AUTOIMMUNE PANCREATITIS — THE SPECIAL FORM OF CHRONIC PANCREATITIS

Y. S. Tsimmerman

Perm State Medical Academy n. a. Y. A. Vagner, Perm, Russia

Key words: autoimmune pancreatitis, definition, pathogenesis, diagnostic criteria, treatment

Autoimmunne pancreatitis (AIP) is a peculiar, original and relatively new form of chronic pancreatitis (CP), which in recent years has been intensively studied by pancreatologists around the world.

Brief history of this problem is as follows. In 1961, one of the leading pancreatologists of that time N. Sarles [27] first identified the "primary inflammatory sclerosis of the pancreas, with flowing hypergammaglobulinemia and evolving, apparently after consequence autoimmunization". However, this publication did not somehow attract the attention of researchers.

Only in 1995 K. Yoshida et al. [28] noted existence of a particular form of CP, due to the autoimmune disorders, which can be successfully treated with corticosteroids. In the subsequent following years the description of cases of AIP, the peculiarities of its pathogenesis, diagnostics and treatment were represented mainly in the studies of the number of Japanese pancreatologists [14, 15, 17, 19, 26, 28].

In 2000 K. Okazaki et al. [24] suggested that the underlying pathologic processes in the pancreas in AIP were autoimmune reactions directed against carbonic anhydrase-II and lactoferrin. In the same year, K. Hahm et al. [40] found that one of the pathogenic mechanisms of AIP was a block of TGF-signaling system, and its origin was confirmed by an autoimmune response to treatment with corticosteroids.

In 2001 V. Etamad and D. C. Whitcomb [33] for the first time included AIP in their proposed etiological classification of CP, received classification known as "TIGAR-O" (the initial letters of the selected etiological factors: Toxic ; Idiopathic; Genetic; Autoimmuna; Recurrent; Obstructive). It should be noted that the etiology

of AIP is still unknown, but we are talking about the autoimmune pathogenesis of this form of CP (AIP).

In the following years criteria of AIP diagnosis and methods (strategy and tactics) of its treatment were developed [36].

Terminology. At various times, to denote of AIP different terms were used: 1) non-alcoholic CP with the destruction of pancreatic ducts; 2) lymphoplasmacytic sclerosing pancreatitis; 3) chronic sclerosing pancreatitis; 4) pseudotumorous CP; 5) CP with narrowing of the main pancreatic duct; 6) ductal idiopathic CP, and finally 7) autoimmune pancreatitis [1], having international recognition.

Definition. In 2009, at the joint meeting of the American and Japanese associations of pancreatology (4-7.11.2009, Honolulu, Hawaii, USA) the following definition was given [20]: "AIP is a special form of CP, in the pathogenesis of which autoimmune mechanisms are involved, hypergammaglobulinemia is observed, levels of IgG and IgG4 in serum are elevated, antinuclear antibodies are present, distinct positive affirmative answer to corticosteroid treatment is registered".

In 2010, at the joint meeting of the International Association of Pancreatology (11-13.07.2010, Fukuoka, Japan) AIP definition was changed: "AIP is a special form of CP, which is clinically characterized by the frequent development of obstructive jaundice, occurs with increasing or without increasing size of the pancreas; histologically — periductal lymphoplasmacytoid infiltration and moire-form fibrosis; therapeutically — with rapid and pronounced response to corticosteroids [36]".

AIP definition is likely to be reviewed more than once

Prevalence. Due to the difficulties of diagnosis of AIP, it is completely difficult to establish its true distribution. Different numbers are named: from 4,8-5,8% (0,71 cases per 100,000 population) [20] to 5-7% and 3-11% [13, 41]. Men suffer more often than women (1,5-2 times). The predominant age of patients is over 40-45.

Etiology and pathogenesis. Etiology of AIP has not yet been established. One time there were assumptions on possible link of its development with a viral infection, specifically with Coxsackie B virus kind of enteroviruses. Patients with

enterovirus infection were found to have antibodies to the structural elements of the pancreas (antinuclear, antismooth-muscle), as well as lactoferrin and carbonic anhydrase-II, typical of AIP [42, 44]. It was suggested the concept of viral lesion o pancreatic tissue and transformation of its cells in the antigens, formation of autoantibodies reacting with pancreatic cells and thereby contributing to the progression of the disease [1].

