IgG4-Related Sclerosing Cholangitis

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Introduction

IgG4-related sclerosing cholangitis (IgG4-SC) is the biliary manifestation of IgG4-related disease (IgG4-RD), a systemic fibro-inflammatory condition that manifests as organ dysfunction or mass lesions.

IgG4-SC often occurs alongside the pancreatic manifestation of IgG4-RD, autoimmune pancreatitis type 1 (AIP). It commonly presents with obstructive jaundice; however it may be found incidentally when liver function tests or imaging suggest biliary involvement in a patient with IgG4-RD in other organs. Once diagnosed, the disease has a good response to steroid therapy in the inflammatory phase, but patients often relapse. Progressive fibrosis and cirrhosis can develop if the disease is not well controlled.

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Clinicians face several challenges in the diagnosis of IgG4-SC. Firstly, clinical, biochemical, and radiological findings can mimic biliary and pancreatic malignancy (cholangiocarcinoma (CCA) and pancreatic adenocarcinoma) or primary sclerosing cholangitis (PSC). Furthermore, although the majority of IgG4-SC patients will have an increased serum IgG4, this is not specific to the disease and there is no available noninvasive diagnostic test. Finally, if a biopsy specimen is obtained, there is often insufficient material to identify all of the characteristic histological features seen in IgG4-RD lesions. As a result, many patients are not treated appropriately or undergo unnecessary surgical resection for presumed malignancy.

This chapter outlines the clinical, biochemical, radiological, and histological characteristics of IgG4-SC, as well as its treatment, natural history, and pathogenesis.

The Discovery of IgG4-Related Sclerosing Cholangitis

Cases of sclerosing cholangitis associated with fibrosis outside the bile duct in the retroperitoneum or thyroid gland were first reported in 1963 [6]. Subsequently, pancreatitis and sclerosing cholangitis were observed together [96]. Although associations were made between sclerosing cholangitis, chronic pancreatitis, and inflammation in a variety of other organs, they were not considered

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to be a single disease entity and their pathophysiology remained elusive. In 1995 it was proposed that chronic pancreatitis was autoimmune in etiology, based on the observation that the disease was steroid responsive and associated with a serum hypergammaglobulinemia [97]. It was later demonstrated that serum IgG4 in particular was raised in the disease [29].

The concept that AIP was part of a systemic disease was not suggested until 2003. Histopathological data showed the infiltration of T-Cells, and IgG4-positive plasma cells seen in the pancreatic lesions of AIP were also present in the bile ducts of the same patients [37]. Evidence that sclerosing cholangitis and AIP shared a distinct histological phenotype supported the idea that sclerosing cholangitis was the biliary manifestation of IgG4-RD [99]. In 2007, it was proposed that this form of cholangitis should be termed IgG4-associated cholangitis (IAC), and this nomenclature is still recommended in the European Association for Study of the Liver (EASL) clinical practice guidelines [7, 21]. Currently, the term IgG4-related sclerosing cholangitis (IgG4-SC) is used, after a consensus agreement at the International Symposium on IgG4-RD in 2014.

Epidemiology

There is a paucity of good epidemiological data to estimate the true incidence and prevalence of IgG4-SC. Data collected on AIP captures some patients with coexistent IgG4-SC. It suggests that patients with IgG4-SC are likely to have concurrent AIP. In Japan, the most recent population survey of AIP in 2011 estimated the annual incidence rate to be 1.4 per 100,000 population and prevalence to be 4.6 per 100,000 population, an increase on previous estimates from the 2007 survey [42, 43]. In the 2011 cohort of 918 patients with both new and existing diagnoses of AIP, 95 (10.3 %) had IgG4-SC at the porta hepatis, and 216 (23.5 %) had intrahepatic IgG4-SC [43]. In Western Countries data suggests a stronger co-occurrence of AIP and IgG4-SC. One report from the United States found that in a group of 53 patients with IgG4-SC, 49 (92 %) of them had coexistent AIP and only 4 (8 %) had IgG4-SC alone [26]. Recent analysis of a cohort of 115 patients with AIP and/or IgG4-SC in the United Kingdom found that of the 106 patients with AIP, 60 (56 %) had concurrent IgG4-SC and 9 patients (8 %) had isolated IgG4-SC [32].

