Virchows Arch (2011) 458:761–765
DOI 10.1007/s00428-011-1073-2

CASE REPORT

IgG4-associated cholangitis with cholangiocarcinoma

Beate K. Straub · Irene Esposito · Daniel Gotthardt · Boris Radeleff · Dalibor Antolovic · Christa Flechtenmacher · Peter Schirmacher

Received: 8 October 2010 / Revised: 8 March 2011 / Accepted: 30 March 2011 / Published online: 12 April 2011

Abbreviations

AIP	Autoimmune pancreatitis
AIPC	Autoimmune pancreatocholangitis
ANA	Antinuclear antibodies
IAC	IgG4-associated cholangitis
CC	Cholangiocarcinoma
HPF	High-power field
MRCP	Magnetic resonance cholangiopancreatography
PSC	Primary sclerosing cholangitis

B. K. Straub (✉) · C. Flechtenmacher · P. Schirmacher
Institute of Pathology, University Hospital,
Im Neuenheimer Feld 220/221,
69120 Heidelberg, Germany
e-mail: beate.straub@med.uni-heidelberg.de

I. Esposito
Institute of Pathology, Technische Universität München,
Ismaningerstr. 22,
81675 Munich, Germany

I. Esposito
Institute of Pathology, Helmholtz Zentrum München,
Ingolstädter Landstraße 1,
85764 Neuherberg, Germany

D. Gotthardt
Department of Internal Medicine IV, University Hospital,
Im Neuenheimer Feld 410,
69120 Heidelberg, Germany

B. Radeleff
Department of Diagnostic and Interventional Radiology,
University Hospital,
Im Neuenheimer Feld 110,
69120 Heidelberg, Germany

D. Antolovic
Department of Surgery, University Hospital,
Im Neuenheimer Feld 110,
69120 Heidelberg, Germany

Introduction

Autoimmune pancreatitis (AIP) was first described by Sarles and coauthors [1] as a primary inflammatory sclerosis of the pancreas and is currently subclassified into two clinical entities named type 1 and type 2 AIP [2]. Clinical features of type 1 AIP include elevated IgG4-levels in the serum and excellent response to steroids, whereas in type 2 AIP, IgG4 levels are not elevated. Histologic criteria for type 1 AIP include periductal lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative venulitis, whereas the hallmark of type 2 AIP is the presence of epithelial granulocytic lesions. Extrapancreatic disease occurs in more than 45% of patients with AIP, and especially intra- and extrahepatic biliary tree involvement has been described as a peculiar form of sclerosing cholangitis [3–5]. Less frequently, the disease may only involve the intra- and/or extrahepatic bile ducts, then termed IgG4-associated cholangitis (IAC) [6]. Currently, IAC and AIP are seen as manifestations of a systemic IgG4-disease [6], often occurring together as autoimmune pancreatocholangitis (AIPC) [7]. While in primary sclerosing cholangitis (PSC), an association with malignancy, i.e., cholangiocarcinoma (CC), is well established with an incidence rate of 1.5% per year [8], an association of IAC/AIPC with invasive carcinoma of the biliary tree has not been demonstrated so far. Only recently, a case of biliary intraepithelial neoplasia in the common bile duct in the presence of bile duct affection of AIPC has been described [9]. Here, we demonstrate the first case of co-occurrence with a potentially correlated malignancy, i.e., intrahepatic CC.

