Tumor-Like Fibrosclerotic Lesions of the Hepatobiliary Tract

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Abstract

A spectrum of idiopathic tumor-like fibrosclerotic lesions can involve the biliary tract and cause stenotic lesions. Idiopathic retroperitoneal fibrosis denotes a group of still not well-defined disorders that include Albarran-Ormond syndrome, chronic periaortitis, inflammatory aortic aneurysms, sclerosing mesenteritis, sclerosing mediastinitis, orbital pseudotumor, and Riedel's thyroiditis. The mass-producing effect of fibrosing processes taking place in the retroperitoneal space or the mesentery can encroach upon the extrahepatic biliary tree and result in biliary obstruction. A second group of conditions is summarized under the term IgG4-related sclerosing disease, characterized by infiltrations of IgG4-expressing plasma cells associated with a chronic fibrosclerosing process. In the hepatobiliary tract, these disorders mainly present as IgG4-related cholangitis, IgG4-realted pseudotumors, and bile duct alterations secondary to IgG4-related autoimmune pancreatitis.

Hepatobiliary Involvement in Idiopathic Retroperitoneal Fibrosis and Related Disorders

Introduction

Idiopathic retroperitoneal fibrosis (IRPF; Albarran-Ormond syndrome; Gerota syndrome; Ormond's disease; fibrous retroperitonitis) denotes a group of progressive fibrosclerotic disorders now characterized by the development of fibrosis in several tissue compartments, i.e., not only in the retroperitoneal space as was previously thought. The eponyms associated with idiopathic retroperitoneal fibrosis (Albarran-Ormond syndrome and Gerota syndrome or Gerota's fasciitis) are John Kelso Ormond (1886–1978), an American urologist; Joaquin Maria Albarran y Dominguez (1860–1912), a Cuban urologist; and Dimitrie D. Gerota (1867–1939), a Romanian anatomist and surgeon. Dr. Albarran y Dominguez studied histology with Louis-Antoine Ranvier (Ranvier's nodes), and together with Halle, he described the Bacillus pyogenes, later to be named Bacterium coli. In 1906 he became the chairman of the Clinic of Urology at the Paris Necker Hospital and described the periureteric lesions found in the syndrome in 1905 (Albarran 1905). Ormond also published his findings based on the ureteral involvement in the disease in question (Ormond 1948). He summarized the main features of the syndrome in 1965, naming the condition idiopathic retroperitoneal fibrosis (Ormond 1965). Dr. Gerota was, in addition to his function as a professor of surgical anatomy and experimental surgery, also a professor at the Art Academy of Bucharest and teacher to the well-known sculptor Constantin Brancusi. Together, they performed the famous carved muscles study known as The Ecorché (1905). Gerota's fascia is named after him. Since the first descriptions of the condition, it has been recognized that retroperitoneal fibrosis and its variants makes part of a group of what is now called fibroinflammatory disorders, comprising retroperitoneal fibrosis sensu strictiori, chronic periaortitis and part of inflammatory aortic aneurysms, sclerosing mediastinitis, sclerosing mesenteritis, orbital pseudotumor, and Riedel's thyroiditis (reviews: Dehner and Coffin 1998; Alberti 2007). Fibrotic processes in the retroperitoneal space and the aortic/periaortic compartment are now recognized to cover an entire spectrum of lesions (Bulkley 1960; Sethia and Darke 1983; Mitchinson 1984, 1986; Martina et al. 1993; Amiya et al. 2005; Table 1).

Table 1 Idiopathic retroperitoneal fibrosis (IRPF) and the spectrum of fibroinflammatory disorders

Idiopathic retroperitoneal fibrosis sensu strictiori (Albarran-Ormond syndrome)
Chronic periaortitis/perianeurysmal retroperitoneal fibrosis
Inflammatory aortic aneurysms
Sclerosing mesenteritis
Sclerosing mediastinitis
Orbital pseudotumor
Riedel's thyroiditis
Several lesions from the spectrum of systemic IgG4-related sclerosing disease

More recently, chronic periaortitis has been proposed to represent a term under which the several manifestations of the disease may be listed, including idiopathic retroperitoneal fibrosis (the previous Albarran-Ormond or Gerota syndromes), perianeurysmal retroperitoneal fibrosis, and inflammatory abdominal aortic aneurysm (Jois et al. 2004; Vaglio and Buzio 2005; Vaglio et al. 2006a, 2007).

Fibroinflammatory Disorders Are Often Manifestations of Systemic IgG4-Related Sclerosing Disease

The aetiology and pathogenesis of the retroperitoneal fibrosis complex are only partially clarified. It has been reported that asbestos exposure is a risk factor for idiopathic retroperitoneal fibrosis. In addition, an increasing number of studies showed an association between these fibrotic disorders and autoimmune processes (Vaglio et al. 2003, 2006b). At least part of these conditions are pathogenetically related to an entity termed, IgG4-related autoimmune disease (IgG4-associated multifocal systemic fibrosclerosis; IgG4-related sclerosing disease; systemic IgG4-related plasmacytic syndrome, SIPS; Hyper-IgG4 disease; Neild et al. 2006). In this disorder, a moderate to marked infiltration of IgG4-positive plasma cells together with CD4- and/or CD8-positive T lymphocytes is noted in the target tissues, including peripancreatic, retroperitoneal, lung, salivary gland, and large bile duct tissues (-Kamisawa et al. 2003a; Hamed et al. 2007). Retroperitoneal fibrosis and chronic periaortitis develop in conjunction with the IgG4-related autoimmune disease (Yamashita et al. 2008), and a subset of inflammatory abdominal aortic aneurysms has a close relationship to IgG4-related periaortitis (Kasashima et al. 2008; Matsumoto et al. 2008; Sakata et al. 2008).