Previous data suggested that IgG4-SC is second only to AIP as the most common site of IgG4-RD. This is being challenged by more recent data from several IgG4-RD cohorts, depending on the referral practices and specialists involved (Table 5.1). As IgG4-RD is diagnosed more frequently, differences in patterns of organ involvement between geographical locations may become more apparent.

Disease Pathogenesis

The pathological mechanisms underlying IgG4-SC are not yet fully understood. The raised serum IgG4, lymphoplasmacytic infiltration seen

Table 5.1 Reported frequency of IgG4-SC and AIP

Study	Country	Cohort	N. of patients	IgG4-SC N (%)	AIP N (%)
Kanno et al. [43]	Japan	AIP	91 8	311 (33.8)	918 (100)
Ghazale et al. [26]	USA	IgG4-SC and AIP	53	53 (100)	49 (92)
Huggett et al. [32]	UK	AIP and IgG4-SC	115	69 (60)	106 (92)
Lin et al. [53]	China	IgG4-RD	118	21 (17.9)	45 (38.1)
Inoue et al. [34]	Japan	IgG4-RD	235	(13)	142 (60)
Fernandez-Codina et al. [22]	Spain	IgG4-RD	55	30 (4)	142 (60)
Campochiaro et al. [10]	Italy	IgG4-RD	41	4 (10)	17 (41)

Key: *N* number, *AIP* autoimmune pancreatitis, *IgG4-SC* IgG4-sclerosing cholangitis

in disease lesions, and the response to steroids and immunosuppressive agents indicate that aberration of the immune response is central. What triggers and sustains the inflammatory process is not clear, but several mechanisms have been proposed including autoimmunity against a self-antigen, molecular mimicry, or chronic antigen exposure triggering immune dysregulation. Advances in our understanding of the genetic background and the immunological environment of patients, are beginning to unravel disease pathogenesis.

Genetic Susceptibility

No studies to date have focused on the genetics of IgG4-SC patients specifically. Evidence is growing that AIP patients have a genetic background that makes them susceptible to disease development. Single nucleotide polymorphisms in genes encoding immune factors including cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and Fc receptor-like 3 (FcR-3) have been reported to be associated with AIP development or recurrence [14, 88, 90]. Class II human leukocyte antigen (HLA) alleles HLA DRB1_0405 and DQB1_0401 were identified to be associated with AIP [44]. A Korean study found that substitution on position 57 on HLA DQB1 was associated with disease relapse in AIP [71]. It is likely that variation in class II alleles involved in antigen presentation can influence predisposition to disease and its course.

Autoantigens

A role for autoimmunity is supported by the presence of a T-Cell, B cell, and antibody-rich infiltrate in disease lesions. Multiple candidate autoantibodies and autoantigens have been investigated in AIP, although none have been found to be specific for the disease. Antibodies against carbonic anhydrase II and lactoferrin, which are expressed widely in exocrine organs, have been reported in 73% and 54% of AIP patients, respectively [4, 69]. Anti-carbonic anhydrase II antibodies were found to correlate with serum IgG4 levels [4]. Another purported mechanism of disease pathogenesis is molecular mimicry between sequences found in alpha-carbonic anhydrase of the bacterium *Heliobacter pylori* and carbonic anhydrase II [28]. Other candidate antibodies detected at lower levels in AIP include anti-carbonic anhydrase IV, pancreatic secretory trypsin inhibitor, amylase IV, heat-shock protein 10 and plasminogen binding protein [5, 19, 23, 52, 82].

The Role of B Cells and the IgG4 Molecule

The presence of IgG4-positive plasma cells in disease lesions and raised serum IgG4 levels seen in the majority of patients are indications that B cells and antibody production are important in IgG4-SC pathogenesis. The B lymphocyte-depleting agent rituximab has been used with success to treat IgG4-SC patients refractory to steroids and conventional immunosuppressants [11, 12, 45, 46, 55]. Recent work has identified circulating oligoclonal IgG4-positive plasmablasts in patients with active IgG4-RD, which remit after treatment with rituximab and re-expand during relapse [56, 57, 94, 95]. Relapse of IgG4-RD after B-cell depletion with rituximab infers that the reemergence of IgG4-positive plasmablasts are derived from either a subset of memory B cells that survive rituximab therapy or newly generated naïve B cells that interact with a yet unidentified antigen or pathogenic T-Cell repertoire, unaffected by rituximab.