Clinical history

A 75-year-old male patient with coronary heart disease, high blood pressure, and hypercholesterolemia, but no

known preexistent disease of the pancreas or of the liver, presented with a tumor in the left lobe of the liver. CEA and CA19-9 levels in the serum were not or only slightly elevated (CEA 2.3 μg/l, CA19-9 40.8 U/ml). The liver enzyme levels were moderately elevated (AP 96 U/l, AST 65 U/l, ALT 41 U/l, GGT 496 U/l), lipase levels were normal. While the level of IgG4 in the serum was normal (0.84 g/l), ANA titer was positive (1:1,280). There was no known preexisting chronic inflammatory bowel disease. In magnetic resonance cholangiopancreatography, the left lobe of the liver (segment 4b) presented with a subcapsular tumor characteristic of cholangiocarcinoma and accompanying cholestasis/cholangitis which was interpreted as being secondary to the tumor (Fig. 1). The pancreas did not show any abnormalities. By CT-guided liver biopsy, the diagnosis of adenocarcinoma of the pancreatobiliary system was made and left hemihepatectomy was performed. After surgery, cholestasis disappeared rapidly, the patient was not treated with steroids. More than 2 years after hemihepatectomy, the patient is well, CT scan of thorax and abdomen show no relapse, osseous, or pulmonary metastases; CA19-9-levels in serum are normal.

Results

At gross examination of the hemihepatectomy specimen, liver segment 4b presented with a whitish and compact subcapsular tumor with bilobated aspect measuring 4.5 cm in diameter, in continuity with the bile ducts (Fig. 2). In addition, some larger intra- and extrahepatic bile ducts were surrounded by whitish tissue with tumorlike appearance. The liver parenchyma was not cirrhotic.

At microscopic examination, the larger intrahepatic bile ducts showed chronic cholangitis with marked storiform fibrosis and periductal lymphoplasmacellular infiltrates with few eosinophilic granulocytes. Part of the bilobated tumorous lesion in segment 4b resembled inflammatory pseudotumor (Fig. 3) but actually represented a tumorous manifestation of the cholangitis. The ductal epithelium appeared intact; no biliary intraepithelial neoplasia was detected. Additionally, the lymphoplasmacellular infiltrate surrounded veins and arteries as well as nerves. Lymph follicles were present in the periphery. No granulocytic epithelial lesions were present, nor were stigmata of PSC such as onion-skin-like periductal fibrosis, ductopenia, or degenerative changes of the bile duct epithelium. In conclusion, due to its typical histomorphology, the cholangitis was classified as IAC. Immunohistochemistry was performed to identify IgG4-positive plasma cells. More than 10 IgG4-positive cells/high-power field were detected in the inflammatory infiltrate surrounding intrahepatic bile ducts as well as vessels and nerves (Fig. 3) with little regional heterogeneity, further confirming the diagnosis of IgG4-associated cholangitis. The second, subcapsular part of the bilobated tumor situated in direct continuity to the pseudotumorous manifestation of IAC represented an intrahepatic cholangiocarcinoma, peripheral type, with tubular growth pattern, without angioinvasion (pT1, pN0, pMx, and G2; Fig. 3). No biliary intraepithelial neoplasia was detected in proximity of the cholangiocarcinoma. In the surrounding liver parenchyma, marked hepatocellular siderosis (siderosis index 3/4) was detected suggesting iron storage disease without cirrhosis. Bidirectional sequencing of exons 2 and 4 of the *HFE* gene showed no mutations in codon 63 and codon 282, excluding HFE-related hereditary