Pathology

The macroscopic presentation of retroperitoneal fibrosis is most frequently that of a firm or rubbery, unencapsulated fibrous plaque or flat mass of gray to whitish color, this mat with indistinct borders being sometimes several centimeters thick, firmly adherent to the posterior peritoneum and displacing it anteriorly. The main portion of the plaque is commonly at the level of the sacral promontorium, with variable extension upward and to the sides. Typically, the process envelopes the retroperitoneal structures, in particular the large- and medium-sized vessels and the ureters, but it may also involve the extrahepatic bile ducts.

Histologically, the tissue shows a chronic inflammation with lymphocytes, macrophages, and plasma cell infiltrates of variable density associated with fibrosis, which is cellular in early or active phases and later becomes hypocellular and sclerotic. The lymphocytic infiltrates are chiefly located around blood vessels, often with central core of CD20-positive B cells and a peripheral zone of CD3-positive T cells. Generally, T cells predominate in diffuse lymphocyte infiltrates (Corradi et al. 2007). Eosinophil and neutrophil granulocytes are present in variable numbers. In some phase of the disease, macrophages (in part foamy cells) predominate (Hughes and Buckley 1993). In the setting of adipose tissue invasion/replacement by the fibrotic process, lipogranulomas can develop. In cases associated with IgG4-related multifocal fibrosclerosis, many of the plasma cells are IgG4 positive and usually occur together with T lymphocytes, both CD4- and CD8-positive. In regard to mesenchymal cells found in the lesions of the disease spectrum, it has been suggested that myofibroblasts are involved in the development of inflammatory aortic aneurysm (Sakata et al. 2007).

Bile Duct Involvement in Idiopathic Retroperitoneal Fibrosis

The mass-producing process of IRPF can encroach upon the extrahepatic biliary system and sometimes mimic bile duct cancer. In the course of anterior extension of fibrosclerosis, it can involve the tissue of the hepatoduodenal ligament, the peripancreatic tissue, and tissues of the hepatic hilum, thus causing encasement and stenosis of extrahepatic bile ducts and leading to biliary obstruction with jaundice.

Selected References Hardy (1962), Schneider (1964), Renner et al. (1980), Lundström (1983), Wetter et al. (1991), Laitt et al. (1992), Cappell (1994), Chutaputti et al. (1995), Pereira-Lima et al. (1996), Dejaco et al. (1999), Lechiche et al. (2001), Tamura et al. (2003), Zhao et al. (2004), Fukui et al. (2005), Kamisawa et al. (2006a), Matsushita et al. (2009), and Quante et al. (2006).

The necropsy case of Schneider (1964) showed a plaque-like mass which completely surrounded several large retroperitoneal vessels, both ureters, body and head of the pancreas, the retroperitoneal part of the duodenum, and the distal end of the common bile duct. The liver was described as green owing to biliary obstruction. The 46-year-old male patient described by Dejaco et al. (1999) was presented with jaundice, and ultrasonography revealed a solid tumor in the porta hepatis about 2 cm in diameter and dilated intrahepatic bile ducts. Subsequent ERCP demonstrated a stenosis of the common bile duct, and a presumptive diagnosis of Klatskin tumor was made. Resection of the lesion histologically showed a manifestation of Ormond's disease, with chronic inflammatory and fibrotic fatty tissue surrounding a narrowed bile duct. Quante et al. (2006) described involvement of the hepatic ducts by the fibrotic process, causing a duct stricture suggesting malignancy. Extrahepatic bile duct stenosis caused by retroperitoneal fibrosis may thus mimic sclerosing cholangiocarcinoma (Klatskin tumor; Wetter et al. 1991; Dejaco et al. 1999). Apart from large bile ducts, extending retroperitoneal fibrosis may also compromise the venous inflow tract of the liver, causing portal hypertension and hypoplasia (or rather atrophy) of a liver lobe (Hisatomi et al. 2004).

IRPF can involve the pancreas and the peripancreatic tissues and subsequently the distal-most part of the common bile duct, causing biliary obstruction (Cappell 1994). In some cases, IRPF encased the pancreatic head, with formation of firm and grayish-white tissue that compressed the distal bile duct, or with generation of a fibrous pseudotumor (Chutaputti et al. 1995; Zhao et al. 2004). Apart from autoimmune pancreatitis, autoimmune disorders of bile ducts, in part related to IgG4 disease, occur in the setting of IRPF. The process can be associated with primary biliary cirrhosis (Sevenet et al. 1985), primary sclerosing cholangitis (Hellstrom and Perez-Stable 1966; Laitt et al. 1992; De Suray et al. 2009), and hepatobiliary inflammatory pseudotumors (De Suray et al. 2009). Also IRPF with concomitant autoimmune pancreatitis has been found to be associated with sclerosing cholangitis (Alpert and Jindrak 1972; Fukui et al. 2005).

Chronic periaortitis (or perianeurysmal retroperitoneal fibrosis) has been observed to sometimes be complicated by common bile duct obstruction (Quante et al. 1991; Remedios et al. 1991). In the 67-year-old female patient reported by Remedios and coworkers, an inflammatory abdominal aortic aneurysm with surrounding retroperitoneal fibrosis was resected. The patient died of a ruptured perinephric abscess, and autopsy revealed a firm 4 cm mass in the pancreatic head severely constricting the pancreatic duct and infiltrating part of the wall of the common bile duct adjacent to the ampulla. Histology of the mass showed extensive dense fibrosis in the peripancreatic tissue adjacent to the site of the previously resected inflammatory aneurysm (Remedios et al. 1991).