An important question in understanding IgG4-RD pathogenesis is why IgG4 immunoglobulin and IgG4-positive plasma cells are expanded in a great majority of patients. Although it has been postulated that autoantibodies might induce an inappropriate immune response, candidates thus far are of the IgG1 rather than IgG4 subclass. Oligoclonal IgG4-positive clones have been identified in sequencing of whole blood in IgG4-SC patients, suggesting that only specific B cells are expanded [54]. However a generalized polyclonal IgG4 response to multiple common antigens has been demonstrated in IgG4-RD patients. This supports the alternative theory that increased IgG4 is an epiphenomenon, occurring as a result of the expansion of preexisting IgG4-switched B cells rather than being driven by a specific autoantigen [13].

It is unknown as to whether the IgG4 immunoglobulin is directly involved in driving the inflammation seen in disease lesions. IgG4 has anti-inflammatory properties due to its unique structure that allows exchange of its Fab arm, producing functional monomers that are unable to form large immune complexes [91]. Unlike the other gamma immunoglobulin subclasses, IgG4 is unable to activate complement [92]. Under physiological conditions, specific IgG4 responses occur to generate humoral tolerance after repetitive antigen stimulation, for example, in beekeepers that are repeatedly exposed to bee venom [1]. These tolerogenic properties argue that IgG4 molecules themselves are unlikely to be intrinsically harmful.

However, in other immune conditions including pemphigus vulgaris and myasthenia gravis, IgG4 antibodies are thought to be directly pathogenic [24, 33]. In a small study, IgG4 in sera from AIP patients bound with normal pancreatic and biliary epithelial tissue, indicating an interaction between IgG4 antibodies with a yet unidentified antigen [3].

T-Cell Immunological Response

CD4-positive T-Cells are necessary to support and coordinate IgG4-switched B-cell responses, but their role in IgG4-SC pathogenesis has not been fully elucidated. T-Cells are a component of the lymphoplasmacytic infiltrate in disease lesions and are likely to interact with the B cells when in close proximity.

T-helper type 2 (Th2) cells have been implicated in IgG4-RD pathogenesis. The Th2 cytokines IL-4, IL-5, and IL-13 have been detected at the messenger RNA level in IgG4-RD disease lesions, blood CD4-positive T-Cells in IgG4-RD patients, and in the bile of IgG4-SC patients [41, 60, 83, 100, 101]. A skew of circulating CD4-positive T-Cells towards a Th2 phenotype has also been reported [73]. It has been suggested that Th2 cells in IgG4-RD promote peripheral eosinophilia, raised serum immunoglobulin E (IgE), and IgG4 predominance, as Th2-associated cytokines IL-4 and IL-13 have been shown to promote immunoglobulin class switch toward the IgG4 subtype [72, 87]. However a recent report that blood Th2 cell expansion is restricted to IgG4-RD patients with atopy challenges the hypothesis of a Th2-driven response in IgG4-RD [56, 57]. Mast cells have been suggested as an alternative source of Th2 cytokines, based on their colocalization with IL-4 and IL-13 in IgG4-RD lesions from salivary glands [79, 80].

T follicular helper cells, which support B-cell differentiation into antigen-secreting cells in germinal centers, have also been implicated in IgG4-RD pathogenesis. Next-generation sequencing of the B-cell receptor immunoglobulin heavy chain repertoire of circulating plasmablasts in IgG4-RD patients has shown they have undergone extensive somatic hypermutation, a process for which T follicular helper cells are integral [56, 57]. A recent study has shown that circulating type 2 T follicular helper (Tfh2) cells are expanded in patients with IgG4-RD [2]. Tfh2 cells preferentially secrete Th2 cytokines [59] and could be the driver of the B-cell differentiation to IgG4-positive plasmablasts and plasma cells.

