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Autoimmune pancreatitis - role of intestinal microbiota in pathogenesis. Review of the literature

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Abstract

Introduction: Autoimmune pancreatitis is a type of chronic autoimmune inflammation that can be divided into two types. Type 1 is a clinical manifestation of IgG4-mediated disease, while type 2 may coexist with inflammatory bowel diseases.

Objective: The aim of the study is to review the literature on the role of the intestinal microbiota in the pathogenesis of autoimmune pancreatitis.

Methods: A literature review was conducted on databases such as PubMed and Google Scholar using the terms: ”autoimmune pancreatits”, “intestinal dysbiosis”, “intestinal microbiome”, and “pathogenesis”.

Conclusions: The intestinal microbiota has an impact on the development of autoimmune pancreatitis, but it is not the main pathogenic factor, but rather a risk factor.

Keywords: autoimmune pancreatitis, intestinal microbiome, intestinal dysbiosis

Background

Autoimmune pancreatitis (AIP) is a relatively rare disease. In accordance with the 2010 ICDC criteria autoimmune pancreatitis is a distinct type of pancreatitis characterized clinically by obstructive jaundice with the presence or absence of a tumor in the pancreas, histologically by lymphoplasmacytic infiltration and a therapeutically rapid response to steroid treatment [1]. Histologically, we distinguish two types of AIP: type 1 and type 2 (Table 1).

Autoimmune pancreatitis type 1 (LPSP) is histologically a lymphoplasmacytic fibrosing pancreatitis and is a clinical manifestation of an IgG4-dependent disease. It is characterized by lymphoplasmacytic infiltration with more than 10 IgG4-positive plasma cells at the highest magnification, storiform fibrosis and obliterative phlebitis [2].

Autoimmune duct-centric pancreatitis type 2 (IDCP) is associated with idiopathic inflammation around the main pancreatic duct and, unlike AIP type 1, it is not a systemic disease and the pancreas is the only organ affected. Histologically, it is characterized by a fibroinflammatory process with neutrophilic infiltration affecting mainly medium and small ducts. The pathognomonic histological feature is the presence of granulocytic changes in the epithelium in medium and small ducts, as well as in alveolar cells. In approximately 15-30% of cases, AIP type 2 is associated with inflammatory bowel diseases, mainly ulcerative colitis. A common clinical manifestation is acute pancreatitis (AP) in relatively young people [2].

Symptoms of autoimmune pancreatitis

The clinical symptoms of AIP are very non-specific, one of the most common symptoms is jaundice. Patients may also report abdominal pain, which in AIP type 2 is more severe than in AIP type 1, where the pain is quite mild. Additionally, back pain, weight loss and fatigue may occur. Sometimes patients also present symptoms of diabetes and symptoms from other organs in the case of AIP type 1 [3].

Diagnostics of autoimmune pancreatitis

Both laboratory and imaging tests are important in the diagnosis of autoimmune pancreatitis. Every patient with suspected autoimmune pancreatitis should have their serum IgG4 level checked, which may be elevated in patients with AIP type 1, but may also remain normal [2]. It is also worth performing protein electrophoresis, which may show a band connecting the ß and γ fractions. Patients may also have hypocomplementemia, positive ANA antibodies and rheumatoid factor, but these tests do not clearly indicate the disease [2,3].

Imaging plays an important role in the diagnosis of AIP. Magnetic resonance imaging (MRI), computed tomography (CT) or endoscopic ultrasound (EUS) is usually performed. In an MRI examination, a typical change is the so-called "sausage-like" pancreas, other characteristic changes include hypointense signal on T1-weighted images, decreased signal intensity in the presence of extensive fibrosis, or relatively hyperintense signal on T2-weighted images in the case of minimal fibrosis [3]. CT examination most often shows diffuse morphological

enlargement of the pancreatic parenchyma, but focal enlargement of the pancreas or a pancreas with normal structure may also be visible. A characteristic feature is the visible so-called capsule-like-rim[3]. EUS examination can also primarily visualize an enlarged pancreas, which is usually hypoechoic, and sometimes it is also possible to visualize hypoechoic masses within the organ [3]. Endoscopic retrograde cholangiopancreatography (ERCP) also plays a role in the diagnosis; a characteristic feature is narrowing of the main pancreatic duct, and in 80-90% of patients there is also narrowing of the common bile duct [3].

