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IgG4 cholangiopathy – Current concept, diagnosis, and pathogenesis

Kazuichi Okazaki*, Kazushige Uchida, Masanori Koyabu, Hideaki Miyoshi, Tsukasa Ikeura, Makoto Takaoka

The Third Department of Internal Medicine, Division of Gastroenterology and Hepatology, Kansai Medical University, Osaka, Japan

Summary

IgG4 related cholangiopathy, a distinctive type of cholangitis of unknown origin, is characterized by increased serum levels of IgG4, massive infiltration of IgG4-positive plasma cells with storiform fibrosis and/or obliterative phlebitis in the thickened bile duct wall, and good response to steroids. Patients with IgG4-cholangiopathy are frequently associated with autoimmune pancreatitis; IgG4-cholangiopathy is recognized as a biliary manifestation of IgG4-related disease. This condition can be diagnosed by a combination of imaging, serology, histopathology, and steroid responsiveness; however, cholangiographic features are often difficult to differentiate from primary sclerosing cholangitis, pancreatic cancer, or cholangiocarcinoma. The Japanese clinical diagnostic criteria for IgG4-related sclerosing cholangitis established in 2012 are useful in the diagnosis of IgG4-cholangiopathy. Although the precise pathogenic mechanism remains unclear, the development of IgG4-cholangiopathy may involve: susceptible genetic factors, abnormal innate and acquired immunity, decreased naïve regulatory T cells, and specific B cell responses.

Further studies on genetic backgrounds, disease specific antigens, and the role of IgG4 are necessary to clarify the pathogenesis.

Introduction

IgG4 related cholangiopathy is a distinctive type of cholangitis of unknown origin, which is characterized by increased serum levels of IgG4 [1], massive infiltration of IgG4-positive plasma cells with storiform fibrosis and/or obliterative phlebitis in the bile duct wall and good response to steroids [1–3]. Patients with IgG4-cholangiopathy are frequently associated with autoimmune pancreatitis (AIP) [2,3], the concept of which was originally proposed by Yoshida *et al.* [4], and Hamano *et al.* reported increased serum levels of IgG4 in Japanese patients with AIP [1]. Now, it is recognized as a biliary manifestation of IgG4-related disease (IgG4-RD) [2–6]. Clinically, it is important to distinguish IgG4-cholangiopathy from malignancy such as cholangiocarcinoma, pancreas cancer, or a benign counterpart, PSC [2]. The organizing committee of the first international symposium on IgG4-RD in 2009 [6] proposed the nomenclature of "IgG4-related sclerosing cholangitis" (IgG4-SC) instead of "IgG4-associated cholangitis" which was recommended by the European Association for the Study of the Liver (EASL) [6]. Recently, the Japanese clinical diagnostic criteria 2012 for IgG4-SC have been proposed, although the pathogenic mechanisms remain unclear [2]. Here, we introduce the current concept, diagnosis, and recent advances in the pathogenesis of IgG4-SC.

Current concept and diagnosis of IgG4-SC

Classification of sclerosing cholangitis

Sclerosing cholangitis is classified into a primary type of unknown origin such as PSC or IgG4-SC, and secondary type with obvious pathogenesis (e.g., common bile duct (CBD) stone, cholangiocarcinoma, trauma, operation of biliary tract, congenital biliary anatomy, corrosive cholangitis, ischemic bile duct stenosis, AIDS-related cholangitis, or biliary injury of intra-arterial chemotherapy) (Table 1).

Prevalence of IgG4-SC

The prevalence of IgG4-SC still remains unclear. About 80% of AIP patients suffer complications with stenosis of the distal CBD with wall thickness [2,3,5]. This stricture might be due to both the thickening of bile duct and the effect of inflammation and/or edema of pancreas without CBD wall thickness. Based on these propositions, a recent Japanese national study analyzed 197 PSC and 43 IgG4-SC patients without AIP [7]. The male/female ratio was 106:91 (1.16:1) in PSC and 33:10 (3.3:1) in IgG4-SC and the mean age [min–max] was 48.1 [4.0–86.3] in PSC and 69.3

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* Corresponding author. Address: The Third Department of Internal Medicine, Division of Gastroenterology and Hepatology, Kansai Medical University, Shinmachi, Hirakata, Osaka 573-1197, Japan. Tel.: +81 72 804 0101x3223; fax: +81 72 804 2061.
E-mail address: okazaki@hirakata.kmu.ac.jp (K. Okazaki).
Abbreviations: AIP, autoimmune pancreatitis; ANA, anti-nuclear antibody; CA-II, carbonic anhydrase-II; CBD, common bile duct; *CTLA-4*, cytotoxic T lymphocyte antigen-4; ERCP, endoscopic retrograde cholangio-pancreatography; FCRL, Fc-receptor-like; IFN-γ, interferon-γ; IgG4-RD, IgG4-related disease; IgG4-SC, IgG4-related sclerosing cholangitis; IL-4, interleukin-4; LF, lactoferrin; LPSP, lymphoplasmacytic sclerosing pancreatitis; PSC, primary sclerosing cholangitis.

Table 1. Classification of sclerosing cholangitis.