The T regulatory (Treg) cell-associated cytokine IL-10 and tumor growth factor beta (TGF-β) have been found in IgG4-RD lesions [87, 100, 101]. There is also evidence that Tregs are expanded in the circulation and tissue lesions in IgG4-SC and AIP [49, 51, 61]. IL-10 has been shown to preferentially switch immunoglobulin toward IgG4 rather than IgE, and TGF-β has been purported to contribute to the fibrosis seen in late stage disease [36, 78].

Regional Factors Promoting Lymphocyte Recruitment

It has been suggested that factors local to the pancreatobiliary system may be at play in IgG4-SC, as it often occurs alongside AIP. Pathological specimens of IgG4-SC show severe inflammation in the peribiliary glands, which contain pancreatic acini [27]. In tissue specimens from AIP and IgG4-SC, the chemokine CCL1 was expressed highly at the messenger RNA level and was localized to the peribiliary glands and pancreatic duct epithelium. The expression of CCR8, the receptor for CCL1 found on Th2 and Treg lymphocytes,

was also upregulated in IgG4-SC disease lesions [102]. Another study found that CXCR5, expressed on Tfh cells, and its ligand CXCL13 were upregulated in AIP tissue [20]. A variety of other chemokines have been found to be overexpressed in AIP and IgG4-SC tissue including CCL1, CXCL13, CCL17, CCL19, and CCL21, but their role in the disease is not yet clear [74].

Clinical Features and Natural History

Clinical Presentation

Patients with IgG4-SC are predominantly males in their seventh decade and most commonly present with obstructive jaundice, weight loss, and abdominal pain. Patients with concomitant pancreatic involvement can present with steatorrhea, indicative of exocrine insufficiency and/or diabetes [26, 32]. In others, biliary involvement might be found incidentally on cross-sectional imaging performed for another reason.

Patients should be asked about previous occupational exposure, especially "blue-collar work" and history of allergy and/or atopy. Both have been observed at increased rates in IgG4-RD, although their significance in disease pathogenesis remains unclear [16, 17, 38, 39].

Laboratory Findings

There is no single laboratory test that can accurately diagnose IgG4-SC. Liver function tests are often deranged. An obstructive pattern of raised alkalinephosphatase,gamma-glutamyltransferase, and bilirubin is most commonly observed. In addition, patients can also have a polyclonal hypergammaglobulinemia and raised serum IgG.

Serum IgG4 is raised in 70–74 % of patients at time of diagnosis [26, 32]. However, an elevated serum IgG4 is not specific to IgG4-RD and can also be raised in PSC and pancreatobiliary malignancy, which mimic IgG4-SC both clinically and radiologically [11, 12, 58, 70, 94, 95]. Several studies have investigated whether using a higher cutoff value for serum IgG4 increases its ability to distinguish IgG4-SC from PSC or CCA. Using a higher IgG4 value over four times the upper limit of normal increases the specificity or positive predictive value (PPV) to almost 100 % for IgG4-SC. Alternatively when serum IgG4 is raised between one and two times the upper limit of normal, using an IgG4 to IgG1 ratio rather than IgG4 in isolation has been shown to increase PPV and sensitivity for IgG4-SC in Dutch and UK cohorts [8, 70]. However these methods do not detect the group of IgG4-SC patients with a normal serum IgG4.

Serum IgE levels are raised in between 35 and 95 % of IgG4-RD patients. Furthermore, 25–30 % of patients have a peripheral blood eosinophilia. There is conflicting evidence as to whether patients with a history of allergy are more likely to have a raised IgE and/or eosinophilia, compared to nonallergic patients [17, 38, 39, 98].

No autoantibody has been found to be specific to IgG4-SC [76]. The tumor marker CA19-9 can be raised in both pancreatobiliary malignancy and IgG4-SC, making it a poor differentiator between the conditions [26]. Although bile IgG4 levels can be elevated in patients with IgG4-SC compared to other biliary disorders including PSC and CCA, it is not specific [93].

Imaging Features

Imaging alone is unable to make a firm diagnosis of IgG4-SC as features can mimic PSC, CCA, and pancreatic carcinoma. Imaging of the biliary tree via magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) can reveal IgG4-SC biliary strictures.

