Ursodeoxycholic Acid as an Alternative Therapy for Autoimmune Pancreatitis

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Since Sarles et al reported a case of particular pancreatitis with hypergammaglobulinemia (1), the occasional coexistence of pancreatitis with other autoimmune diseases such as Sjögren’s syndrome (SjS), primary sclerosing cholangitis (PSC) or primary biliary cirrhosis (PBC), has been reported. These findings lead us to the concept of an autoimmune-related pancreatitis, so called “autoimmune pancreatitis (AIP)” (2-4). The clinical characteristics of AIP are (i) increased levels of serum gammaglobulin, IgG, IgG4, and the IgG4 subclass of immune complexes (5); (ii) presence of autoantibodies; (iii) diffuse enlargement of the pancreas; (iv) diffusely irregular narrowing images of the main pancreatic duct; (v) fibrotic changes with lymphocyte infiltration; (vi) no or only mild symptoms; (vii) rare pancreatic calcification or pancreatic cysts; (viii) occasional association with other autoimmune diseases, and (ix) effective steroid therapy.

AIP is a rare disorder, although the exact prevalence is unknown. More than 150 cases have been reported as AIP or pancreatitis with a diffusely narrowing pancreatic duct (PNPD) in the Japanese literature (3, 4). Males are usually predominant over females. Genetically, HLA DRB 10405-DQB 10401 haplotype is reported to be associated in the Japanese population (6). The mean age at diagnosis is over 55 years. The long-term prognosis of AIP is unknown. The patients with AIP usually have no or only slight discomfort in the epigastrium or back, in addition to the symptoms related to other associated diseases. Obstructive jaundice due to the stenosis of intra-pancreatic CBD is characteristic for AIP, which is rare in other types of pancreatitis.

Patients with AIP often show narrowing of the biliary duct, mainly in the intra-pancreatic common bile duct with increased serum bilirubin and hepato-biliary enzymes. In these cases, other liver diseases such as viral hepatitis, autoimmune hepatitis or PBC should be ruled out. Different from PSC, administration of steroid usually shows therapeutic effects on many abnormal laboratory and biliary findings (3, 4). Therefore, the mechanism of the development of biliary lesions in AIP may be different from typical PSC (3, 4, 7).

Diabetes mellitus (DM) is often (43-68%) observed in patients with AIP (3, 4, 8). The majority of diabetic patients associated with AIP is type 2 or other non-specified type. Interestingly, some DM patients associated with AIP improve after steroid therapy (8). Although the mechanism is obscure, cytokines from T cells and macrophages suppressing the function of islet β-cells may be down regulated by steroids. Retropertitoneal fibrosis with sclerosing cholangitis and pancreatitis with a dramatic response to corticosteroid therapy, has been observed (7, 9), although the mechanism of pathophysiology is unclear.

The pathogenetic mechanism is still unclear. Several autoantibodies such as antinuclear antibody, anti-lactoferrin (LF) antibody, anti-carbonic anhydrase-II (CA-II) antibody and rheumatoid factor were frequently detected in patients with AIP, but anti-mitochondrial (M2) antibody specific for PBS is rarely observed (3, 10). CA-II and LF are distributed in the ductal cells of several exocrine organs, including the pancreas, salivary gland, biliary duct and distal renal tubules. Detection of these antibodies may be helpful for the diagnosis of AIP. The effector cells in AIP have been still unclear. The activated T-cells bearing HLA-DR predominantly increase in the peripheral blood lymphocytes and infiltrate into pancreas of AIP (10), although B cells, plasma cells and follicles are occasionally observed in the pancreas.

Even though the standard therapy of AIP is still not established, steroid therapy is usually effective for pancreatic lesions and its complicated lesions such as biliary narrowing, retropertitoneal fibrosis or DM (2–5, 8). In cases of jaundice, percutaneous transhepatic or endoscopic biliary drainage is often necessary prior to steroid therapy, especially in cases of bacterial infection. In the patients unresponsive to steroid therapy, surgical operation is often necessary not only for the relief of symptoms but also for differentiation from malignancy. In this issue (11), Tsubakio K et al reported a 51-year-old female with AIP, in whom treatment with ursodeoxycholic acid (UDCA) was effective for DM and the pancreatic swelling, as well as the liver dysfunction.

See also p 1142.

UDCA is well known to be effective for PBC through bile flow increment and immune-modulation activity. Therefore, UDCA may be an alternative therapy of AIP, especially in cases of involved biliary tract.

In conclusion, recent studies support a unique clinical entity, autoimmune-related pancreatitis. Further studies for clarifying the pathogenesis and establishment of the standard therapy are necessary.
References