**COMMENTARY**
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# Diagnosis of Immunoglobulin G4-Related Sclerosing Cholangitis

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See "IgG4 Levels in Bile for Distinguishing IgG4-Associated Cholangiopathy from Other Biliary Disorders: A Single Blinded Pilot Study) by Udayakumar Navaneethan, Norma G. Gutierrez, Ramprasad Jegadeesan, et al., on page 555-559

Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) is a characteristic type of SC with increased serum IgG4 levels and dense infiltration of IgG4-positive plasma cells with extensive fibrosis in the bile duct wall.[1] IgG4-SC is now recognized within the spectrum of systemic IgG4-related diseases. IgG4-SC is well resolved by steroid therapy, which is a characteristic feature of IgG4-related disease. IgG4-SC is frequently associated with type 1 autoimmune pancreatitis (AIP) and IgG4-related sialadenitis; retroperitoneal fibrosis can also occasionally be observed in IgG4-SC. However, some IgG4-SC cases do not involve any other organs. The cholangiographic abnormalities observed in IgG4-SC may resemble those of primary sclerosing cholangitis (PSC) and hilar cholangiocarcinoma. Since obstructive jaundice is frequently observed in IgG4-SC, and IgG4-SC is most common in elderly men, the differential diagnosis compared to that for hilar cholangiocarcinoma is sometimes very difficult. Secondary SC also should be ruled out.

An elevated serum IgG4 level is a characteristic feature of IgG4-SC and can effectively detect patients with IgG4-SC.[2] However, IgG4-SC patients without pancreatic involvement displayed no marked increase in serum IgG4 levels compared to patients with AIP-associated IgG4-SC.

Even though an IgG4 cutoff level of 135 mg/dL is widely used as part of the diagnostic criteria for AIP, a few reports concerning the IgG4 cutoff level in the diagnosis of IgG4-SC have been published.[3,4]

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Oseini et al.[3] reported that among 126 patients with cholangiocarcinoma, 17 (13.5%) had elevated serum IgG4 levels (>140 mg/dL), while four (3.2%) had a >2-fold increase (>280 mg/dL) in serum IgG4 levels. They concluded that diagnosis using a 2-fold higher cutoff serum IgG4 level may not reliably distinguish IgG4-SC from cholangiocarcinoma, but a cutoff level 4-fold higher than the normal upper limit had 100% specificity for IgG4-SC. A recent Japanese study, which included 344 IgG4-SC patients, established a cutoff value of serum IgG4 to differentiate IgG4-SC from other diseases in nine high-volume centers in Japan.[4] The cutoff obtained from receiver-operator characteristic curves displayed similar sensitivity and specificity to a cutoff of 135 mg/dL, when IgG4-SC cases were compared with controls. A cutoff of 182 mg/dL increased the specificity for distinguishing IgG4-SC from cholangiocarcinoma to 96.6%. A cutoff of 207 mg/dL might be more useful for unambiguously distinguishing IgG4-SC from all cholangiocarcinoma, but the sensitivity was only 68.4%.

Only three diagnostic criteria for IgG4-SC have been proposed[5-7] and no standard international diagnostic criteria have been defined until now. IgG4-SC should be discriminated from all three intractable diseases, namely, pancreatic cancer, PSC, and cholangiocarcinoma. The Japanese criteria were derived from a combination of characteristic clinical, serological, morphological, and histopathological features with cholangiographic classification.[6,7]

Recently, Navaneethan et al.[8] performed a single center pilot study on the diagnostic role of biliary IgG4 in IgG4-SC. They enrolled 54 patients in total, and bile was directly aspirated from the common bile duct during endoscopic retrograde cholangiography. The median biliary IgG4 levels were markedly elevated in patients with IgG4-SC (5.5 mg/dL) compared to patients with other diseases such as PSC (1.2 mg/dL) and cholangiocarcinoma (0.9 mg/dL). A cutoff value of 3.8 mg/dL distinguished IgG4-SC from PSC and cholangiocarcinoma with

 

a 100% and 76.9% sensitivity and specificity, respectively. However, the limitations of this study were the small number of patients enrolled (three patients with IgG4-SC and nine patients with cholangiocarcinoma) and a possibility of type II errors. Therefore, the number of patients is too small to derive a definite cutoff value at present. Another limitation was that serum IgG4 levels were not obtained from the enrolled patients. Despite these limitations, this study suggested a potential role for biliary IgG4 measurement as a diagnostic tool in patients with IgG4-SC. Thus, biliary IgG4 levels can be included in new diagnostic criteria for a prospective large multicenter study.

## Conflicts of Interest

The author has no financial conflicts of interest.

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