	Autoimmune pancreatitis type 1	**Autoimmune pancreatitis type 2**
IgG4 level	Increased or normal	Normal
Co-occurrence with inflammatory bowel disease	No co-occurence	Yes, more common with ulcerative colitis
Relapse	Relatively often	Rare
Characteristic histological changes	„storiform fibrosis”	Granulocytic changes in the epithelium in medium and small ducts
Pain symptoms	Less severe	More severe

Table 1. Comparison of AIP type 1 and AIP type 2 [1,2,3].

Treatment of autoimmune pancreatitis

We start treatment of autoimmune pancreatitis in symptomatic patients: 1) with pancreatic involvement - mechanical jaundice, abdominal or back pain; 2) with involvement of other organs, e.g. jaundice caused by narrowing of the bile ducts. In asymptomatic patients, treatment may be initiated in the presence of a persistent mass in the pancreas or persistently elevated liver parameters in patients with IgG4-dependent sclerosing cholangitis[4]. Spontaneous remission of the disease occurs in 10-25% of patients [4]. The first line of treatment in patients with AIP is steroid therapy. In case of contraindications, another drug effective in inducing remission is rituximab [4]. Complete remission is defined as resolution of symptoms, normalization of IgG or IgG4 levels, resolution of pancreatic enlargement and narrowing of the pancreatic duct. Incomplete remission occurs when only 1 or 2 of the above are met[5]. In patients with diffuse pancreatic enlargement, delayed radiological remission or

persistently elevated IgG4 levels, it is advisable to maintain therapy with low doses of glucocorticosteroids, rituximab or immunomodulators[4].

Pathogenesis of autoimmune pancreatitis

The pathogenesis of AIP type 1 is not fully understood, but immune system disorders, which contribute to the development of an IgG-dependent disease, undoubtedly play a large role. Toll-like receptors (TLRs) present in the pancreas and salivary glands, which are activated, among others, by intestinal bacteria, play a significant role [2,6]. Ishiguro et. Al. showed overexpression of TLR-7 in macrophages of patients with AZT type 1 and IgG4-dependent disease, which stimulates interleukin 33 (IL-33), which is responsible for the activation of fibroblasts, leading to the fibrosis characteristic of this disease [2,7,8] . Il-33 also stimulates a Th2-type immune response, which results in the production of intereleukin 4 and 13, which are fibrogenic [2,9]. Plasmacytoid dendritic cells also play a role in pathogenesis by producing type 1 interferon, which is involved in host defense against infections [2,10].

The pathogenesis of AIP type 2 is much less well understood than in the case of type 1. The main histological changes found in this case are changes in the granulocytic epithelium (GELs), in particular neutrophilic infiltrates of the ducts [11]. Overexpression of IL-8 was also found in the pancreas of patients with AIP type 2, whose main function is angiogenesis and neutrophil chemotaxis to the site of inflammation [2, 12]. IL-8 overexpression has also been found in patients with ulcerative colitis, which often co-occurs with AIP type 2 [13]. The involvement of Th17 lymphocytes, which produce cytokines such as IL-17A, IL-21, IL-22 and IL-23, is also suggested. Dong et al. suggested a genetic hypothesis, he found mutations in the MEN1 and PKHD1 genes in patients with AIP type 2 [2,14].

The role of intestinal microbiota in the development of autoimmune pancreatitis

The involvement of antigens in the pathogenesis of autoimmune pancreatitis is also likely, but they have not been defined. In times of extensive research on the intestinal microbiota, work is currently being carried out on its involvement in the development of AIP type 1 [2,15].

