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IgG4 associated autoimmune hepatitis: a differential diagnosis for classical autoimmune hepatitis

Autoimmune pancreatitis is characterised by raised serum levels of IgG4 and IgG4-bearing plasma cells in the inflammatory tissue.[1] Similar pathology can also occur in the larger bile ducts, resembling sclerosing cholangitis.[2] We report a patient with hepatitis and chronic cholecystitis, raised IgG4 level, and IgG4-bearing plasma cells in the liver and gall bladder wall, but no evident pancreatic disease.

In January 2003, a cholecystectomy was undertaken on a 54 year old woman for chronic cholecystitis. The extracted gall bladder showed lymphoplasmacytic infiltration and subserosal fibrosis. A liver biopsy was done because of abnormal liver function tests and showed severe lobular hepatitis with mild portal inflammation. Plasma cell infiltration was observed in the portal tracts and parenchyma, though fibrosis was not significant. IgG4 bearing plasma cell infiltration was found both in the liver and the gall bladder wall. After six months, liver function was still abnormal: aspartate aminotransferase, 234 IU/l (reference range, 12 to 37); alanine aminotransferase, 487 IU/l (7 to 45); alkaline phosphatase, 478 IU/l (124 to 367); γ-glutamyl transpeptidase, 581 IU/l (6 to 30); total bilirubin, 46.2 μmol/l (5 to 20); IgG, 2403 mg/dl (870 to 1700). The antinuclear antibody titre (1:80 on rodent tissue) was abnormal, and tests for autoantibodies to smooth muscle, double stranded DNA, and mitochondria were negative. Infection with hepatitis viruses A, B, and C, cytomegalovirus, and Epstein-Barr virus was excluded. HLA DRB1 alleles were *1302 and *1501.

She denied taking medicines or herbal remedies.

Ultrasonography, abdominal computed tomography, endoscopic retrograde cholangiography, and magnetic resonance cholangiopancreatography showed no abnormalities in the extrahepatic bile ducts or pancreas. A second liver biopsy, which was done six months after the first, showed changes associated with autoimmune hepatitis, interface hepatitis, lobular hepatitis, rosette formation, syncytial multinucleated giant cell change, and marked plasma cell infiltration (fig 1, panels A to C). Biliary features, such as cholangitis and periductal fibrosis, were not evident. Immunostaining of liver tissue showed abundance of plasma cells with strong immunohistochemical reactivity to IgG4 (fig 1D). The International Autoimmune Hepatitis Group (IAIHG) disease score was 18, identifying definite autoimmune hepatitis[3] (table 1). Treatment was successful with prednisolone 40 mg daily for four weeks, tapered by 5 mg weekly to 5 mg daily. Serum IgG4 concentrations were 557 mg/dl pretreatment (reference range <135 mg/dl), 226 mg/dl after one month, and 44 mg/dl after one year. Serum aspartate aminotransferase and alanine aminotransferase were 94 and 278 IU/l after one month, 31 and 73 IU/l after two months, and 22 and 25 IU/l after one year, respectively.

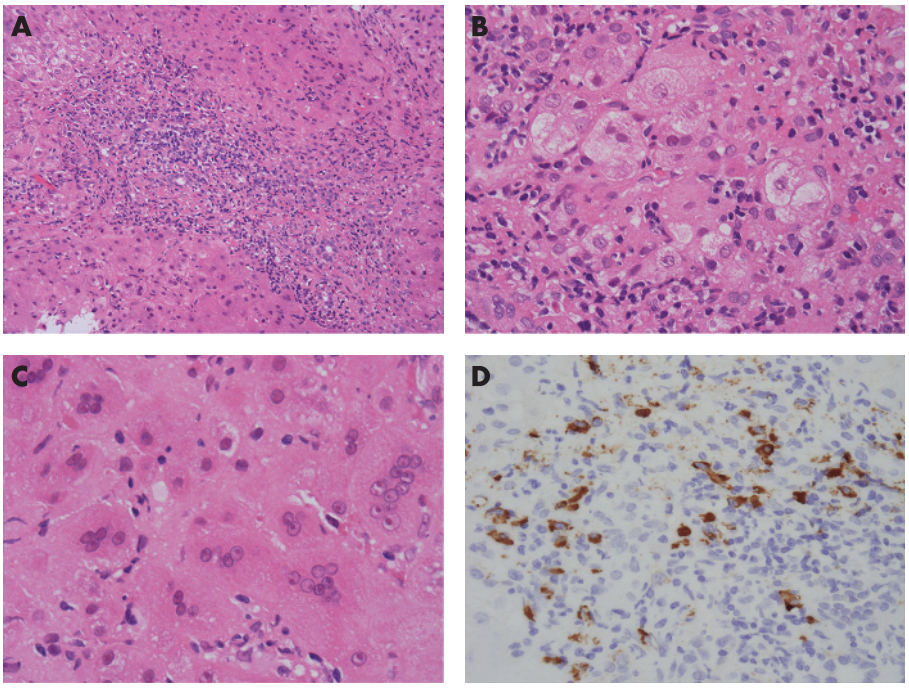

Figure 1 Pathological findings of the second liver biopsy. (A) Portal tracts are enlarged with severe inflammatory cell infiltration. Interface hepatitis is also observed (H&E, ×200). (B) Hepatocytes show rosette formation (H&E, ×400). (C) Syncytial multinucleated giant cell change of hepatocytes is observed (H&E, ×400). (D) Immunostaining for IgG4 reveals abundant IgG4 bearing plasma cells in a portal tract (IgG4 immunostaining, ×400).