Bile Duct Disease in Sclerosing Mesenteritis

Sclerosing mesenteritis has rarely been found to be associated with an idiopathic form of stenosing bile duct fibrosis closely mimicking hilar/perihilar cholangiocarcinoma (Klatskin tumor; Medina-Franco et al. 2001). In this 64-year-old jaundiced male patient, abdominal ultrasound showed intrahepatic biliary dilatation without extrahepatic dilatation. ERCP demonstrated a hilar stricture compatible with Klatskin tumor. Dynamic contrast-enhanced helical CT scans revealed focal thickening of extrahepatic bile ducts as well as an infiltrative mass measuring 8.4 × 4.6 cm in the root of the mesentery. Laparotomy showed a dense infiltration in the proximal mesentery, extending to the hepatic hilar region. Histologically, the mesenteric lesion was sclerosing

mesenteritis, and the bile duct was extensively encased by this inflamed sclerotic tissue.

What Is Sclerosing Mesenteritis?

Sclerosing mesenteritis (SCM), first described in 1924 (Jura 1924), is known in the literature under several other terms, including retractile mesenteritis, fibrosing mesenteritis, liposclerotic mesenteritis, xanthogranulomatous mesenteritis, mesenteric lipodystrophy, mesenteric lipogranuloma, and mesenteric panniculitis (Panniculitis mesenterialis). Jura (1924) already employed the term, retractile and sclerosing mesenteritis (in the Italian publication: mesenterite retrattile e sclerosante). These different terms have caused considerable confusion, but they are currently thought to reflect different evolution phases and/or severity grades of the same disease process (Durst et al. 1977; Ghosh and Kum 2007). It is a chronic inflammatory process of unknown aetiology, located to the mesenteric adipose tissue (more frequently involving the small bowel meso than the colonic meso; in the small bowel mesenterium chiefly the mesenteric root), with a tendency to progress to extensive lipofibrosis or liposclerosis. The disease rarely involves the peripancreatic tissue, the omentum, or the pelvic adipose tissue. The disease may occur in conjunction with retroperitoneal fibrosis, which in this disease most probably reflects an extension of the disease from the mesenteric root to the retroperitoneal space (Sabaté et al. 1999). Peripancreatic involvement may cause the clinical presentation of pancreatic pseudotumor (Sheikh et al. 1999). That SCM may belong to the spectrum of multiorgan fibrosclerosing disorders is supported by the observation that SCM occurs in conjunction with idiopathic orbital inflammation (Sharma et al. 2006). The incidence of the disorder is not known, but postmortem studies have reported an incidence of up to 1 % (Streuli and Stamm 1994). The peak incidence is in the sixth to seventh decades, and males are more frequently affected than females (2:1). Patients usually present with abdominal discomfort or pain, nausea, weight loss, and, less commonly, fever of unknown origin. Probably caused by remodeling of the mesenteric lymph vessels by the inflammatory process, multiple mesenteric lymphatic cysts (Johnson et al. 1997) and/or chylous ascites may develop (Ehrenpreis et al. 2008). SCM may produce tumor-like mesenteric lesions; a palpable mass has been reported to be found in 50 % of the patients. The etiology and pathogenesis of SCM remain unclear. Potential causes that have been discussed include autoimmune causes, infections, and vascular disorders.

Idiopathic Sclerosing Peritonitis

Idiopathic sclerosing (encapsulating) peritonitis (idiopathic encapsulating peritonitis; abdominal cocoon syndrome) is a rare condition characterized by intraperitoneal fibrosclerosis, mainly reported in young adolescent women as a cause of small bowel obstruction. In this disorder, which can be associated with ascites, the small bowel is encased in an encapsulating fibrous sac or saclike membrane termed abdominal cocoon (Masuda et al. 1993). The firm nacreous fibrotic membrane may wrap the intestine in a concertina-like fashion (Da Luz et al. 2011). Apart from the idiopathic form, secondary sclerosing peritonitis occurs to be caused by intraperitoneal chemotherapy, peritoneal dialysis, practolol therapy, meconium peritonitis, tuberculous peritonitis, or the positioning of a peritoneal-jugular shunt in cirrhotic patients with refractory ascites (reviews: Cleffken et al. 2008; Minutolo et al. 2008). The idiopathic form, which is the main cause of abdominal cocoon, was first described in 1978 based on observation on ten girls with a narrow age range of 13–18 years (Foo et al. 1978). As the fibrous cocoon is associated with extensive adhesions, it may be expected that the structure of the hepatoduodenal ligament can be compromised.

Segmental Pericholangial Fibrosis

This is a rare benign fibrotic disorder observed in a child who underwent surgery to remove a hepatic hilar mass suspected to be malignant. It represents a fibrous disorder of unknown etiology located to the bifurcation of the hepatic duct, where the bile

duct wall and the surrounding tissue were markedly fibrotic. Histologically the resected lesion was characterized by a loose connective tissue containing myofibroblasts and chronic inflammatory cells, while more advanced fibrosis was noted in the adjacent soft tissues (Takabe et al. 1997). The potential relationship of this disorder to the spectrum of IRPF is currently unknown.

Fibrosing Thyroid Disease and Sclerosing Cholangitis

Riedel's thyroiditis, an IgG4-related disorder with or without associated multisystemic sclerosis (Dahlgren et al. 2010), may be combined with sclerosing cholangitis (Bartholomew et al. 1963; Brihaye et al. 2008).

