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Autoimmune Pancreatitis: Pathological Findings

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Summary

In recent years, autoimmune pancreatitis 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 and granulocytic epithelial lesions with consequent destruction of the duct epithelium and venulitis. Autoimmune pancreatitis has therefore also been called lymphoplasmacytic sclerosing pancreatitis, duct-destructive chronic pancreatitis, or sclerosing pancreatitis. Autoimmune pancreatitis most commonly involves the head of the pancreas and the distal bile duct. Occasionally, masses are formed and it has been described as an inflammatory myofibroblastic tumor.

Introduction

Similarly to other solid organs, such as the liver and thyroid, it has long been suggested that a type of pancreatitis with an autoimmune etiology exists. The first reports describing such pancreatitis date back more than fifty years. Ball and Baggenstoss [1] described patients with pancreatitis in conjunction with ulcerative colitis. In 1961, Sarles [2] reported on a case of sclerosing pancreatitis with hypergammaglobulinema. The term autoimmune pancreatitis (AIP) was coined in the 1990s [3]. Meanwhile a number of reports on single cases or small series of cases which used various other terms such as "lymphoplasmacytic sclerosing pancreatitis with cholangitis" [4], "non-alcoholic duct-destructive chronic pancreatitis" [5], and "chronic sclerosing pancreatitis" have been published [6]. Here we will adhere to the name autoimmune pancreatitis, since this term has recently been widely recognized [7], although the evidence for an autoimmune pathogenesis is so far only circumstantial [8, 9, 10]. This short review will deal with the pathology of autoimmune pancreatitis focusing on duct changes and storiform fibrosis.

Pathology

Information about the pathology of AIP is available from case reports and several small series which have recently been published [4, 5, 6, 11, 12, 13, 14, 15]. Our knowledge is based on a series of 63 cases which were reported in Germany, Belgium and Italy [16].
The gross appearance of AIP mimics pancreatic ductal carcinoma because the inflammatory process, like 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 the tail of the pancreas. Diffuse

involvement of the pancreas may also be seen, but so far 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 some macrophages and occasionally also neutrophilic and eosinophilic granulocytes [18]. Immunocytochemical typing of the lymphocytes reveals that most of them are CD8 and CD4 positive T lymphocytes with B lymphocytes present to a lesser degree. 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.

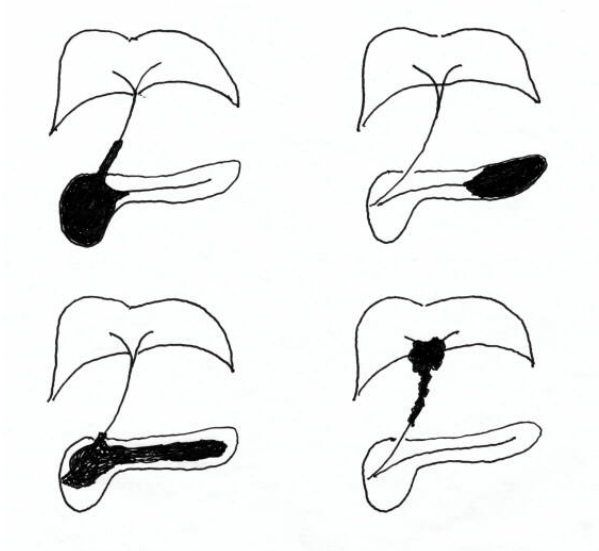

Figure 1. Scheme showing the variable involvement of the pancreas and the biliary tract which may be observed in patients with autoimmune pancreatitis (from [38], with modifications).

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. The granulocytic infiltration sometimes extends into the small intralobular ducts and acini. Though these acute duct changes may be severe, total duct destruction leaving scars which replace the ducts seems to be a rare event.

The extension and severity of the chronic and acute 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 in which the pancreatic tissue is even 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] which may contain scattered B cell-rich small lymphoid follicles. The acinar cells are then more or less replaced by inflammatory cells and fibrosis, and the lobular architecture of the pancreas is almost lost. If the fibrotic changes occupy large areas which show myofibroblasts in a storiform arrangement, they may mimic the features of an inflammatory pseudotumor [20].

In addition to the duct changes and the sclerotic process, there are vascular changes. Vasculitis affecting the small veins is the most frequent while obliterative arteritis is less common.

If the inflammatory process affects the head of the gland (as in approximately 80% of the 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 (Figure 1). 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 involving the pancreatic duct as well as the distal common bile duct [22], some associated with retroperitoneal fibrosis [23, 24, 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 certain 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 (Figure 1).

Inflammatory and sclerosing changes of the distal bile duct (which sometimes also involve the gallbladder) are very frequent and almost an integral part of AIP. Because of their similarity to extrahepatic primary sclerosing cholangitis (PSC), a relationship with this autoimmune liver disease has been discussed. However, the PSC-like changes in the extrahepatic bile duct system have so far 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 different disease and distinct from PSC.

Pathogenesis

The inflammatory duct changes seen in AIP point to potential antigens within the duct epithelium which 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, 27]. Increased numbers of these T cells bearing HLA-DR were also found in the peripheral blood [28]. Subtyping of the CD4+ cells according to their cytokine production profiles revealed a predominance of CD4+Th1 cells over Th2 cells in some cases [28], similar to what has been reported in Sjögren's disease [29] and PSC [30]. HLA-DR antigens have also been detected on pancreatic duct cells [5, 27]. Finally, similar to other autoimmune diseases, AIP patients show a particular HLA haplotype, namely DRB1*0405-DQB1*0401 [31]. 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 antibodies against carboanhydrase II and nuclear antigens [28], the elevated IgG4 serum levels and IgG4 positive plasma cells [32, 33], the oligoclonal pattern of T cell receptor gamma gene rearrangements [20] and the responsiveness to steroid therapy [34, 35, 36, 37]. What is unclear is 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.

Conclusions

Autoimmune pancreatitis, which has been described morphologically under the terms non-alcoholic 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. Recent studies suggest a role for biopsy in the establishment of the diagnosis of AIP, but the value of this procedure needs to be confirmed in a prospective study [16].

Keywords Autoimmune Diseases; Cholangitis, Sclerosing; Pancreatitis; Pathology

Abbreviations AIP: autoimmune pancreatitis; PSC: primary sclerosing cholangitis

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