There were attempts to somehow link the development of AIP and Helicobacter pylori — noninvasive low-virulent bacterium, viability of which is limited to the gastric compartment [5]. However, they turn to be absurd, not having any evidence [8]. Even authors of Maastricht consensus-4 (2011) were forced to admit: "There is no sufficient evidence of the relationship between Helicobacter pylori-infection and other (out-gastric) diseases [7]".

Among the proposed hypotheses of the pathogenesis of AIP, the concept can be named that the first step in the development of the disease is antigenic damage of pancreatic ducts or acinar cells, in particular aberration expression of HLA-DR. Subsequently, CD4+ T-cells may recognize complex HLA II class and autoantigen peptides, homoanalogous to carbonic anhydrase-II or lactoferrin, with helper or cytotoxic functions, inducing apoptosis. CD8+ T-cells are regarded to be cytotoxic cells [6].

In 2010, G. Kloppel et al. [23] proposed to consider AIP pathogenesis as the primary damage ductal epithelium of the pancreas by the immune complexes consisting of yet unknown antigen complement components and antibodies belonging to IgG (predominantly to IgG 4).

This hypothesis is confirmed by the results of immunohistochemical analysis of pancreas tissue obtained during surgical intervention in patients with AIP: they defined C3-component of complement (3+) and positive stain on IgG 4. Involved in this process is an interleukin-6, which induces a production of acute phase proteins (C-reactive protein, fibrinogen, α_2-macroglobulin, ceruloplasmin, α_1-antitrypsin) and C3-component of complement.

To confirm or reject mentioned hypotheses, of course, we need further in-depth studies.

Nevertheless, AIP autoimmune pathogenesis is shown by both clinical and (especially) the laboratory and histological data, and the effectiveness of corticosteroid therapy [1, 18, 30].

Clinically, AIP is often associated with other diseases of the autoimmune nature: primary and (mostly) secondary sclerosing cholangitis, flowing with stenosis of the terminal part of the common bile duct, which runs through the head of the pancreas; obstructive jaundice; with sclerosing sialoadenitis; Sjogren-Gougerat syndrome; with autoimmune thyroiditis, ulcerative colitis (UC) and (rarely) with terminal ileitis — Crohn's disease (CD), etc.

Significant frequency of extrapancreatic autoimmune diseases and syndromes in AIP is noted: sclerosing cholangitis — 60%, sclerosing sialoadenitis — 13%, retroperitoneal fibrosis — 9%, autoimmune thyroiditis — 7%, lymphadenopathy — 9% [1, 18, 30]. According to Kamisawa T. et al., extrapancreatic lesions occur more frequently: sclerosing cholangitis — 100%, sclerosing sialoadenitis — 44.4%; retroperitoneal fibrosis — 11.1%; lymphadenopathy — 55.5% [37, 39].

Laboratory parameters upon AIP show of hypergammaglobulinemia, elevated levels of IgG and IgG4 in serum, higher titers of autoantibodies (antinuclear, antismooth-muscle) [35].

Histologically, diffuse or focal reveal periductalar lymphoplasmocytic infiltration of the pancreas is found [34].

Therapeutically we note fast and clear effect of corticosteroid treatment.

K. Uchida et al. [30] in patients with AIP found autoantibodies to structural elements of the pancreas (antinuclear — ANA and antismooth-muscle — SMA), as well as lactoferrin and carbonic anhydrase-II; hypergammaglobulinemia. Endoscopic retrograde cholangiopancreatography macroscopic (ERCP) detected segmentary stenosis of the main (Wirsung's) pancreatic duct. Histological study of biopsy specimens revealed periductal lymphoplasmocytic infiltration of the pancreas with

the participation of CD4+ T-helper lymphocytes and expression of HLA-DR (immunogenetic factor) on the CD4+ cells and ductal epithelium of the pancreas.

L. Aparisi et al. [10] identified a reliable link between the development of AIP, lymphoplasmocytic infiltration of the pancreatic tissue, obtained upon surgery, and increased levels of IgG4 in serum (response to IgG4-positive cells) [9, 24, 30, 40].