IgG4-Related Disease of the Hepatobiliary Tract

Introduction

IgG4-related disease (synonyms: IgG4-related systemic disease; IgG4 syndrome; IgG4-related sclerosing disease; IgG4-reated systemic sclerosing disease; multifocal fibrosclerosis) is a systemic disorder that is characterized by extensive IgG4-positive plasma cells and T-lymphocyte infiltration of various organs, followed by a variable fibrosing process and obliterative phlebitis of the target tissues (reviews: Bateman and Deheragoda 2009; Cheuk and Chan 2010; Okazaki et al. 2010; Sato et al. 2010; Takahashi et al. 2010; Khosroshahi and Stone 2011a, b; Smyrk 2011; Zen and Nakanuma 2011; Carruthers et al. 2012; Divatia et al. 2012; Stone 2013; Mahajan et al. 2014). The disease was first identified based on the observation that patients with sclerosing pancreatitis (now autoimmune pancreatitis) have high serum IgG4 concentrations (Hamano et al. 2001) and that autoimmune pancreatitis is characterized by the presence of numerous IgG4+ plasma cells (Hamano et al. 2002). Clinical manifestations mainly involve the pancreas, the biliary tract, and the salivary glands, but also the retroperitoneal tissues, kidney, lung, prostate, and numerous other organs and tissues (review: Kamisawa and Okamoto 2008). The disorder has also been termed multifocal idiopathic fibrosclerosis, IgG4-related sclerosing disease, IgG4-related systemic disease, IgG4-related autoimmune disease, IgG4-related syndrome, IgG4-related plasmacytic syndrome (SIPS), and IgG4-related multiorgan lymphoproliferative syndrome. Also the term, hyper-IgG4 disease, has been proposed (Neild et al. 2006). The Japanese Research Committee for Systemic IgG4-related Sclerosing Disease appointed the term, IgG4-related disease, as a minimal consensus to all conditions of the disorder (review: Okazaki et al. 2010). The disorder is usually associated with an elevation of serum IgG4 levels, and the serial measurement of these levels is useful to determine the disease activity (Tabata et al. 2011). IgG4-related disease manifesting in the biliary tract is typically associated with stenosing duct lesions that mimic malignancy. On the other hand, IgG4-related disease of the pancreas and bile ducts cause significant morbidity, organ dysfunction, and malignancy (Huggett et al. 2014). The clinical entities associated with this disease are numerous, and a selection is shown in the Table 2. In all of these disease entities, the presence of IgG4-containing plasma cells in the lesions is a characteristic and diagnostically significant feature (Deheragoda et al. 2007).

Selected References Saeki et al. (2006), Tanabe et al. (2006), Chen and Montgomery (2008), Ito et al. (2008), Miwa et al. (2008), Takato et al. (2008), Kamisawa et al. (2003a, 2006a,b), Neild et al. (2006), Ohara et al. (2007), Kamisawa and Okamoto (2008), Zen and Nakanuma (2010), Khosroshahi and Stone (2011a,b), and Smyrk (2011).

IgG4-Associated Sclerosing Cholangitis

Sclerosing cholangitis (SC) is a heterogeneous disease entity with different etiologies and pathogenic pathways. The spectrum of SC chiefly

Table 2 Selection of reported organ manifestations of IgG4-related disease

Central nervous system
Sclerosing pachymeningitis
Pseudotumoral hypophysitis
Head and neck region
IgG4-related orbital inflammatory disease
IgG4-related scleritis
Sialadenitis (sometimes with Küttner tumor)
Sclerosing dacryoadenitis
IgG4-related Mikulicz's disease
Chronic rhinosinusitis
Thoracic organs
IgG4-related thyroiditis
IgG4-related esophagitis
Mediastinal fibrosis
Interstitial pneumonia (IgG4-positive pulmonary disease)
Cardiovascular system
Thoracic inflammatory aortic disease
Inflammatory aortic aneurysm
IgG4-related arteritis and periarteritis
IgG4-related pericarditis
Abdominal organs
IgG4-related autoimmune pancreatitis
IgG4-related cholangitis/cholangiopathy
IgG4-related hepatobiliary pseudotumors
Sclerosing mesenteritis
IgG4-related inflammatory bowel disease
Retroperitoneal space
Retroperitoneal fibrosis
Genitourinary tract
Tubulointerstitial nephritis
Ureteral inflammatory pseudotumor
IgG4-related epididymo-orchitis
IgG4-related prostatitis
Skin and associated structures
IgG4-related skin diseases
IgG4-related mastitis
Skeletal-articular system
IgG4-related arthritis
Peripheral nervous system
Perineural IgG4(+) plasma cell infiltration
Lymphoreticular system
IgG4-related lymphadenopathy

