Is IgG4-associated Multifocal Systemic Fibrosis the Same Disease Entity as Autoimmune Pancreatitis?

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It is suspected that the pathogenesis of autoimmune pancreatitis (AIP) is still unknown, although it has become recognized as a distinct entity worldwide. The characteristic findings in most cases of AIP can be summarized as follows: (i) mild abdominal symptoms, usually without acute attacks of pancreatitis; (ii) occasional existence of obstructive jaundice; (iii) increased levels of serum gammaglobulin, IgG or IgG4; (iv) presence of autoantibodies; (v) enlargement of the pancreas; (vi) sometimes pseudotumors, (vii) irregular narrowing of the pancreatic duct (sclerosing pancreatitis) often with intra-pancreatic biliary stenosis or coexistence of biliary lesions (sclerosing cholangitis) similar to primary sclerosing cholangitis (PSC) on endoscopic retrograde cholangiopancreatographic (ERCP) images; (viii) fibrotic changes with prominent lymphocyte and IgG4-positive plasmacyte infiltration, and obliterative thrombophlebitis; (ix) occasional association with other systemic lesions such as sialoadenitis, retroperitoneal fibrosis, interstitial renal tubular disorders, and (x) effective steroid therapy (1). Other nomenclature such as “chronic inflammatory sclerosis of the pancreas”, “lymphoplasmacytic sclerosing pancreatitis (LPSP)”, “pancreatitis showing the narrowing appearance of the pancreatic duct (PNPD)”, and “sclerosing pancreato-cholangitis”, “inflammatory pseudotumor of the pancreas”, “tumefactive chronic pancreatitis”, or “non-alcoholic duct destructive chronic pancreatitis” have also been proposed for the pancreatic lesions (1). Although the prognosis of AIP is still unclear, a few long follow-up studies have suggested occasional formation of pancreatic stone. Dense infiltration of lymphocytes and IgG4-positive plasma cells with prominent fibrosis, occasionally with lymphoid follicles, are characteristic histopathologic findings of AIP. As it is usually difficult to obtain a sufficient pancreatic specimen, most AIP are currently diagnosed based on a combination of the characteristic radiological findings (irregular narrowing of the main pancreatic duct and enlargement of the pancreas), serological findings (increased levels of serum gamma-globulin, IgG, or IgG4, along with the

presence of autoantibodies) and histopathological findings. Based on these findings, recently, some diagnostic criteria for AIP have been proposed; (i) the revised version of the clinical diagnostic criteria of autoimmune pancreatitis proposed by the Research Committee of Intractable Diseases of the Pancreas supported by the Japanese Ministry of Health, Labor, and Welfare and the Japan Pancreatic Society (2), (ii) Mayo criteria (3), and (iii) Korean criteria (4). Patients with AIP often show dense infiltration of IgG4-positive plasma cells as well as CD4- or CD8-positive T lymphocytes and fibrosis in the bile duct wall, gallbladder wall, periportal area of the liver, salivary glands, or peripancreatic retroperitoneal tissue, as well as the pancreatic lesions. These extra-pancreatic manifestations were termed as sclerosing cholangitis, sclerosing cholecystitis, sclerosing sialadenitis, and retroperitoneal fibrosis, which are also dramatically responsive to steroid (1, 2). On the other hand, AIP patients with sclerosing sialadenitis are negative for both anti-SSA and anti-SSB antibodies which are disease-specific autoantibodies for Sjögren’s syndrome. Patients with primary sclerosing cholangitis (PSC) rarely respond to steroid therapy and show different prognoses from those with sclerosing cholangitis accompanying with AIP. Moreover, IgG4-positive plasma cells rarely infiltrate into the involved organs in patients with PSC, or Sjögren’s syndrome (1, 2). Therefore, these findings may lead us to a new clinicopathological concept such as “IgG4-related sclerosing disease” (5) or “IgG4-associated multifocal systemic fibrosis” (6). Although most IgG4-related sclerosing diseases have been found to be associated with AIP, some without pancreatic involvement have been reported. Recently, Tanabe et al (7) reported in this journal a patient with combined sclerosing sialadenitis, hypophysitis, and retroperitoneal fibrosis, but lacking pancreatic lesions, in whom steroidal replacement was effective. This case supported a concept of IgG4-associated systemic disease such as “IgG4-related sclerosing disease” or “IgG4-associated multifocal systemic fibrosis. In some previous cases, only 1 or 2 organs were clinically involved, while in

others 3 or 4 organs were affected. Therefore, if this concept is acceptable, classification of clinical subtypes based on the predominantly involved organs is necessary. Clinical manifestations usually depend on the mainly involved organs such as the pancreas, bile duct, salivary glands, and retroperitoneum, in which infiltration of IgG4-plasma cells and tissue fibrosis with obliterative phlebitis are pathologically observed. However, different from these organs, the stomach and colon usually show no sclerotic changes including fibrotic or destructive mucosa in spite of prominent infiltration of IgG4-positive plasma cells (8). These findings sug-

gest that infiltration of IgG4-positive plasma cells may not be involved in the development of tissue destruction or fibrosis. At the moment, the roles of IgG4-infiltrating plasma cells and antigens against serum IgG4 are unknown, although several autoantibodies against systemic distributed proteins such as carbonic anhydrase, lactoferrin or pancreatic secretory trypsin inhibitor (PSTI) are observed in some AIP (9). Further studies are necessary to clarify the role of IgG4 or IgG4-positive plasma cells in the development of AIP.

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