Review Article

IgG4 Related Sclerosing Cholangitis

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Received 7 August 2014; Revised 13 October 2014; Accepted 15 October 2014; Published 10 November 2014

Academic Editor: Sharon DeMorrow

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IgG4 related disease (IgG4-RD) is a multisystemic disorder which has only recently been recognized. IgG4 related sclerosing cholangitis (IgG4-SC) is the biliary manifestation of the disease, often in association with autoimmune pancreatitis (AIP). In this review, we provide an overview of IgG4-RD, with a focus on the biliary manifestations. In particular, we describe the important differential diagnoses of IgG4-SC that need to be considered, namely, primary sclerosing cholangitis (PSC) and cholangiocarcinoma, and provide a management algorithm. Finally, we highlight future directions and unanswered questions which will provide new insights into this exciting and evolving disease entity.

1. Introduction

IgG4 related disease (IgG4-RD) is a new and emerging disease entity. It was first identified as a multisystemic disease in 2003, in patients with autoimmune pancreatitis (AIP) [1, 2]. Multiorgan involvement has been reported to occur in more than 60% of patients with IgG4-RD [3, 4], with a wide range of organs affected, including pancreas, kidneys, biliary tree, liver, salivary gland, orbit, breast, pericardium, aorta, skin, lungs, prostate, meninges, and pituitary [5–8]. Asymptomatic lymphadenopathy can also occur, affecting 80% of patients with AIP [9]. The epidemiology of IgG4-RD is difficult to determine as it depends on the primary organ at presentation. Extrapolating data from patients with type-1 AIP, IgG4-RD appears to be a disease predominantly affecting middle aged/older men (60 years) [10, 11]. This seems to be the case in patients that present with either single organ disease or multiorgan disease [10].

2. IgG4 Related Disease

Previously recognized conditions are unified by the diagnosis of IgG4-RD and include Ormond's disease (retroperitoneal fibrosis), Riedel's thyroiditis, Mikulicz's disease (salivary gland enlargement), and Kuttner's tumour (sclerosing sialadenitis). Patients often present with tumefactive (mass-forming) lesions and, therefore, are suspected to have

malignancy [12]. Clinical features at presentation depend upon the organ that is involved. Constitutional symptoms such as pyrexia and weight loss affect less than 10% of patients [12].

The pathogenesis of IgG4-RD is incompletely defined, but evidence would suggest a possible role for autoimmunity and allergy. Inflammation and subsequent fibrosis in IgG4-RD appear to be driven by T helper 2 (Th2) cells and regulatory T cells (Treg cells) compared to Th1 or Th17 subsets in other autoimmune diseases [13]. The proposed role of allergy appears to have originated from the considerable overlap of symptoms and positive histories for concurrent allergic disorders, that is, rhinitis, eosinophilia, and asthma in addition to the Th2 and Treg response [14]. However, no firm conclusions can be drawn at present. The role of IgG4 also remains unclear and whether the characteristic increased infiltrate is a primary or secondary phenomenon. Proposed hypotheses include that IgG4 is upregulated in response to microbial and nonmicrobial antigens or due to increased production of anti-inflammatory cytokines at the site of chronic inflammation [15–17]. The latter seems credible, as IgG4 levels fall spontaneously and in response to steroid therapy [18]. No risk factors for IgG4-RD are currently known.

2.1. Diagnosis. Over recent years a number of diagnostic criteria for IgG4-RD have been proposed, most recently

TABLE 1: HISORt criteria for IgG4 associated cholangitis [26].

Feature	Characteristics
Histology of bile duct	Lymphoplasmacytic sclerosing cholangitis on resection specimens (lymphoplasmacytic infiltrate with >10 IgG4-positive cells/high powered field within and around bile ducts with associated obliterative phlebitis and storiform fibrosis)
Imaging of bile duct	(i) One stricture or more strictures involving intrahepatic, proximal extrahepatic, or intrapancreatic bile ducts (ii) Fleeting/migrating biliary strictures
Serology	Increased levels of serum IgG4
Other organs involvement	pancreas, retroperitoneal fibrosis, renal lesion, and salivary/lacrimal gland
Response to steroid therapy	Normalization of liver enzymes or resolution of stricture (radiologically)

