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## Review

# IgG4-related disease: a systemic condition with characteristic microscopic features

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**Summary.** During the first decade of the 21st century, IgG4-related disease (IgG4-RD), a fibroinflammatory condition occurring at multiple sites of the body, has been newly recognized. As indicated by its name, elevation of IgG4 in the serum and tissue is a common denominator of IgG4-RD. Since the observation that many patients suffering from autoimmune pancreatitis (AIP), a specific type of chronic pancreatitis, had elevated serum levels of IgG4, it was reported that these patients also had increased numbers of IgG4-positive cells in the inflamed pancreatic tissue. In 2003, it was noted that a significant proportion of the AIP patients had a variety of extrapancreatic fibroinflammatory lesions, and that AIP therefore was the pancreatic manifestation of a systemic disease. Among these extrapancreatic manifestations, the extrahepatic bile ducts, salivary glands, thyroid, lymph nodes and retroperitoneum were most frequently reported, and infiltration of the tissue with IgG4-positive cells was also noted at these sites. During the following years, a multitude of other conditions have been added to the spectrum of IgG4-RD. While some of these organ manifestations were once believed to represent diseases on their own, others have been included under the umbrella of "multifocal fibrosclerosis". Biopsies or resection specimens from affected organs in IgG4-RD reveal several common microscopic features irrespective of the site of the lesion. Cellular and storiform fibrosis, lymphoplasmacytic infiltration, increased numbers of IgG4-positive cells and obliterative phlebitis are among the most characteristic histological changes in IgG4-RD. The detailed etiology, pathophysiology, epidemiology and clinical long-term outcome have at present yet to be fully elucidated. This paper focuses on the microscopic features, diagnosis and differential diagnosis of the different organ manifestations of IgG4-RD, and the current concepts of its pathogenesis will also be addressed.

**Key words:** IgG4-related disease, Obliterative phlebitis, Autoimmune pancreatitis, Chronic sclerosing sialadenitis, Storiform fibrosis

### Introduction

Historically, the concept of IgG4-related disease (IgG4-RD) was preceded by the discovery of autoimmune pancreatitis (AIP) as a new and distinct type of chronic pancreatitis. In 1995, Yoshida and coworkers (Yoshida et al., 1995) coined this term, but the main features of AIP have likely been described already by Ball et al. in 1950 and by Sarles et al. in 1961 (Ball et al., 1950; Sarles et al., 1961). In 1991, the histopathology of two cases of "lymphoplasmacytic sclerosing pancreatitis with cholangitis" were reported, which later were found to also represent AIP (Kawaguchi et al., 1991). Histologic criteria for distinguishing AIP from the most common type of chronic pancreatitis in western countries, alcoholic chronic pancreatitis, were established in 1997 (Ectors et al., 1997; Klöppel et al., 2004). During the last decade, Asian and Western research groups established criteria for the diagnosis of AIP (Japan Pancreas Society, 2002; Chari et al., 2006, 2009; Kim et al., 2006; Otsuki et al., 2008; Okazaki et al., 2009).

In 2003, Kamisawa et al. reported 21 AIP patients whom they had followed and treated. Seven of these patients had other autoimmune diseases: two had sclerosing cholangitis, two retroperitoneal fibrosis, two rheumatoid arthritis and one had Sjögren's syndrome, and he concluded that AIP was a systemic autoimmune

**Abbreviations:** AAA, abdominal aortic aneurysm; AIP, autoimmune pancreatitis; CT, computed tomography; H&E, hematoxylin and eosin; HPF, high power field; IBD, inflammatory bowel disease; IgG4-RD, IgG4-related disease; IMT, inflammatory myofibroblastic tumor; IPT, inflammatory pseudotumor; PSC, primary sclerosing cholangitis; RF, retroperitoneal fibrosis; SANT, sclerosing angiomatoid nodular transformation; SC, sclerosing cholangitis; TIN, tubulointerstitial lymphoplasmacytic nephritis.

disease and termed it IgG4-related systemic disease (Kamisawa et al., 2003a,b). However, for several years it had been noted at microscopy, that AIP is a heterogeneous disease, and at the consensus conference on AIP in Honolulu in november 2009, it was agreed that the type of AIP formerly called lymphoplasmacytic sclerosing pancreatitis should be labeled type 1 AIP, while the type formerly designated as idiopathic duct-centric chronic pancreatitis would be called type 2 AIP (Notohara et al., 2003; Zamboni et al., 2004; Deshpande et al., 2006; Chari et al., 2010). Type 1 AIP is one of the main manifestations of IgG4-RD, while type 2 AIP is associated with inflammatory bowel disease and does not belong to the IgG4-RD entity (Chari et al., 2010; Klöppel et al., 2010; Sah et al., 2010; Deshpande et al., 2011; Detlefsen et al., 2011, 2012; Maire et al., 2011). Names formerly used for IgG4-RD are "IgG4-related autoimmune disease", "IgG4-associated multifocal systemic fibrosis", "IgG4-related sclerosing disease", "Hyper-IgG4 disease", "systemic IgG4 plasmacytic syndrome" (SIPS), "IgG4-related multi-organ lymphoproliferative syndrome" (IgG4-MOLPS) and "IgG4-associated disease" (Kamisawa et al., 2003b,

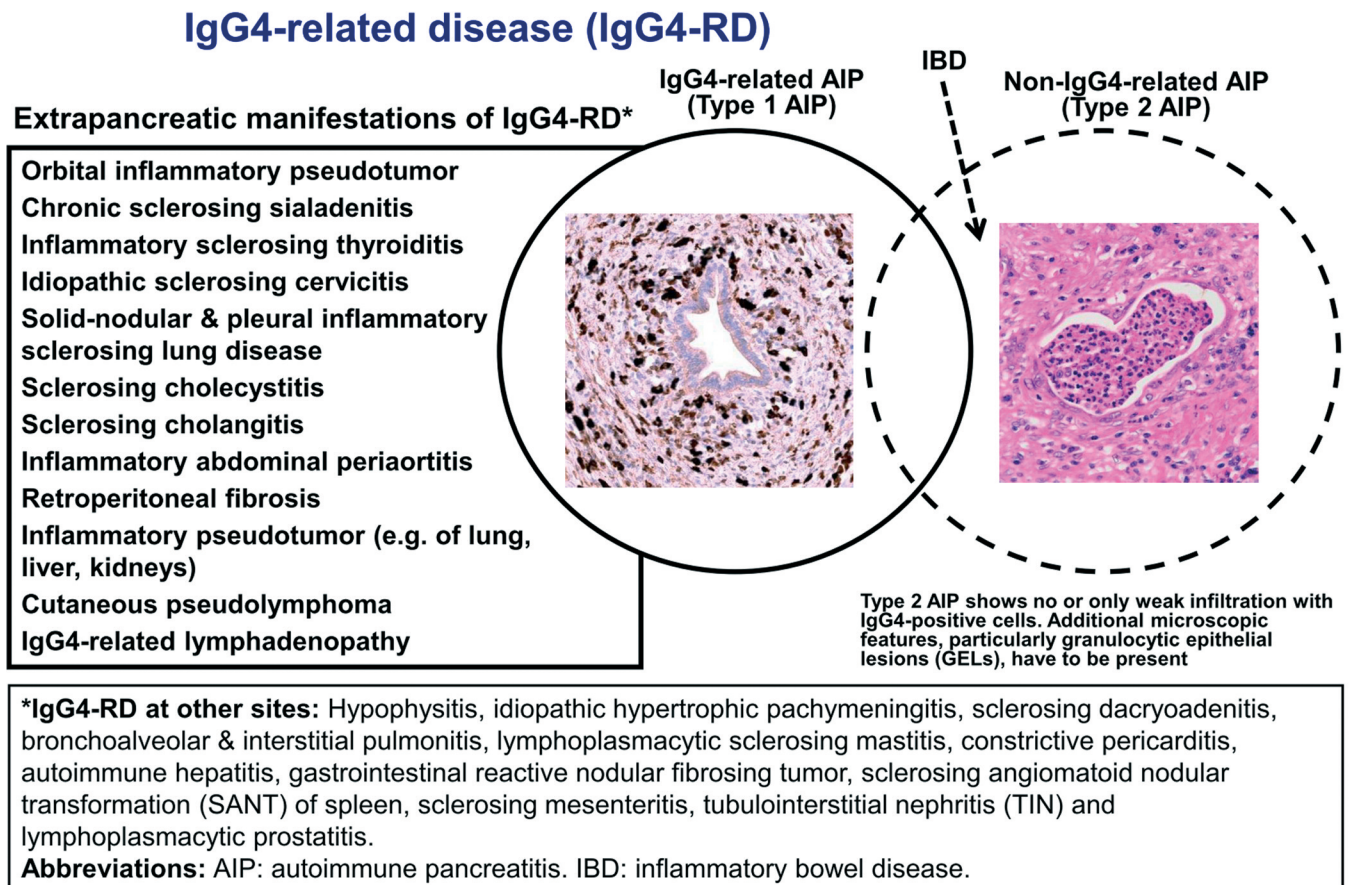
2004, 2006b; van der Vliet and Perenboom, 2004; Neild et al., 2006; Zen et al., 2007b; Masaki et al., 2009; Geyer et al., 2010; Yamamoto et al., 2010). However, there is international consensus on using the unifying term IgG4-RD (Stone et al., 2012a; Umehara et al., 2012a). However, as our knowledge of this disease and particularly its pathogenesis increases, the name will likely change to a more specific name at some point in the future (Khosroshahi et al., 2011b).

