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REVIEW ARTICLE

Advances in the diagnosis and treatment of IgG4-related sclerosing cholangitis: a review

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Abstract

Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) is an IgG4-related disease characterized by bile duct fibroinflammatory wall-thickening and stenosis, resulting in obstruction jaundice, weight loss. Different regions of the bile duct can be involved, with the distal region being the most common. IgG4-SC can also have other organ involvement, such as the pancreas, urinary tract, salivary glands and lacrimal glands. In clinical practice, the manifestation of IgG4-SC is very similar to cholangiocarcinoma (CC) and primary sclerosing cholangitis (PSC), as well as pancreatic malignancies, while the treatment and prognosis are totally different. Japanese researchers ever established the clinical diagnostic criteria in 2012: (1) characteristic biliary imaging findings; (2) elevated serum IgG4 concentrations; (3) the coexistence of IgG4-related diseases except those of the biliary tract; and (4) characteristic histopathological features. According to our observations, IgG4-SC can be distinguished from CC with 100% specificity only at a cutoff of six times the upper normal limit. Imaging findings have low specificity for diagnosis, with the exception of intraductal ultrasonography, which can reflect the lesion with relatively high specificity. IgG4 plasma cell infiltration can be found in bile duct biopsy tissue, although this procedure is difficult. According to recent studies, the treatment of IgG4-SC relies mainly on corticosteroids. Following steroid treatment, most IgG4-SC patients can recover and their symptoms are resolved although a few patients relapse after steroid withdrawal. Maintenance of steroid therapy or alternative drugs is necessary in such cases. There is, however, no strong evidence for malignant transformation in IgG4-SC.

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Immunoglobulin G4-related disease (IgG4-RD) is a fibroinflammatory disorder that can be associated with several histological patterns and increases in the absolute number and ratio of IgG4-positive plasma cells. IgG4-related sclerosing cholangitis (IgG4-SC) has been recognized as an IgG4-related disease since 2003 [1]. Patients often present with obstructive jaundice, weight loss, and other organ involvement. The concept of IgG4-SC was first described in 2004. Numerous IgG4-positive plasma cells are found in bile duct lesions [2]. Several cases can involve different regions of the bile duct, with the distal region being the most common [3], while few cases are limited to the intrahepatic [4] or intrapancreatic [5] regions.

Few large epidemiological studies of IgG4-SC have been conducted. Some reports suggest that IgG4-SC patients are predominantly older men [6–7]. Furthermore, more than 90% of patients with IgG4-SC have type 1 autoimmune pancreatitis (AIP) [8–9], with more abundant IgG4-positive plasma cell infiltration in those tissues than is observed in other IgG4-RD-related diseases [9–11] and increased serum IgG4 levels [12]. IgG4-SC may have other organ involvement, such as periaortitis [13], and hemolytic anemia [14], even after long periods of clinical remission from AIP [15] without relapse [16]. In such cases, serum IgG4 levels are also increased [17].

The pathogenesis of IgG4-SC is still unclear. According to previous studies [18–19], T-lymphocytes, macrophages, and total plasma cells can be found in the lesions, with high levels of interleukin (IL) 4/interferon-gamma (IFN-γ), IL-5/IFN-γ, IL-13/IFN-γ, IL-10/CD4, and transforming growth factor (TGF)-beta/CD4. The overproduction of T-helper (Th) 2-type and regulatory cytokines may

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be followed by IgG4 class switching of B cells [11] and fibroplasia. The increased levels of Th2 cytokines in bile can disrupt the tight junctions of biliary epithelial cells and contribute to inflammation [20]. Interactions between chemotactic factors such as chemokine (C-C motif) ligand 1 (CCL1) and chemokine receptor 8 (CCR8), and B-cell responses may be important in the pathogenesis of IgG4-SC [12, 21–22]. However, further studies are required to fully elucidate this.

Diagnosis of IgG4-SC

In clinical practice, the diagnosis of IgG4-SC is extremely challenging. It is difficult to distinguish IgG4-SC from cholangiocarcinoma (CC) and primary sclerosing cholangitis (PSC), as well as pancreatic malignancies, which have similar symptoms but different treatments and prognoses. In 2012, Japanese researchers established the following clinical diagnostic criteria for IgG4-SC [23]: (1) characteristic biliary imaging findings; (2) elevated serum IgG4 concentrations; (3) the coexistence of IgG4-related diseases except those of the biliary tract; and (4) characteristic histopathological features. In addition, highly effective steroid therapy can be useful to confirm the diagnosis. Based on these criteria, the diagnosis of IgG4-SC includes radiological, biochemical, clinical and histomorphological features, and preoperative treatment such as steroids. Endoscopic biliary decompression can also be used to inform the diagnosis and avoid unnecessary surgery [24–25].

Based on the regions of stricture, IgG4-SC can be classified into four types [26]. In type I, stenosis is located only in the lower part of the common bile duct. In type 2, stenosis is diffusely distributed in the intrahepatic and extrahepatic bile ducts. In type 3, stenosis is detected in both the hilar hepatic lesions and lower part of the common bile duct. In type 4, strictures of the bile duct are detected only in the hilar hepatic lesions.