the international consensus diagnostic criteria (ICDC) [19]. The HISORt criteria from the Mayo Clinic were initially proposed for the diagnosis of AIP and include diagnostic histology, characteristic imaging, elevated serum IgG4 levels on serological testing, other organ involvement, and response to steroid therapy [20]. The 3 histological hallmarks of IgG4 related disease (IgG4-RD) are an IgG4 positive lymphoplasmacytic tissue infiltrate (>10–50 IgG4-positive cells per high powered field (with threshold dependent on organ involved)), storiform fibrosis (cartwheel or whorled appearance), and obliterative phlebitis [21]. Tissue eosinophilia may also be present. Serum IgG4 levels should be measured but are normal in up to 40% of patients [12]. Elevated serum IgG4 levels (>135 mg/dL) may aid in the diagnosis but are not considered to be diagnostic. IgG4-RD should be considered and actively excluded in patients with cryptogenic pancreatitis, sclerosing cholangitis, and bilateral/lacrimal gland enlargement. Another unifying characteristic is the improvement and response to immunosuppression in particular steroid therapy [21].

2.2. Treatment. Optimal treatment regimens remain ill-defined, and there are no randomized placebo controlled studies. At present, the mainstay of treatment is steroid therapy (e.g., prednisone 30–40 mg once/day for 4 weeks and then reduction by 5 mg every 14 days) which has been extrapolated from experience and data in patients with type-1 AIP. A response is usually seen within 4–6 weeks and is determined by improvement in organ function, reduction in size of the mass in the affected organ and/or other radiological improvements, decrease in serum IgG4 levels, and an improvement in symptoms. Patients that are symptomatic at the time of diagnosis often benefit from treatment. It is unclear whether maintenance therapy should be commenced in all patients, but it should certainly be used in patients with multiorgan involvement. Whilst Japanese groups often use single-agent low dose maintenance steroids, azathioprine (1–2 mg/kg/day) can be used as a steroid-sparing agent. Mycophenolate mofetil and more recently rituximab have been used in patients with steroid-refractory disease [22–24], with the latter showing particular promise in small case series.

2.3. Prognosis. The natural history of IgG4-RD remains unclear; some patients may improve spontaneously without treatment whilst others adopt a relapsing phenotype. Relapses occur in approximately 50% after discontinuation of treatment, particularly in patients with multiorgan involvement, suggesting a role for maintenance therapy. The risk of malignancy appears to be increased compared to age and sex matched controls [25].

3. IgG4 Related Sclerosing Cholangitis

The biliary manifestation of IgG4-RD is IgG4 related sclerosing cholangitis (IgG4-SC) [26], which is the commonest extrapancreatic manifestation of type-1 AIP, occurring in 20–88% of cases [9, 20, 22, 26–29]. IgG4-SC has a male preponderance and usually presents in 5th and 6th decades of life with obstructive jaundice, weight loss, and abdominal pain. Jaundice is the most common presenting symptom affecting 70–80% of patients [29]. IgG4-SC may be diagnosed asymptotically in a patient presenting clinically with AIP.

3.1. Diagnosis. We use the HISORt criteria to establish the diagnosis of IgG4-SC (Table 1) [26]. Most of patients will have undergone an abdominal ultrasound and this may identify extrahepatic biliary stenosis but more importantly can exclude other causes of biliary obstruction, that is, intraductal stones. Computed tomography (CT) is invaluable and is able to demonstrate biliary strictures with associated wall thickening and inflammation (enhancement). It can also identify other organs involvement and generalized lymphadenopathy [30, 31]. Cholangiography obtained at ERC (endoscopic retrograde cholangiography) or MRC (magnetic resonance cholangiography) plays an important role in the initial evaluation and diagnosis (Figure 1). Any part of the biliary tree can be involved but the distal (intrapaneatic) lower common bile duct is the most commonly affected site. IgG4-SC can be divided into 4 subtypes based upon the position of the stricture (Table 2) [32]. ERCP and MRCP may also demonstrate characteristic pancreatic ductal features of AIP, including long main duct strictures (>1/3rd the length of the duct), multiple strictures, and lack of upstream dilatation [33]. Endoscopic ultrasound and intraductal US can also

TABLE 2: Classification of IgG4 related sclerosing cholangitis (IgG4-SC), differential diagnosis, and investigations (modified from the study by Nakazawa et al. [32]).