comprises primary sclerosing cholangitis (PSC), autoimmune-related SC, and secondary sclerosing cholangitis (SSC) caused by stenosing lesions of the biliary tract. One subset of autoimmune-related SC is associated with or caused by IgG4-related disease, with or without other manifestations of this disorder (IgG4-SC; Hamano et al. 2005; Hamed et al. 2007; Hayashi et al. 2007; Nakanuma and Zen 2007; Cheung and Lo 2008; Erdogan et al. 2008; Alderlieste et al. 2009; Fujita et al. 2010; Mizutani et al. 2012; Naitoh et al. 2012; Nakazawa et al. 2012, 2013; Novotny et al. 2012; Nowatari et al. 2012; Boonstra et al. 2014; Saito et al. 2013; Silveira 2013; Graham et al. 2014; Joshi and Webster 2014; Okazaki et al. 2014). The diagnostic criteria for this distinct type of cholangiopathy have recently been reviewed (Ohara et al. 2012). IgG4-SC typically affects patients 60–80 years old, 80–85 % being male, and usually manifests as obstructive jaundice and organ swelling mimicking cancer (Beuers et al. 2014). This type of SC is mostly found in conjunction with autoimmune pancreatitis (AIP) discussed in the following paragraph and may be associated with other IgG4-related disorders, such as retroperitoneal fibrosis and sclerosing sialadenitis (Hamed et al. 2007). IgG4-related SC without pancreatic manifestations is rare. Even less common are types of autoimmune but non-AIP-related SC without elevation of serum IgG4 (Sawai et al. 2011). IgG4-SC can clinically and radiologically mimic hilar cholangiocarcinoma/Klatskin tumor (Hamano et al. 2005; Cheung and Lo 2008; Nguyen-tat et al. 2012; Tabata et al. 2013) or other cholangiocarcinomas (Lytras et al. 2012; Maeda and Shimada 2012) and, in case of lesions in the distal common bile duct, resemble ampullary cancer (Aomatsu et al. 2012). Intrahepatic IgG4-related SC can result in sepsis caused by secondary suppurative cholangitis and can sometimes result in recurrent liver failure (Clendenon et al. 2011). The disorder is sometimes associated with hepatic inflammatory pseudotumors (Zen et al. 2004). IgG4-SC may show similar manifestations as eosinophilic cholangitis (Iwamuro et al. 2009). The disorder can be associated with other lesions found in IgG4-related sclerosing disease, such as autoimmune pancreatitis/AIP (discussed in the following paragraph), retroperitoneal fibrosis, and sclerosing sialadenitis (Hamed et al. 2007). IgG4-related SC has been observed together with

retroperitoneal fibrosis in the absence of AIP (Miura and Miyachi 2009; Rompa et al. 2010). Similar to type 1 autoimmune pancreatitis, IgG4-SC is associated with significant morbidity and mortality due to malignancy and organ failure involving the liver, kidney, and brain. In one study, malignancy occurred in 11 % shortly before or after the diagnosis of IgG4-related disease, with development of pancreatobiliary cancers (Huggett et al. 2014).

IgG4-SC presents with a characteristic pathology. Similar to PSC, bile ducts show a chronic fibrosclerosing process that results in marked stenosis of the involved parts. In the patients reported by Hamano and coworkers (Hamano et al. 2005), ERCP showed long-segment, smooth narrowing of the common bile duct, and in one case MRI revealed a mass-like lesion around the common bile duct that involved the portal vein. In contrast to PSC, where cellular infiltrates in the florid inflammatory phase are mainly lymphocytes, IgG4-SC shows IgG4-expressing plasma cells at high density, typically >50 IgG4-positive cells per high-powered field. In part of patients, dense infiltrates of IgG4-positive plasma cells were noted in portal tracts and associated with destructive cholangitis, suggesting an overlap between IgG4-SC and primary biliary cirrhosis (Takemoto et al. 2014). The presence of high-density infiltrates of IgG4-positve plasma cells in hilar areas of liver explants from patients with PSC was significantly associated with dominant biliary strictures and need for biliary stenting (Fischer et al. 2014), suggesting a causal relationship between IgG4(+) plasma cells and the pathogenesis of marked fibrosclerosing biliary changes.

IgG4-Related Sclerosing Cholangitis in Autoimmune Pancreatitis (AIP-Associated Sclerosing Cholangitis)

Autoimmune pancreatitis (AIP) is one of the chief manifestations of IgG4-related sclerosing disease (Kamisawa et al. 2003b; Kojima et al. 2007; Blejter et al. 2008; Okazaki et al. 2008; Smyrk 2011). AIP has been reported in 1961 as a peculiar type of pancreatitis associated with hypergammaglobulinemia (Sarles et al. 1961) and described in more detail in 1995 (Yoshida et al. 1995), and consensus diagnostic criteria for AIP have since been worked out (Asian Diagnostic Criteria, Japan-Korea Consensus: Otsuki et al. 2008; Mayo Clinic Diagnostic Criteria/HISORt Criteria: Chari et al. 2006; International Consensus Diagnostic criteria: Shimosegawa et al. 2011). AIP occurs in two histologic variants, i.e., lymphoplasmacytic sclerosing pancreatitis (LPSP; type 1 AIP, associated with elevated serum IgG4) and idiopathic duct-centric pancreatitis (IDCP; type 2 AIP) or granulocytic epithelial lesion-positive pancreatitis (Honolulu Consensus Document; Chari et al. 2011). In contrast to type 1 AIP, type 2 AIP seems to be confined to the pancreas (Deshpande et al. 2011). AIP was localized to the pancreatic head in 94 % of cases, with possible extension into the periphery of the gland and/or into the biliary tract (Esposito et al, 2008). It has later been found that AIP is closely related to the HLA DRB1*0405-DQB1*0401 haplotype (Kawa et al. 2002) and associated with inflammatory infiltrates rich in IgG4-containing plasma cells and that it is accompanied by elevated serum IgG4 levels (Hamano et al. 2001; Sadler et al. 2011). Immunohistochemically, deposition of IgG4 together with IgG and complement C3s has been detected at the basement membrane of pancreatic ducts and acini in AIP (Detlefsen et al. 2010). AIP can cause plasma cell-rich sclerosing mass lesions (pseudotumors) that may closely mimic pancreatic malignancy (Kajiwara et al. 2008).