Intestinal bacteria present in the human gastrointestinal tract are necessary for the development of the immune system in the mucosa, as well as for digestion, absorption and modulation of glucose metabolism [16]. Intestinal dysbiosis is a change in the composition and disruption of the functioning of the intestinal microbiota [16,17]. Studies show a

relationship between intestinal dysbiosis and the development of inflammatory bowel diseases, which is related to the pro-inflammatory cytokine response to intestinal bacteria [16, 17, 18]. Intestinal microbiota disorders cause a chronic fibroinflammatory process in the pancreas by activating plasmacytoid dendritic cells producing large amounts of IFN-α and IL-33 [19].

Kamata et al. in his studies on the microbiota, he noticed the complete disappearance of Klebsiella pneumonii after the use of steroids in 2 patients [2,20]. Yamaki et al. conducted research on mice immunized with a mixture of pancreas extract from syngeneic mice and capsular polysaccharide of the Kasuya strain of Klebsiella pneumoniae type 1. He obtained histological changes characterized by infiltration of plasma cells and lymphocytes, destruction of the acinar architecture, which was replaced by adipose tissue and fibrosis [2,21] A similar experiment on mice was performed by Kamata et al. stating that oral administration of heat-killed K. pneumoniae promoted the development of pancreatitis [2,20]. The role of H. pylori infection in the pathogenesis of AZT is also suggested, as antibodies against plasminogen-binding protein (PBP) were detected in 93% of patients, however, due to the common carriage of H. pylori, this contribution is controversial [2]. Yoshikawa et al. conducted a study on mice, based on which he concluded that intestinal barrier disorders favor the translocation of Staphylococcus sciuri to the pancreas, which resulted in the intensification of AIP as a result of the secretion of greater amounts of IL-33 and IFN-α by plasmacytoid dendritic cells [22].

These studies strongly suggest the involvement of intestinal dysbiosis in the development of AIP type 1, however, it should be emphasized that intestinal dysbiosis increases the sensitivity, but does not itself cause the development of the disease, it acts rather as a factor enhancing the development of the disease rather than the main pathogenic factor.

The molecular mechanisms of the role of intestinal dysbiosis in the development of AIP are not fully understood. However, plasmacytoid dendritic cells and M2 macrophages are probably activated. Studies on mice suggest that intestinal bacteria are translocated to the pancreas and there stimulate dendritic cells and macrophages [20]. However, research does not clearly confirm this and a theory is also suggested regarding the activation of immune cells in the intestine and their subsequent movement to the pancreas, where they cause fibro-inflammatory changes [20].

Metabolites of the intestinal microbiota

Although there are no studies on the involvement of intestinal microbiota metabolites in the immune response and pathogenesis of AIP, intestinal dysbiosis may cause disturbances

in the composition of metabolites. Short-chain fatty acids produced by the microbiota as a result of fiber fermentation facilitate the polarization and functioning of M2 macrophages [23]. Bile acids activate transmembrane G protein-coupled receptor 5 (TGR5) and farnesoid X receptor (FXR) present on macrophages, which leads to the differentiation into M2 of macrophages, which play a role in the development of AIP [24]. Testing whether short-chain fatty acids and bile acids promote the secretion of IL-33 by M2 macrophages remains unexplored, and further research must be conducted on the disturbances of intestinal microbiota metabolites and their role in the pathogenesis of AIP [16].

Conclusions

Autoimmune pancreatitis type 1 and type 2 have different pathogenesis. Intestinal dysbiosis has a greater share in the pathogenesis of AIP type 1 than AIP type 2. Changes in the composition of the intestinal microbiota play a role in the development of AIP, but they are not the main cause of the disease, but only a factor increasing the risk of development through the activation of plasmacytoid dendritic cells and M2 macrophages. It should be noted, however, that the studies conducted so far have focused on small groups of patients, and therefore further studies need to be conducted to further investigate the relationship between changes in the composition of the intestinal microbiota and the development of AIP.

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