Autoimmunity and Chronic Pancreatitis: A Concealed Relationship

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Chronic pancreatitis is an inflammatory disease well known for its epidemiological and clinical aspects, but still obscure as to its aetiology and pathogenesis [1]. Alcohol has been identified to be the cause of the disease, since the largest number of patients suffering from chronic pancreatitis were found to have consumed large quantities of wine or spirits over a long period of time [2, 3, 4]. The French school furnished the mechanism by which alcohol caused injury to the pancreas, namely, the lithostathine hypothesis [5]. From this point of view, chronic pancreatitis should be a calcifying-calcified disease caused by alcohol-induced and/or genetically-induced alterations of lithostatine, a protein able to solubilize the calcium present in the pancreatic juice. Unfortunately, there are no experimental models for this hypothesis, and all attempts failed to reproduce chronic pancreatitis-like lesions in alcoholic fed animals [6]. Furthermore, there is clinical [7] and biochemical evidence [8] that does not support the lithostatine hypothesis.

In the late 1990s, new concepts emerged regarding the pathogenesis of chronic pancreatitis. First, chronic pancreatitis is not a single disease but probably many different diseases, with different pathogenesis and with many different epidemiological, clinical and instrumental aspects [9]. In the last 20 years, many clinical entities involving the pancreas have been identified histologically or instrumentally, such as obstructive pancreatitis [9], pancreatitis associated with cystic dystrophy of the duodenal wall [10, 11, 12, 13], pancreatitis associated with mutations of the cystic fibrosis trans-membrane conductance regulator (CFTR) gene [14, 15, 16] and hereditary pancreatitis [17, 18, 19]. But the newest “radical” concept in the pancreatic field is the possibility that acute pancreatitis may evolve into chronic pancreatitis [20]. This was especially demonstrated in inherited pancreatitis and in pancreatitis associated with mutations of the CFTR gene, but some Authors postulated this evolution in all patients suffering from chronic pancreatitis [20]. The main consequence of this hypothesis is not to use the terms acute recurrent and chronic pancreatitis, but to introduce the more general term “pancreatitis” for patients suffering from recurrent episodes of pancreatitis.

The second consequence is the identification of the cause of acute pancreatitis, because, if we know the cause, we may be able to remove it and stop the progression of the inflammatory process in the pancreas.

Therefore, we strongly believe that chronic pancreatitis is an heterogeneous disease, with different mechanisms of damage and we would like to introduce the term “inflammatory pancreatic diseases” to identify the inflammatory diseases involving the pancreas.

The Pathogenesis: A “Hydraulic” Problem

Until a few years ago, the only experimental model of chronic pancreatitis was the obstruction of the main pancreatic duct. The partial obstruction of the pancreatic duct in dogs [21, 22], rats [23] and pigs [24] results in lesions of the pancreatic parenchyma very similar to those observed in human chronic
pancreatitis. Chronic alcoholic intake aggravates the pancreatic lesions, accelerates their onset and makes them irreversible [25]. Experimental studies also showed: 1) the longer the obstruction is in place, the more serious the pancreatic lesions are; 2) ductal obstruction causes the formation of pancreatic calculi in half of the animals; 3) complete obstruction determines an atrophy of the pancreatic parenchyma; 4) the restoration of the pancreatic outflow prevents the formation of calculi and the histological modifications.

We may therefore postulate that most etiological factors act in the same way, the obstruction of the pancreatic duct system. The stasis of the pancreatic juice facilitates the precipitation of the calcium crystal into the lumen duct, with the onset of calcifications that aggravate the obstruction. The acinar component undergoes deep ultra-structural alterations that reduce the enzyme production and stimulate an inflammatory process and fibrosis involving all the glands above the stricture.

In the presence of lithogenetic factors, such as alcohol and cigarette smoking, or in genetically predisposed patients (low levels of lithostathine), the process may be accelerated, with the early onset of calcifications and of exocrine and endocrine insufficiency [26].

The obstruction may involve the main pancreatic duct (“big duct hypothesis”) or the secondary ducts (“little duct hypothesis”). The main common cause of the stricture may be a stenosis of the papilla of Vater, possibly caused by biliary lithiasis, as postulated at the beginning of the century by Opie [27]. Other possible causes are tumors of the pancreas (adenocarcinoma, mucinous-producing tumors, cystic tumors, endocrine tumors, tumors of the papilla of Vater), and stenosis of the main pancreatic duct secondary to acute necrotizing pancreatitis. In patients suffering from inherited pancreatitis, the obstruction is caused by relapsing acute pancreatitis secondary to mutations of the trypsinogen gene, whereas in those suffering from pancreatitis associated with CFTR mutations the disease starts with an obstruction of the ducts secondary to the formation of intraductal mucous aggregates.