Elevated serum IgG4 is always described as the hallmark of IgG4-RD and IgG4-SC [27–28]. Based on current reports, 100% of IgG-SC patients exhibit elevated sIgG4 before any treatment, with a cutoff value of 135 mg/dL. Based on a Japanese cohort study [29], elevated cutoff values can increase the specificity of serum IgG4 concentrations for distinguishing IgG4-SC from CC. In this study, it was greatly useful in distinguishing IgG4-SC from CC and PSC, while a cutoff value of four times the normal upper limit was 100% specific for the diagnosis of IgG4-SC [30]. However, according to our observations, IgG4-SC can be distinguished from CC with 100% specificity only at a cutoff of six times the upper normal limit. Although serum IgG4 concentrations are important in the diagnosis of IgG4-RD, the positive predictive value of this factor is not universally accepted [31]. The pathogenesis of IgG4-SC is not yet clear. IgG4 may be one factor, with no initial or direct injury stimulus currently recognized, as some other types of disease can also produce elevated sIgG4 levels. Nevertheless, some studies suggest that IgG4 levels [32] in the bile duct tissues provide higher sensitivity for the diagnosis of IgG4-SC.

Although the conventional imaging method is commonly used and highly important in clinical practice, it has low specificity in the diagnosis of IgG4-SC. Under computed tomography (CT), the features of biliary duct involvement in IgG4-SC include dilatation, increased wall thickness, smooth margins, and narrow but visible lumen [33]. Delayed enhancement is also a characteristic feature [34]. Magnetic resonance (MR) imaging (MRI) with MR cholangiography is helpful in the noninvasive evaluation of patients with obstructive jaundice or biliary duct dilatation [35]. Furthermore, this approach may be useful for excluding malignant causes with features of increased wall thickness, long-segment involvement, asymmetry, indistinct outer margins, luminal irregularity, and hyperenhancement relative to the liver parenchyma. Based on our experience, CT and MRI are highly useful for the diagnosis of bile obstruction, although the specificity for IgG4-SC is low.

In addition to routine imaging examinations, endoscopic retrograde cholangiography (ERC) is always used for the diagnosis of bile-related disease. However, no single feature of ERC is sufficient for the diagnosis of IgG4-SC [36]. Segmental or long biliary strictures, isolated strictures, beading, diverticulum-like formations, shaggy bile duct, and pruned-tree appearance can be found and the type of IgG4-SC depends on the manifestation. However, the specificity and sensitivity of ERC are not well balanced for the diagnosis of IgG4-SC [36].

Compared with ERC, endoscopic transpapillary intraductal ultrasonography (IDUS) may have higher specificity. According to IDUS findings [37–38], IgG4-SC has consistently larger regions of circular-symmetric wall thickness with smooth outer and inner margins than are observed in CC. Thus, this feature is useful in distinguishing IgG4-SC from CC. A bile duct wall thickness exceeding 0.8 mm in regions of nonstricture on cholangiography provides high sensitivity and specificity for the diagnosis of IgG4-SC. Based on our clinical observations, IDUS revealed significant differences in manifestations such as wall-thickening and duct-occupying lesions between IgG4-SC and CC.

Histopathological examination has been the gold standard and definitive method for the diagnosis of IgG4-SC, with the bile duct wall consistently showing infiltration by numerous IgG4-positive plasma cells [9–11, 39]. However, surgical biopsy of bile tissue is too difficult for this method to be routinely adopted in clinical practice and noninvasive methods are preferable.

Owing to the similarity in the manifestations of IgG4-SC and other IgG4-RD, abnormal findings in other organs can be useful in the diagnosis of IgG4-SC [40]. Pancreatic involvement [38], termed lymphoplasmacytic sclerosing pancreatitis or type 1 AIP, is characterized by a lymphoplasmacytic infiltration around small ducts, swirling fibrosis centered around ducts and veins (storiform fibrosis), and obliterative phlebitis wherein the infiltrate surrounds pancreatic venules while sparing arterioles. According to a national survey in Japan, IgG4-SC patients without pancreatic involvement were all older than 45 years [41]. Other organs such as the urinary tract [33], salivary and lacrimal glands, lung, gallbladder, retroperitoneum, kidney, prostate, and lymph node can also be involved with abnormal manifestations, including abnormal function, swelling, and of lymphocyte infiltration.

Differentiation from CC

Diagnosis of IgG4-SC is differentiated from that of CC based on serum IgG4 levels [29, 40, 42]. However, because of the significant IgG4-positive plasma cell infiltration of the extrahepatic bile duct in CC [37, 43–44], both of these diseases are associated with elevated serum IgG4 level. Therefore, a cutoff of four times the normal upper limit, which increases the specificity for diagnosing IgG4-SC to 100%, is commonly adopted [30]. However, after observation of 30 IgG4-SC and 275 CC cases, we found that a cutoff of six times the upper normal limit for sIgG4 was required to achieve 100% specificity in the diagnosis of IAC. Nevertheless, the sIgG4 level related to 100% specificity may be revised based on the analysis of more samples.