Pancreatic tissue fibrosis in AIP is due to activation of stellate cells which synthesize transforming growth factor (TGFα and TGFβ), and PDGF, stimulating the synthesis of collagen and fibronectin by lymphoblasts. It is increased production of growth factors (primarily TGFβ) that is a key component of fibrogenesis in the pancreas.

Clinical picture. AIP can't be diagnosed solely on the basis of clinical data. It is important to emphasize that this is a disease of pancreas, which was highlighted in a special form of CP not due to the presence of typical clinical symptoms, and in connection with its histological and laboratory-instruments features.

Clinical symptoms of AIP are nonspecific. The most frequent manifestations include jaundice (60%) and increasing size of the pancreas due to its diffuse edema. Uncharacteristic clinical symptoms can be considered: weight loss associated with anorexia (70-80%), up to cachexia, low tolerance to food, abdominal discomfort and pain (35%), which is never intensive and does not require the use of analgesics. Occasionally there are nonspecific symptoms of dyspepsia (10%). Patients may also indicate the presence of asthenia (weakness, fatigue, etc.).

In addition, it is necessary to take into account the frequent combination of AIP with other above-mentioned autoimmune diseases.

Diagnostics. Due to the considerable difficulties of AIP diagnostics in 2010 during the 14th Congress of the International Association of Pancretology (11-13.07.2010, Fukuoka, Japan), an international group of experts elaborated "The diagnostic criteria of autoimmune pancreatitis" (Autoimmune Pancreatitis International Cooperative Study Group — APICS) [20, 36]. It was suggested to distinguish two types of AIP.

The first type is characterized histologically as "lymphoplasmocytic sclerosing pancreatitis (LPSP)" or "AIP without granulocyte epithelial lesions (GEL)." It is distinguished by four histological features:

1. Dense lymphoplasmacytic infiltration localized predominantly in the periductal areas of the pancreas.
2. Specific moire-form fibrosis ("moire" — similar to a dense silk fabric with wavy designs).
3. Lymphoplasmocytic venulitis often with obliteration of the affected veins.
4. Significant increase (more than 10 in the field of view) IgG4-positive plasmatic cells [11, 12, 22, 31].

The first AIP type is revealed by lesion of the pancreas within IgG4-systemic disease with elevated IgG4 in serum and a number of outpancreatic diseases and syndromes (sclerosing cholangitis, sclerosing sialoadenitis, retroperitoneal fibrosis, etc.) with a massive infiltration of the pancreas by IgG4-positive plasmatic cells.

The first AIP type more often affects older men over the age of 45-50; clinically it proceeds normally with mechanical yellow jaundice, responds well to the trial (within 2 weeks) corticosteroid therapy. Diagnosis in some cases can be set without histological investigation of the pancreatic tissue.

The second type, more common in Europe and the United States, received the name "idiopathic ductal-concentric pancreatitis (IDCP)" or "idiopathic ductal pancreatitis (IDP) with granulocyte epithelial lesions (GEL)".

As the first AIP type (LPSP), the second AIP type (IDCP) proceeds with periductal lymphoplasmocytic inflammatory infiltration and moire-form fibrosis of the pancreas.

Distinctive features of the second AIP type:

1. Presence of GEL as clusters of neutrophils in the lumen of medium and small pancreatic ducts, also located intraepithelially in the pancreatic acini, leading to obliteration of the ducts and their lesion.

2. Number of IgG4-positive plasmatic cells in many patients is not increased (less than 10 in the field of view); IDCP is not a systemic pathological process, but the specific disease of the pancreas.
3. Involvement of other (outpancreatic) organs in the disease is not usually observed, but in 30% of cases this type of AIP is associated with UC.

Age of patients with a second type of AIP is about 10 years less, and the frequency of its development does not depend on gender.

Serological markers of the second AIP type have not yet been detected [23].

Thus, LPSP and IPCP are two different serological AIP types.

Autoimmune pathogenesis of the second AIP type causes certain doubts among the part of pancreatologists. However, the similarity of clinical manifestations (jaundice) and histologic features, as well as a positive response to trial corticosteroid therapy give enough reason to include IDCP to AIP.