Four patterns of strictures have been recognized [66]. Type 1 describes a single distal common bile duct (CBD) stricture which can mimic pancreatic carcinoma or CCA. This appearance commonly occurs in IgG4-SC, particularly in association with AIP where the stricture may be caused by inflammation of both the pancreas and biliary wall [31]. Type 2 lesions can be divided into type 2a intrahepatic strictures with

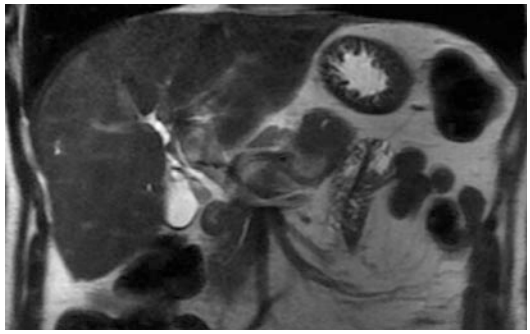

Fig. 5.1 MRCP of a patient with type 2 IgG4-SC with intra- and extrahepatic biliary dilatation

prestenotic dilatation and type 2b intrahepatic strictures without prestenotic dilatation and reduced bile duct branching. Both type 2 patterns can exhibit additional extrahepatic strictures, and appearances can be similar to PSC (Fig. 5.1). Unlike PSC, IgG4-SC strictures often show biliary dilation of over 10 mm proximal to a confluent narrowing in the distal CBD. Characteristic PSC features such as a beaded and pruned-tree appearance of the bile ducts are often absent in IgG4-SC [65]. A recent study of biliary appearance using MRI found continuous rather than skip lesions, and a single wall CBD thickness of over 2.5 mm favored IgG4-SC over PSC [85].

Type 3 IgG4-SC describes a distal CBD stricture and hilar hepatic stricture. Type 4 strictures involve the hilum only (Fig. 5.2). In a Japanese survey of IgG4-SC patients without pancreatic lesions, this was the commonest subtype [84]. Both type 3 and type 4 can mimic hilar CCA.

Other characteristic features of IgG4-SC lesions include symmetrical biliary wall thickening, smooth inner and outer margins, and a homogenous echo appearance of the internal bile duct wall. These can be characterized using conventional abdominal ultrasound, computed tomography (CT), endoscopic ultrasound (EUS), and intraductal ultrasonography (IDUS). Lesions can occur in regions where there is no identifiable biliary stricture on cholangiography [35, 50, 62]. Cross-sectional imaging can identify mass lesions in other organs caused by systemic IgG4-RD. CT pancreas can show a characteristic sausage-shaped appearance or mass lesions within the pancreatic parenchyma representative of AIP [35]. In one series, pancreatic abnormalities were the strongest predictor of correctly distinguishing IgG4-SC from PSC and malignancy [25].

Histopathological Features

Inflammatory lesions in IgG4-SC are usually distributed in the extrahepatic, hilar, and perihilar bile ducts but can also affect the small intrahepatic ducts and gallbladder.

Macroscopically the affected areas of the bile duct are diffusely thickened, with stenotic lumens, and in some cases appear as tumorous lesions [64, 100, 101]. In contrast to PSC, the biliary epithelium is relatively well preserved but inflammation can extend into local veins, glands, and nerves [99].

Microscopically, classical IgG4-SC lesions share the lymphoplasmacytic infiltrate, obliterative phlebitis, and storiform pattern of fibrosis seen in other IgG4-RD conditions [26, 99]. The lymphoplasmacytic infiltrate is T-Cell predominant with scattered B-cell aggregates (Fig. 5.3 left). Germinal centers are sometimes seen and many specimens have an eosinophilia. The presence of IgG4-positive plasma cells, however, is not sufficient for diagnosis, as they can be seen in other conditions. A biopsy specimen with a mean of >10 IgG4 plasma cells per high-power field (HPF) (Fig. 5.3 right) or an IgG4/IgG plasma cell ration of >40 % is suggestive and incorporated into diagnostic guidelines for IgG4-RD and IgG4-SC [15, 68, 75]. It should also be noted that some classical histopathological features might not be present on biopsy if insufficient amounts of tissue are obtained. In one series of transpapillary biopsy specimens collected from IgG4-SC strictures using IDUS, obliterative phlebitis was absent and >10 IgG4-positive cells per HPF was only observed in a minority [62].

