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Diagnostic Dilemma in a Patient with Jaundice: How to Differentiate between Autoimmune Pancreatitis, Primary Sclerosing Cholangitis and Pancreas Carcinoma

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Key Words
Autoimmune pancreatitis · Immunoglobulin G4-associated cholangitis · Pancreas carcinoma · Primary sclerosing cholangitis

Abstract
A 68-year-old male patient was referred to our institution in May 2011 for a suspected tumor in the pancreatic head with consecutive jaundice. Using magnetic resonance imaging, further differentiation between chronic inflammation and a malignant process was not possible with certainty. Apart from cholestasis, laboratory studies showed increased values for CA 19-9 to 532 U/ml (normal <37 U/ml) and hypergammaglobulinemia (immunoglobulin G, IgG) of 19.3% (normal 8.0–15.8%) with an elevation of the IgG4 subtype to 2,350 mg/l (normal 52–1,250 mg/l). Endoscopic retrograde cholangiopancreatography revealed a prominent stenosis of the distal ductus hepaticus communis caused by pancreatic head swelling and also a bihilar stenosis of the main hepatic bile ducts. Cytology demonstrated inflammatory cells without evidence of malignancy. Under suspicion of autoimmune pancreatitis with IgG4-associated cholangitis, immunosuppressive therapy with steroids and azathioprine was started. Follow-up endoscopic retrograde cholangiopancreatography after 3 months displayed regressive development of the diverse stenoses. Jaundice had disappeared and blood values had returned to normal ranges. Moreover, no tumor of the pancreatic head was present in the magnetic resonance control images. Due to clinical and radiological similarities but a consecutive completely different prognosis and therapy, it is of

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fundamental importance to differentiate between pancreatic cancer and autoimmune pancreatitis. Especially, determination of serum IgG4 levels and associated bile duct lesions induced by inflammation should clarify the diagnosis of autoimmune pancreatitis and legitimate immunosuppressive therapy.

Introduction

It is at present known and accepted that immunoglobulin G4 (IgG4)-associated cholangitis (IAC) is one of several diseases associated with autoimmune pancreatitis (AIP) [1–3]. However, IAC may occur in 20–90% of cases of AIP whereas a study of the Mayo Clinic recently revealed that 92.5% of patients with IAC suffer from AIP [4–6]. A possible involvement of *Helicobacter pylori* in the initiation of the autoimmune process is speculated [7–9]. Typical results concerning blood values are high IgG4 concentrations, which can be seen as a useful indicator to differentiate between other pancreatic or bile duct diseases [1–4, 10]. IgG4-related diseases such as AIP and IAC have typical histopathological features in common showing a diffuse infiltration with lymphocytes and IgG4-positive plasma cells [1, 2, 4, 7, 10].

The acute syndrome appears with obstructive jaundice (30–100%), diabetes mellitus (40–70%), abdominal pain (35%), and weight loss (30%) [1, 3, 4, 7, 10, 11]. Typical changes in pancreatic tissue are diffuse pancreatic swelling ('diffuse type') or a focal pancreatic mass ('focal type') with local lymphadenopathy and peri-pancreatic capsule-like rim [7, 11–13]. IAC is characterized by bile duct wall thickening and biliary strictures, which are, in contrast to primary sclerosing cholangitis, predominantly located in the lower bile ducts [1, 7, 11, 14–16].

Both AIP and IAC respond well to steroid therapy [3, 11, 14, 17, 18]. Although there is no accepted consensus concerning the dose of steroid therapy, an initiation of prednisolone with 0.6 mg/kg/day followed by steroid dose tapering has been demonstrated to be effective [1, 7, 11, 19, 20]. The need for maintaining immunosuppression (e.g. with azathioprine) after resolution has been documented [4, 7, 19]. Based on clinical and radiological similarities to primary sclerosing cholangitis, cholangiocarcinoma or pancreatic neoplasm but with completely different prognosis and therapeutic strategies, it is of major importance for the physician to differentiate between these entities and AIP/IAC.

