New Thoughts on Immunoglobulin G4–Related Sclerosing Cholangitis

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KEYWORDS

• IgG4-related sclerosing cholangitis • IgG4-associated cholangitis
• IgG4-related disease • Autoimmune pancreatitis

KEY POINTS

- Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) is the biliary manifestation of a multisystem disease known as IgG4-related disease.
- IgG4-SC may present with biliary strictures and/or masses, which makes it extremely difficult to differentiate from primary sclerosing cholangitis or malignancies, such as cholangiocarcinoma and pancreatic cancer.
- Diagnosis of IgG4-SC is based on a combination of clinical, biochemical, radiological, and histologic findings.
- A gold standard diagnostic test for IgG4-SC is still lacking, warranting the identification of more specific disease markers to aid clinicians.

SYNOPSIS

Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) is a distinct form of chronic cholangitis characterized by infiltration of lymphocytes and abundant IgG4-positive plasma cells in the bile duct wall, elevated IgG4 serum levels in the majority, and a strong response to corticosteroid therapy. It is the biliary manifestation of IgG4-related disease (IRD), a recently recognized fibro-inflammatory multisystem condition.[1] IgG4-SC is most often found in association with autoimmune pancreatitis (AIP), the pancreatic manifestation of IRD. To date, there is no gold standard

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diagnostic test for IgG4-SC; diagnosis is made through a combination of clinical, biochemical, radiological, and histologic features. These features, however, can present similarly to primary sclerosing cholangitis (PSC), cholangiocarcinoma (CCA), or pancreatic cancer (PCa), which complicates and usually delays the diagnostic process. When IgG4-SC is treated during the initial (inflammatory) phase of disease, corticosteroid therapy is very effective. Delayed treatment in a patient with persistent inflammation can eventually lead to irreversible fibrosis and end-stage liver disease. Thus, correctly diagnosing IgG4-SC is critical to avoid unnecessary interventions due to a mistaken diagnosis (for example, surgery or chemotherapy for presumed malignancy) and to prevent fibrotic complications of disease.[2] However, it is essential to exclude malignant disease by adequate imaging and tissue sampling. Evidence suggests that the pathogenesis of IgG4-SC differs from other immune-mediated cholestatic liver diseases like PSC and primary biliary sclerosis (PBC), although fundamental insight into the cause of IgG4-SC is currently lacking. This review provides a comprehensive overview of the current knowledge of the prevalence, clinical features, radiology and histology findings, diagnosis, treatment, natural history, and pathophysiology of IgG4-SC.

Concept of Immunoglobulin G4–Related Disease

IRD is a multisystem disease characterized by unique histopathologic features that include a dense lymphoplasmacytic infiltrate, obliterative phlebitis, and storiform fibrosis, with prominent IgG4-positive plasma cell infiltration in affected organs. Various organs may either simultaneously or consecutively be involved. Almost all organ systems except the brain parenchyma have been reported to be affected.

Brief History

Initial reports of the pancreatobiliary manifestations of IRD date back to 1961, when Sarles and colleagues[3] described an inflammatory disease of the pancreas termed "chronic inflammatory sclerosis of the pancreas." Two years later, Bartholomew and colleagues[4] described cases of sclerosing cholangitis associated with Riedel thyroiditis and "fibrous retroperitonitis". In the 4 decades thereafter, several cases of sclerosing cholangitis were reported in association with inflammation of other organs, such as the pancreas, salivary and lacrimal glands, orbit, mediastinum, and lymph nodes. An association with elevated levels of serum IgG4 was demonstrated in 2001 in patients with AIP.[5] In 2003, after multiple extrapancreatic lesions with similar histologic findings were observed in patients with AIP, the systemic nature of IRD was finally recognized.[6]

Terminology

Several descriptive terms for IRD with concomitant cholangitis have been used through the last decade.[1] The European Association for the Study of the Liver's clinical practice guidelines for cholestatic liver diseases recommended using *IgG4-associated cholangitis*, as clear histologic evidence of sclerosing disease is often absent.[7] However, in 2014 at an international symposium on IRD, the name *IgG4-SC* was agreed on given the fibrotic and potentially irreversible nature of the later stages of the disease, which is the term that is used in this article. With respect to AIP, 2 types have now been recognized (type I and II). Type I AIP is the pancreatic manifestation of IRD and is discussed in this article.[8] Type II AIP has distinct clinical and histologic manifestations (duct-centric sclerosing pancreatitis with granulocytic epithelial lesions) that are unrelated to IRD and are not considered here (**Table 1**).