Liver biopsy can demonstrate small duct involvement in IgG4-SC in up to 26 % of cases. Specimens typically show portal inflammation and IgG4-positive plasma cell infiltration [63, 89]. Some specimens also have portal-based micro-inflammatory nodules of lymphocytes,

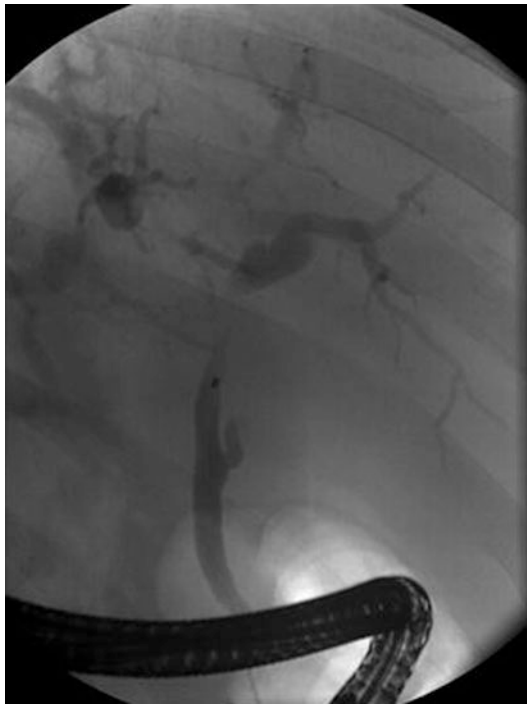

Fig. 5.2 MRCP of a patient with type 4 IgG4-SC with a hilar stricture, which is difficult to differentiate from hilar CCA

plasma cells, eosinophils, and a myxoid stroma, a feature not present in PSC [18].

Diagnosis

There is no single diagnostic test to confirm IgG4-SC. Therefore, diagnosis should be based on a combination of clinical, radiological, laboratory, and histological findings. Several guidelines have been developed. These include the HISORt criteria (histology, imaging, serology, other organ involvement and response to therapy), originally developed for AIP and adapted for IgG4-SC (Table 5.2; [15, 26]). In Japan, clinical diagnostic criteria for IgG4-SC classify the diagnosis as being definite, probable, or possible depending on the features of the case [68]. For definitive diagnosis both guidelines include typical imaging findings of a thickened bile duct wall with segmental or diffuse biliary strictures, raised serum IgG4 titers, coexistence of other organ involvement, and the typical histological features (lymphoplasmacytic infiltrate, >10/HPF IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis). If steroid therapy has been effective in improving clinical, radiological, or histological features, this is supportive for diagnosis, although improvement with steroids can also occur in other malignant and inflammatory conditions. It is imperative to exclude malignancy.

Table 5.2 HISORt diagnostic criteria for IgG4-SC

Histology	(i) Lymphoplasmacytic infiltrate
	(ii) >10 IgG4-positive cells per high-power field
	(iii) Obliterative phlebitis
	(iv) Storiform fibrosis
Imaging	Strictures of the biliary tree including
	(i) Intrahepatic ducts
	(ii) Extrahepatic ducts
	(iii) Intrapancreatic ducts
Serology	Serum IgG4 levels above the upper limit of normal
Other organ involvement	Including
	(i) Pancreas
	(ii) Retroperitoneal fibrosis
	(iii) Kidney
	(iv) Salivary or lacrimal gland
Response to steroid treatment	Defined as
	(i) Normalization of liver enzymes (ii) Stricture resolution)

Adapted from Ghazale et al. [26]

Treatment

The aims of treatment in IgG4-SC are to alleviate symptoms and prevent disease complications and irreversible fibrosis. Spontaneous resolution of IgG4-SC lesions without treatment has been described. However, oral steroids have been shown consistently to hasten the resolution of clinical jaundice, itch and abdominal discomfort, radiological strictures, serum IgG4, and microscopic inflammation ([26, 32, 48, 67, 81]; Fig. 5.4). Japanese guidelines recommend biliary drainage in patients with obstructive jaundice prior to the commencement of steroid therapy [40]. A recent international consensus of experts on the