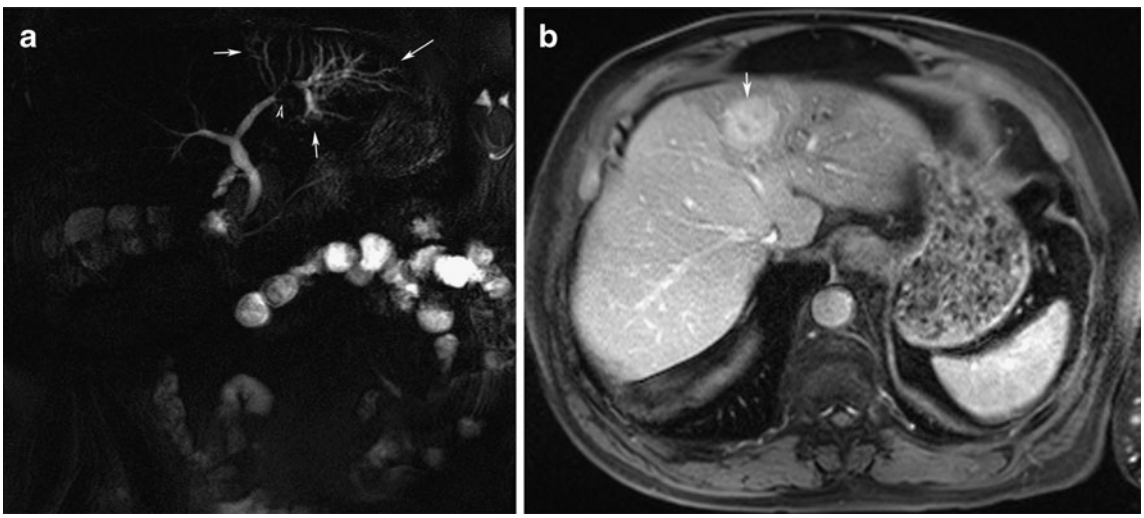

Fig. 1 Preoperative magnetic resonance cholangiopancreatography (MRCP) images. **a** MRCP showing cholestasis/cholangitis (*arrows*) and infiltration by an intrahepatic cholangiocarcinoma (*arrowheads*). **b** Transversal sections of MRCP in portal-venous, contrast medium-enhanced phase, showing an intrahepatic cholangiocarcinoma in the left lobe of the liver (*arrow*)

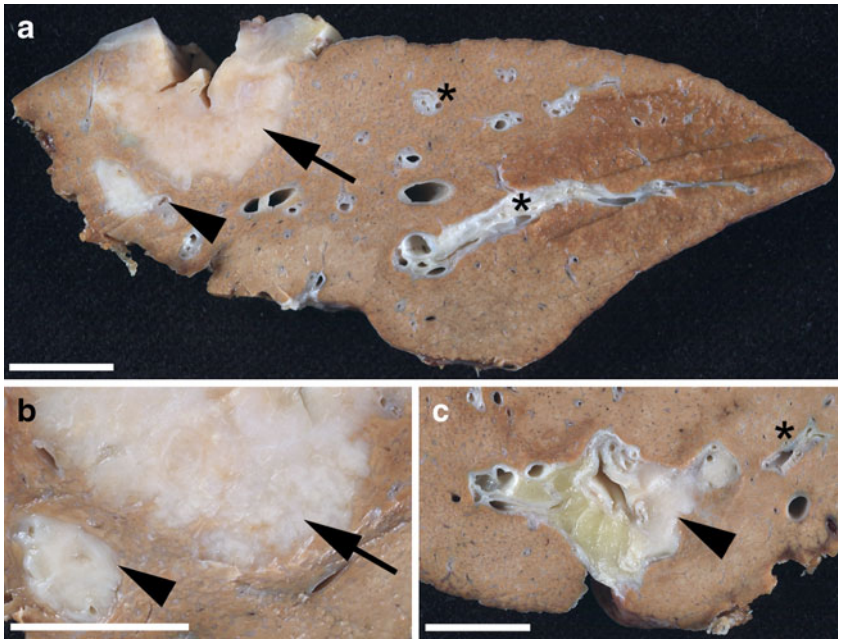

Fig. 2 Gross findings in the hemihepatectomy specimen. **a** Hemihepatectomy specimen showing 4.5-cm subcapsular cholangiocarcinoma (*arrow*) and neighbouring whitish bile ducts with tumorlike manifestation of IAC (*arrowhead*). **b** Enlarged image of cholangiocarcinoma and IAC. Note rounded enlarged whitish portal tracts in **a** and **c** (*asterisks*). Bars, each 2 cm

hemochromatosis; the cause of the significant siderosis could not be defined further.