It should be noted that both types require conduction of differential diagnostics with pancreatic cancer.

According to the recommendations of the International Consensus on the diagnostics of AIP, the diagnostics of AIP should consider the following [3, 4, 20, 36]:

- the most frequent acute manifestation of AIP is obstructive jaundice and/or increased size of the pancreas due to its swelling (diffuse or focal) — by ultrasound or computed tomography (CT). In the presence of jaundice, ERCP or magnetic resonance cholangiopancreatography (MRCP) determines local beaded strictures of intrapancreatic (distal) part of the common bile duct as a "prune tree";
- the decrease in echogenicity of pancreatic parenchyma (ultrasound) is observed. In the later stages of AIP atrophy, increased pancreatic ducts are revealed, but no pain and clinical manifestations of disease relapse.

Uncharacteristic clinical AIP manifestations:

- dramatic weight loss, up to cachexia;
- low tolerance to food;

– occurrence of abdominal pain, demanding narcotic drugs, which gives reason to suspect pancreatic cancer.

It is proposed to include at least 2 of the following 5 criteria in the diagnostics of AIP:

1. Lesion of the ducts and pancreatic parenchyma (by CT or MRI, ERCP or MRCP). Marked one extent (more than 6 cm) or multiple segmental strictures of the main pancreatic duct without suprastenotic dilatation, simultaneously affected side branches of the Wirsung's duct coming from the area of its restriction.
2. Serological studies indicate elevated levels of IgG and IgG4 in the serum and the presence of antinuclear antibodies.
3. Pathological process involves other (outpancreatic) organs.
4. Observed characteristics of histopathology (periductal lymphoplasmocytic infiltration, etc.).
5. Positive response to a trial of corticosteroids [10, 34].

Differential diagnostic criteria of the first and second AIP types [3, 4]:

1. Typical serological indicators and involvement of other (outpancreatic) organs in the pathological process are found only in the first AIP type, but inflammatory bowel diseases (UC and BC) are associated with both types of AIP.
2. Absence of serological markers and/or involvement in the pathological process of other (outpancreatic) organs is characteristic only of the second type of AIP, but the first AIP type in some cases may be seronegative and flow without involvement of other organs.
3. Diagnosis of the first AIP type can be set on the basis of simplified criteria that do not include histological examination of tissue of the pancreas. At the same time, the diagnosis of AIP of the second type requires mandatory morphological confirmation.

4. In cases when CP does not meet the basic criteria for the AIP diagnosis and is not confirmed histologically, there is a reason to assume the existence of the latter, "possible AIP" should be diagnosed.
5. Results of pancreatic visualization and positive answer to a trial of corticosteroids do not allow differentiating AIP of the first and second types.

The diagnosis of AIP and its differentiation with malignant neoplasm are only possible upon using the imaging of the pancreas (CT and MRI, ERCP and MRCP)

1. In the differential diagnosis of AIP and the pancreatic cancer, CT and/or MRI are the most informative, which are carried out with the use of an even parenterally administered dose of secretin with the induction of 0,1 N HCl through nasobiliary drainage (ENBD) at a speed of 2.2 ml/min every 2 min for 20 min. This method can detect the presence of ductal hypertension in the pancreas. In the diffuse increase in the size of the pancreas and thickening of its capsule, presence of mechanical jaundice without sharp narrowing (or expansion) of pancreatic ducts and reducing density of the pancreatic tissue, with a high probability AIP could be diagnosed without additional criteria.
2. Upon detection of the typical signs of malignant tumors (presence in the pancreatic tissue of formation with low density of the contrast, sharp narrowing or widening of pancreatic ducts with or without atrophy of organ) pancreatic cancer should be diagnosed.
3. In cases when pancreatic cancer is excluded (it is especially important to exclude the presence of obstructive jaundice), you have to diagnose AIP.
4. Upon the absence of the characteristic features of AIP and malignant neoplasm, firstly pancreatic cancer should be excluded, and the presence of AIP can be assumed only when the diagnosis of cancer will be completely rejected. Upon ERCP or MRCP, diagnostic pancreatogram at AIP indicates the presence of an extended (more than 1/3) stricture of the main pancreatic

duct with its suprastenotic dilation (or not). However, we must not forget that ERCP is an invasive method of investigation, the use of which is fraught with the danger of severe complications (acute pancreatitis develops in 5.3% of cases), so the use of MRCP or endoscopic ultrasonography (EUS) with contrast enhancement using infusion SANAZOID (CE-US) is more favorable. Standard positron emission tomography (FDG-PET) is also used.