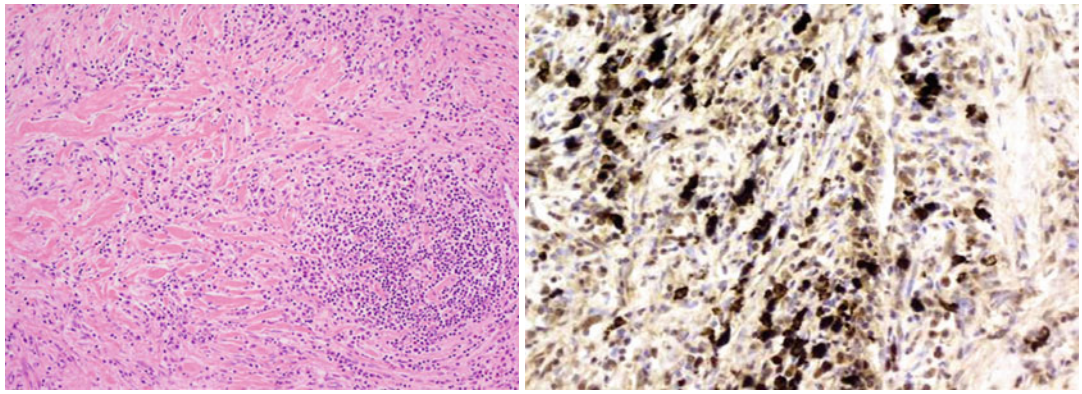

Fig. 5.3 Microscopic appearance of IgG4-SC showing a lymphoplasmacytic infiltrate (*left panel*) and IgG4-positive plasma cells >50/HPF (*right panel*)

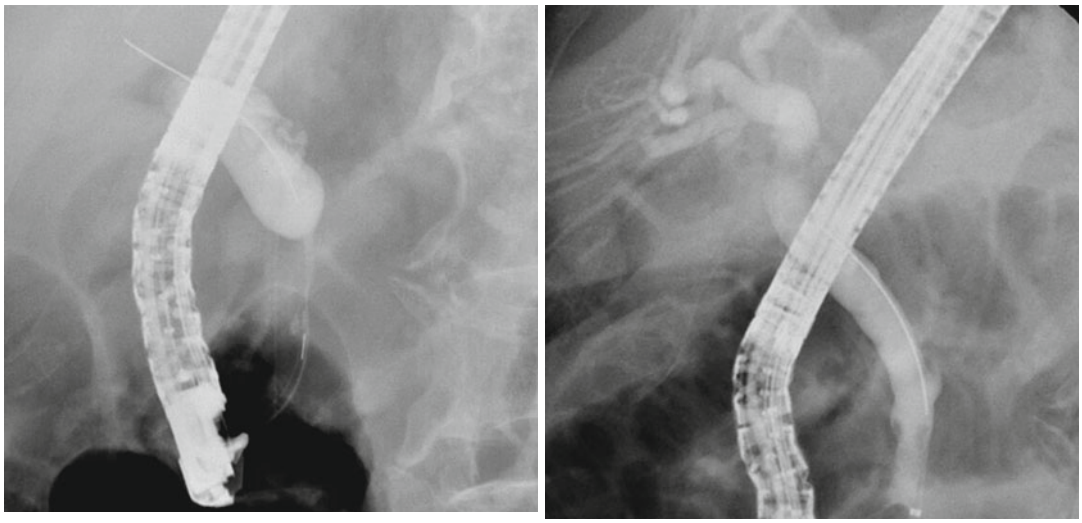

Fig. 5.4 ERCP showing a distal CBD stricture before (*left image*) and after treatment with biliary stenting and corticosteroid therapy (*right image*)

management of IgG4-RD concluded that urgent treatment is appropriate in biliary disease even when asymptomatic, to prevent infectious cholangitis and permanent fibrosis that may complicate untreated disease [47].

No randomized clinical trial has been conducted to determine the dose or duration of steroid treatment, and regimes are based on published clinical experience. Starting doses range from 30 to 40 mg of prednisolone or 0.6 mg/kg once a day for 2–4 weeks; after which the dose is tapered. Tapering regimes vary, but a dose reduction by 5 mg every 1–2 weeks depending on clinical response with a total treatment period of between 3 and 6 months is typical. In Japan guidelines recommend tapering to a maintenance dose between 5 and 10 mg per day to continue for up to 3 years.