Discussion

IgG4-associated cholangitis is a recently described steroid-responsive disease comprising chronic inflammation and storiform fibrosis of the intra- and extrahepatic bile ducts. It is often associated with AIP and involvement of pancreas and bile ducts is termed AIPC [3, 4]. In patients with primary sclerosing cholangitis, the development of intrahepatic cholangiocarcinoma is a known consequence [8]. While IAC or AIPC or AIP may present as a tumor mass mimicking cholangiocarcinoma or ductal adenocarcinoma of the pancreas [10] by imaging techniques, these diseases have not been demonstrated to be associated with an increased risk of developing cancers of the liver or pancreas so far.

To date only a few cases of synchronous autoimmune pancreatitis and infiltrating pancreatic ductal adenocarcinoma have been reported [11, 12] as well as one case of a patient with salivary duct carcinoma arising in IgG4-related autoimmune disease of the parotid gland [13]. Additionally, one report describes epithelial atypia in the common bile duct (suggestive of biliary intraepithelial neoplasia) in the presence of bile duct affection of AIPC [9].

The cholangitic lesion was classified as IAC type 1 due to the presence of several classical histological features: typical duct lesion with storiform periductal fibrosis but intact ductal epithelium, lymphoplasmacytic infiltrate with sufficient content of IgG4 positive plasma cells, simultaneous vascular and nerval affections, and focal inflammatory myofibroblastic tumorlike manifestation. Besides IAC, the hemihepatectomy specimen also showed significant siderosis. Iron storage disease in general carries an increased risk of hepatic malignancy, with HCC by far outscoring intrahepatic CC [14]. A contribution of increased iron storage to the genesis of CC has to be considered in principle, but it is certainly not the predominant cause of CC in our case, since hepatic malignancy in iron storage disease almost exclusively occurs at stage 4 (cirrhosis).

The rarity of IgG4 disease and the fact that IAC and AIPC have been described only recently may have obscured a potential causal relationship between these chronic inflammatory processes and tumor development in the affected organs. It is also possible that previous cases of IAC/AIPC (with CC) may have been diagnosed as PSC, which may share overlapping morphological characteristics with IAC [15].

Affection of the same target structure and close topographical correlation of CC and maximal (tumorlike) manifestation of IAC in the absence of other known relevant causes fuels the suspicion that IAC may have contributed to CC development in our case. Of course an inverse relationship, i.e., that intrahepatic CC may have triggered IAC cannot be ruled out. Nevertheless, as the tumor was localized in the subcapsular periphery of the liver and as the larger and hilar bile ducts were affected, IgG4-associated cholangitis in our case is unlikely a secondary cause of physical blockage or recurrent cholangitis. Yet, further observation and investigation are required to establish or rule out a possible relation between IAC/AIPC and the development of CC.