Upon serological study, AIP is confirmed by:

1. Elevated levels of IgG and antinuclear and (rarely) antismooth-muscle antibodies, but these figures can't be considered pathognomonic for AIP. Furthermore, hypergammaglobulinemia and HLA-specific haplotype DRB1*0405 — DQB1*0401 are defined [31].
2. The best and probably the only one serological marker of AIP should be considered as an increased level of IgG4 in serum. It is recommended to carry out its assessment not in absolute terms (they are variable), but in multiple increase in normal values (e.g., more than 2 times). The content of serum IgG4 is considered to be high when its level is over 140 mg/dl. This index has special significance when AIP occurs with obstructive jaundice.
3. Serological methods of AIP diagnostics for greater reliability are recommended to combine with imaging techniques of the pancreas and its ductal system.

Involvement of other (outpancreatic) organs upon AIP:

1. AIP of the first type as a manifestation of IgG4-systemic disease is often associated with other autoimmune diseases (seropositive Sjogren-Gougerat syndrome, rheumatoid arthritis, autoimmune thyroiditis, sclerosing sialoadenitis, etc.).
2. For the diagnosis of other autoimmune diseases that occur simultaneously with the AIP, imaging techniques (ultrasound and EUS, CT and MRI, ERCP and MRCP) should be used together with full clinical examination of patients.

Histological diagnosis of AIP:

1. AIP of the first type can be diagnosed without histological study of pancreatic tissue, but for the diagnosis of AIP of the second type the latter is mandatory.
2. Biopsy specimens can be obtained by fine-needle targeted biopsy under ultrasound control or in pancreatic resection.
3. AIP diagnosis is confirmed upon the presence of typical histological changes in pancreatic tissue (periductal lymphoplasmocytic infiltration, moire-form fibrosis etc.).

Response to corticosteroid treatment:

1. Trial corticosteroid therapy involves prescription of prednisolone (metipred, budesonide) in a dose of 0.6-1.0 mg per 1 kg of body weight per day for 2 weeks with a diagnostic assessment of results of pancreatic visualization and tumor marker CA-19-9 (carboantigen) determination before and after treatment [11]. Any patient with cancer of pancreas responds to a trial of corticosteroid (unlike patients with AIP).
2. CA-19-9 level does not normally exceed 37-40 U/ml. Upon AIP level of oncomarker remains normal, and upon pancreatic cancer it rises 3 times or more. Analysis of gene mutations κ-ras and immunnohistochemical studies indicate that AIP is a risk factor of pancreobiliary cancer [12, 22, 32].
3. Upon corticosteroids reduction of IgG4 in serum is observed [45].
4. Evaluation of trial therapy by corticosteroids should be done with caution — it should not replace other methods of confirming the diagnosis of AIP. You can’t say, "If corticosteroids are helpful, it is AIP", you need other proofs [38].
5. Upon treating of AIP with mechanical jaundice, the appointment of ursodeoxycholic acid at a dose of 13-15 mg/kg/day for 2-3 weeks is justified [16, 21].
6. Additional prescription AIP antioxidants seems appropriate: antioxicaps (α-tocopherol acetate 30 mg + selenium 30 mcg + ascorbic acid 1000 mg + β-

carotene 6 mg) or betamora (selenium 600 mg + ascorbic acid 540 mg + β-carotene 9000 ME + α-tocopherol acetate 270 ME + α-methionine 2000 mg) — 1 capsule daily after meals in a long period (2-3 months) [9, 43].

7. Surgical treatment (proximal pancreatoduodenal or distal pancreatectomy) are permitted only in cases when after using all previously listed diagnostic criteria you can't distinguish AIP and pancreatic cancer.