Remission, defined as normalization of liver enzymes or stricture resolution, is achieved in 82–100 % of patients after steroid treatment. The diagnosis of IgG4-SC should be reconsidered in steroid nonresponders, but some long-standing strictures may be only partially responsive or unresponsive to treatment if fibrosis has developed, and in these patients, biliary stenting can be used to improve symptoms.

After withdrawal of steroid therapy, relapse rates between 50 and 57 % have been reported; the majority of which occur within 6 months of discontinuation of steroid treatment. In Japan it is commonplace to maintain low-dose steroid for up to 3 years after remission induction. This is based on evidence that relapse rates are significantly lower while on low-dose steroid compared to complete cessation of therapy [38, 39]. The presence of IgG4-SC as opposed to AIP in isolation is a risk factor for relapse [32, 77]. Proximal strictures are more likely to reoccur than distal strictures [26].

For the minority of patients who do not achieve remission on initial treatment induction and for those who relapse after withdrawal of therapy, further treatment is necessary. Steroids can be reintroduced or the dose increased, but long-term high-dose steroid therapy is associated with an adverse side-effect profile. For this reason, steroid-sparing agents including azathioprine, mycophenolate mofetil, 6-mercaptopurine, methotrexate, and tacrolimus have all been used to maintain remission in patients who relapse during steroid tapering or are at high risk of relapse [9, 26, 30, 32, 77]. There is no randomized evidence to support the use of these agents or the type or duration of treatment.

More recently the B-cell-depleting agent rituximab has been shown to be effective in inducing remission in patients with IgG4-RD relapse with promising results [86]. In an open-label trial where two doses of 1 g of intravenous rituximab were administered to IgG4-RD patients, 97 % achieved disease response by 6 months, and 77 % saw an improvement in disease activity, did not need to use oral steroid and did not exhibit any evidence of disease relapse by the end of 6 months. Remission, defined as no use of steroid and no evidence of disease activity, was achieved by 47 % at 6 months and 46 % at 12 months after rituximab therapy [11, 12].

Side effects associated with treatment are largely unexplored in IgG4-SC. In a cohort of 56 patients with IgG4-RD, over 50 % of patients receiving drug treatment reported adverse effects. Most were steroid related including weight gain, hyperglycemia, and cataracts, which are of particular relevance in the older male demographic at risk of IgG4-RD (unpublished data). Side effects in IgG4-RD patients treated with azathioprine and 6-merceptopurine have been reported and include nausea, vomiting, transaminitis, rash, and myelosuppression [30]. In the recent trial of rituximab therapy for IgG4-RD, two patients were hospitalized for bacterial infection [11, 12].

Prognosis

The long-term natural history of IgG4-SC is not yet well defined due to a paucity of cohorts with sufficient follow-up. It is clear that relapse in the bile duct or in another organ is likely to occur despite treatment. In a series of 53 patients with IgG4-SC, three treatment-naïve patients and one nonresponder developed cirrhosis and portal hypertension between 9 and 62 months after IgG4-SC diagnosis [26]. In a UK cohort of 115 patients with AIP and/or IgG4-SC, 5 % developed liver cirrhosis. There is also an increased incidence of all cancers, and all cause mortality compared to the general population [32].

Summary

IgG4-SC remains a diagnostic challenge with the key issue remaining differentiation from pancreatobiliary malignancy and other forms of sclerosing cholangitis. Current therapy follows an international expert consensus but is not supported by randomized controlled trials. More recently, the B-cell-depleting agent rituximab has given clues into disease pathogenesis as well as providing an option in those experiencing adverse effects with, or becoming refractory to, conventional therapy. The longer-term consequences of irreversible fibrosis, cirrhosis, and an increased risk of malignancy are now becoming apparent. Studies have implicated both dysregulation of the immune system and genetic susceptibility in IgG4-SC disease pathogenesis. Further work to establish risk factors and determinants of fibrotic disease and the mechanisms underlying this is essential.

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