Case Report

A 68-year-old male Caucasian patient was referred to our institution in May 2011 for a suspected tumor in the pancreatic head with consecutive stenosis of the hepatico-choledochic duct. Anamnestically, the patient complained of progressive fatigue and slight weight loss of 4 kg in the past 3 months accompanied by a painless jaundice. Laboratory studies were significant for total bilirubin of 5.5 mg/dl (normal 0.3–1.2 mg/dl), alkaline phosphatase (AP) of 294 U/l (normal 25–124) and γ-glutamyltransferase (γ-GT) of 359 U/l (normal <55 U/l). Pancreatic lipase was within normal ranges. Advanced diagnostic examinations revealed a hypergammaglobulinemia of 19.3% (normal 8.0–15.8%) with a significant elevation of the IgG4 subtype to 2,350 mg/l (normal 52–1,250 mg/l), while titers for anti-nuclear, anti-mitochondrial and anti-neutrophilic cytoplasmic antibodies were all negative. Furthermore, the tumor marker CA 19-9 was elevated to 532 U/ml (normal <37 U/ml).

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Abdominal ultrasound demonstrated extended extrahepatic bile ducts. Magnetic resonance imaging (MRI) presented a swelling of the processus uncinatus, conspicuous cholestasis, and a ductus wirsungianus with many cystic lesions. Differentiation between a chronic process of inflammation or a malignant process was not possible with certainty (**fig. 1**a). Consecutive endoscopic retrograde cholangiopancreatography (ERCP) showed a stenosis of the distal ductus hepaticus communis (DHC) caused by pancreatic head swelling and also a bihilar stenosis of the main hepatic bile ducts (fig. 1b). Endoscopic dilatation, lavage and insertion of two stents were carried out. Cytology of the bile duct stenosis revealed inflammatory cells without evidence of malignancy. Under suspicion of AIP with IAC, immunosuppressive therapy with an initial steroid dose of 50 mg prednisolone was started. Steroids were tapered down slowly by scheme to 5 mg/day prednisolone conservation dose in combination with azathioprine 1 mg/kg/day.

At follow-up 3 months later, the patient was in excellent general condition, had no complaints, had gained weight, and jaundice was no longer detectable. ERCP revealed a significant regression of the stenosis of the DHC and the main right and left bile ducts (**fig. 2**b). Total serum bilirubin (0.2 mg/dl), γ-GT (107 U/l), AP (48 U/l), IgG4 (1,110 mg/l), and finally CA 19-9 (9 U/ml) were within normal ranges (**fig. 3**). Likewise, MRI control examination 3 months after initiation of immunosuppressive therapy demonstrated regressive largeness of the bile ducts and pancreatic head. A malignant tumor of the pancreas was no longer detectable (fig. 2a).

Discussion

We herein describe a patient who was referred to our institution with the suspicion of a carcinoma of the pancreatic head with consecutive cholestasis. Clinical signs which encouraged the diagnosis were weight loss, progressive fatigue and painless jaundice. MRI showed a swelling of the processus uncinatus with conspicuous cholestasis. Moreover, the tumor marker CA 19-9 was significantly elevated, while pancreatic enzymes were within normal ranges. According to the literature, elevated levels of CA 19-9 are not common in patients with AIP, while levels >100 U/ml are often associated with pancreatic cancer [21].

The most common clinical features of AIP are weight loss and painless jaundice, the last being reported to occur in up to 100% of patients [1, 3, 4, 7, 10, 11, 22, 23]. AIP is frequently associated with extrapancreatic organ involvement, especially of the biliary tract, so-called IAC. Elevated levels of serum IgG4 are a characteristic feature of AIP with a sensitivity of 76% and a specificity of 93% [21, 22]. To distinguish AIP from pancreas carcinoma, Oseini et al. [24] recently described a specificity of 97% for a >2-fold increase in serum IgG4, while the specificity for a >4-fold increase was even 100%. In our case, serum IgG4 was significantly elevated to 2,350 mg/l (normal 52–1,250 mg/l). ERCP displayed a stenosis of the distal DHC caused by pancreatic head swelling without evidence of malignant cells in cytology.

Due to clinical and radiological similarities but a completely different prognosis and therapy, it is of major importance to differentiate between pancreatic cancer and AIP. Especially, determination of serum IgG4 levels with associated inflammatory bile duct changes should clarify the diagnosis of AIP and legitimate initiation of immunosuppressive therapy. This case report highlights the features of an emerging disease which is diagnostically challenging for the physician. To date, there are no international validated diagnostic criteria for this entity.