This review gives an overview of the microscopic features of IgG4-RD. The pathogenesis, diagnosis and differential diagnosis of this evolving rheumatologic disease are also discussed.

### IgG4-related disease: general features and diagnosis

#### *IgG4-RD: a systemic condition*

The number of conditions which are part of IgG4-RD has increased immensely, and the main manifestations are given in Figure 1 and Table 1. Since many of the organ manifestations of IgG4-RD are also affected in multifocal fibrosclerosis, it has been



**Fig. 1.** Schematic illustration of the relationship between the IgG4-related type of autoimmune pancreatitis (AIP), other manifestations of IgG4-related disease (IgG4-RD), and non-IgG4-related AIP.

suggested that there may be an overlap of this disease, particularly of Riedel's thyroiditis, and IgG4-RD (Comings et al., 1967; Dahlgren et al., 2010; Khosroshahi and Stone, 2011). However, as is known particularly from the pancreas and bile ducts, lymphoplasmacytic lesions similar to IgG4-RD but negative for IgG4 and with slightly different histology are common. Therefore, this issue should be addressed in future studies.

#### *Histological features of IgG4-RD*

The main histological features of IgG4-RD have initially been described in type 1 AIP patients:

A) A prominent infiltration of lymphocytes and plasma cells in the tissue (Yoshida et al., 1995; Ectors et al., 1997; Notohara et al., 2003; Zamboni et al., 2004).

B) A characteristic type of lymphoplasmacytic, cellular fibrosis, named "storiform" or "swirling" fibrosis (Fig. 2A) (Kamisawa et al., 2003c; Notohara et al., 2003; Zamboni et al., 2004). The term "storiform" means that the fibrotic fascicles of fibroblasts and myofibroblasts are arranged in a cartwheel-like pattern.

C) Evidence of obliterative phlebitis, meaning inflammation of the veins in the tissue (phlebitis) (Fig. 2B) (Kamisawa et al., 2003c; Notohara et al., 2003; Zamboni et al., 2004). It seems that the phlebitis begins at the periphery of the venous wall and later spreads through the wall, involving also the central part. The most characteristic lesions are those showing further increase of inflammation and fibrosis in the venous wall, resulting in stenosis or obstruction of the lumen.

D) Abundant infiltration of IgG4-positive plasma cells (Fig. 2C) in the respective organ (Kamisawa et al., 2003b; Deshpande et al., 2005). To avoid overdiagnosis of IgG4-RD, due to the fact that the mere infiltration with IgG4-positive cells can occur in many other diseases than IgG4-RD, it is important to employ both a cut-off for the number of infiltrating IgG4-positive cells and a ratio of IgG4- over IgG-positive cells (Fig. 2C-D). These ratios vary, dependent on the affected organ (see below) (Deshpande et al., 2012). However, a cut-off of 10 IgG4-positive cells/high power field (HPF) and a ratio of more than 40% has been recommended as a rough rule, even though it is appreciated that this could lead to overdiagnosis of IgG4-RD (Okazaki et al., 2011; Deshpande et al., 2012; Umehara et al., 2012b). Hence, for most of the manifestations of IgG4-RD, specific cut-off values for IgG4-positive cell infiltration and IgG4/IgG-ratios have been developed (Deshpande et al., 2012).

If all the four listed criteria are met, a diagnosis of IgG4-RD is highly suggested. If not all these criteria are met, a diagnosis of IgG4-RD is still probable, but additional non-microscopic criteria, particularly elevated serum levels of IgG4 and proof of other organ involvement of IgG4-RD, are necessary for the diagnosis (Deshpande et al., 2012).

#### *Diagnosis and treatment of IgG4-RD*

In the first study to show elevation of serum IgG4 in AIP, the sensitivity of IgG4 was 90.9% compared to 70.5% for IgG (Hamano et al., 2001). The specificity of IgG4 in differentiating between AIP and pancreatic cancer was 98% (Hamano et al., 2001). Reported other autoantibodies in another landmark study of type 1 AIP were antinuclear antibody in 76%, anti-lactoferrin in 76%, anti-carbonic-anhydrase II in 59%, rheumatoid factor in 29% and anti-smooth muscle antibody in 18% (Okazaki et al., 2000). The sensitivity of serum gammaglobulins was estimated 59.1% (Kawa and Hamano, 2003). A few years later, elevation of serum IgG4 was also reported in patients with Mukulicz disease (MD) and later also in patients with other manifestations of IgG4-RD (Yamamoto et al., 2004; Masaki et al., 2009). Some of the other markers mentioned above were later also found to be increased in some patients with extrapancreatic manifestations of IgG4-RD (Nishi et al., 2007, 2010; Masaki et al., 2009). Also, hypergammaglobulinaemia, an increase of IgE, hypocomplementaemia and the detection of immune

**Table 1.** The different organ manifestations of IgG4-related disease (IgG4-RD), listed successively as discussed in the text.

Manifestations of IgG4-RD
Type 1 autoimmune pancreatitis (IgG4-related pancreatitis)
IgG4-related sclerosing cholangitis (SC)
IgG4-related sialadenitis (including Küttner's tumor)
IgG4-related thyroiditis (including fibrosing Hashimoto's thyroiditis and Riedel's thyroiditis)
IgG4-related retroperitoneal fibrosis (RF)
IgG4-related periaortitis
Multifocal fibrosclerosis
IgG4-related cervical sclerosis (syn. idiopathic sclerosing cervicitis, cervical fibrosclerosis)
IgG4-related inflammatory pseudotumor (IPT)
IgG4-related mastitis
IgG4-related prostatitis
IgG4-related lung and pleural disease
IgG4-related lymphadenopathy
IgG4-related kidney disease
IgG4-related hepatopathy
IgG4-related hypophysitis
IgG4-related pachymeningitis
IgG4-related orbital inflammatory pseudotumor
IgG4-related dacryoadenitis
IgG4-related pericarditis
Gastrointestinal reactive nodular fibrosing tumor
Sclerosing angiomatoid nodular transformation (SANT)
IgG4-related mesenteritis (sclerosing mesenteritis)
IgG4-related skin disease (cutaneous pseudolymphoma)

Nomenclature adapted from: Stone et al. (2012a). Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. *Arthritis Rheum.* 64, 3061-3067.

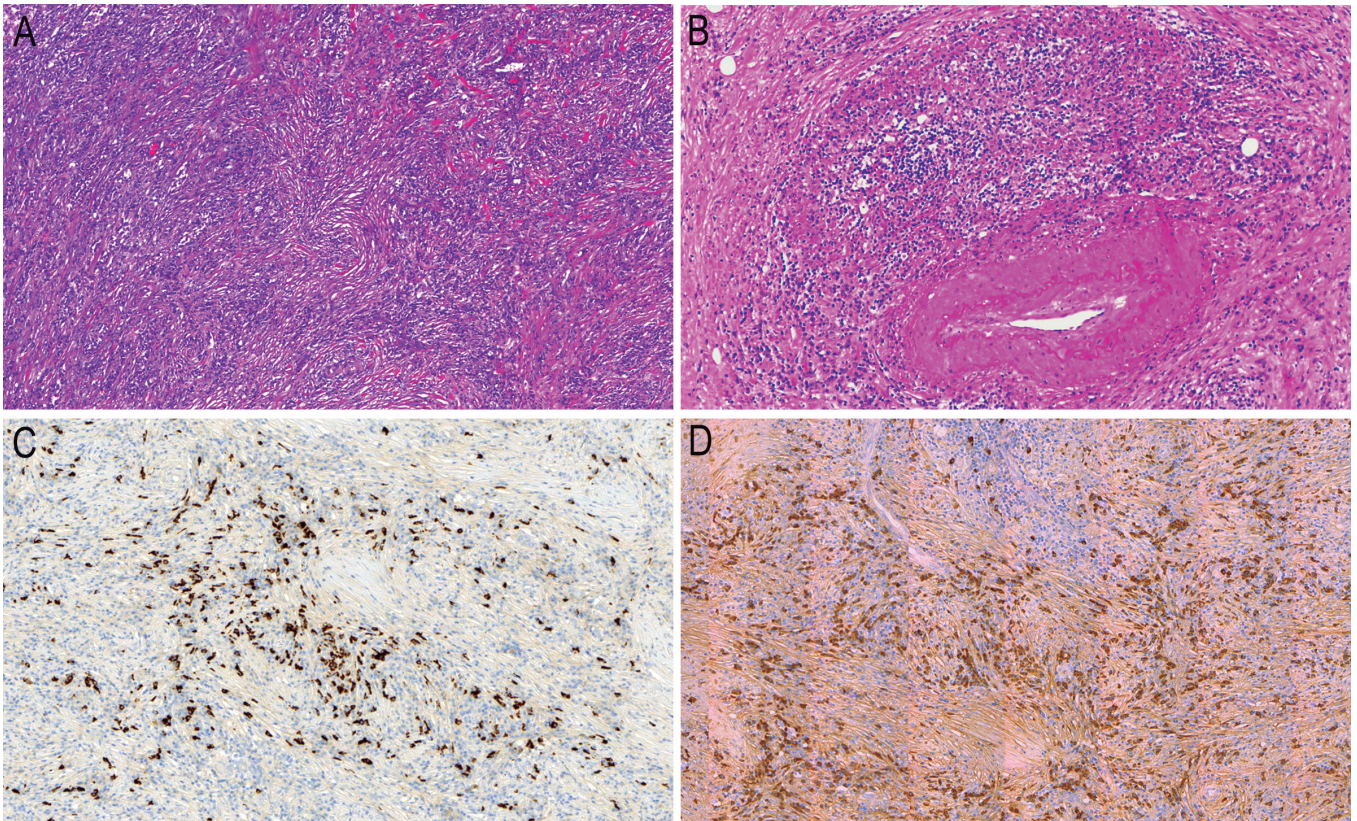
complexes can be employed in establishing the diagnosis (Umehara et al., 2012a). Hence, the diagnosis can in many instances be made based on serum IgG4 (cut-off 135 mg/dL) together with either typical histopathological findings or evidence of diffuse or focal enlargement, or a massforming lesion in the respective organ (Masaki et al., 2009; Zen and Nakanuma, 2010; Umehara et al., 2012a). However, as serum IgG4 is not elevated in all patients, serologically negative patients can also be diagnosed with IgG4-RD, if there is strong microscopic evidence (Okazaki et al., 2011; Umehara et al., 2012a). Also, histology alone can provide the diagnosis, but only if features (A), (B), (C) and (D) mentioned above are noted (Okazaki et al., 2011; Umehara et al., 2012a).