AIP has been observed in association with several forms of IgG4-related sclerosing disease (reviews: Hirano et al. 2004; Kamisawa et al. 2010; Zhang and Smyrk 2010) and in particular with bile duct lesions mimicking primary sclerosing cholangitis (IgG4-associated cholangitis, see above; review: Björnsson et al. 2007), primary biliary cirrhosis, and Sjögren syndrome (Takuma et al. 2011). In 1963, two cases of PSC with pancreatic involvement seen at the Mayo Clinic were reported, and these cases may represent the first published examples of SC associated with AIP (Bartholomew et al. 1963). Sclerosing cholangitis can in fact develop subsequent to chronic

pancreatitis associated with Sjögren syndrome (Montefusco et al. 1984; Versapuech et al. 1986) and with AIP proper (Erkelens et al. 1999; Nakazawa et al. 2001, 2005; Horiuchi et al. 2002; Kuroiwa et al. 2002; Hirano et al. 2003; Pickartz et al. 2004; Prasad et al. 2004; Nishino et al. 2005, 2007; Kawa et al. 2007; Beristain et al. 2008; Esposito et al. 2008; Ong et al. 2011). In patients with this constellation, serum IgG4 levels are significantly higher than those in patients with primary sclerosing cholangitis (Hirano et al. 2006; Nishino et al. 2007; Hochwald et al. 2008), and the disease in these patients does not show an association with inflammatory bowel disease (Nakazawa et al. 2005). In one study, intra- and/or extrahepatic biliary tract involvement in AIH was 64 % (Esposito et al. 2008), and in another investigation on 16 patients with AIP, stricture of the extrahepatic bile duct was detected in 88 % and duct wall thickening in 94 % of the patients (Nishino et al. 2005). The overall rate of extrahepatic bile duct involvement in AIP is around 70 % (Zhang and Smyrk 2010). Sclerosing cholangitis associated with AIP seems to be a distinct disease that differs from classical primary sclerosing cholangitis (PSC), although there is some overlap (Webster et al. 2009). This has led to the concept of "AIP-associated sclerosing cholangitis" (AIP-SC; Uehara et al. 2005). The mean age at presentation was significantly higher in AIP associated with bile duct disease than in PSC (Kim et al. 2006). Radiologically, the extrahepatic duct was involved in AIP-SC, while both extrahepatic and intrahepatic bile ducts were involved in PSC. Cholangiography can discriminate PSC from AIP-SC, in that band-like stricture, beaded or pruned-tree appearance and diverticulum-like formation were significantly more frequent in PSC, and segmental stricture, long stricture with prestenotic dilatation, and stricture of the distal common bile duct were more common in AIP-SC (Nakazawa et al. 2004). These authors therefore classified cholangiograms of IgG4-related SC into four types. Stenosis with type 1 is located only in the lower part of the common bile duct; stenosis type 2 is diffusely distributed throughout the intrahepatic and extrahepatic bile ducts; type 3 stenosis occurs in both the hilar hepatic region and the lower part of the common bile duct; and type 4 stenosis is detected only in the hilar region.

The clinical, radiological, and pathological features of IgG4-related SC and PSC are different (Zen et al. 2004; Nakanuma and Zen 2007; Deshpande et al. 2009; Cheuk and Chan 2010; Smyrk 2011). IgG4-related sclerosing cholangitis has a more marked male preponderance, involves middle-aged to elderly individuals (PSC: more commonly young adults), and often presents with obstructive jaundice. IgG4 cholangiopathy is histologically characterized by an inflammation with infiltrates showing a transmural and homogeneous distribution within the bile duct wall, whereas inflammatory changes in PSC tend to involve the inner parts of the duct wall. In contrast to PSC, erosive or ulcerous lesions, and onion-skin-type concentric periductal fibrosis, and/or xanthomatous changes are not features of AIP-SC. The diffuse transmural lymphoplasmacytic infiltration in AIP-SC is associated with marked interstitial fibrosis with a focal storiform pattern (similar to that seen in AIP) and occasional obliterative phlebitis. The biliary epithelium is usually spared of injury. Immunohistochemically, IgG4-containing plasma cells are frequent in the infiltrates of AIP-SC (Nishino et al. 2005; Nakanuma and Zen 2007; Ghazale et al. 2008; Naitoh et al. 2009) and can be assessed in biopsies from Vater's ampulla and the common bile duct (Kawakami et al. 2010), and the IgG4-positive plasma cell/mononuclear cell ratio was significantly higher in AIP-SC than in PSC (Uehara et al. 2005). Patients with AIP-SC have significantly higher numbers of IgG4+ plasma cells in ampullary biopsies than patients with PSC and pancreatobiliary carcinomas. In one study, 18 out of 27 patients (67 %) with AIP had more than 10 IgG4+ plasma cells in their ampullary biopsies (Kubota et al. 2008). PSC occurs in younger and AIP-SC in older patients, obstructive jaundice is more often found in AIP-SC, and whereas PSC is associated with inflammatory bowel disease, AIP-SC is associated with extrapancreatic manifestations of AIP (Kawa et al. 2007). AIP-SC may cause stenosing lesions closing mimicking hilar sclerosing carcinoma/Klatskin tumor (Cheung and Lo 2008). Sclerosing cholangitis may

develop in patients having developed a AIP-related pancreatic pseudotumor (Toosi and Heathcote 2004). Rarely, IgG4-negative sclerosing cholangitis is associated with AIP (Sewkani et al. 2005).