Table 1 Autoimmune hepatitis score using IAIHG scoring system

Variable/feature	Score
Female sex: female	+2
ALP:AST ratio: 0.2 (<1.5)	+2
Serum IgG above normal: 1.4 g/dl (1.0 to 1.5)	+1
ANA: 1:80	+2
AMA positive: negative	0
Hepatitis viral markers: negative	+3
Drug history: negative	+1
Average alcohol intake: <25 g/day	+2
Liver histology:	
Interface hepatitis	+3
Predominantly lymphoplasmacytic infiltrate	+1
Rosetting of liver cells	+1
Total	+18

ALP, alkaline phosphatase; AMA, anti-mitochondrial antibodies; ANA, antinuclear antibody; AST, aspartate aminotransferase; IAIHG, International Autoimmune Hepatitis Group.

Raised serum IgG4 concentration and IgG4-bearing plasma cell infiltrates have a high sensitivity and specificity for the diagnosis of autoimmune pancreatitis[1] and associated diseases, including sclerosing cholangitis.[2] In the present case, the clinical and histological criteria for definite autoimmune hepatitis were met and, additionally, both biopsies showed hepatitis with abundant IgG4-bearing plasma cells in the liver and gallbladder.

We previously studied 17 patients with classic autoimmune hepatitis. Both serum IgG4 and IgG4-bearing plasma cells were completely absent in the liver of 13, and a minor increase in only one index was seen in four.[4] Thus we can identify a new disease entity—IgG4 associated autoimmune hepatitis—which can be differentiated from other recognised types. Our present case implies that IgG4 related inflammatory processes can occur in the hepatic parenchyma in the same way as in the pancreatobiliary system, and such cases may resemble autoimmune hepatitis both clinically and pathologically. As such, detection of IgG4 and assessment of liver histology using IgG4 immunostaining may be useful for differentiating IgG4 related diseases from definite autoimmune hepatitis. Further studies are needed on this possible new disease entity and its impact on the diagnostic guidelines for autoimmune hepatitis.

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T Umemura
Department of Internal Medicine, Division of Hepatology and Gastroenterology, Shinshu University School of Medicine, Matsumoto, Japan

Y Zen
Division of Pathology, Kanazawa University Hospital, Kanazawa, Japan

H Hamano, T Ichijo
Department of Internal Medicine, Division of Hepatology and Gastroenterology, Shinshu University School of Medicine, Matsumoto, Japan

S Kawa
Centre for Health, Safety and Environmental Management, Shinshu University, Matsumoto, Japan

Y Nakanuma
Department of Human Pathology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

K Kiyosawa
Department of Internal Medicine, Division of Hepatology and Gastroenterology, Shinshu University School of Medicine, Matsumoto, Japan

Correspondence to: Dr Takeji Umemura, Department of Internal Medicine, Division of Hepatology and Gastroenterology, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390–8621, Japan; t-ume@hsp.md.shinshu-u.ac.jp

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The morphine–prostigmine provocation (Nardi) test for sphincter of Oddi dysfunction: results in healthy volunteers and in patients before and after transduodenal sphincteroplasty and transampullary septectomy

Sphincter of Oddi dysfunction is a complex and poorly understood syndrome that usually manifests as pain of apparently biliary or pancreatic origin in the absence of an organic cause after conventional investigations. Transduodenal sphincteroplasty with transampullary septectomy (TDS/TAS) is a therapeutic option.[1] Although biliary manometry is the gold standard diagnostic test, the morphine–prostigmine provocation (Nardi) test is sometimes used to screen patients. A fourfold increase in either serum amylase or lipase and reproduction of pain after intramuscular injection of 10 mg morphine (to induce sphincteric spasm) and 1 mg prostigmine (to stimulate pancreatic exocrine secretions) is considered a positive test.[2 3] However, the enzymatic changes may also occur in healthy subjects and in patients with irritable bowel syndrome,[3 4] bringing the clinical value of the test into question. Conversely, when the Nardi test was carried out on 70 patients with chronic abdominal pain, enzyme elevation was detected in only 23 patients (33%), 16 (70%) of whom had ampullary stenosis.[5]

We undertook these studies to characterise the response to the Nardi test in 20 healthy young adult subjects and 24 patients with sphincter of Oddi dysfunction before and after TDS/TAS. Our diagnosis of sphincter of Oddi dysfunction was based on clinical history, HIDA scanning, cross sectional imaging, endoscopic retrograde cholangiopancreatography, and exclusion of luminal pathology. All patients had significant debilitating upper abdominal pain requiring regular strong analgesia and had a poor quality of life. Patients were Milwaukee class I or II and had microscopic stenosis/fibrosis, but biliary manometry was not done routinely. We excluded from the healthy subject study those with recurrent abdominal pain, gallstones, or previous abdominal surgery, and those on regular medicines or with allergies.

