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Autoimmune pancreatitis: histo- and immunopathological features

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In recent years autoimmune pancreatitis (AIP) has been established as a special type of chronic pancreatitis. It is characterized by its histopathological and immunological features. The morphological hallmarks are periductal infiltration by lymphocytes and plasma cells, granulocytic epithelial lesions with focal destruction of the duct epithelium, venulitis, and diffuse sclerosis in advanced stages. AIP has therefore also been called lymphoplasmacytic sclerosing pancreatitis, duct-destructive chronic pancreatitis, or sclerosing pancreatitis. AIP most commonly involves the head of the pancreas and the distal bile duct. Occasionally it is mass-forming, and has been described as an inflammatory myofibroblastic tumor. The presence of more than 20 IgG4-positive plasma cells per high-power field is of high specificity for the tissue diagnosis of AIP.

Key words: autoimmune pancreatitis, histopathology, IgG4 expression

Introduction

What are probably the first reports of autoimmune pancreatitis (AIP) date back more than fifty years. Ball et al.[1] described patients with pancreatitis in conjunction with ulcerative colitis. In 1961, Sarles et al.[2] reported on a sclerosing pancreatitis with hypergammaglobulinemia. The term autoimmune pancreatitis was first used in an article by Yoshida et al. in 1995.[3] Other names that were proposed in reports on single cases or small series of cases included "lymphoplasmacytic sclerosing pancreatitis with cholangitis,"[4] "nonalcoholic duct-destructive chronic pancreatitis,"[5] and "chronic sclerosing pancreatitis."[6] Here we will adhere to the term autoimmune pancreatitis (AIP), because this term has recently been widely recognized,[7] although the evidence for an autoimmune pathogenesis is so far only circumstantial.[8–10] This review will deal with the pathology of autoimmune pancreatitis, focusing on the duct changes, the sclerosis and storiform myofibroblastic fibrosis in the late stages of the disease, and the significance of immune cells, in particular IgG4 plasma cells, in the pathogenesis and diagnosis of AIP.

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Histopathology

Information about the pathology of AIP is available from case reports and several series that have recently been published in Japan, the United States, and Europe.[4–6,11–16]

The gross appearance of AIP mimics pancreatic ductal carcinoma because the inflammatory process, like the carcinoma, commonly focuses on the head of the pancreas and leads to a gray to yellowish-white induration of the affected tissue with loss of its normal lobular structure. The involved portions may be enlarged. These changes cause obstruction of the main pancreatic duct and usually also of the distal bile duct. In a minority of cases the inflammatory process is concentrated in the body or tail of the pancreas. Diffuse involvement of the pancreas may also be seen, but to date it is not known how frequently and to what extent the entire pancreas is affected in AIP. In contrast to other types of chronic pancreatitis, such as alcoholic chronic pancreatitis, hereditary pancreatitis, and tropical pancreatitis, there are no pseudocysts. Calculi (i.e., intraductal calcifications) are usually absent, but if they occur, they seem to occur late in the course of the disease.[17]

The hallmark of the histological changes in the pancreas in AIP is an intense inflammatory cell infiltration around medium-sized and large interlobular ducts.[4,5,13,16] Smaller ducts may also be involved, but only in

advanced cases. The inflammatory infiltrate consists mainly of lymphocytes and plasma cells, but also contains macrophages, and neutrophilic and eosinophilic granulocytes.[18] Immunocytochemical typing of the lymphocytes reveals that most of them are CD4- and CD8-positive T lymphocytes with fewer B lymphocytes. The infiltrate completely encompasses the ducts and may narrow their lumen by infolding of the epithelium, often giving the lumen a star-like structure. In later stages, the duct wall is thickened by periductal fibrosis.

In a number of cases the chronic changes in the pancreas are overlain by "granulocytic–epithelial" lesions of the ducts. This acute inflammatory component of AIP is characterized by focal detachment, disruption and destruction of the duct epithelium due to invading neutrophilic, and occasionally also eosinophilic, granulocytes, which may also cluster immediately beneath the duct epithelium. A granulocytic infiltration may also be seen in and between the small intralobular ducts and acini.

The extension and severity of the histopathological changes in AIP vary from case to case, and even from one area to another within a single pancreas. In some cases the inflammatory process occupies only a relatively small part of the pancreas and alternates abruptly with areas in which only minimal inflammation is found or even where the pancreatic tissue is normal. If the tissue is only slightly affected, the inflammation focuses almost entirely on the ducts, while in severely affected pancreases the inflammatory process involves the acinar parenchyma, in addition to the ducts, and leads to diffuse sclerosis.[19] At this stage the acinar cells are more or less replaced by inflammatory cells and fibrosis, and the lobular architecture of the pancreas is almost lost. In addition, there are scattered B-cell-rich small lymphoid follicles. If the fibrotic changes occupy large areas, numerous myofibroblasts may appear in a storiform arrangement, mimicking the features of an inflammatory pseudotumor.[20]

In addition to the duct lesions and the sclerotic process, there are vascular changes. Most frequent is vasculitis affecting the small veins. Less common is obliterative arteritis.

If the inflammatory process affects the head of the gland (as it does in approximately 80% of cases), it usually also involves the distal common bile duct, where it leads to a marked thickening of the bile duct wall due to a diffuse lymphoplasmacytic infiltration combined with fibrosis. In some cases the inflammation also extends to the hepatic ducts of the liver hilus and the gall bladder wall.[21] The inflammatory process is usually well demarcated from the surrounding fatty tissue. The peripancreatic and peribiliary lymph nodes are enlarged and show follicular hyperplasia.

