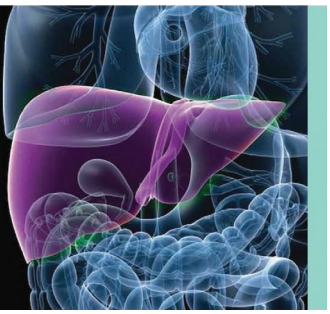

Hepatic Manifestations of Immunoglobulin G4-Related Disease

Kaveh Sharzehi, M.D., M.S.

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated fibroinflammatory condition affecting multiple organs presenting with mass-forming lesions leading to tissue destruction and organ failure.[1] This disease can affect one or multiple organs, synchronously or metachronously.[2] Previously different organ involvements were classified as separate entities, such as autoimmune pancreatitis (AIP) and Riedel thyroiditis. These diseases were eventually classified as IgG4-RD given the expression of IgG4 in involved tissue (Fig. 1).[3]

The hepatobiliary presentation of IgG4-RD includes IgG4-related sclerosing cholangitis (IgG4-SC) and IgG4-related hepatopathy. They can present with biliary strictures and/or mass-like lesions, making them difficult to differentiate from primary sclerosing cholangitis (PSC) or other hepatobiliary malignancies.[4] In retrospect, some cases with the diagnosis of PSC could have been IgG4-SC.

EPIDEMIOLOGY

There is a paucity of data on the prevalence of IgG4-RD in North America. A slight male predilection has been identified, with mean age of presentation being 55 years.[5] The incidence and prevalence of IgG4-RD is not well known, but the prevalence of pancreatobiliary involvement is 4.6 per 100,000 in Japanese studies.[6] Similar to other IgG4-RDs, IgG4-SC is seen more often in the blue-collar workforce.[2]

About 4% to 10% of IgG4-RDs have hepatobiliary involvement. The majority of patients with biliary IgG4-RDs have concurrent AIP. Isolated biliary disease is uncommon and seen in only 8% to 17% of patients.[7] Six to ten percent of patients with IgG4-SC have inflammatory bowel disease, predominantly ulcerative colitis.

CLINICAL FEATURES

Patients with IgG4-SC typically present with obstructive jaundice, in particular in those with concurrent AIP. Less common symptoms include pruritis and abdominal pain. In some instances, unrelated symptoms trigger abdominal imaging leading to the diagnosis of this condition. Unlike PSC, which is often diagnosed at the advanced stage, this presentation is uncommon in

Abbreviations: AIP, autoimmune pancreatitis; IgG4-RD, immunoglobulin G4-related disease; IgG4-SC, immunoglobulin G4-related sclerosing cholangitis; PSC, primary sclerosing cholangitis.

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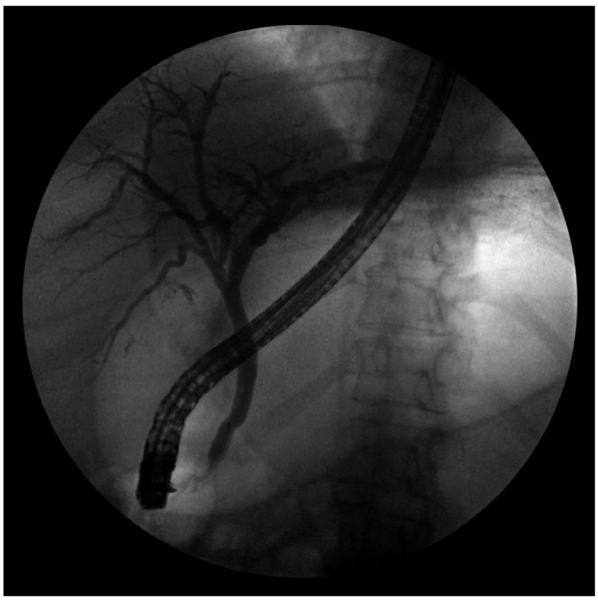

FIG 1 IgG4-SC with isolated left-sided biliary stricture (type 2).

IgG4-SC. Decompensated liver disease is extremely rare with IgG4-SC.[8]

In regard to laboratory abnormalities, serum alkaline phosphatase is elevated in most patients (80%). Serum IgG4 levels are greater than normal range (<140 mg/dL) in more than 80% of patients, hence a normal IgG4 does not exclude the diagnosis.[8] IgG4 greater than 140 mg/dL has a 90% sensitivity, 85% specificity, and 59% positive predictive value in diagnosing IgG4-SC over PSC. By moving the cutoff to 280 or 560 mg/dL, the positive predictive value increases to 88% and 100%, respectively, for diagnosing IgG4-SC over PSC.[9] IgG4 may be elevated in cholangiocarcinoma (as high as 15%) or other biliary pathology. Other nonspecific inflammatory or autoimmune markers, such as ANA, can be elevated but are not diagnostic.

RADIOGRAPHIC FINDINGS

Cholangiograms (endoscopic or magnetic resonance) are the most valuable tools in diagnosing IgG4-SC. Findings on cholangiograms are classified as intrapancreatic strictures (type 1) in 60% to 70%, hilar or perihilar lesions (type 4) in 10%, intrapancreatic and hilar lesions (type 3) in 10%, and intrahepatic strictures (types 2a and 2b) in 5% of patients (Fig. 1).[10] Biliary strictures may be the only radiological features, although these lesions may also be associated with a biliary wall thickening or mass-like lesions in the pancreas and the liver. Therefore, cross-sectional imaging, such as contrast-enhanced computed tomographic scan and magnetic resonance imaging, remain vital in the diagnosis. Certain magnetic resonance imaging features have been used to differentiate IgG4-SC over PSC, such as continuous bile duct involvement (rather than skip disease), common bile duct wall thickness >2.5 mm, and the presence of gallbladder involvement.[11] Even in expert hands, distinguishing IgG4-SC from PSC and bile duct carcinoma based on radiographic findings alone remains challenging.