Subjects abstained from alcohol for at least 24 hours. After sampling blood for baseline concentrations of amylase and lipase, subjects were given 1 ml of 0.9% saline intramuscularly as a sham test. Blood was resampled one hour after this injection. Subjects were then given 10 mg morphine and 1 mg prostigmine intramuscularly simultaneously and blood samples were

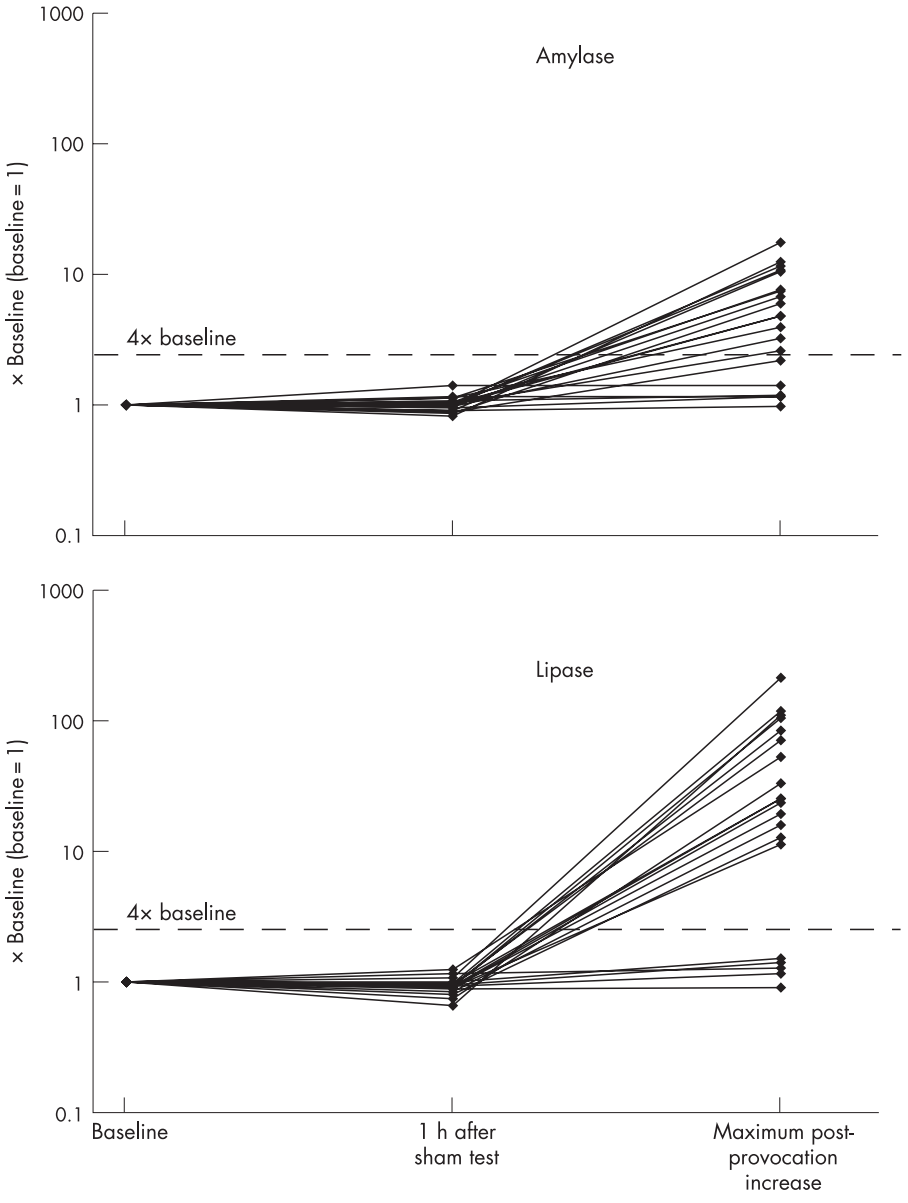

Figure 1 Scatter plot showing maximum increase in serum amylase (top) and lipase (bottom) over baseline values one hour after the sham test and after provocation with morphine and prostigmine in healthy subjects. The baseline value has arbitrarily been defined as 1 and increases are shown as multiples of the baseline value. The dashed line represents 4× baseline. A smaller than fourfold increase over baseline in both amylase and lipase was seen in only four of the 20 subjects.