Primary Sclerosing Cholangitis Mimicking IgG4-Related Disease

Zen and coworkers described two patients of PSC associated with ulcerative colitis and typical bile duct histology, including duct erosion and xanthogranulomatous reaction, having undergone liver transplantation. The explants showed marked infiltration of IgG4-positive plasma cells, mainly in duct-associated xanthogranulomatous tissue, in the absence of typical features of IgG4-related SC (Zen et al. 2011).

Small Bile Duct Involvement in IgG4-Related Sclerosing Cholangitis

This disorder has been defined as damage of small intrahepatic bile ducts associated with infiltration of >/= 10 IgG4+ plasma cells per HPF and has been observed in 5 out of 22 (26 %) patients with IgG4-related disease. Patients with small duct involvement showed a higher incidence of intrahepatic bile duct strictures on cholangiography. Conversely, 57 % of patients with intrahepatic bile duct strictures on cholangiography had histologically evident small duct involvement. The number of IgG4+ plasma cells was correlated with the site of the most proximal stricture (Naitoh et al. 2011).

IgG4 Hepatopathy and IgG4-Related Hepatitis

IgG4 hepatopathy is a recently described disorder which presents with five histologic patterns: (1) evident portal tract inflammation with or without interface hepatitis, (2) large bile duct obstructive features, (3) portal sclerosis, (4) lobular hepatitis, and (5) canalicular cholestasis (Umemura et al. 2007). A subset of patients with interface hepatitis showing the features of autoimmune hepatitis (AIH) reveal high densities of IgG4+ plasma cells in the cellular infiltrates (IgG4-associated autoimmune hepatitis). This type of AIH was identified in 2007 (Umemura et al. 2007) in one patient showing an International Autoimmune Hepatitis Group (IAIHG) score of 18 and a high serum IgG4 concentration and was later confirmed in other patients (Chung et al. 2010; Castillo-Rama et al al. 2013; Yada et al. 2013) and found in over 3 % of Japanese patients with type 1 AIH (Umemura et al. 2011).

Hepatobiliary Pseudotumors in IgG4-Related Sclerosing Disease

Inflammatory pseudotumors developing in association with IgG4-related disease usually show histologic features that resemble those of ALK rearrangement-positive inflammatory myofibroblastic tumors (IMTs). Inflammatory pseudotumors occurring in patients with IgG4-related disease contain numerous IgG4-positive plasma cells, albeit there is considerable histologic overlap between these two lesion groups. It has been demonstrated that a subset of IMT exhibits an IgG4/IgG ratio that is within the range for IgG4-related sclerosing disease, a feature that is useful for the distinction of two types of IMT (Saab et al. 2011).

Hepatobiliary pseudotumors with high IgG4 plasmocyte cellularity have been observed by several authors, sometimes, but not always, in association with autoimmune pancreatitis/AIP (Sato et al. 2004; Kanno et al. 2005; Sasahira et al. 2005; Martin Malagon et al. 2006; Uchida et al. 2007; de Suray et al. 2009; Kim et al. 2011; Ahn et al. 2012; Hastir et al. 2014). In the case reported by Martin Malagon et al. (2006), a lesion of the inflammatory myofibroblastic tumor type was located in the distal common bile duct of a 51-year-old female patient suffering from lymphoplasmacytic sclerosing pancreatitis. In AIP, pseudotumoral masses have been observed synchronously in the pancreas and the gallbladder (Gumbs et al. 2005). In

another patient with AIP, multiple inflammatory pseudotumors were detected in the liver, associated with peripheral eosinophilia (Sasahira et al. 2005). Hepatic inflammatory pseudotumor may, apart from AIP, synchronously occur with other manifestations, including sclerosing cholangitis, retroperitoneal fibrosis, and sialadenitis (de Suray et al. 2009). Intrahepatic IgG4-related pseudotumor can clinically and radiologically mimic hepatocellular carcinoma (Hastir et al. 2014). Zen and coworkers (Zen et al. 2007) defined two types of hepatic inflammatory pseudotumors, fibrohistiocytic and lymphoplasmacytic. The lymphoplasmacytic type is histologically characterized by diffuse inflammatory cell infiltration, mainly by lymphocytes and plasma cells. The inflammatory cells may infiltrate perineural spaces. Parts of these pseudotumors reveal a significant eosinophil infiltration. Obliterative phlebitis with or without recanalization may be present. IgG4+ plasma cells were significantly more frequent in the lymphoplasmacytic variant. Some areas of pseudotumors display entrapped small bile ducts.

IgG4-Associated Ampullitis

In rare cases, ampullitis is characterized by an infiltrate showing numerous IgG4-positive plasma cells. This disorder was also observed in patients with inflammatory bowel disease, including Crohn's disease (Navaneethan et al. 2011). On the other hand, plasma cells can be increased in ampullary tissue due to extension of IgG4-related autoimmune pancreatitis into the ampullary region (Kawakami and Zen 2010).

