IgG4 related disease in pancreas, bile duct and liver

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IgG4-related disease is a unique systemic inflammatory condition characterized by pseudotumorous formation or swelling of affected organs and high-serum IgG4 concentrations. Further studies have demonstrated that IgG4-related disease can involve a variety of organs including the pancreas (type 1 autoimmune pancreatitis) , bile duct (IgG4-related sclerosing cholangitis), liver (IgG4-related hepatitis and inflammatory pseudotumor), gallbladder (IgG4-related cholecystitis), salivary gland (IgG4-related sialadenitis),retroperitoeneum (IgG4-related retroperitoneal fibrosis), kidney (IgG4-related tubulointerstitial nephritis), lung (IgG4-related interstitial pneumonia, inflammatory pseudotumor), prostate (IgG4-related prostatitis), lymph node (IgG4-related lymphadenopathy) et al. Presence of typical histopathological features, including the existence of numerous IgG4 positive plasma cells within affected tissue, is the gold standard for the diagnosis of IgG4-related disease. Responsiveness to glucocorticoid is particularly characteristic early in the disease course, before the onset of significant tissue fibrosis. Increasing prevalence of IgG4 disease is reported worldwide.

Autoimmune pancreatitis (AIP) is a very unique type of chronic pancreatitis among all types of chronic pancreatitis which characterized by swelling of pancreas, irregular narrowing of main pancreatic duct, histological evidence of lymphoplasmacytic inflammation, and a good response to steroid therapy. AIP could mimic pancreatic malignancy in their clinical manifestation. To keep a high suspicion of AIP could avoid unnecessary pancreatic resection/ surgery. AIP are now categorized into type 1 and type 2 according to consensus of international diagnostic criteria proposed in 2011. **Type 1 AIP is a prototype of IgG4 related disease.** The incidence of AIP is usually about 2-5% among chronic pancreatitis population worldwide. We have analyzed hospitalized patients with validated diagnosis of chronic pancreatitis in National Taiwan University Hospital.Between1994 to 2005, AIP accounted for 2 % in our clinical databases and 5 % of our pathological database. Up to now, we have successfully treated over hundreds cases of AIP by our team, the largest cohort in Taiwan and also in Chinese. The demographic data and clinical presentation of AIP in our population is similar to other countries. Male gender slightly predominantly (57% male patient). The mean age was between 50-60 years old. Elevated IgG4 (>140) was observed in 90.7% of cases with blood sampling available. Elevated IgG (>1800) was observed in 44.2% of cases with blood sampling available. Presence of autoantibody (all screened by at least

ANA, RA, anti-SSA/SSB) was observed in 44.7% of cases. About 60 % AIP patients received steroid treatment (30-40 mg/day by tapering 5 mg every week). The longest follow up period is 96 months. The relapse rate of patients with AIP was 35.9%.The organs with extra-pancreatic involvement included biliary (intrahepatic), liver, salivary, lymphadenopathy, kidney, orbial pseudotumors, retroperitoneum et al.

The pathogenesis of IgG4 related disease is still unclear. Regarding the genetic factors of AIP, our team had firstly reported cytotoxic T lymphocyte- associated antigen 4 (CTLA-4) was associated with risk of AIP in 2007. The significant increase in CTLA-4 49A carriers among AIP patients, compared with the healthy population. The 2318C/+49A/CT60G haplotype was associated with higher susceptibility to AIP. The association was also confirmed in other studies/ethic population later. In our study, we also found tumor necrosis factor a (TNFa) promoter 2863A was correlated with extrapancreatic involvement in patients with AIP. About the pathogenesis, a potential role of *Helicobacter pylori (H pylori)* infection in the pathogenesis of AIP via molecular mimicry has been proposed. Our team had also analyzed the association of HP with AIP. The result could not demonstrate the positive *H pylori* status associated with the AIP in our population

Bile duct involvement of IgG4 disease is known as IgG4-associated cholangitis or IgG4 sclerosing cholangitis (IgG4-SC). It appears to be the second most common manifestation of IgG4 systemic disease, following AIP. IgG4-SC can manifest as diffuse sclerosing cholangitis or a hilar pseudotumourous mass. The former should be differentiated from primary sclerosing cholangitis, whereas the latter radiologically resembles hilar cholangiocarcinoma. IgG4-SC usually present with obstructive jaundice due to a pancreatic head mass (autoimmune pancreatitis) or severe biliary stricture. Other patients are sometimes discovered to have IgG4-SC during a workup for other IgG4-related conditions. The gold standard for the diagnosis of IgG4-SC is histology including characteristic features on H&E and extensive infiltration by IgG4+ plasma cells on immunostaining. Patients with Autoimmune Pancreatitis are mostly easily to be diagnosed with IgG4-SC compared to IgG4-SC alone without pancreatic manifestation. The diagnosis could be established by HISORt criteria (histology, Imaging, Serology, other organ involvement, response to steroid) if no sufficient tissue to be immunostained with IgG4. It is great challenging to diagnose IgG4-SC not associated with pancreatitis. In fact, most patients have been surgically treated for suspected biliary malignancy preoperatively in this situation. The diagnosis of IgG4-associated cholangitis requires a very high index of suspicion and should be entertained in all patients with unexplained biliary strictures. The biliary strictures of IgG4-associated cholangitis are responsive to glucocorticoids, a characteristic that distinguishes them from other causes of biliary tree disorders with similar presentations, such as primary sclerosing cholangitis, cholangiocarcinoma.

A term named “IgG4-hepatopathy” is proposed to indicate liver involvement of IgG4 disease, which includes pseudotumorous or non-tumorous presentation. Many features of IgG4 hepatitis are similar to autoimmune hepatitis except for the presence of abundant IgG4 plasma cells. Some histological patterns are proposed to differentiate with other liver inflammation, including portal inflammation, large bile-duct obstructive features, portal sclerosis, lobular hepatitis, and canalicular cholestasis. IgG4-hepatopathy lack of usual autoantibodies such as antimitochondrial and smooth muscle antibody compared to traditional autoimmune hepatitis. The cardinal difference between IgG4 hepatitis and non-IgG4 autoimmune hepatitis is the dramatic response to steroid.