Concluding the review on AIP problem, it should be noted that there are still many unknown and controversial issues that require further comprehensive study.

References

1. Аутоиммунный панкреатит: оперировать или нет? / В. И. Егоров, В. А. Вишневсий, Г. Г. Кармазановский [и др.] // Consilium medicum. Прил. Гастроэнтерология. — 2008. — № 1. — С. 14–19.
2. Васильев Ю. В. Аутоиммунный панкреатит / Ю. В. Васильев // Экспер. клин. гастроэнтерол. — 2005. — № 2. — С. 83–86.
3. Губергриц Н. Б. Новости американской и японской панкреатологии (Материалы объединенной встречи Американской и Японской Ассоциации панкреатологов. Гонолулу, ноябрь 2009) / Н. Б. Губергриц // Вестник Клуба Панкреатологов. — 2010. — № 1. — С. 6–9.
4. Губергриц Н. Б. Новости мировой панкреатологии (Материалы объединенной встречи Международной Ассоциации панкреатологов и Японского панкреатологического общества. Фукуока, июль 2010) / Н. Б. Губергриц // Вестник Клуба Панкреатологов. — 2010. — № 4. — С. 6–13.
5. Маев И. В. Аутоиммунный панкреатит / И. В. Маев, Ю. А. Кучерявый // Рос. журн. гастроэнтерологии, гепатологии, колопроктологии. — 2004. — № 6. — С. 47–55.
6. Маев И. В. Аутоиммунный панкреатит : учеб. пособие / И. В. Маев, Ю. А. Кучерявый, Т. С. Оганесян. — М. : ФИРО, 2011. — 78 с.
7. Циммерман Я. С. «Маастрихтский консенсус-4» (2011): основные положения и комментарии к ним / Я. С. Циммерман // Клин. мед. — 2012. — № 9. — С. 28–34.
8. Циммерман Я. С. Helicobacter pylori-инфекция: внежелудочные эффекты и заболевания (критический анализ) / Я. С. Циммерман // Клин. мед. — 2006. — № 4. — С. 63–67.
9. Циммерман Я. С. Хронический панкреатит / Я. С. Циммерман // Гастроэнтерология / Я. С. Циммерман. — М. : ГЭОТАР-Медиа, 2012. — С. 415–444.

10. Antibodies to carbonic anhydrase and IgG4 level in idiopathic chronic pancreatitis. Relevance for diagnosis of autoimmune pancreatitis / L. Aparisi, A. Farre, L. Gomez-Cambronero [et al.] // Gut. — 2005. — Vol. 54. — P. 703–709.
11. Asian diagnostic criteria for autoimmune pancreatitis : consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis / M. Otsuki, J. B. Chung, K. Okazaki [et al.] // J. Gastroenterol. — 2008. — Vol. 43. — P. 403–408.
12. Autoantibodies against the exocrine pancreas in autoimmune pancreatitis : gene and protein expression profiling and immunoassays inenfiti pancreatic enzymes as a major target of the inflammatory process / J.-M. Lohr, R. Faissner, D. Koczan [et al.] // Am. J. Gastroenterol. — 2010. — Vol. 105. — P. 2060–2071.
13. Autoimmune chronic pancreatitis / K. P. Kim, M. U. Kim, M. H. Song [et al.] // Am. J. Gastroenterol. — 2004. — Vol. 99. — P. 1605–1616.
14. Autoimmune chronic pancreatitis simulating pancreatic lymphoma / A. Horiuchi, T. Kaneko, N. Yamamura [et al.] // Am. J. Gastroenterol. — 1996. — Vol. 91. — Vol. 2607–2609.
15. Autoimmune pancreatitis : radiologic findings in three histologically proven cases / N. Furukawa, T. Muranaka, K. Yasumory [et al.] // J. Comput. Assist. Tomogr. — 1998. — Vol. 22. — P. 880–883.
16. Autoimmune pancreatitis and multiple bile duct strictures treated effectively with steroid / E. Kojirna, K. Kimura, Y. Noda [et al.] // J. Gastroenterol. — 2003. — Vol. 38. — P. 303–307.
17. Autoimmune pancreatitis as a new clinical entity : three cases of autoimmune pancreatitis with effective steroid therapy / T. Ito, I. Nakano, S. Koyanagi [et al.] // Dig. Dis. Sci. — 1997. — Vol. 42. — P. 1458–1468.
18. Autoimmune pancreatitis associated with idiopathic retroperitoneal fibrosis / Y. Fukukura, F. Fujiyochi, F. Nakamara [et al.] // Am. J. Roentgenol. — 2003. — Vol. 181. — P. 993–995.
19. Autoimmune pancreatitis detected as a mass in the trial of the pancreas / T. Taniguchi, S. Seko, K. Azuma [et al.] // J. Gastroenterol. Hepatol. — 2000. — Vol. 15. — P. 461–464.