Sclerosing cholangitis of unknown origin
Primary sclerosing cholangitis (PSC)
IgG4-related sclerosing cholangitis (IgG4-SC)
Secondary sclerosing cholangitis
Biliary lesion in AIDS patients
Cholangiocarcinoma
CBD stone
Postoperative/bile duct injury
Congenital biliary disorders
Chemical agents/drug-induced cholangitis
Ischemic biliary stenosis
Others

[47.6–87.4] in IgG4-SC [7]. Cholangiographic classification of IgG4-SC (Fig. 1) according to the clinical diagnostic criteria of IgG4-SC in 2012 [2] demonstrated that type IV, in which strictures of the bile duct are detected only in the hepatic hilar lesions similar to cholangiocarcinoma was the most common in cases of IgG4-SC without AIP [7].

Bile duct images of IgG4-SC

Cholangiogram

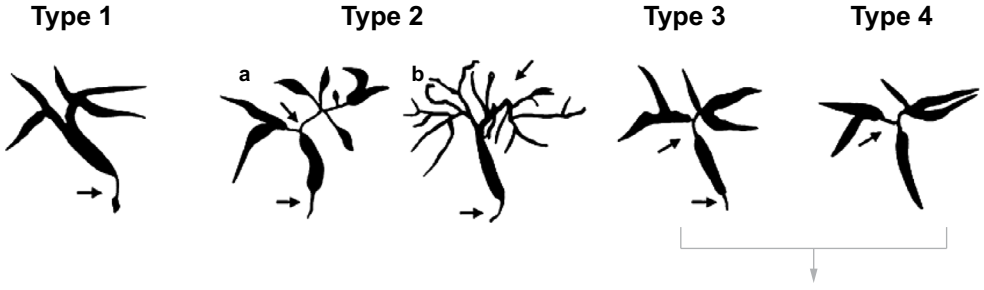
Four types of the characteristic cholangiographic features of IgG4-SC have been proposed based on the regions of stricture (Fig. 1) [2]. Type 1 IgG4-SC shows stenosis only in the distal CBD, which is often observed in pancreas cancer. Type 2 IgG4-SC, in which stenosis is diffusely distributed throughout the intrahepatic/proximal bile ducts, should be differentiated from PSC. Type 3 and type 4 of IgG4-SC show stenosis in the hilar hepatic bile duct similar to hepatic hilar cholangiocarcinoma.

Circular/symmetric thickening of the bile duct

Circular and symmetric thickening of the bile duct wall, smooth outer and inner margin, and homogenous internal echo demonstrated by abdominal ultrasonography (US), abdominal computed tomography (CT), abdominal magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS), and intraductal ultrasonography (IDUS) are most characteristic images of the bile duct [2]. These characteristic features are recognized not only in the stenotic areas or occasionally in the gallbladder but also in areas without stenosis that appear normal in a cholangiogram [2].

Characteristic hematological findings

More than 80% of the patients with IgG4-SC show elevation of serum hepatobiliary enzymes, total bilirubin in cases of obstructive jaundice, and serum IgG4 levels (higher than the upper limit of normal value (ULN) of 135 mg/dl) [1,2]. However, elevation of serum IgG4 levels is not necessarily specific to IgG4-SC; it is also observed in atopic dermatitis, pemphigus, asthma, and some malignant cholangio-pancreatic diseases [2–6]. Cut-off values of serum IgG4 higher than x 2 ULN may be useful for more precisely differentiating IgG4-SC from PSC or cholangiocarcinoma [2,7].



Differential diagnosis			
	Pancreatic cancer Bile duct cancer Chronic pancreatitis	Primary sclerosing cholangitis	Bile duct cancer Gallbladder cancer
Useful modalities			
	IDUS* (bile duct) EUS-FNA** (pancreas) Biopsy (bile duct)	Liver biopsy Colonoscopy (R/O co-existence of IBD***)	EUS (bile duct, pancreas) IDUS (bile duct) Biopsy (bile duct)

Fig. 1. Classification of cholangiography in IgG4-related sclerosing cholangitis. The characteristic features of IgG4-SC can be classified into 4 types based on the regions of stricture as revealed by cholangiography and differential diagnosis. Type 1 IgG4-SC shows stenosis only in the lower part of the common bile duct, and it should be differentiated from chronic pancreatitis, pancreatic cancer, or cholangiocarcinoma. Type 2 IgG4-SC, in which stenosis is diffusely distributed throughout the intrahepatic and extrahepatic bile ducts, should be differentiated from PSC. Type 2 is further subdivided into 2 types. Type 2a, with narrowing of the intrahepatic bile ducts with prestenotic dilation and Type 2b, with narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches, which is caused by marked lymphocytic and plasmacyte infiltration into the peripheral bile ducts. Type 3 IgG4-SC is characterized by stenosis in both the hilar hepatic lesions and the lower part of common bile duct. Type 4 IgG4-SC shows strictures of the bile duct only in the hilar hepatic lesions. Cholangiographic findings of type 3 and type 4 need to be discriminated from those of cholangiocarcinoma. *IDUS, intraductal ultrasonography; **EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; ***IBD, inflammatory bowel disease. Modified from Hepatobiliary Pancreat Sci. 2012;19:536–542 [2], Copyright © 2013, with permission.