

PANCREAS NEWS

New Insights into the Pathology and Treatment of Autoimmune Pancreatitis

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It is well-known that the frequency of new diagnoses of autoimmune pancreatitis has increased in the past few years [1, 2]. Autoimmune pancreatitis is characterized by diffuse or focal pancreatic swelling with a narrowing of the pancreatic duct and/or common bile duct. The histological hallmark of this type of pancreatitis is lymphoplasmacytic infiltration, especially concentrated on the pancreatic ducts [3, 4, 5]. However, we have no clear pathological classification of this disease and, because of the difficulty, case studies are still limited. One of the first attempts to classify the various pathological aspects of autoimmune pancreatitis came from Mayo Clinic researchers in Rochester, MN [6] who reviewed the histological features of 35 patients resected for chronic pancreatitis. These authors identified two histologic groups: lymphoplasmacytic sclerosing pancreatitis and idiopathic duct-centric chronic pancreatitis. Lymphoplasmacytic sclerosing pancreatitis was found in 22 cases and was characterized by a fibrosing process with diffuse lymphoplasmacytic infiltrates involving pancreatic lobules and ducts, adipose tissue, blood vessels and the common bile duct; obliterative phlebitis was found in all but one. The histologic features were similar to other idiopathic fibrosclerosing disorders, and one patient also had retroperitoneal fibrosis. Idiopathic duct-centric chronic pancreatitis was found in 13 cases and was characterized by inflammatory

infiltrates denser in the lobules than in interlobular fibrotic areas. Neutrophils were prominent in the ducts, and destruction of the duct epithelium was commonly seen. More recently, a cooperative pathological study carried out by European pathologists has been published [7]. The authors reviewed the histological specimens of 53 resected patients who were found to have chronic pancreatitis lacking pseudocysts, calculi, irregular duct dilatations, pancreas divisum and/or duodenal wall inflammation. They recorded histopathological criteria and clinical features of these patients; most importantly, the severity of the chronic inflammation was graded from 1 to 4, and the activity of the acute inflammatory component and the granulocytic epithelial lesion were determined. Furthermore, pancreatic biopsy specimens from 9 patients with suspected autoimmune pancreatitis were assessed. Periductal lymphoplasmacytic infiltration was identified in all cases, followed in order of frequency by periductal fibrosis and venulitis. These changes were absent in 147 pancreatic specimens of "traditional" chronic pancreatitis associated with pseudocysts, calculi, pancreas divisum and/or duodenal wall inflammation. In 90% of the autoimmune pancreatitis cases, these chronic changes were graded as 3 or 4 and, in 81% of patients, the inflammatory process was found to be in the head of the pancreas and involved the common bile duct. Granulocytic epithelial lesions were present in 42% of the patients,

who had a mean age of 40.5 years, an almost equal male-female ratio and a high coincidence of ulcerative colitis or Crohn's disease. Patients without granulocytic epithelial lesions were older, had a mean age of 64 years, were predominantly male, frequently had Sjögren's syndrome and often developed recurrent bile-duct stenosis. Diagnostically relevant lesions were present in two of five wedge biopsy specimens and three of four fine-needle specimens. Periductal lymphoplasmacytic infiltration and fibrosis, preferential occurrence in the pancreatic head and venulitis characterize autoimmune pancreatitis. In brief, the conclusion of this paper was that granulocytic epithelial lesions predominantly occur in a subset of patients who are younger, more commonly have ulcerative colitis and Crohn's disease, and seem to have fewer recurrences than patients without granulocytic epithelial lesions; more importantly, for good management of patients with this disease, pancreatic biopsy material is helpful in establishing the diagnosis of autoimmune pancreatitis.

From a therapeutic point of view, steroids are a well-known efficacious treatment of autoimmune pancreatitis, as demonstrated by a recent paper coming from Japan [8] which demonstrated, in two cases of autoimmune pancreatitis, the regression not only of the inflammatory infiltration but also of pancreatic fibrosis after a short course of oral steroid therapy. Furthermore, long term steroid treatment [9] has been demonstrated to be a good therapeutic approach in 21 patients having autoimmune pancreatitis with a rate of 19% of clinical recurrence of the disease. Other therapeutic strategies have appeared in recent years such as treatment with ursodeoxycholic acid [10]. However, we need an experimental model of autoimmune pancreatitis to explore not only the pathogenesis of autoimmune pancreatitis but also to test new therapeutic approaches. A Japanese group [11] has found that MRL/Mp^{+/+} (MRL^{+/}) mice, 34 weeks of age or older, develop pancreatitis spontaneously by an autoimmune mechanism. Because this disease

might be a model for multi-factorial diseases controlled by genetic and environmental factors, beginning at 6 weeks old, the researchers injected polyinosinic:polycytidylic acid into MRL^{+/} mice and in addition, into MRL/Mp mice bearing the Fas deletion mutant gene, lpr (MRL/lpr) [12]. Polyinosinic:polycytidylic acid induced chronic severe pancreatitis in all the MRL^{+/} mice and, to a lesser extent, in the MRL/lpr mice by 18 weeks of age. Activated T cells and macrophages, and high levels of cytokines suggest that the progression of chronic pancreatitis might be associated with an autoimmune mechanism in polyinosinic:polycytidylic acid-treated mice. MRL^{+/} mice treated with polyinosinic:polycytidylic acid developed chronic pancreatitis but not other severe lupus diseases, indicating that treated MRL^{+/} mice might be a suitable model for certain aspects of human chronic pancreatitis. Thus, this model should facilitate elucidation of the immune mechanisms and the pathology of chronic pancreatitis, and contribute to the development of effective new therapies.

In conclusion, further knowledge has been acquired in understanding the various aspects of autoimmune pancreatitis. In the near future we hope to obtain more information in order to better care for our patients who have this challenging disease.

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