Most patients respond well to steroid treatment (Stone et al., 2012b). However, if steroid treatment is tapered too early or relapse occurs, another course of steroids or low-dose steroid treatment for maintenance therapy should be given (Masaki et al., 2009). In difficult cases azathioprine, methotrexate or rituximab have also been used in IgG4-RD (Khosroshahi et al., 2010; Stone et al., 2012b). In some patients, it is urgent to initiate steroid treatment, as irreversible organ damage

can otherwise occur.

#### Malignancy in IgG4-RD

In all cases of IgG4-RD, it is of the utmost importance to exclude a malignant neoplasm, even if there is evidence of serum IgG4 elevation, because serum IgG4 can also be increased in a minor number of patients suffering from malignant disease in a variety of organs (Ghazale et al., 2007; Raina et al., 2008; Yamamoto et al., 2012). Also, tissue infiltration with IgG4-RD itself is not specific, as Strehl et al. pointed out (Strehl et al., 2011). They demonstrated significant numbers of IgG4-positive cells and also elevated IgG4 to IgG ratios in inflammatory lesions of the oral cavity (Strehl et al., 2011). Furthermore, at other sites, particularly in inflammatory bowel disease of the lower gastrointestinal tract, synovitis and carcinomas, sometimes high numbers of IgG4 positive cells were observed, but a IgG4/IgG ratio above 0.4 was not noted in these non-IgG4-RD conditions (Strehl et al., 2011). However, the occurrence of storiform fibrosis or obliterative phlebitis was not reported in this study. Furthermore, in every case, a manifestation of



**Fig. 2.** Characteristic histological findings in IgG4-related disease (IgG4-RD). **A.** A cartwheel-like, cellular and storiform fibrosis is shown (H&E). **B.** Obliterative phlebitis. Note that the arterial vessel located below the venous branch is without significant inflammation (H&E). **C.** Dense infiltration with IgG4-positive cells (IgG4 immunostaining). **D.** IgG-positive cells slightly outnumber the IgG4-positive cells shown in Fig. 2C (IgG immunostaining).

sarcoidosis, granulomatosis with polyangiitis (formerly called Wegener's granulomatosis), lymphoma or inflammatory myofibroblastic tumor should be excluded before establishing the diagnosis (Okazaki et al., 2011; Smyrk, 2011; Umehara et al., 2012a). Of note, serum IgG4 levels were slightly higher in granulomatosis with polyangiitis patients compared to normal controls, and MPO-ANCA IgG4-subclass antibodies may play a role in the development of this disease (Holland et al., 2004; Liu et al., 2008; Vaglio et al., 2012). Besides, for most of the sites which can be affected in IgG4-RD, there are organ-specific differential diagnoses which should be ruled out before establishing the diagnosis.

Malignancies prior to or after diagnosis of IgG4-RD were noted in 10.4% in a 3-year-follow-up study of 104 IgG4-RD patients, and in 11.5% in a 5-year-follow-up study of 63 surgically treated type 1 AIP patients (Detlefsen et al., 2012; Yamamoto et al., 2012). Hence, these data indicate that IgG4-RD patients may be at increased risk for developing malignancies, and, until more precise data on IgG4-RD are available, the thorough search for malignancies during follow-up of these patients is recommended (Yamamoto et al., 2012).

### Organ manifestations of IgG4-related disease

In the following sections, some of the most important manifestations of IgG4-RD will be addressed, with special emphasis on their microscopic features.

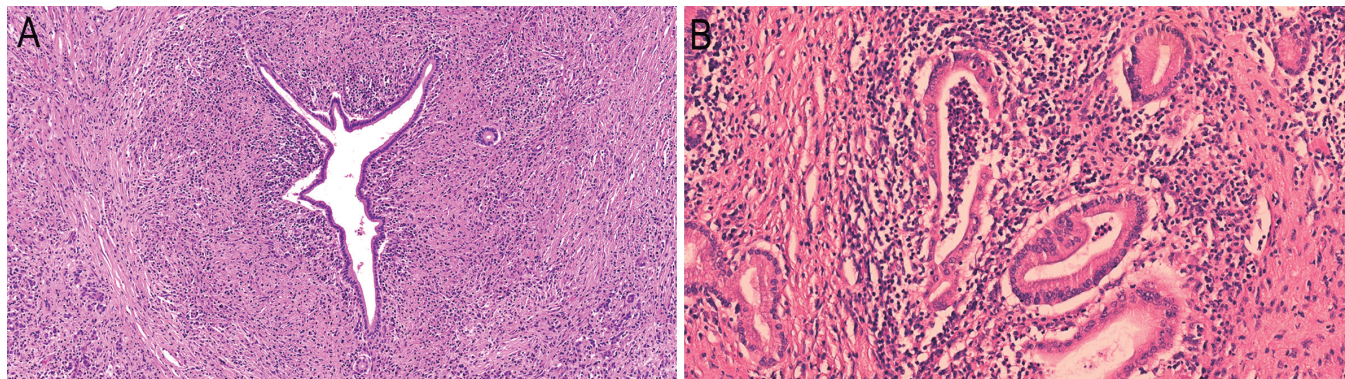
#### *Type 1 autoimmune pancreatitis (IgG4-related pancreatitis)*

Clinically, AIP patients complain of abdominal pain, anorexia and jaundice (Kamisawa et al., 2003c; Kleeff et al., 2006; Church et al., 2007). Macroscopically, AIP sometimes mimics pancreatic cancer because it in some instances forms a tumor-like mass in the pancreatic head, body or tail (Zamboni et al., 2000; Klöppel et al., 2007; Esposito et al., 2008; Detlefsen and Drewes, 2009;

Zamboni et al., 2009). A follow-up study on surgically treated AIP patients reported the inflammatory lesion in the pancreatic head in 76%, pancreatic body in 6%, the tail in 14% and diffusely in the whole gland in 3% of type 1 AIP (Detlefsen et al., 2012). However, the focal type of AIP will naturally occur more frequently in studies based on pancreatic resection specimens, because most of these specimens are resected due to suspected pancreatic cancer. In studies based on a mix of conservatively and surgically treated type 1 AIP patients, roughly 40% show diffuse swelling of the pancreas (Kamisawa et al., 2011). The typical computed tomography (CT) presentation of AIP is a diffuse, sausage-like enlargement of the pancreas with delayed enhancement (Chari et al., 2009). Pseudocysts and calculi are less frequently noted compared to alcoholic chronic pancreatitis (Ectors et al., 1997; Notohara et al., 2003; Zamboni et al., 2004).

Periductal infiltration with lymphocytes and plasma cells is observed in both types of AIP (Fig. 3A). Microscopic features of type 1 AIP can aid as a basis for the diagnosis also in pancreatic core needle biopsy specimens (Zamboni et al., 2004; Chari et al., 2006; Detlefsen et al., 2009). The feature that usually is not observed in IgG4-related pancreatitis but abundantly in the non-IgG4-related type 2 AIP is the granulocytic epithelial lesion (GEL) (Fig. 3B) (Zamboni et al., 2004). This lesion is characterized by penetration of neutrophilic granulocytes through the duct epithelium and their accumulation in the duct lumen (Zamboni et al., 2004).

The differential diagnosis of AIP versus pancreatic cancer is important, because type 1 AIP as the prototype of an IgG4-related disease responds well to steroid treatment. Hence, clinicians should try to differentiate AIP from pancreatic cancer before surgery is performed, even though it of course would be detrimental to treat a patient with a resectable pancreatic carcinoma with steroids. In a core needle biopsy study including 26 patients with AIP, 45% showed GELs and 38% had



