatitis: concept, diagnosis, and pathogenesis. *J Gastroenterology* 2008;43:409-18.
12. Nishimori I, Takakoshi A, Otsuki M. Prevalence of autoimmune pancreatitis in Japan from a nationwide survey in 2002. *J Gastroenterol* 2007;42(Suppl18):6-8.
13. Otsuki M. Autoimmune pancreatitis: a message from Japan. *J Gastroenterol* 2007;42(Suppl18):1-5.
14. Notohara K, Brgart LJ, Yadav D. Idiopathic chronic pancreatitis with periductal lymphoplasmacytic infiltration: clinicopathologic features of 35 cases. *Am J Surg Pathol* 1991;22:1119-27.
15. Zamboni G, Lüttges J, Capelli P. Histopathological features of diagnostic and clinical relevance in autoimmune pancreatitis: a study on 53 resection specimens and 9 biopsy specimens. *Virchows Arch* 2004;445:552-63.
16. Takeda S, Haratake J, Kasai T, Takaeda C, Takazakura E. IgG4-associated idiopathic tubulointerstitial nephritis complicating autoimmune pancreatitis. *Nephrol Dial Transplant* 2004;19:474-6.
17. Yamamoto M, Takahashi H, Sugai S, Imai K. Clinical and pathological characteristics of Mikulicz's disease (IgG4-related plasmacytic exocrinopathy). *Autoimmun Rev* 2005;4:195-200.
18. Komatsu K, Hamano H, Ochi Y, Takayama M, Muraki T, Yoshizawa K. High prevalence of hypothyroidism in patients with autoimmune pancreatitis. *Dig Dis Sci* 2005;50:1052-105.
19. Taniguchi T, Ko M, Seko S, Nishida O, Inoue F, Kobayashi H. Interstitial pneumonia associated with autoimmune pancreatitis. *Gut* 2004;53:770.
20. Ghazale A, Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. *Am J Gastroenterol* 2007;102:1646-53.
21. Kamisawa T, Egawa N, Nakajima H, Tsuruta K, Okamoto A. Extrapaneatic lesions in autoimmune pancreatitis. *J Clin Gastroenterol* 2005;39:904-7.
22. Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Zhang L. Diagnosis of autoimmune pancreatitis: the Mayo Clinic experience. *Clin Gastroenterol Hepatol* 2006;4:1010-6.
23. Kim MH, Lee TY. Diagnostic criteria for autoimmune pancreatitis: a proposal of revised Kim criteria. *J Gastroenterol Hepatol* 2007;22:A104.
24. Okazaki K, Kawa S, Kamisawa T, Naruse S, Tanaka S, Nishimori I. Clinical diagnostic criteria of autoimmune pancreatitis: revised proposal. *J Gastroenterol* 2006;41:626-31.
25. Naitoh I, Nakazawa T, Ohara H, Ando T, Hayashi K, Okumura F, Miyabe K, Yoshida M, Sano H, Takada H, Kanematsu T, Joh T. Comparative evaluation of the Japanese Diagnostic Criteria for autoimmune pancreatitis. *Pancreas* 2010;39:1173-9.
26. Chari ST, Takahashi N, Levy MJ, Smyrk TC, Clain JE, Pearson RK, Petersen BT, Topazian MA, Vege SS. A diagnostic strategy to distinguish autoimmune pancreatitis from pancreatic cancer. *Clin Gastroenterol Hepatol* 2009;7:1097-103.
27. Inoue H, Miyatani H, Sawada Y, Yoshida Y. A case of pancreas cancer with autoimmune pancreatitis. *Pancreas* 2006;33:208-9.
28. Fukuj T, Mitsuyama T, Takaoka M, Uchida K, Matsushita M, Okazaki K. Pancreatic cancer associated with autoimmune pancreatitis in remission. *Intern Med* 2008;47:151-5.