	Cholangiogram	Differential diagnosis	Investigations
Type 1		PCa CCa CP	EUS-FNA Endobiliary brushings Endobiliary biopsies Percutaneous biopsy
Type 2		PSC	Liver biopsy Colonoscopy (i.e. look for concurrent IBD)
Type 3		CCa GB cancer	EUS Endobiliary biopsy Percutaneous biopsy
Type 4

FIGURE 1: IgG4 related sclerosing cholangitis. (a) Cholangiogram taken at ERCP demonstrating stricture of the lower CBD (large arrow) and evidence of intrahepatic structuring and dilatation (small arrow). (b) Evidence of intrahepatic cholangiopathy. CCa: cholangiocarcinoma; CP: chronic pancreatitis; EUS: endoscopic ultrasound; FNA: fine needle aspiration; GB: gall bladder; PCa: pancreatic carcinoma; PSC: primary sclerosing cholangitis; IBD: inflammatory bowel disease.

demonstrate diffuse bile duct wall thickening in stenotic segments [34].

3.2. Endoscopic Retrograde Cholangiography (ERC). ERCP is integral in the investigation and management of patients with suspected IgG4-SC. ERCP allows the acquisition of histological samples as well as playing a therapeutic role. Brush cytology obtained at the time of ERCP, although important in excluding malignancy, does not allow a diagnosis of IgG4-SC to be made [35]. Histology can be obtained via endobiliary biopsies or ampullary biopsies [36]. Direct cholangioscopy allows the operator to gain direct visualization of the biliary mucosa and also to obtain specific targeted biopsies

[37]. Intrabiliary biopsies may show characteristic features of IgG4-RD [37, 38]. We recommend biliary stenting of dominant strictures at ERCP, even if a response to steroids is expected.

3.3. Differential Diagnosis. PSC needs to be considered in the differential diagnosis of IgG4-SC. Cholangiographic features might help distinguish between PSC and IgG4-SC; the cholangiogram in PSC classically demonstrates beading, pruned tree appearance, and short, band-like strictures. In IgG4-SC long strictures and involvement of the lower CBD as well as hilar/intrahepatic cholangiopathy may be seen (Table 2). Despite apparent differences between IgG4-SC and

PSC, data would suggest that cholangiography obtained at ERCP alone is associated with a high specificity (88%) but low sensitivity (45%) in the diagnosis of IgG4-SC [39]. Therefore, using ERCP alone, some patients with IgG4-SC who may benefit from steroids may be misdiagnosed with PSC or CCa. Cholangiogram may lend support to a diagnosis of IgG4-SC but, alone, does not allow a definitive diagnosis to be made. Other organs involvement (OOI), such as pancreatic abnormalities (e.g., enlargement and pancreatic duct irregularity), may provide powerful evidence for IgG4-SC, compared to PSC.

Raised serum IgG4 levels have been described in 9% of patients with PSC compared with 1% for other liver diseases and are unhelpful alone in differentiating between IgG4-SC and PSC [18]. Finally, CCa occurs in up to 30% of patients with PSC but to date has been described rarely in IgG4-SC. A hilar mass may be seen in IgG4-SC (inflammatory pseudotumour), but not in PSC, except when associated with CCa. There may be a role for cholangioscopy in differentiating between PSC and IgG4-SC [38].

Secondary sclerosing cholangitis (SSC) encompasses a broad spectrum of disorders including infection (e.g., AIDS cholangiopathy), vascular (e.g., hepatic artery thrombosis), toxic (e.g., postchemotherapy), congenital (e.g., Caroli's disease), infiltrative (e.g., histiocytosis X), trauma (e.g., postbiliary trauma), and immunological (e.g., eosinophilic cholangitis) etiologies. Relevant features within the patient's history may help identify the likely underlying etiology. Patients with SSC are at risk of recurrent cholangitis which can progress to secondary biliary cirrhosis and the need for liver transplantation. CCa and PCa are other important differentials to consider and actively exclude.