PATHOLOGY

The combination of the characteristic histological features and increased numbers of $IgG4^+$ plasma cells is central to the diagnosis of IgG4-RD. Tissue acquisition for diagnosis in IgG4-SC is a priority and at the same time a challenge. Cytological samples obtained from brushings of biliary strictures or endosonographic sampling of the bile duct wall or pancreas are minute and may not show diagnostic features of IgG4-SC. Cholangiography-guided or cholangioscopic-directed biopsies often yield small samples but might show characteristic features of IgG4-SC. The involvement of small intrahepatic bile ducts in IgG4-SC can be observed from liver biopsy samples.[4] The Boston consensus criteria include three major histological and a few minor criteria for the diagnosis of IgG4-RD. Diagnosis requires two of the three major criteria: (1) dense lymphoplasmacytic infiltrate, (2) storiform fibrosis, and (3) obliterative phlebitis.[12] The diagnosis is often supported by immunohistochemistry showing elevated $IgG4^+$ cells and IgG4/IgG ratio greater than 40% (Fig. 2).

DIAGNOSIS

The diagnosis of IgG4-SC (similar to other IgG4-RDs) depends on the combination of clinical, radiographic, pathological, and laboratory parameters. Several guidelines for diagnosing AIP and IgG4-SC have been developed. The HISORt (histology, imaging, serology, other organ involvement, and response to therapy) criteria are the most widely used.[13] The Japanese clinical diagnostic criteria for IgG4-SC classify the diagnosis as being definite, probable, or possible (Fig. 3).[14]

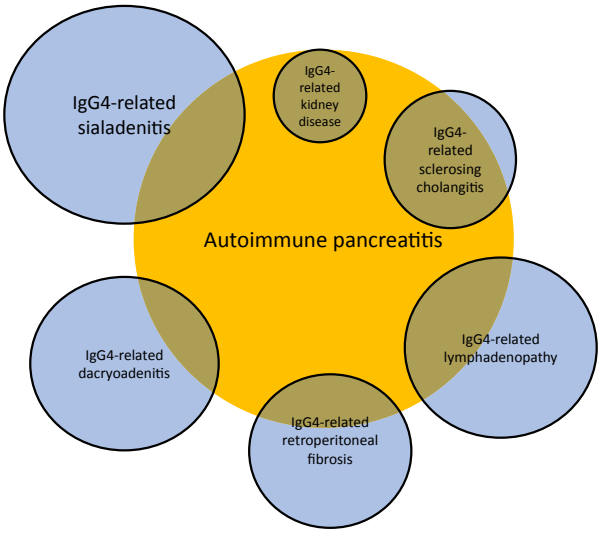

FIG 2 Photomicrograph of IgG4 immunohistochemistry in biliary tissue at 200× original magnification shows extensive IgG4 expression. Courtesy Dr. Aaron Halfpenny, Oregon Health and Science University.

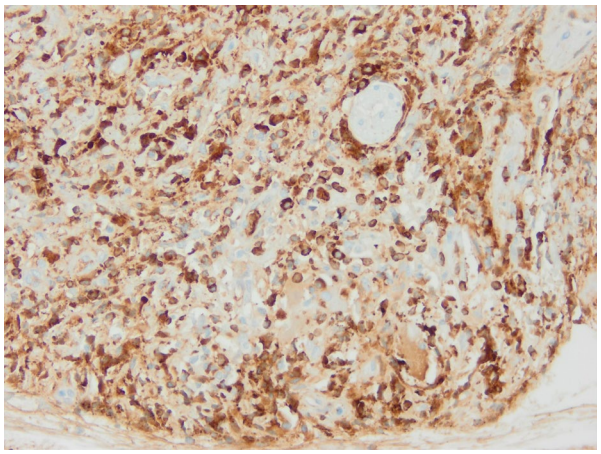

FIG 3 Diagram showing correlation between AIP and other associated IgG4-RDs. Adapted from *Journal of Korean Medicine Science*.[3] Copyright 2015, Korean Academy of Medical Science.

Differentials from IgG4-SC include PSC, secondary sclerosing cholangitis, cholangiocarcinoma, benign and malignant hepatic tumors, and pancreatic adenocarcinoma.

TREATMENT AND OUTCOME

IgG4-SC, similar to other IgG4-RDs, responds promptly to immunosuppressive therapy. Corticosteroids have become the mainstay of treatment even though they have not been studied as well as in AIP. The recommended initial therapy is prednisone at a dosage of 30 to 40 mg daily for 4 weeks, before reducing by 5 mg every 2 weeks depending on response.[15] The absence of a quick response should prompt a thorough evaluation to exclude an alternative diagnosis. More than half of the patients relapse after withdrawal of corticosteroids. Maintenance therapy is often used in Asia (2.5-10 mg/day prednisone for 1-3 years), whereas in North America steroids are withdrawn after the taper.[4] Several steroid-sparing agents have been used in the therapy of IgG4-SC, most prominently rituximab, an anti-CD20 antibody. Limited data suggest a remission rate of 80% to 90%.[2]

In terms of long-term outcomes, it remains unclear whether and how fast IgG4-SC progresses to liver cirrhosis. Limited outcome data suggest end-stage liver disease is uncommon but has been recognized. Risk for cancer (cholangiocarcinoma and hepatocellular carcinoma) is unknown.

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