29. Park DJ, Kim MH, Chari ST. Recent advances in autoimmune pancreatitis. *Gut* 2009;58:1680-9.
30. Erkelens GW, Vleggaar FP, Lesterhuis W, van Buuren HR, van der Werf SD. Sclerosing pancreato-cholangitis responsive to steroid therapy. *Lancet* 1999;354:43-4.
31. Tanaka S, Kobayashi T, Nakanishi K, Okubo M, Murase T, Hashimoto M. Corticosteroid-responsive diabetes mellitus associated with autoimmune pancreatitis. *Lancet* 2000;356:910-1.
32. Kountouras J, Zavos C, Gavalas E, Tzives D. Challenge in the pathogenesis of autoimmune pancreatitis: potential role of *Helicobacter pylori* infection via molecular mimicry. *Gastroenterology* 2007;133:368-9.
33. Ko SBH, Mizuno N, Yatabe Y, Yoshikawa T, Ishiguro H, Yamamoto A, Azuma S, Naruse S, Yamao K, Muallem S, Goto H. Corticosteroids correct aberrant CFTR localization in the duct and regenerate acinar cells in autoimmune pancreatitis. *Gastroenterology* 2010;138:5:1988-96.
34. Hart PA, Topazian MD, Witzig TE. Treatment of relapsing autoimmune pancreatitis with immunomodulators and rituximab: the Mayo Clinic experience. *Gut* Published Online First:30 Aug 2012, doi:10.1136/gutjnl-2012-302886/
35. Chari ST. Current concepts in the treatment of autoimmune pancreatitis. *JOP* 2007;8:1-3.
36. Kamisawa T, Okamoto A. IgG – related sclerosing disease. *World J Gastroenterol* 2008;14:3948-55.
37. Kamisawa T. IgG4-positive plasma cells specifically infiltrate various organs in autoimmune pancreatitis. *Pancreas* 2004;29:167-8.
38. Kamisawa T, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K. A new clinicopathological entity of IgG4 – related autoimmune disease. *J Gastroenterol* 2003;38:982-4.
39. Uomo G. Autoimmune pancreatitis: An autonomous disease or a single entity in a complex puzzle of a multi-organ disorder? *JOP (Online)* 2010;5,11(2):191-2.
40. Masaki Y, Dong L, Kurose N, Kitagawa K, Morikawa Y, Yamamoto M, Takahashi H, Shinomura Y, Imai K, Saeki T, Azumi A, Nakada S, Sugiyama E, Matsui S, Origuchi T, Nishiyama S, Nishimori I, Nojima T, Yamada K, Kawano M, Zen Y, Kaneko M, Miyazaki K, Tsubota K, Eguchi K, Tomoda K, Sawaki T, Kawanami T, Tanaka M, Fukushima T, Sugai S, Umehara H. Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. *Ann Rheum Dis* 2009;68(8):1310-5. doi: 10.1136/ard.2008.089169
41. Chari ST, Kloppel G, Zhang L, Notohara K, Lerch MM, Shimosegawa T. Histopathologic and clinical subtypes of autoimmune pancreatitis: The Honolulu Consensus Document. *Pancreatol* 2010;10:664-72.
42. Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, Kim MH, Kloppel 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 Pancreatolgy. *Pancreas* 2011;40(3):352-8. doi: 10.1097/MPA.0b013e3182142fd2.
43. Kamisawa T, Chari ST, Lerch MM, Kim MH, Gress TM, Shimosegawa T. Recent advances in autoimmune pancreatitis type 1 and type 2. *Gut* 2013;62:1373-80. doi: 10.1136/gutjnl-2012-304224
44. Hart PA, Kamisawa T, Brugge WR, Chung JB, Culvert EL, Czako L, Frulloni L, Go WL, Gress TM, Myung-Hwan K, Kawa S, Lee KT, Lerch MM, Liao W, Lohr 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(12):1771-6. doi: 10.1136/gutjnl-2012-303617