3.4. Treatment

3.4.1. Steroids. The mainstay of treatment in IgG4-SC is the use of steroids, despite the absence of randomized placebo-controlled trials. Although spontaneous remission can occur in AIP, steroids have been shown to induce remission quicker and consistently [40]. Significant spontaneous cholangiographic improvement of types 2–4 IgG4-SC appears to be unusual. At present, there is no agreed consensus regarding steroid regimens. We recommend a starting dose of prednisone 30–40 mg OD for 4 weeks before reducing by 5 mg every subsequent 14 days. Patients are reviewed regularly given the increased risk of cholangitis/sepsis with use of steroids and biliary obstruction. Studies have demonstrated an improvement in bile-duct stricturing and normalization of liver enzymes following the introduction of steroid therapy [26, 29]. In addition, a response to steroid therapy can help support the diagnosis of IgG4-SC and is part of the HISORt diagnostic criteria. Intriguingly, however, a response to steroids may be seen in some patients with IgG4 +ve PSC [41]. Personal experience would suggest that factors predictive of a favorable response to steroids include recent onset disease with acute jaundice and a change in imaging over a short period of time. It remains unclear whether raised serum IgG4 levels pretreatment predicts a favorable response to steroids.

A clinical and cholangiographic improvement should be seen within 4–6 weeks of starting treatment. We recommend repeat imaging (MRCP, ERCP, or CT) in 6 weeks with repeat blood tests. Nonresponse to steroid therapy may be representative of a less inflammatory, fibrotic, “burnt-out” phase of IgG4-SC disease or an alternative diagnosis.

3.4.2. Relapse. Patients with IgG4-SC are at high risk of relapse, either after stopping steroid treatment or during the initial taper [35]. In our study at UCLH of patients with IgG4-SC and AIP, 57% (13 of 23) of patients relapsed [35]. In a further study of 53 patients with IgG4-SC, a similar relapse rate was reported in patients that underwent surgery ($n = 18$) or treatment with steroids ($n = 30$) (44% versus 54%, $P = 0.1$). Factors predictive of relapse included the presence of proximal strictures (extrahepatic or intrahepatic) and increased IgG4 levels [26]. Relapses that occur after steroid withdrawal/reduction may be treated with further steroids followed by additional immunomodulatory drugs, for example, azathioprine (target dose 1–2 mg/kg/day). Mycophenolate mofetil (750–1000 mg twice daily) has also been used as a steroid-sparing agent. In our experience long-term therapy (low dose steroid $\pm$ azathioprine) is also beneficial in patients with evidence of multiorgan disease. Predictors of resistance to immunomodulator therapy include evidence of other organs involvement other than IgG4-SC, retroperitoneal fibrosis, and evidence of other organs involvement ever ($P < 0.03$) [42].

Certain patients may be intolerant of immunomodulatory drugs and become dependent on high-dose steroids in order to maintain remission. In these patients, the use of rituximab, a monoclonal antibody depletion therapy directed against the CD20 antigen on B cells, has been described and may have a role to play. A large study of 116 AIP patients managed at the Mayo Clinic reported 76 relapse episodes in 52 patients over a median followup of 47 months [42]. 12 patients in total were treated with rituximab. Indications for treatment with rituximab were resistance to immunomodulatory drugs with or without steroids ($n = 8$) and steroid intolerance ($n = 4$). Rituximab was given as 375 mg/m² intravenous body surface area for 4 weeks (induction phase) followed by repeat infusions every 2–3 months for 24 months (maintenance phase). The rituximab group was predominantly composed of males (92%), with mean age of 66 years, and had serum IgG4 positivity (67%). Following induction therapy, 10 patients achieved complete remission, 1 patient required treatment to be stopped due to the development of malignancy, and 1 had incomplete remission. Overall, treatment with rituximab was well tolerated with minimal serious side effects. Eight patients of the 10 with radiographic followup had complete radiographic remission at a median of 4.5 months (range 2.3–9.9 months). All patients that achieved complete remission required additional maintenance therapy with rituximab [42]. Rituximab may, therefore, be a suitable alternative in patients that have failed previous steroid therapy or immunomodulatory therapy for relapsing IgG4-SC. To date, we have treated 2 patients with rituximab.

4. IgG4 Related Disease at UCLH

Our first case of IgG4 related disease was in 2004, in a male patient with AIP. Since then we have developed a tertiary referral service for IgG4-RD. We now have a large cohort (110 patients) of prospectively recruited patients with IgG4-RD and work with other centers in the UK. Given our expertise in pancreaticobiliary disease and ERCP, the majority of our patients have biliary, pancreatic, or hepatic involvement. However, we have experience of managing patients with IgG4 related renal, cerebral, bone, pulmonary, and peritoneal disease.