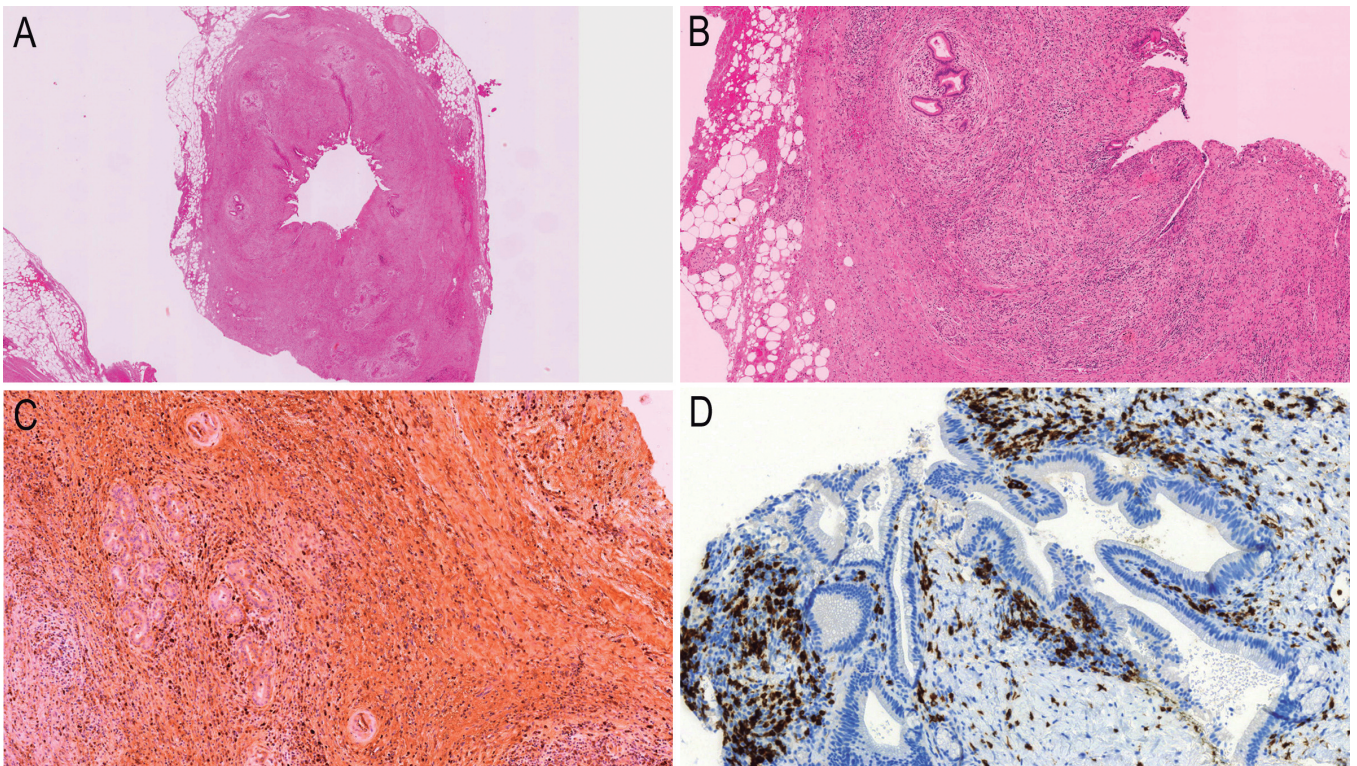
**Fig. 3.** **A.** Periductal lymphoplasmacytic infiltration in IgG4-related autoimmune pancreatitis (H&E). **B.** Granulocytic epithelial lesion in non-IgG4-related AIP (H&E).

infiltration with IgG4-positive cells (Detlefsen et al., 2009). The detection of GELs was indicative of type 2 AIP (Detlefsen et al., 2009). The following microscopic features were assessed: GELs, >10 IgG4-positive plasma cells/ high power field (HPF), >10 eosinophilic granulocytes/HPF, cellular fibrosis with inflammation, lymphoplasmacytic infiltration and venulitis (Detlefsen et al., 2009). All biopsies that showed four or more of the six features were obtained from 21/26 AIP patients. The biopsies from 14 non-AIP patients, taken from lesions showing peritumoral pancreatitis or alcoholic pancreatitis, had only three or fewer of the features (Detlefsen et al., 2009). Hence, these data indicate that the presence of four of the six criteria can be considered as diagnostic for AIP in patients lacking characteristic features of pancreatic cancer clinically, serologically and radiologically. Similarly, the current international consensus diagnostic criteria (ICDC) recommend that for a definitive histological diagnosis of type 1 AIP at least 3 of 4 features (marked lymphoplasmacytic infiltration, storiform fibrosis, obliterative phlebitis and IgG4-positivity) should be present in a core needle biopsy (Shimosegawa et al., 2011). However, it is of the utmost importance to exclude pancreatic cancer in core needle biopsies before suggesting AIP. If necessary,

immunohistochemical stains for markers such as SMAD4, monoclonal CEA, MUC1, p53, Ki67 or S100P can be of valuable help, particularly when considering well-differentiated ductal adenocarcinoma accompanied by inflammation (Klöppel and Adsay, 2009). Of note, several reports of pancreatic cancer occurring synchronously or metachronously in AIP patients are on record (Inoue et al., 2006; Kamisawa et al., 2006a; Fukui et al., 2008; Witkiewicz et al., 2008; Motosugi et al., 2009). Also, non-Hodgkin lymphoma has been reported in an AIP patient (Takahashi et al., 2009).

#### *IgG4-related sclerosing cholangitis*

IgG4-related sclerosing cholangitis (IgG4-related SC) is the most important and most frequently observed extrapancreatic manifestation IgG4-RD in type 1 AIP patients (Kamisawa et al., 2003c, 2009; Sah et al., 2010; Detlefsen et al., 2012). It shows most of the characteristic features of IgG4-RD, even though the storiform fibrosis sometimes is not prominent (Fig. 4). The most important differential diagnosis is primary sclerosing cholangitis (PSC) (Mendes and Lindor, 2010). IgG4-related SC has mostly been observed in adults, while PSC is also sometimes seen in children (Schrumph



**Fig. 4.** IgG4-related sclerosing cholangitis. **A and B.** Cross-section of the extrapancreatic portion of the common bile duct showing stenosis due to diffuse lymphoplasmacytic infiltration and fibrosis (H&E). **C.** Strong infiltration of IgG4-positive cells around peribiliary tubular glands of the bile duct wall (IgG4 immunostaining). **D.** Core needle biopsy specimen showing infiltration of the distal common bile duct mucosa with lymphoplasmacytic inflammatory cells (CD79a immunostaining).

## IgG4-related disease

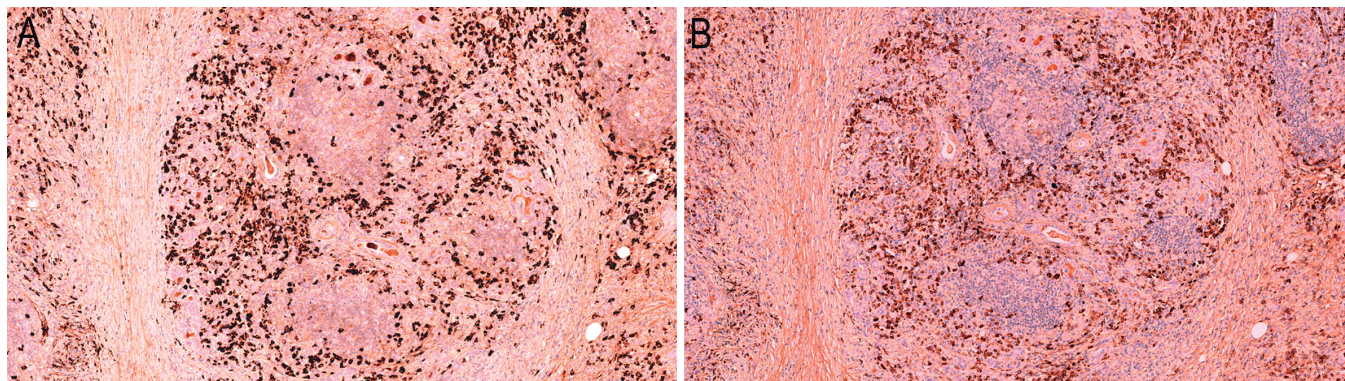
and Boberg, 2001; Mendes and Lindor, 2010). While IgG4-related SC shows association with other manifestations of IgG4-RD, PSC shows concomitant inflammatory bowel disease in 80% of cases (Schrumpf and Boberg, 2001). Besides, IgG4-related SC shows frequently elevated serum IgG4 while 80% of PSC patients show elevated pANCA antibodies, even though a small subgroup of PSC patients also have elevated serum IgG4 levels (Mendes et al., 2006; Mendes and Lindor, 2010). While PSC occurs in both the extra- and intrahepatic bile ducts and is often diffusely distributed, IgG4-related SC is mainly located in the hilum of the liver and in the extrahepatic bile ducts (Björnsson et al., 2007; Mendes and Lindor, 2010; Zen and Nakanuma, 2012). In PSC, fibro-obliterative lesions of the bile ducts as well as ulceration of the mucosa and sometimes also xanthogranulomatous inflammation are often appreciated, while obliterative phlebitis, dense fibrosis (Fig. 4A-B) and strong infiltration with IgG4-positive cells (Fig. 4C) are more characteristic of IgG4-related SC (Björnsson et al., 2007; Silveira and Lindor, 2008; Mendes and Lindor, 2010; Zen and Nakanuma, 2012). Recently, IgG4-negative cases of SC not fitting into the PSC category have been noted (Aoki et al., 2003; Lee et al., 2005; Fujita et al., 2010; Zen et al., 2012). These cases showed strong lymphoplasmacytic infiltration and abundance of lymphoid follicles with activated germinal centers and were called "follicular cholangitis". Obliterative phlebitis and a storiform type of fibrosis as well as IgG4-positivity in the tissue were absent (Fujita et al., 2010; Zen et al., 2012). Zen also noted this type of inflammation in the pancreas in two patients (Zen et al., 2012). The responsiveness to steroids of follicular cholangitis and pancreatitis remains to be elucidated (Zen et al., 2012).