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Disclosure Statement

The authors have nothing to declare.

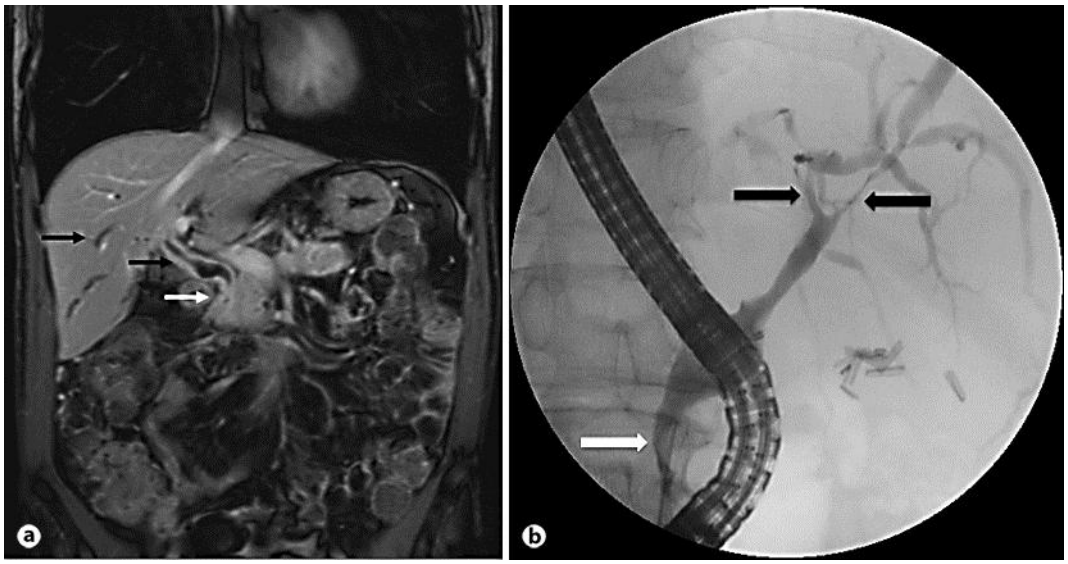

Fig. 1. **a** Initial contrast-enhanced T1-weighted image showing swelling of the processus uncinatus (white arrow) and conspicuous cholestasis (black arrows). **b** Likewise, initial ERCP revealed a significant stenosis of the distal DHC induced by pancreatic head swelling (white arrow) and bihilar strictures of the main hepatic bile ducts (black arrows).