Sclerosing Cholecystitis in Autoimmune Pancreatitis

Sclerosing cholecystitis is now well recognized to occur in association with IgG4-related disease (IgG4-related cholecystitis; Abraham et al. 2003; Fukui et al. 2005; Nishino et al. 2005; Kamisawa et al. 2006c; Wang et al. 2009; Leise et al. 2011; Lee et al. 2013; Feely et al. 2014). Thickening of the gallbladder wall was detected on ultrasonography and/or CT in 32 % of AIP patients (Kamisawa and Okamoto 2008) and in another study in 56 % (Nishino et al. 2005). In a study of gallbladders obtained from patients with lymphoplasmacytic sclerosing pancreatitis, 60 % of the gallbladders contained moderate or marked inflammatory infiltrates and lymphoid nodules, and gallbladders from these pancreatitis patients received the highest scores for deep inflammation of all groups compared (Abraham et al. 2003). IgG4-related sclerosing cholecystitis is most common in patients having AIP with extensive bile duct disease and where stenosis of the extrahepatic bile duct is frequent (Kamisawa et al. 2006c). Histologically, fibrosis/sclerosis is associated with a mucosal or transmural lymphoplasmacytic infiltration, the plasma cells containing IgG4 (Kamisawa et al. 2006c). In case of diffuse and marked plasmacytic inflammatory infiltration of the gallbladder wall, the lesion can mimic gallbladder cancer (Lee et al. 2013; Shin et al. 2013).

Locoregional Lymphadenopathy in IgG4-Associated Sclerosing Disease of the Hepatobiliary Tract (IgG4 Lymphadenopathy)

Lymph nodes draining IgG4-associated sclerosing cholangitis and pancreatitis are often enlarged, because the immune reaction driving the disease causes a marked expansion of the nodal cell populations involved and particularly lymphoblasts and IgG4-expressing plasma cells. In such lymph nodes, three histological patterns have been identified, i.e., interfollicular expansion by immunoblasts and plasma cells, follicular and germinal center hyperplasia, and Castleman-like alterations (Cheuk et al. 2008; Shimizu et al. 2010). Some patients with IgG4-related disease may develop generalized lymphadenopathy, sometimes with a histology mimicking multicentric Castleman's disease (Kamisawa et al. 2006a; Sato et al. 2009; Takenaka et al. 2011; review: Sato et al. 2010).

Malignancy Associated with IgG4-Related Sclerosing Disease

Generally, the incidence of total malignancies in patients with IgG4-related disease seems to not be different from control populations (Hirano et al. 2014), but certain neoplasms have been found in association with this disorder. Mucosa-associated lymphoid tissue lymphoma may arise from ocular adnexal IgG4-related disease and IgG4-producing lymphomas exist (review: Sato et al. 2010). In a study on 111 patients with IgG4-related disease with or without AIP and 331 patient-years of observation, 3 patients developed non-Hodgkin lymphoma 3–5 years after the diagnosis of IgG4-related disease. One of the patients showed lymphoma involvement of the liver (Takahashi et al. 2009). Peripheral T-cell lymphoma has been reported in a patient with IgG4-related disease (Kanda et al. 2011). Marginal zone lymphoma involving the meningeal dura has been observed in IgG4-related disease (Venkataraman et al. 2011). Several cases of ductal adenocarcinoma of the pancreas have been reported in association with IgG4-related AIP, and IgG4-related disease can rarely be complicated by cholangiocarcinoma (Douhara et al. 2013).

Differential Diagnosis

It has to be emphasized that IgG4-containing plasma cells may be observed in a wide array of immune reactions and inflammatory responses, in the absence of other features of IgG4-related disease (Strehl et al. 2011). IgG4-positive plasma cells were also found in peritumoral tissue of patients with hilar cholangiocarcinoma, other cholangiocarcinomas, and gallbladder carcinoma (Resheq et al. 2013; Harada and Nakanuma 2014), suggesting that cholangiocarcinoma cells in their function as nonprofessional antigen-presenting cells may indirectly induce an IgG4 reaction via an Il-10-mediated pathway (Harada and Nakanuma 2014). Interestingly, IgG4-positive plasma cells are also encountered in inflammatory myofibroblastic tumor, a rare mesenchymal neoplasm having an anaplastic lymphoma kinase (ALK) rearrangement in the majority of cases and histologically resembling IgG4-related reactive inflammatory pseudotumor (Saab et al. 2011), eventually suggesting a pathogenic link. Increased numbers of IgG4(+) plasma cells were observed in a subset of Rosai-Dorfman disease cases (Menon et al. 2014). There is one report describing an inflammatory angiomyolipoma of the liver showing dense infiltrates of IgG4-positive plasma cells (Agaimy and Märkl 2013).

Pathogenic Pathways

IgG4 has distinct functional properties (review: Nirula et al. 2011). IgG4 is known to be capable to undergo what is called half-antibody exchange in vivo and what causes the generation of recombined antibodies composed of two different binding specificities. The regulation of IgG4 synthesis in plasma cells is not fully understood but seems to depend on an aberrant acquired immunity based on T2-dominated immune responses. IgG4 production is partially driven by T helper 2 cytokines mediating allergic responses and IgE synthesis. In tissues affected by IgG4-related disease, mast cells are a source of T helper 2 and regulatory T-cell cytokines and are therefore suggested to play a role in pathogenic pathways of this disease (Takeuchi et al. 2014). Increased T-helper 2 cytokines produced in IgG4-related cholangitis disrupted the tight-junction-associated biliary epithelial cell barrier, the subsequent biliary leaks considered to contribute to the pathogenesis of chronic bile duct inflammation (Müller et al. 2013). It has been found that interleukin-13 is a T cell-derived cytokine that efficiently directs naïve human B cells to switch to IgG4 and IgE production (Punnonen et al. 1993). Observations in polyclonal IgG4 hypergammaglobulinemia have, however, shown that stimulation of IgG4 synthesis by plasmacytoid cells may be mediated by soluble T cell factors other than IL-13 (Boulanger et al. 2006). In IgG4-related sclerosing cholangitis, there is evidence that the chemotactic factor/receptor system CCl1-CCR8 is involved in the recruitment of lymphocytes (Zen et al. 2013).

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