### IgG4-related sialadenitis

Involvement of the salivary glands was noted in 14% of resected type 1 AIP, thereby the second most common site of extrapancreatic organ involvement in IgG4-

related AIP (Detlefsen et al., 2012). IgG4-related sialadenitis probably corresponds to the unilateral swelling of the submandibular gland described by Küttner in 1896 (Küttner, 1896; Kitagawa et al., 2005; Geyer et al., 2010; Laco et al., 2011). Macroscopically, IgG4-related sialadenitis sometimes involves the entire submandibular or parotid gland, but more often well circumscribed lesions involving between 30% and 80% of the parenchyma are noted (Geyer et al., 2010). Obliterative phlebitis was noted in roughly 50% of Geyer's 13 cases (Geyer et al., 2010). Cellular interlobular fibrosis and florid lymphoid follicle hyperplasia are observed in most cases (Geyer et al., 2010). The number of IgG4-positive cells usually ranges from 120 to 230 per HPF, and the mean IgG4 to IgG ratio ranges from 0.7 to 0.85 (Fig. 5A-B) (Kitagawa et al., 2005; Geyer et al., 2010). Laco and colleagues reported a lower cut-off of 50 IgG4-positive cells per HPF and an IgG4 to IgG cell ratio of at least 0.40 as useful for the differentiation of IgG4-related sialadenitis from chronic sialadenitis, not otherwise specified (Laco et al., 2011).

Sialolithiasis-related sialadenitis can also show infiltration with lymphocytes and plasma cells, but the inflammatory foci are typically patchily distributed (Seifert et al., 1986a). Furthermore, there are only few IgG4-positive cells, IgG4 to IgG ratios are usually low, and obliterative phlebitis is not characteristic (Kitagawa et al., 2005; Geyer et al., 2010). Sometimes the calculi lead to erosion or squamous metaplasia of the epithelium (Seifert et al., 1986b). In Sjögren's syndrome, the fibrosis is less prominent compared to IgG4-related sialadenitis, while atrophy seems to be more common (Seifert et al., 1986a). In contrast to initial hypotheses, Sjögren's syndrome seems not to be part of IgG4-RD, and IgG4 stains are typically negative or only weakly positive (Kitagawa et al., 2005; Geyer et al., 2010). As in most cases of IgG4-RD, lymphoma has to be considered in the differential diagnosis. This is of particular importance if several salivary glands and/or also the lacrimal glands are involved. Such a scenario is



**Fig. 5.** IgG4-related sialadenitis. **A.** Intralobular infiltration of IgG4-positive cells (IgG4 immunostaining). **B.** A large proportion of the IgG4-positive cells shown in Figure 5A also stain for IgG (IgG immunostaining).



suggestive of multifocal IgG4-RD, but also lymphoma, particularly mucosa-associated lymphoid tissue (MALT) lymphoma, has to be considered. This is highlighted by the fact that the original report of Mikulicz's disease, often referred to in the literature as a benign, chronic inflammatory disease of the salivary and lacrimal glands, has in retrospect been interpreted as a MALT lymphoma by some authors, and it seems that the eponym Mikulicz's disease is better no longer used (Mikulicz, 1892; Ihrlér and Harrison, 2005; Harrison and Rodriguez-Justo, 2011; Laco et al., 2011; Himi et al., 2012).

#### *IgG4-related thyroiditis*

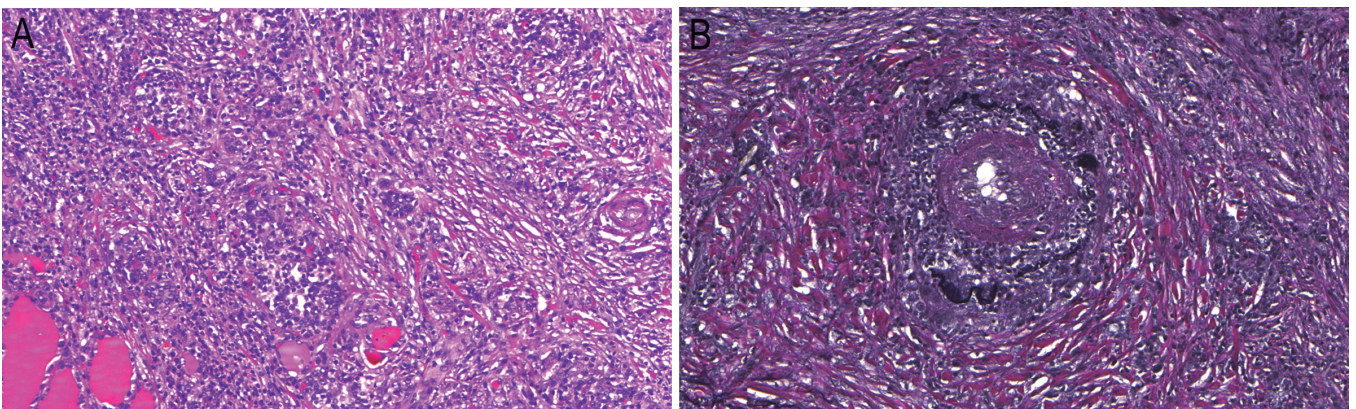
The observation that around 25% of patients with AIP also show hypothyroidism, often accompanied by antibodies to thyroglobulin, preceded immunohistochemical studies of IgG and IgG4 expression in resected thyroid tissue from patients with Hashimoto's thyroiditis (Komatsu et al., 2005; Hamano et al., 2006). Using a threshold of 20 IgG4-positive cells per HPF and an IgG4/IgG ratio of at least 30%, Li et al. separated resection specimens with Hashimoto's thyroiditis into IgG4-positive and IgG4-negative cases (Li et al., 2009). They also showed that IgG4-positive plasma cell infiltrates were associated with a more fibrotic type of Hashimoto's and a shorter interval between onset of disease and surgery (Li et al., 2010). In a series of 70 Hashimoto's thyroiditis cases, 27% were IgG4-positive (Li et al., 2010). At microscopy, storiform fibrosis and diffuse lymphoplasmacytic infiltration (Fig. 6A) are noted. Also obliterative phlebitis is a feature of IgG4-related thyroiditis (Fig. 6B) (Dahlgren et al., 2010).

The differentiation of the fibrosing variant of Hashimoto's thyroiditis from Riedel's thyroiditis can be difficult (Katz and Vickery, 1974; Harach and Williams, 1983; Dahlgren et al., 2010). Riedel's thyroiditis forms a firm and "woody" palpable mass, which extends into the

surrounding structures (Hennessey, 2011). The condition was named after Bernhard Riedel, who published his cases in the last decade of the 19th century (Riedel, 1896, 1897). At microscopy, there is a dense and hyaline fibrosis and diffuse lymphoplasmacytic and eosinophilic infiltration (Harach and Williams, 1983). Obliterative phlebitis seems to be more frequent in Riedel's thyroiditis compared to Hashimoto's thyroiditis (Katz and Vickery, 1974; Harach and Williams, 1983; Li et al., 2009; Dahlgren et al., 2010; Hennessey, 2011). For most authors, it is essential to demonstrate fibrosis and/or inflammation outside the thyroid capsule to establish a diagnosis of Riedel's thyroiditis (Hennessey, 2011). However, Riedel's thyroiditis is extremely rare. In a study on 56,700 thyroidectomies performed at the Mayo Clinic between 1920 and 1984, the frequency of Riedel's thyroiditis was only 0.06%, and between 1976 and 2008, only 21 certain surgical cases of Riedel's thyroiditis were observed retrospectively at this institution (Hay, 1985; Fatourechí et al., 2011). Recently, Riedel's thyroiditis has been linked to IgG4-RD (Dahlgren et al., 2010). The exact relationship between Riedel's thyroiditis and fibrosing Hashimoto's thyroiditis, however, remains to be established, but it is possible that further studies of IgG4-positive cases of both entities will gain further insight (Hennessey, 2011).

#### *IgG4-related retroperitoneal fibrosis*

Albarran described more than a century ago the surgical treatment of idiopathic retroperitoneal fibrosis (RF)-related ureteral obstruction (Albarran, 1905). However, it was not before 1948, when Ormond published two cases of idiopathic RF causing bilateral ureteral obstruction, that this condition became more widely known as an acknowledged disease entity (Ormond, 1948). Since that time, several advances have been made in the understanding and treatment of RF (Vaglio et al., 2006). Microscopically, early-stage RF



**Fig. 6.** IgG4-related thyroiditis. **A.** Thyroid follicles surrounded by lymphoplasmacytic inflammation and fibrosis are shown (H&E). **B.** Inflammation and storiform fibrosis surrounding a vessel with obliterative phlebitis (Verhoeff elastin).

## IgG4-related disease

shows a highly vascular stroma with many lymphocytes and plasma cells, with numerous fibroblasts interspersed between bundles of collagen. Later stages show a pronounced fibrosis with only scattered inflammatory cells and sometimes calcifications (Vaglio et al., 2006). Several reports point out that a substantial number of RF cases are part of IgG4-RD (Yamashita et al., 2008; Zen et al., 2009b). Yamashita found that patients with RF and associated AIP had between 60 and 580 IgG4-positive cells per HPF with IgG4 to IgG ratios between 66% and 80%, while most patients with isolated RF had less than 50 IgG4-positive cells per HPF (Yamashita et al., 2008). Zen examined core needle biopsies from RF patients and separated them into IgG4-positive and IgG4-negative RF. The former had IgG4 to IgG ratios between 35% and 76% and frequent occurrence of lymphoid follicles and obliterative phlebitis. The latter had IgG4 to IgG ratios between 0% and 10%, and lymphoid follicles as well as obliterative phlebitis were sparse (Zen et al., 2009b). He suggested that the IgG4-negative cases may be either burnt out IgG4-RD or that only a subgroup of RF patients belong to the spectrum of IgG4-RD (Zen et al., 2009b). It is recommended that at least 30 IgG4-positive cells per HPF should be present to suggest the diagnosis of IgG4-related RF (Deshpande et al., 2012).