20. The autoimmune pancreatitis International cooperative study group (APICS). Histopathologic and clinical subtypes of autoimmune pancreatitis : the Honolulu consensus document / S. T. Chari, G. Kloppel, L. Zhang, [et al.] // Pancreas. — 2010. — Vol. 39. — P. 549–554.
21. Autoimmune pancreatitis successfully treated with ursodeoxycholic acid / K. Tsubakio, K. Kiriyama, N. Matsushima [et al.] // Intern. Med. — 2002. — Vol. 41, No 12. — P. 1142–1146.
22. Autoimmune pancreatitis with effective steroid therapy / S. P. Hong, S. W. Park, J. P. Chung [et al.] // Yonsey Med. J. — 2003. — Vol. 44, No 3. — P. 534–538.
23. Autoimmune pancreatitis: the clinicopathological characteristics of the subtype with granulocytic epithelial lesions / G. Kloppel, S. Detiefsen, S. T. Chari [et al.] // J. Gastroenterol. — 2010. — Vol. 45. — P. 787–793.
24. Autoimmunerelated pancreatitis is associated with autoantibodies and a Th1/Th2-type cellular immune response / K. Okazaki, K. Uchida, M. Ohana [et al.] // Gastroenterology. — 2000. — Vol. 118. — P. 573–581.
25. A case of autoimmune pancreatitis, associated with sclerosing cholangitis, retroperitoneal fibrosis and Sjogren's syndrome / T. Fukui, K. Okazaki, H. Yochizawa [et al.] // Pancreatology. — 2005. — Vol. 5. — Vol. 86–91.
26. Characteristic pancreatic duct appearance in autoimmune chronic pancreatitis : a case report and review of the Japanese literature / A. Horiuchi, S. Kawa, T. Akamatsu [et al.] // Am. J. Gastroenterol. — 1998. — Vol. 93. — P. 260–263.
27. Chronic inflammatory sclerosis of the pancreas — an autonomus pancreatic disease? / H. Sarles, Y. Sarles, R. Muratore [et al.] // Am. J. Dig. Dis. — 1961. — Vol. 6. — P. 688–699.
28. Chronic pancreatitis caused by an autoimmune abnormality proposal of the concept of autoimmune pancreatitis / K. Yoshida, F. Toni, T. Takeuchi [et al.] // Dig. Dis. Sci. — 1995. — Vol. 40. — P. 1561–1568.
29. Chronic pancreatitis with diffuse irregular narrowing of the main pancreatic duct / T. Wakabayashi, Y. Motoo, Y. Kojima [et al.] // Dig. Dis. Sci. — 1998. — Vol. 43. — P. 2415–2425.