Besides elevated sIgG4 levels, tumor markers such as serum CA199 level are also important indicators for differential diagnosis. Similar to serum IgG4 level, serum CA199 level is elevated in both IgG4-SC and CC. However, serum CA199 levels in CC patients are always significantly higher than those in IgG4-SC patients [42], possibly owing to the elevated expression level of CA199 in adenocarcinoma cells [45].

Although the findings of routine CT and MRI examinations with regard to the biliary strictures, wall enhancement pattern, and pancreas size may help distinguish IgG4-SC from CC [46–47], in clinical practice, this is not a definitive approach. In the hands of an experienced endoscopist, the findings of IDUS can distinguish IgG4-SC from CC [37, 48]. As IgG4-SC is a systemic fibroinflammatory disorder, the involvement of other organs such as the pancreas, salivary glands, kidney, retroperitoneum, and lymph nodes, can be used for the differential diagnosis and avoid unnecessary surgery [40, 42, 49–50]. Distinguishing IgG4-SC from pancreatic cancer is also highly important in patients with pancreatitis. In pancreatic cancer patients, sIgG4 levels will be far lower than those in patients with autoimmune pancreato-cholangitis [51].

Differentiation from PSC

PSC may also have manifestations similar to those of IgG4-SC [52]. Unfortunately, some PSC patients also have elevated sIgG4 levels [12, 53–55], and the use of IgG4/IgG1 ratios for the purposes of differentiation is recommended by some clinicians. The sIgG4 level combined with the diagnostic algorithm based on an IgG4/IgG1 ratio of 0.24 can increase the specificity for IgG4-SC diagnosis [55]. Immunohistochemical staining of IgG4 can also help distinguish IgG4-SC from PSC [56–57].

According to some CT and MRI retrospective analyses [58–59], the bile duct wall is thicker in IgG4-SC than in PSC. In cholangiographic findings, band-like strictures, a beaded or pruned-tree appearance, and diverticulum-like outpouching can be observed in cases of PSC, but in SC with AIP segmental strictures, dilation after confluent stricture, and strictures of the lower common bile duct are observed with significantly greater frequency [9, 60]. The performance of ERC alone is uniformly poor [36]. Peroral video cholangioscopy can reveal scarring and pseudodiverticula in PSC, while dilated and tortuous vessels are more frequently observed in IgG4-SC [61]. Compared with IgG4-SC, IDUS findings such as irregular inner margins, diverticulum-like outpouching, and the disappearance of the three layers are more specific to PSC [62].

Compared with IgG4-related sclerosing cholangitis, PSC does not respond well to corticosteroid therapy [9]. This phenomenon can also be useful for differential diagnosis. In some cases, the features of IgG4-SC overlap with those of PSC, although this association remains to be fully elucidated [63].

Treatment of IgG4-SC

According to recent studies, the treatment of IgG4-SC relies mainly on corticosteroids. IgG4-SC responds well to steroid therapy, which may result in dramatic improvements of bile duct stenosis and blood chemistry data [64–65]. According to published data, oral prednisolone should be used at an initial dosage of 30 mg/day or 0.5 mg/kg/day, followed by a tapering period of varying duration [66–67]. Maintenance therapy is required in cases without complete morphological and serological resolutions. Widely used regimens are low-dose prednisone (2.5–5 mg/day) and/or azathioprine (1–2 mg/kg/day) over a period of 2 to 3 months [66–68]. For patients with refractory or recurrent IgG4-SC, rituximab and azathioprine or tacrolimus may

also be a treatment option [67, 69–70].

Prognosis of IgG4-SC

After steroid treatment, most IgG4-SC patients recover and their symptoms are resolved, although some patients relapse after steroid withdrawal [71–72]. Relapse may be associated with less frequent use of maintenance steroid therapy, more frequent extrapancreatic and multiple bile duct strictures (especially those located proximally), increased bile duct segment involvement, and thicker bile duct walls during the initial episode [7, 73].

Unlike PSC, IgG4-SC is not a definite risk factor of the development of CC [3], and it has better prognosis than PSC [41]. However, according to recent studies [72, 74–77], the risks of cancer and death are increased, and further prospective, adequately controlled studies are needed to evaluate this relationship.

In conclusion, IgG4-SC is an IgG4-related disease characterized by bile duct fibroinflammatory wall thickening and stenosis, resulting in obstruction jaundice. The involvement of other organs such as the pancreas, urinary tract, and salivary and lacrimal glands may be uncommon. Serological manifestations are characterized by elevated serum IgG4 level. IgG4 plasma cell infiltration can be found in bile duct biopsy tissue, although this procedure is difficult. Imaging findings have low specificity for diagnosis, with the exception of IDUS, which can detect lesions with relatively high specificity. Patients respond well to steroid therapy, although a few patients relapse after steroid withdrawal. Maintenance of steroid therapy or alternative drugs is necessary in such cases. There is, however, no strong evidence of malignant transformation in IgG4-SC.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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