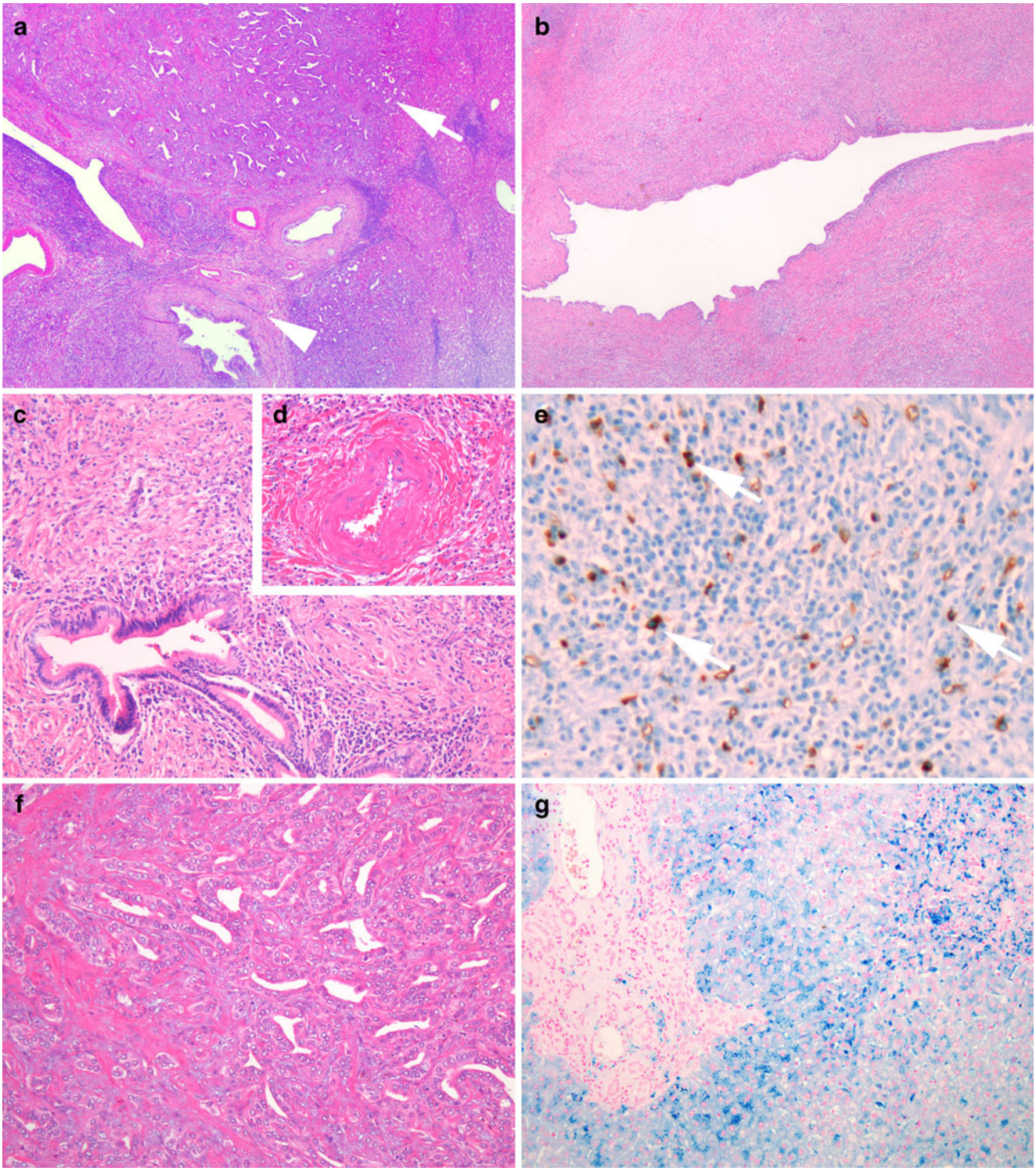

Fig. 3 Microscopic images of the intrahepatic cholangiocarcinoma and of the tumorlike manifestation of IAC. **a** Overview over the intrahepatic cholangiocarcinoma (*arrow*) and IAC (*arrowhead*). **b** Large bile duct in the centre with surrounding inflammatory cells, **c** smaller bile ducts with periductal lymphoplasmacytic infiltration with lack of duct destruction, and excessive storiform fibrosis with **d** encasement of a small artery. **e** Immunohistology for IgG4 demonstrated significantly elevated number of IgG4-positive plasma cells (>10/HPF). **f** Moderately differentiated intrahepatic cholangiocarcinoma. **g** The surrounding liver parenchyma with grade 3 siderosis. Magnification: ×12.5 (**a**), ×40 (**b**), ×200 (**c**, **d**, and **f**), ×400 (**e**), and ×100 (**g**)

Acknowledgment BKS was supported by a stipend of the Olympia-Morata program of the Medical Faculty of Heidelberg University.

Disclosure statement The authors declare that no financial or other conflict of interest exists in relation to the content of the article.

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