30. Clinical analysis of autoimmune-related pancreatitis / K. Uchida, K. Okazaki, Y. Konichi [et al.] // Am. J. Gastroenterol. — 2000. — Vol. 95. — P. 2788–2794.
31. Diagnosis of autoimmune pancreatitis : the Mayo clinic experience / S. T. Chari, T. C. Smyrk, M. J. Levy [et al.] // Clin. Gastroenterol. Hepatol. — 2006. — Vol. 4. — P. 1010–1016.
32. A diagnostic strategy to distinguish autoimmune pancreatitis from pancreatic cancer / S. T. Chari, N. Takahashi, M. J. Levy [et al.] // Clin. Gastroenterol. Hepatol. — 2009. — Vol. 7. — P. 1097–1103.
33. Etamad B. Chronic pancreatitis: diagnosis, classification, and new genetic developments / B. Etamad, D. C. Whitcomb // Gastroenterology. — 2001. — Vol. 120. — P. 682–707.
34. Histopathologic features of diagnostic and clinical relevance in autoimmune pancreatitis : a study 53 resection specimes and 9 biopsy specimes / G. Zamboni, J. Luttges, P. Capelli [et al.] // Virchow's Arch. — 2004. — Vol. 445. — P. 552–553.
35. Immunohistochemical study of autoimmune pancreatitis using anti-IgG4-antibody and patients sera / S. Aoki, T. Nakazawa, H. Ohara [et al.] // Histopathology. — 2005. — Vol. 47. — P. 147–158.
36. International consensus diagnostic criteria for autoimmune pancreatitis / T. Shimosegawa, S. T. Chari, L. Frulloni [et al.] // Pancreas. — 2011. — Vol. 40. — P. 352–358.
37. Involvement of pancreatic and bile ducts in autoimmune pancreatitis / T. Kamisawa, Y. Tu, N. Egawa [et al.] // World J. Gastroenterol. — 2006. — Vol. 12, No 4. — P. 612–614.
38. Is a 2-week steroid trial after initial negative investigation for malignancy useful in differentiating autoimmune pancreatitis from pancreatic cancers? : a prospective outcome study / S.-H. Moon, M. H. Kim, D. H. Park [et al.] // Gut. — 2008. — Vol. 57. — P. 1704–1712.

39. Kamisawa T. Autoimmune pancreatitis associated with retroperitoneal fibrosis / T. Kamisawa, M. Matsukawa, M. Ohkawa // JOP. — 2005. — Vol. 6, No 3. — P. 260–263.
40. Loss of TGF-signaling contributes to autoimmune pancreatitis / K. Hahm, Y. Im, C. Lee [et al.] // J. Clin. Invest. — 2000. — Vol. 105. — P. 1057–1065.
41. Nishimori I. Prevalence of autoimmune pancreatitis in Japan from a nationwide survey in 2002 / I. Nishimori, A. Tomakoshi, M. J. Otsuki // Gastroenterology. — 2007. — Vol. 42, Suppl. 18. — P. 6–8.
42. Ozsvar Z. Possible role of Coxsackie B virus infection in pancreatitis / Z. Ozsvar, J. Deak, A. Pap // Int. J. Pancreatol. — 1992. — Vol. 11. — P. 105–108.
43. A randomized controlled trial of antioxidant supplemention for pain relief in patient with chronic pancreatitis / P. Bhardway, P. K. Sarg, S. K. Maulik [et al.] // Gastroenterology. — 2009. — Vol. 136, No 1. — P. 325–333.
44. Transient exocrine pancreatic insufficiency as a possible complication of a enterovirus infection / S. van Biervliet, K. de Waele, M. van Winckel, E. Roberecht // Eur. J. Pediatr. — 2003. — Vol. 162, No 12. — P. 872–874.
45. Treating patients with autoimmune pancreatitis : results from a long-term fallow-up study / T. Kamisawa, M. Yoshike, N. Egawa [et al.] // Pancreatology. — 2005. — Vol. 5. — P. 234–238.

Autoimmune pancreatitis — the special form of chronic pancreatitis

Y. S. Tsimmerman

Perm State Medical Academy n. a. Y. A. Vagner, Perm, Russia

Key words: autoimmune pancreatitis, definition, pathogenesis, diagnostic criteria, treatment

The aim of review. To present features of clinical presentation, diagnostics and treatment of special form of chronic pancreatitis — *autoimmune pancreatitis* (AIP).

Key points. The etiology of AIP is investigated insufficiently, the role of infection (in particular, viral), antigenic damage of pancreatic ducts and acinar cells is considered. AIP is frequently combined to other autoimmune diseases. The most typical serological marker of AIP is elevation of serum IgG4 level. Now 2 types of AIP are defined. AIP of the second type requires mandatory morphological confirmation. AIP is characterized by good treatment response by corticosteroids.

Conclusion. The issue of AIP remains actual and requires further studies.