### IgG4-related periaortitis

Walker et al. coined the term inflammatory abdominal aortic aneurysm (AAA) in 1972 (Walker et al., 1972). Among 187 resected AAA patients, 19 showed thickening of the aneurysm walls and periaortic adhesions (Walker et al., 1972). At microscopy, these cases had marked fibrosis and lymphoplasmacytic inflammation in the adventitia and/or outer media. Lymphoid aggregates, lymphoid follicles and perivascular inflammatory infiltrates were also noted (Walker et al., 1972). Inflammatory AAA often coexists with RF, as the fibroinflammatory lesions may extend into the retroperitoneal periaortic tissue (Leu, 1990).

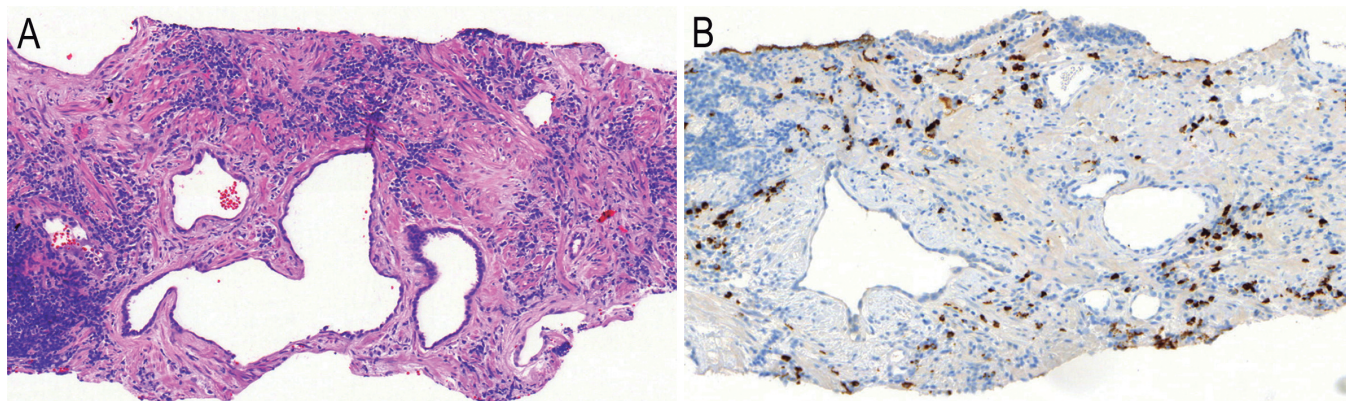
Inflammatory AAA can be subclassified, depending on the severity of IgG4-positive cell infiltration (Kasashima et al., 2009). Higher IgG4 to IgG ratios and more pronounced obliterative phlebitis are observed in IgG4-related periaortitis compared to non-IgG4-related inflammatory AAA (Kasashima et al., 2009). It is recommended that at least 50 IgG4-positive cells per HPF should be present to suggest the diagnosis of IgG4-related inflammatory AAA (Deshpande et al., 2012).

### Multifocal fibrosclerosis and idiopathic cervical sclerosis

The systemic entity known in the literature as multifocal fibrosclerosis was put forward by Comings and coworkers in 1967, but their paper was anticipated by a few publications focusing on inflammatory fibrosing mediastinitis causing obstruction of the superior vena cava and its association with RF, inflammatory pseudotumor of the orbit and Riedel's thyroiditis (Tubbs, 1946; Barrett, 1958; Comings et al., 1967). Comings reported orbital inflammatory pseudotumor, sclerosing cholangitis, RF, mediastinal fibrosis and Riedel's thyroiditis in two brothers who had consanguineous parents (Comings et al., 1967). Also, idiopathic cervical fibrosis has been linked to multifocal fibrosclerosis (Rice et al., 1975). As mentioned in the respective sections, in most of these entities a significant proportion of cases is now known to be part of IgG4-RD, and this also holds for idiopathic cervical fibrosis (Cheuk et al., 2010). Hence, it seems that there is at least a partial overlap between multifocal fibrosclerosis and IgG4-RD (Dahlgren et al., 2010).

### IgG4-related inflammatory pseudotumor

Inflammatory pseudotumors (IPT) have traditionally been defined as mass-forming, non-neoplastic lesions in various organs and at various sites, particularly in the lung, liver and abdominal soft tissue (Umiker and Iverson, 1954; Anthony, 1993). IPT produces grey or



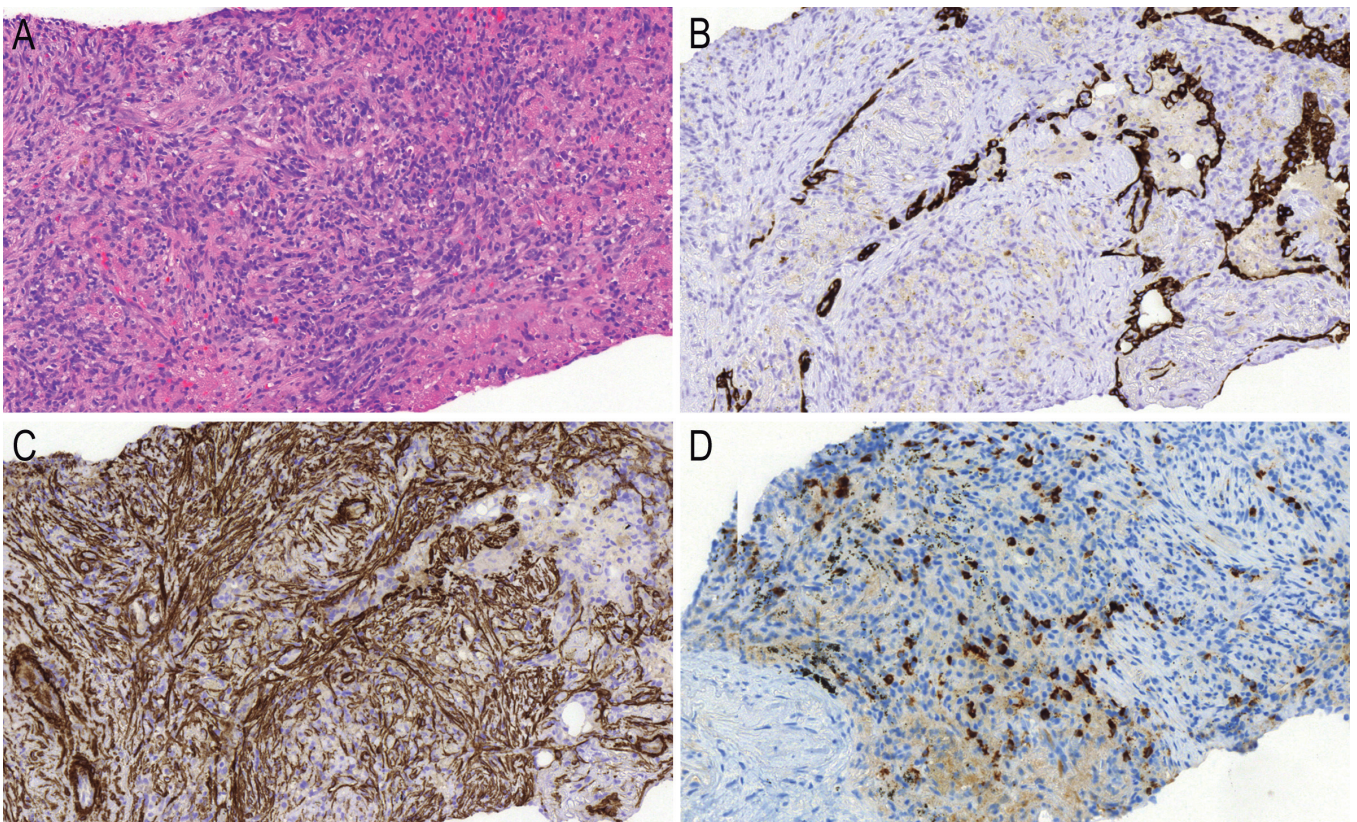
**Fig. 7.** Prostatic core needle biopsy showing IgG4-related prostatitis. **A.** Lymphoplasmacytic infiltration and a slightly storiform fibrosis is appreciated (H&E). **B.** Many of the plasma cells are IgG4-positive (IgG4 immunostaining).

whitish tumor-like lesions (Palazzo and Chang, 1993). At microscopy, a proliferation of fibroblasts and myofibroblasts accompanied by lymphocytes, plasma cells, eosinophils and a swirling fibrosis is noted (Anthony, 1993; Palazzo and Chang, 1993). After identification of the myofibroblast as the main proliferating cell, cytogenetic banding studies showing that unequivocal clonal mutations are present in some IPTs, and after recognition of chromosomal rearrangements involving the ALK receptor tyrosin-kinase locus region (chromosome band 2p23), the term "inflammatory myofibroblastic tumor" has been increasingly used for these tumors (Treisman et al., 1994; Coffin et al., 1995, 1998; Sciot et al., 1997; Griffin et al., 1999). However, it is still believed that not all IPTs are neoplastic IMTs (Yi and Aubry, 2010). Some of these true IPTs have been shown to belong to the IgG4-RD entity, for example in the breast, liver, lung and spleen (Zen et al., 2005a,b, 2007a,b; Cornell et al., 2007; Kuo et al., 2009). Yamamoto et al. compared ALK-positive IMT cases with typical cases of IgG4-RD (Yamamoto et al., 2009). Patients with IMT were younger and showed aberrant expression of ALK in roughly 70% of the cases, but lacked obliterative phlebitis and significant infiltration with IgG4-positive cells. On the other hand,

no aberrant ALK expression was found in IgG4-RD (Yamamoto et al., 2009). Whether ALK- and IgG4-negative IPTs represent an entity on their own remains to be elucidated.