Relationship to inflammatory pseudotumor and primary sclerosing cholangitis

There are a number of reports on inflammatory (myofibroblastic) pseudotumors occurring in the head of the pancreas that involved the pancreatic duct as well as the distal common bile duct,[22] and some of which were associated with retroperitoneal fibrosis.[23–25] Judging from the descriptions and illustrations of these cases, these changes appear to be compatible with those seen in AIP. As the clinical features of the reported inflammatory pseudotumors of the pancreas are also very similar, it is likely that these lesions may represent an advanced stage of AIP in which the fibrotic changes predominate and the disease focuses on a specific area.[16] The fact that inflammatory pseudotumors showing sclerosing cholangitis have been observed in the liver hilus[26] suggests that there is possibly an idiopathic pancreatobiliary inflammatory disease complex whose facets include AIP, extrahepatic sclerosing cholangitis, and inflammatory pseudotumor of the pancreas and/or the common bile duct.

Inflammatory and sclerosing changes of the distal bile duct (which sometimes also involve the gallbladder) are very frequent and are almost an integral part of AIP.[27] Because of the similarity of these changes to extrahepatic primary sclerosing cholangitis (PSC), a relationship with this autoimmune liver disease has been discussed. However, to date the PSC-like changes in the extrahepatic bile duct system have never been found to be accompanied by intrahepatic PSC. Moreover, unlike typical PSC, they appear to respond to steroid therapy. Therefore it is likely that AIP, even if it involves the extrahepatic bile ducts, is a disease which is different and distinct from PSC.

Immune phenomena and cells

The inflammatory duct changes seen in AIP point to potential antigens within the duct epithelium that have become targets of an immune process. Typing of the inflammatory duct-associated cells revealed CD4+ and CD8+ T cells to be the most common.[5,28] Increased numbers of these T cells bearing HLA–DR were also found in the peripheral blood.[29] Subtyping of the CD4+ cells according to their cytokine production profiles revealed a predominance of CD4 + Th1 cells over Th2 cells in some cases,[29] which is similar to what has been reported in Sjögren's disease[30] and PSC.[31] HLA–DR antigens have also been detected on pancreatic duct cells.[5,28] Finally, similar to other autoimmune diseases, AIP patients show a particular HLA haplotype, namely DRB1*0405-DQB1*0401.[32] Taken together, these findings strongly suggest that autoimmune mechanisms may be involved in the pathogenesis of AIP. This concept is

further supported by the common association of AIP with other autoimmune diseases, notably Sjögren's syndrome,[3] the frequent occurrence of various autoimmune antibodies such as those against carboanhydrase II and nuclear antigens,[29] the elevated IgG4 serum levels and IgG4-positive plasma cells,[33,34] the oligoclonal pattern of T cell receptor γ-gene rearrangements,[20] and the responsiveness to steroid therapy.[35–38]

To date it is unclear how this immune process is triggered in the pancreas and why it is usually focal and not diffuse, as might be expected from an autoimmune disease. Moreover, the significance of the IgG4-positive plasma cells as a pathogenetic and/or diagnostic marker remains to be elucidated. When we studied the presence, distribution, and frequency of IgG4-positive plasma cells in our series of 51 AIP resection specimens and compared the results with those in non-AIP CP cases, we found that IgG4-positive cells were absent from one-third of our AIP cases, and if present, were not specific for AIP, because IgG4-positive plasma cells were also detected in non-AIP CP cases.[39] A further analysis of the infiltration of the IgG4-expressing plasma cells in the inflamed pancreas revealed a patchy distribution exhibiting a preference for certain areas such as the periductal or perivenular zones, but occasionally without any structural associations. When we focused our quantitative evaluation on the periductal areas, using a cut-off level of 20 cells per high-power field HPF, we found that this value was not exceeded in non-AIP CP cases. In terms of specificity and sensitivity, this implied that IgG4 expression by more than 20 cells per HPF (using a 40× ocular lens) was of moderate sensitivity (43%) but high specificity (100%) for the diagnosis of AIP. In a recently published abstract on the significance of IgG4-positive plasma cells for the diagnosis of AIP, a cut-off level of 50 cells per 3 HPF was reported to be associated with a sensitivity of 70%.[39] As the number of cases studied in this series was smaller than in our study, it is conceivable that the discrepancy between the results of the two studies is due to the sample size. Despite these discrepancies, the available data show that a demonstration of IgG4-positive cells helps to establish the diagnosis of AIP in approximately half to two-thirds of cases. A troublesome point may be that in core needle biopsy specimens, the diagnostic sensitivity of the IgG4-positive cells is most likely lower than in pancreatectomy specimens because of the patchy distribution of these cells, which may lead to a considerable sampling error.

Conclusions

Autoimmune pancreatitis, which is also known under the terms nonalcoholic duct-destructive chronic pancreatitis[4,5] and lymphoplasmacytic sclerosing pancreatitis, is a distinct type of chronic pancreatitis. Ductal and periductal inflammatory infiltration, predominantly composed of lymphocytes, plasma cells, and granulocytes, is the histopathological hallmark of AIP. Extension of the inflammatory process to the acinar tissue leads to diffuse fibrosis. Immunohistologically, the demonstration of increased numbers of IgG4-positive plasma cells is of diagnostic help. Recent studies suggest a role for biopsy in the establishment of a diagnosis of AIP, but the value of this procedure needs to be confirmed in a prospective study.[16]

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