The evidence for this hypothesis is provided by cystic dystrophy of the duodenal wall [10, 11, 12, 13]. At the beginning of the disease the inflammatory process is limited to the head of the pancreas, near the duodenum, inasmuch as it starts from the islet of pancreatic tissue, normally found in the duodenal wall. Later, in the presence of large cysts (cystic variant) [10, 11] or when the progress of the inflammation involves structures in addition to the choledocus (solid variant or “groove pancreatitis”) [12, 13], an obstruction of Wirsung’s duct determines a secondary chronic obstructive pancreatitis on the tail of the gland, with dilatation of the duct, onset of intraductal calcifications and, finally, involvement of the entire pancreas. An early resection of the head of the pancreas may therefore be curative.

The obstructive hypothesis points out the importance of derivative surgery for patients suffering from disease involving the main pancreatic duct, but it is also important to remove the cause of the disease, whenever possible.

An Experimental Model for Autoimmune Pancreatitis

In 1996, Puig-Divi and co-workers demonstrated that the instillation of tri-nitrobenzene sulfonic acid (TNBS) in the pancreatic duct of rats induced morphologic pancreatic changes similar to those observed in human chronic pancreatitis [28]. This chemical substance acts as a hapten, altering the membranes of the epithelium and changing the antigenic profile of the pancreatic ducts. The new formatted antigen then stimulates an immune T cell-mediated response, with mononuclear and polymorphonuclear cell infiltration in the pancreas in the first three weeks and a consequent fibrosis in the most advanced stages (6 weeks) with progressive acinar atrophy. The authors used alcohol as a “barrier breaker” to facilitate the action of the TNBS. Then, the same authors demonstrated
that ethanol feeding aggravates pancreatic gland injury secondary to the intraductal instillation of TNBS in rats [29]. In particular, alcohol accelerates the injury of the exocrine component of the pancreas and induces the alteration of the islet of Langherans, with loss of the endocrine function which is normally not involved or partially involved in the TNBS model of experimental chronic pancreatitis. Interestingly, the intra-choledochal administration of the same substance in rats induces chronic cholangitis of the small ducts, very similar to that observed in sclerosing cholangitis [30]. The TNBS is also able to induce alterations similar to ulcerative colitis in rats when instilled in the colon [31, 32].

The TNBS model of experimental chronic pancreatitis, the first obtained without partial obstruction of the main pancreatic duct, brings up some points to consider. First, an immune-mediated mechanism may be involved in the aetiology and/or pathogenesis of chronic pancreatitis. Second, alcohol seems to have an important additional role in facilitating the onset of pancreatic lesions and in aggravating the loss of pancreatic function, particularly for the endocrine component. Third, the possibility of inducing alterations of the biliary tree, the colon and the pancreas with the same substance may indicate a possible relationship between the immune-mediated diseases of these organs.

Clinical and Biochemical Evidence for Autoimmune Pancreatitis

The possibility of an autoimmune mechanism in the pathogenesis of chronic pancreatitis has been stressed since the 1950s [33]. However, this hypothesis has never been demonstrated. There is some difficulty with this purpose, as encountered in other postulated autoimmune diseases of the gastrointestinal tract, such as diseases of the liver (primary sclerosing cholangitis, primary biliary cirrhosis) or the bowel (Crohn’s disease, ulcerative colitis). Despite the possibility of obtaining pathological specimens, other than from the pancreas, the immune-mediated disease is yet an hypothesis in these diseases.

Strictly speaking, the classification of a disease as autoimmune requires some biochemical/clinical and experimental criteria not applicable to human diseases [34]. Some criteria have been suggested as indicative for an autoimmune pathogenesis [34]: 1) the presence of auto-immune antibodies specific for the disease and/or the presence of non-specific auto-antibodies; 2) association with other autoimmune disease; 3) association with HLA aplotype; 4) lymphocytic infiltrate in the site of the disease, where HLA type II antigens are expressed; 5) responsiveness to steroid therapy. In patients suffering from chronic pancreatitis, antibodies against carbonic anhydrase type I and II have been reported [35, 36]. Carbonic anhydrases (CA) are a family of zinc metal enzymes that catalyze the reversible hydration of carbon dioxide to bicarbonate and hydrogen ions. The enzymes are largely distributed in the gastrointestinal tract, in particular in the salivary glands, stomach, duodenum, colon and biliary tract [37]. CA II antigens are characteristically present in the pancreatic ductal epithelium [37, 38], and, therefore, the presence of antibodies against this isoenzyme may provide evidence of an immune reaction to a pancreatic target antigen.

Non-specific auto-antibodies, such as antinuclear antibodies and antineutrophil cytoplasmic antibodies (ANCA), were found to be present in some patients suffering from chronic pancreatitis [36].