#### *IgG4-related mastitis*

IgG4-RD of the breast presents typically as a uni- or bilateral mass-forming lesion, and breast cancer is an important initial differential diagnosis (Zen et al., 2005a; Cheuk et al., 2009a; Ogiya et al., 2010). At microscopy, there is a dense lymphoplasmacytic infiltrate which can mimic lymphoma. The fibrosis is of the more patchy type but can also show a storiform pattern. There is atrophy of the normal breast parenchyma (Zen et al., 2005a; Cheuk et al., 2009a; Ogiya et al., 2010). The differential diagnosis versus lymphocytic mastitis is mainly based on the fact that this type of mastitis mainly shows infiltrates of small lymphocytes with only few plasma cells and that the fibrosis is of the keloid type (Valdez et al., 2003). In IgG4-related mastitis, there are many IgG4-positive cells. IgG4/IgG ratios between 0.5 and 0.85, and total numbers of 270 to 500 IgG4-positive cells per HPF were reported (Cheuk et al., 2009a). Some of the cases diagnosed in the past as granulomatous



**Fig. 8.** IgG4-related lung disease, nodular type. **A.** Fibrosis is accompanied by lymphocytes, plasma cells and histiocytes (H&E). **B.** Interspersed lung epithelium at the periphery of the lesion is noted (cytokeratin KL1 immunostaining). **C.** Numerous myofibroblasts are shown (alpha-smooth muscle actin immunostaining). **D.** Many of the plasma cells express IgG4 (IgG4 immunostaining).

## IgG4-related disease

mastitis seem to fit well in the category of IgG4-related mastitis (Ogura et al., 2010). In some of the published cases, histology was based on a core needle biopsy or excision biopsy of the breast, while the diagnosis in others was established postoperatively, on a lumpectomy specimen (Zen et al., 2005a; Cheuk et al., 2009a; Ogiya et al., 2010).

### IgG4-related prostatitis

Several reports of IgG4-related prostatitis are on record (Yoshimura et al., 2006; Nishimori et al., 2007). Uehara et al. examined six patients with AIP-associated prostatitis and compared their pathologic features with 10 patients who were clinically suspicious for prostatic cancer but only had focal inflammation without carcinoma (Uehara et al., 2008). In IgG4-related prostatitis, lymphoplasmacytic infiltration without granuloma formation, scattered eosinophils, obliterative phlebitis, atrophy of the parenchyma and fibrosis were appreciated (Fig. 7A). There are numerous IgG4-positive cells and IgG4/IgG ratios between 0.5 and 0.7 (Fig. 7B) (Uehara et al., 2008). In unspecific prostatitis, the inflammatory infiltrate also consisted of lymphocytes and plasma cells, but they were focally distributed in the gland, and fibrosis and IgG4-positive cells were sparse, while eosinophilic infiltration was lacking (Uehara et al., 2008).

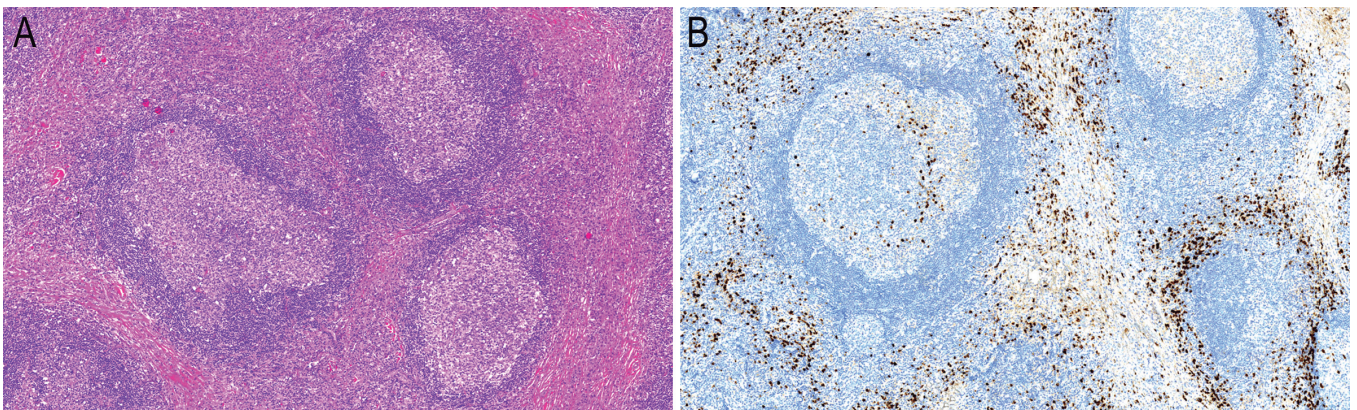
### IgG4-related lung and pleural disease

IgG4-related lung disease does not always produce symptoms, but it can give rise to cough, hemoptysis, dyspnea and pleural effusion (Ryu et al., 2012). At imaging, IgG4-related lung disease may present as solitary or multiple nodules or as peribronchial consolidation (Ryu et al., 2012). Histologically, a solid nodular pattern, a bronchovascular pattern, an alveolar interstitial pattern or pleural disease can be encountered (Zen et al., 2009a). The solid nodular pattern corresponds to the IgG4-related IPT of the lung and is

typically located either peripherally or in the hilus region (Fig. 8) (Zen et al., 2005b, 2009a). In the bronchovascular type, the lymphoplasmacytic infiltrate is distributed along the bronchovascular bundles and interlobular septa, and in the alveolar interstitial type in the alveolar interstitium. In pleural IgG4-RD, fibroinflammatory thickening of the visceral or parietal pleura is noted (Zen et al., 2009a). Obliterative phlebitis was more frequent in the solid nodular and pleural types. At least 50 IgG4-positive cells per HPF should be present to suggest the diagnosis of IgG4-related lung disease in surgical specimens, and at least 20 IgG4-positive cells/HPF in lung biopsies (Deshpande et al., 2012).

### IgG4-related lymphadenopathy

Already in one of the first descriptions of AIP, it was noted that some of the patients had enlarged peripancreatic and intraabdominal lymph nodes (Kawaguchi et al., 1991). Cheuk and Chan suggested that IgG4-related lymphadenopathy may only reflect the immune disturbance that is causing IgG4-RD (Cheuk and Chan, 2010). Five different histologic patterns of IgG4-related lymphadenopathy have been observed (Cheuk et al., 2008; Sato et al., 2009, 2011; Cheuk and Chan, 2010). Type I has been called the multicentric Castleman disease-like type, owing to its similarity to this condition (Cheuk et al., 2008). Hyperplastic lymphoid follicles with frequent penetration by hyalinized blood vessels, numerous high endothelial venules and many IgG4-positive plasma cells in the interfollicular region are appreciated (Fig. 9). Multicentric Castleman disease, however, lacks increased IgG4-positivity in the tissue (Sato et al., 2009). IgG4-related lymphadenopathy type II shows unspecific reactive hyperplasia, with varying interfollicular plasmacytosis (Cheuk et al., 2008). Type III is characterized by interfollicular expansion and sparse or atrophic lymphoid follicles (Cheuk et al., 2008). In type IV, progressive transformation of lymphoid follicles is



**Fig. 9.** IgG4-related lymphadenopathy, type I. **A.** Hyperplastic lymphoid follicles and an interfollicular zone containing high endothelial venules and numerous lymphocytes and plasma cells is shown (H&E). **B.** Strong interfollicular infiltration with IgG4-positive cells (IgG4 immunostaining).

noted, and some lymphoid follicles contain plasma cells in their germinal centers (Sato et al., 2009). Type V has been called nodal IPT-like, due to the focal replacement of the nodal tissue with fibrosis, accompanied by lymphocytes, plasma cells and eosinophils (Cheuk and Chan, 2010; Sato et al., 2011). An IgG4/IgG-ratio between 45% and 73% and at least 100 IgG4-positive cells should be noted per HPF for a given case to be highly suggestive of IgG4-related lymphadenopathy (Sato et al., 2009; Deshpande et al., 2012).

#### *IgG4-related kidney disease*

IgG4-related kidney disease often results in a rather mild impairment of kidney function. At CT, sometimes multiple renal low-attenuation lesions are observed (Sahani et al., 2004; Uchiyama-Tanaka et al., 2004). Of note, IgG4 is the predominant component of glomerular subepithelial immune deposits in membranous nephropathy (Imai et al., 1997). Saeki et al. suggested that membranous nephropathy may represent one of the renal diseases appearing secondary to IgG4-RD, like tubulointerstitial nephritis (TIN) (Saeki et al., 2009a). TIN secondary to IgG4-RD shows by definition a fibroinflammatory interstitial infiltrate with varying grades of (not always storiform) fibrosis and more than 10 IgG4-positive cells per HPF, while obliterative phlebitis is not so common, particularly in core needle biopsies (see also Figure 10) (Cornell et al., 2007; Raissian et al., 2011; Deshpande et al., 2012). In a significant proportion of cases with TIN secondary to IgG4-RD, there is deposition of complement C3, IgG and/or IgG4 along the tubular basement membrane (Cornell et al., 2007; Raissian et al., 2011; Deshpande et al., 2012). Storiform fibrosis and obliterative phlebitis do not have to be present for the diagnosis. A plasma cell-rich TIN with increased IgG4-positive cells is the main diagnostic criterion, together with at least one of the criteria imaging, serology and other organ involvement

(Cornell et al., 2007; Raissian et al., 2011; Deshpande et al., 2012).