The management of IgG4-RD requires a multidisciplinary team approach. We have close working relationships with our surgeons, radiologists, histopathologists, and rheumatologists, all of whom have an interest in IgG4-RD. Our patients are discussed in a weekly multidisciplinary meeting. This approach ensures that patients presenting with biliary strictures or pancreatic masses are assessed appropriately by experienced teams and avoid potentially unnecessary surgical procedures as highlighted by our study in 2012 [43].

In 2007 we described our initial experience and management of AIP in 11 patients [44]. Our data demonstrated a response to steroid therapy in all patients, improvement in ALT and mass lesions. However, we also demonstrated a high rate of relapse (6 patients, 55%) over a median of 18 months. We reported our increasing experience in 2009 in 28 patients, 23 (82%) of whom had IgG4-SC [35]. Our data demonstrated the presence of extra pancreatic disease, in particular IgG4-SC predicted the likelihood of disease relapse after an initial steroid course. Remission was, however, achievable in relapsing patients with azathioprine-based therapy [35].

Our most recent study included 115 patients (74% males) followed prospectively from diagnosis for a median of 33 months (range 1–107) [45]. IgG4-SC again was an important predictor of relapse ($P < 0.01$). Our data demonstrated the common occurrence of end organ failure including pancreatic exocrine insufficiency (53% of patients), diabetes (37% of patients), and renal dysfunction (stages 2–4 CKD) (12% of patients). Perhaps the key findings, however, were the increased risk of developing any cancer (odds ratio 2.25, $P = 0.02$) and an increased risk of death (odds ratio 2.07, $P = 0.02$) when compared to matched national statistics.

5. Future Directions

IgG4-RD as a disease entity remains in its infancy in terms of etiopathogenic and clinical understanding. Certain questions remain unanswered which should influence future research directions. The underlying pathogenetic mechanisms of IgG4-RD remain to be elucidated. Studies are currently ongoing which are attempting to identify pathways involved in the pathoimmunogenesis of IgG4-RD. Currently, we only have short-term outcome data with regard to treatment response.

Steroids therapy remains the mainstay of treatment but, as alluded to above, no consensus treatment regimens exist

within the international community. An agreed steroid treatment regimen would remove the heterogeneity of patient care and improve the interpretation of response rates as well as identify robust predictors of response. The next step is then to identify optimal immunomodulatory drugs and doses. Multicentre collaboration is required also to identify predictors of relapse and the timing of immunomodulatory drugs.

At present, no randomized placebo-controlled study has been performed to identify optimal treatment regimens, the role of immunomodulatory drugs, or the role of maintenance steroid therapy. A multicenter study may shorten the time required to suitably power these studies. Currently, 2 studies are registered with ClinicalTrials.gov but are both single-centre open-label studies [46, 47].

Current data would suggest that rituximab is appropriate for patients with steroid resistant diseases or intolerance to immunomodulatory therapy. A phase 1-2 dual-center study performed at the Mayo Clinic (Rochester, USA) and the Massachusetts General Hospital (Boston, USA) is still ongoing [46]. Eligible patients include those who are steroid naïve, those who are steroid dependent, or those who are refractory to steroid therapy. Patients will receive two doses of rituximab 1000 mg intravenously separated by 15 days. The primary efficacy outcome—disease remission and successful completion of steroid taper—will be assessed at 6 months. This study may provide important insights into the optimal doses of rituximab and the role of maintenance therapy.

6. Conclusion

IgG4-RD is a multisystemic disease. IgG4-SC is a common manifestation of IgG4-RD and diagnostic criteria are available. The liver related manifestations of IgG4-RD are heterogeneous and at present less well described. Steroids remain the basis of current treatment regimens. Ongoing research and future studies will help improve our understanding of the pathogenesis and natural history of this exciting and emerging disease.

Abbreviations

AIP:	Autoimmune pancreatitis
CP:	Chronic pancreatitis
CCa:	Cholangiocarcinoma
Ig:	Immunoglobulin
IgG4-SC:	IgG4 related sclerosing cholangitis
IgG4-RD:	IgG4 related disease
LT:	Liver transplantation
PCa:	Pancreatic cancer
PSC:	Primary sclerosing cholangitis
SSC:	Secondary sclerosing cholangitis
UCLH:	University College London Hospital.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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