The association between chronic pancreatitis and postulated autoimmune diseases of the gastrointestinal tract has been widely reported in the literature [39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65]. Pathological findings in patient with autoimmune pancreatitis seem to show a typical pattern. We can observe a notable inflammatory cellular infiltration, mainly localized around the pancreatic ducts, but also involving the other pancreatic structures (acini, vessels, and nerves). We may also observe lymphocytes and...
granulocytes around the ducts involved, with rupture of the basal membrane and, in some cases, with infiltration into the ducts and their complete destruction [66, 67, 68, 69]. Cytological material, obtained by fine needle aspiration biopsy (FNAB), may also show the presence of a rich component of lymphocytes, plasma cells and granulocytes associated with epithelial aggregates [70]. An increased production of the major antigen of histocompatibility type II (HLA-DR) may be observed in the epithelial cells of the pancreatic ducts which normally do not express this antigen [71, 72, 73].

**Terminology for Autoimmune Pancreatitis: “The Tower of Babele”**

Many terms have been used in the literature to identify auto-immune pancreatitis. “Primary chronic pancreatitis” [7], “non-alcoholic duct destructive chronic pancreatitis” [68], “lymphoplasmacytic sclerosing pancreatitis” [69], “autoimmune pancreatitis” [66, 67], “granulomatous pancreatitis” [58] and “sclerosing pancreato-cholangitis” [74] are the terms commonly used to identify particular forms of pancreatitis which have a similar histological aspect and fulfill the criteria for a pathogenesis involving the immune system. Some Authors defined autoimmune exocrinopathy [75] as the simultaneous involvement of the pancreas, the salivary glands and the liver (primary biliary cirrhosis) by means of an immune-mediated inflammatory process. The terminology was mainly used to identify the pathologic characteristics of the inflammatory process (duct destructive, sclerosing, lymphoplasmatic, granulomatous), but some definitions describe the postulated immune-mediated pathogenesis (primary, autoimmune) rather than the histological pictures.

In our opinion, perhaps *autoimmune* is a better term to use for this disease in order to stress the pathogenesis and to suggest that physicians use steroids for the treatment of this particular form of chronic pancreatitis. However, we need a general consensus to set up the criteria to diagnose and to treat autoimmune pancreatitis.

**The Diagnosis: An Unresolved Problem**

The diagnosis of autoimmune pancreatitis remains a problem. Some diagnostic criteria have been described. The gold standard is histology, with the presence of a dense lymphocytic infiltration topographically centered around the main and/or secondary pancreatic ducts, with focal or diffuse duct destruction and the prevalence of T lymphocytes. However, histological specimens may be obtained only by surgery (surgical specimens and surgical biopsies) and, of course, this appears to be too invasive. Therefore the most important criteria seem to be the clinical association with other postulated autoimmune diseases of the gastrointestinal tract (such as primary sclerosing cholangitis, primary biliary cirrhosis, ulcerative colitis, Crohn’s disease and Sjögren’s syndrome). Other criteria are: a) the presence of non-organ specific autoantibodies at high titre (anti-nuclear, anti-mitochondria, anti-smooth muscle, anti-neutrophil cytoplasmic); b) the presence of antibodies to carbonic anhydrase type I and II; c) aberrant expression of HLA-DR molecules by the pancreatic duct cells; d) cytology obtained by FNAB, ultrasound-guided and characterized by the presence of a notable inflammatory infiltration constituted by lymphocytes, plasmacells and granulocytes and sparse epithelial aggregates; e) clinical response to steroids; f) radiology: morphological characteristics of the CT scan in different contrastographic phases [76, 77], ductal alterations observed at ERCP and at MR-cholangiography [76, 77]. The diagnosis of a fully-manifested disease is easier and more than one of the diagnostic criteria may be observed. However, when the clinical expression of the disease is less pronounced (mild to moderate forms), it may be
Conclusions

We think that an autoimmune mechanism may be present in some of the patients suffering from chronic pancreatitis. Autoimmune pancreatitis is a clinical entity can be identified on the basis of experimental, clinical, histological and biochemical evidence. The diagnosis of the disease is difficult, but it may be reached using the history of the patients, biochemical alterations and radiological findings. The histological findings (biopsy and fine-needle biopsy) are the gold standard for the diagnosis, but we do not yet have any data for the sensibility and specificity of these procedures. Surgical specimens are probably the gold standard for diagnosing the disease, but the diagnosis can be obtained only after resective surgery and/or explorative laparoscopy, generally only in patients with suspected pancreatic cancer. Fine needle biopsy of the pancreas is another potential procedure which can be used, but its role in the diagnosis of autoimmune pancreatitis should be defined. Therapy with steroids is effective in reducing pancreatic inflammation, but we do not know the long-term effects of steroids in the evolution of autoimmune pancreatitis. We need to examine these patients, because it is possible to misdiagnose autoimmune pancreatitis and perform a pancreatic resection by mistake, but, on the other hand, pancreatic cancer may be erroneously treated using steroids.

Key words Autoimmunity; Pancreatitis (diagnosis, therapy)

Abbreviations ANCA: antineutrophil cytoplasmic antibodies; CA: carbonic anhydrases; CFTR: cystic fibrosis transmembrane conductance regulator; FNBA: fine needle aspiration biopsy; TNBS: tri-nitrobenzene sulfonic acid

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