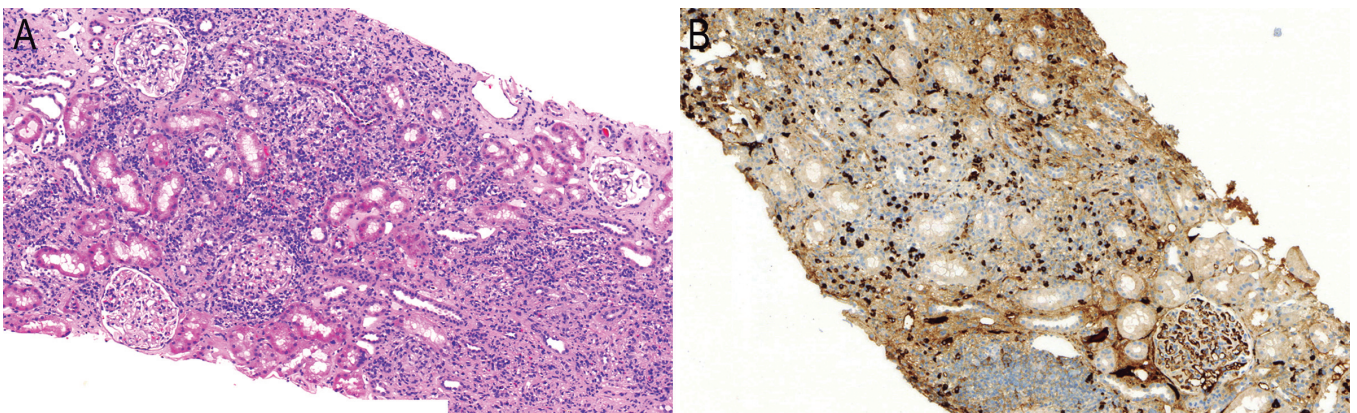
#### *Other manifestations of IgG4-RD*

Figure 1 gives a schematic illustration of the main manifestations of IgG4-RD. IgG4-related hepatopathy occurs most often in patients with IgG4-related SC and appears at imaging as nodular lesions (Nakanuma and Zen, 2007). Of note, an IgG4-positive subtype of autoimmune hepatitis has been described (Chung et al., 2010; Umemura et al., 2011). Nodular lesions show microscopic features of the hepatic type of inflammatory pseudotumor (Zen et al., 2007b; Naitoh et al., 2009).

IgG4-related hypophysitis (Wong et al., 2007; Shimatsu et al., 2009), IgG4-related pachymeningitis (Chan et al., 2009), IgG4-related orbital inflammatory pseudotumor (Plaza et al., 2011) and IgG4-related dacryoadenitis (Takahira et al., 2007) are other important manifestations. Also, constrictive pericarditis (Sugimoto et al., 2008; Sakamoto et al., 2012), gastrointestinal reactive nodular fibrosing tumor (Chetty et al., 2011), sclerosing angiomatoid nodular transformation (SANT) (Kashiwagi et al., 2008; Nagai et al., 2008; Kuo et al., 2009), sclerosing mesenteritis (Chen and Montgomery, 2008; Nomura et al., 2011) and a subgroup of cutaneous pseudolymphoma (Cheuk et al., 2009b; Khosroshahi et al., 2011a) have been added to the spectrum of IgG4-RD.

#### **Pathogenesis of IgG4-RD**

The pathogenesis of IgG4-RD has not yet been fully elucidated, but autoimmune mechanisms are suggested (Stone et al., 2012b). It is still unclear whether IgG4 itself plays a role in the pathogenesis. As the human subclasses of IgG are numbered due to their plasma concentration, IgG4 is the least common antibody. IgG1, on the other hand, represents more than 50% of the total IgG (Pezzilli and Morselli-Labate, 2010). IgG2



**Fig. 10.** Tubulointerstitial nephritis (TIN) secondary to IgG4-RD. **A.** Diffuse lymphoplasmacytic infiltration between the tubuli and glomeruli. Atrophy of the renal tissue and fibrosis are noted (H&E). **B.** TIN with less pronounced fibrosis than in Fig. 10A. IgG4-positivity of numerous plasma cells (IgG4 immunostaining).

antibodies are the main source of antibodies to bacterial polysaccharides, while IgG4 antibodies are mainly related to allergen-induced antibody production (van der Giessen et al., 1976). In IgG4-RD, also total IgG, IgG1, IgG2 and IgE are increased (Masaki et al., 2009; Taguchi et al., 2009). IgM and IgA, on the other hand, are often decreased, but elevated in some of the diseases which have to be considered in the differential diagnosis (Masaki et al., 2009; Taguchi et al., 2009). IgG4 antibodies do not usually precipitate and behave like monovalent antibodies (van der Zee et al., 1986). However, biochemically, they are best described as hetero-bivalent antibodies, because they tend to interchange one of the two heavy-light chain pairs with the heavy-light chain pair of another molecule, resulting in two different antigen-combining sites (van der Neut et al., 2007). In pemphigus vulgaris, IgG4 antibodies to desmoglein, the autoantigen which triggers this disease, play a major role at least in its initial phase (Stanley and Amagai, 2006). Of note, monoclonal IgG4 proteins in myeloma patients show the capacity to act like rheumatoid factor (Cohen et al., 1987). Kawa et al. elucidated whether the polyclonal IgG4 from the serum of AIP patients also acts like rheumatoid factor regarding the ability to recognize the constant portion of IgG through its own variable segment (Kawa et al., 2008). They found, however, that IgG4 binds to the constant portion of IgG using its own constant portion (Kawa et al., 2008). Hence, it is yet unclear whether IgG4 acts autoantibody-like in IgG4-RD (Kawa et al., 2008).

Several disease-related antibodies have been reported in IgG4-related pancreatitis, for example antibodies to lactoferrin, carbonic anhydrase-II and pancreatic secretory trypsin inhibitor (Kino-Ohsaki et al., 1996; Okazaki et al., 2000; Asada et al., 2006; Löhr et al., 2010). Amylase-alpha-2A and heat-shock protein-10 antibodies are also elevated in some AIP patients, and most of the antibodies just mentioned belong to the IgG1 subclass. Furthermore, some of these antigens are expressed in the ductal cells of several exocrine organs in which IgG4-RD has been described (Okazaki et al., 2000; Uchida et al., 2000; Nishimori et al., 2005; Asada et al., 2006; Nishi et al., 2007; Endo et al., 2009; Frulloni et al., 2009; Takizawa et al., 2009). Hence, it is tempting to speculate that these antigens may trigger the disease.

Increased circulating immune complexes accompanied by hypocomplementaemia and tissue deposition of C3, IgG and IgG-subclasses, including IgG4, were observed in the kidneys and pancreata from IgG4-RD patients (Deshpande et al., 2006; Cornell et al., 2007; Saeki et al., 2009b; Detlefsen et al., 2010; Yamamoto et al., 2010). However, IgG4 is not able to activate complement by the classical pathway, and data indicate that the classical pathway of complement activation through IgG1 possibly plays a more important role in the development of AIP than mannose-binding lectin or alternative pathways through IgG4 (Muraki et

al., 2006). Interestingly, experiments in mice showed that non-complement activating subclasses of antibodies can synergize with other IgG subclasses to activate complement through the lectin pathway (Murata et al., 2007). Because IgG4 is bound to the constant portion of IgG1 via its own constant portion in AIP, it may contribute to the clearance of immune complexes or even to the prevention of formation of large immune complexes by blocking those effector functions of IgG1 that are mediated through the constant portion of IgG1 (Kawa et al., 2008; Okazaki et al., 2011).

While early studies suggested a predominance of CD4-positive T helper (Th)1 cells over Th2 cells in AIP (Okazaki et al., 2000) and Mikulicz's disease (Yamamoto et al., 2005), the immune reaction in type 1 AIP and IgG4-related sclerosing cholangitis was later reported to be mainly based on Th2 cells and CD4+CD25+Foxp3 regulatory cells (Zen et al., 2007a). Okazaki and colleagues recently summarized their unifying hypothesis on the pathogenesis of IgG4-RD (Okazaki et al., 2011): In early stages of IgG4-RD, autoantigens may contribute to a decrease in the suppressive effect of naïve natural regulatory T cells. Afterwards, a Th1-type immune response may lead to an increase of the proinflammatory cytokines interferon-gamma, interleukin (IL)-2 and TNF-alpha (Kroemer et al., 1996; Okazaki et al., 2011). According to Okazaki's hypothesis, Th2-type immune responses, based on the secretion of IL-4, -5 and -10, may then upregulate IgG, IgG4 and autoantibodies. The latter may then contribute to the progression of the disease (Kroemer et al., 1996; Okazaki et al., 2011). Upregulation of transforming growth factor  $\beta$ , amongst others, seems to contribute to fibrogenesis during later stages of IgG4-RD (Detlefsen et al., 2008; Okazaki et al., 2011).

## Conclusion

IgG4-related disease is a rapidly evolving fibroinflammatory disease occurring at multiple sites of the body. It is important for the pathologist to be familiar with the characteristic microscopic features of this disease because many patients initially are suspected of suffering from malignancy. IgG4-RD patients, however, do not need surgery in most cases. The characteristic histological features of IgG4-RD are well recognized, but contrasted by the need for a better understanding of the etiology, pathophysiology and long-term outcome of this systemic condition.

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