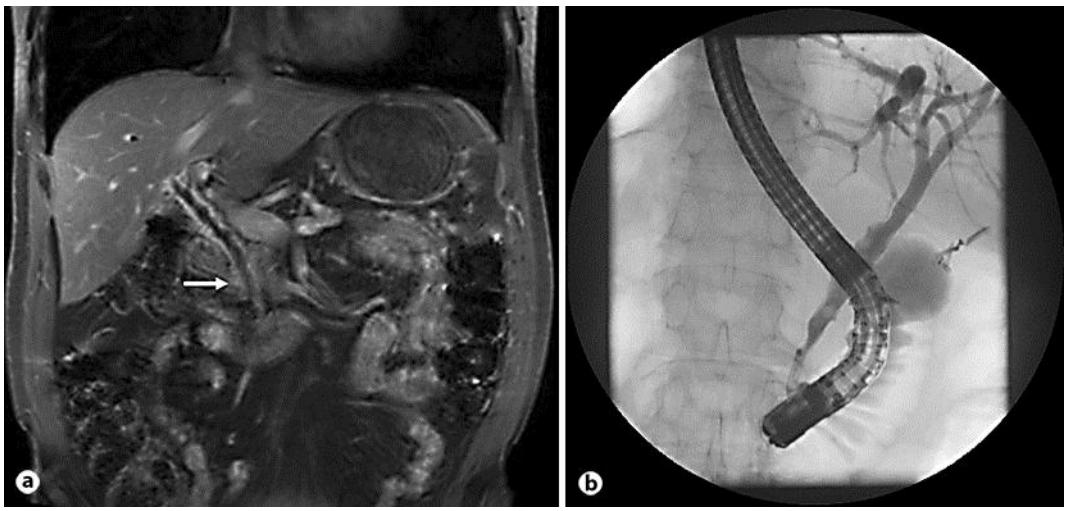

Fig. 2. **a** Following 3 months of immunosuppressive therapy, coronal contrast-enhanced T1-weighted image displayed normal pancreas morphology without malignancy and regressive cholestasis with thin DHC (white arrow). **b** Follow-up ERCP demonstrated a completely regressive development of the diverse stenoses of the DHC and the main right and left bile ducts.

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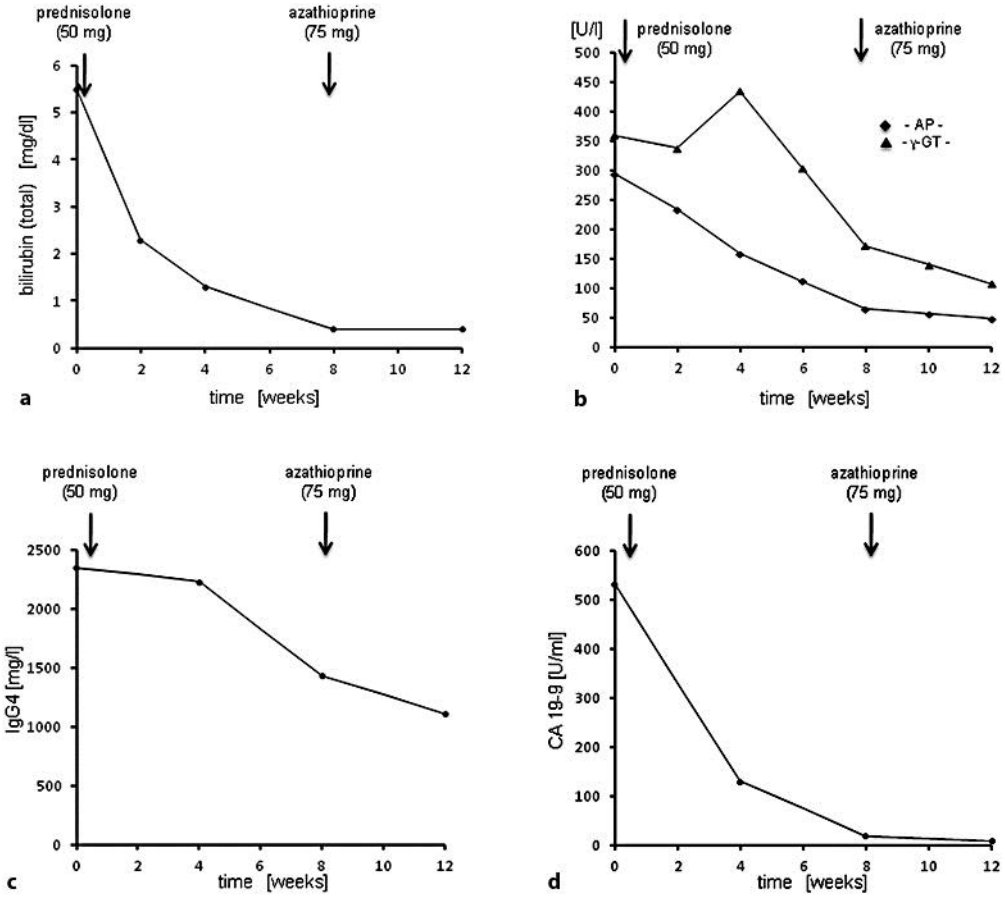

Fig. 3. a Total bilirubin continuously decreased from 5.5 to 0.4 mg/dl during immunosuppressive therapy. **b** γ-GT significantly decreased from 359 to 107 U/l during immunosuppressive therapy. Likewise, AP continuously decreased from 294 to 48 U/l during immunosuppressive therapy. **c** IgG4 continuously decreased from 2,350 to 1,110 mg/l during immunosuppressive therapy. **d** Finally, CA 19-9 continuously decreased to normal values from 532 to 9 U/ml during immunosuppressive therapy.

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