Peer reviewed article

Serum immunoglobin G4 (IgG4): an important marker in autoimmune pancreatitis?

Michael C. Sulz, Martin Geyer, Shajan Peter, Lukas Degen

Department of Gastroenterology and Hepatology, University Hospital of Basel, Basel, Switzerland

Summary

A unique form of chronic pancreatitis has recently become widely recognised as an important clinical entity in the spectrum of pancreatic diseases under the term autoimmune pancreatitis (AIP) [1]. This entity is characterised by irregular narrowing of the pancreatic duct, swelling of parenchyma, lymphoplasmacytic infiltration and fibrosis as well as favourable response to corticosteroid treatment. In addition, increased concentration of serum immunoglobulin G4 (IgG4) is a notable characteristic marker [2]. Some patients undergoing pancreaticoduodenectomy for presumed pancreatic ductal adenocarcinoma have instead been found to have AIP [3, 4]. Early recognition of AIP can prevent pancreaticoduodenectomy in these patients and effective treatment with steroids can be introduced.

Based on an interesting case, we discuss the entity of AIP with the rare combination of sclerosing cholangitis and we focus on the relevance of serum IgG4 as a factor in diagnosis and monitoring therapy of AIP.

Key words: autoimmune pancreatitis; immunglobulin G4 (IgG4)

Case

A 50-year-old man of oriental ethnic origin who lived in Switzerland for a long time, presented in our hospital with symptoms of cholestatic jaundice. The past medical history contained dyslipidaemia and arterial hypertension (under therapy with amiloride). He recently had stopped drinking alcohol. Liver function tests revealed a cholestatic pattern with preserved synthetic function (figure 1). The serological results showed an elevated level of ferritin 426 ng/ml (range 10–200 ng/ml), an elevated antinuclear antibody (ANA) titer 1:320 (normal <1:40) and slightly elevated serum gammaglobulins 18.5 g/l (range 6.2–14.4 g/l). A screening for liver diseases including viral hepatitis serology was negative. The liver biopsy demonstrated a nonspecific infiltration of lymphoplasmacellular cells without signs of steatosis or siderosis. The immunohistochemical examination with cytokeratin 19 noted presence of normal bile ducts.

Two months later, the patient presented with worsening symptoms, ie weight loss of 10 kg, loss of appetite, pruritus and pain in the right upper abdomen. Physical examination revealed a deeply jaundiced patient. Liver function tests this time showed progressive elevation of the bilirubin (243 umol/l), enzymes and cholestatic parameters (figure 1). Abdominal computed tomography (CT) exhibited an enlarged head of pancreas with dilatation of the biliary system. The endoscopic ultrasonography (EUS) confirmed the presence of a hypoechogenic mass measuring 4 cm in diameter within the head of pancreas. An Endoscopic Retrograde Cholangio Pancreaticogram (ERCP) was performed which revealed a single 25 mm long smooth stricture of the distal common bile duct with normal intrahepatic ducts. A plastic stent (8.5 French) was inserted in the bile duct across the stricture. Fine needle biopsies and brushings of the stricture were negative for malignancy.

Considering the mass lesion within the pancreatic head along with the history of weight loss, cholestasis, and mildly elevated cancer antigen (CA) 19–9 (189 U/ml; range <34 U/ml), a pancreatic carcinoma could not be definitely excluded. Therefore a partial duodenopancreatectomy (Traverso) was done. The histology of the resected pancreas showed a lymphoplasmacellular sclerosing inflammation without signs of malignancy (figure 2A and 2B).

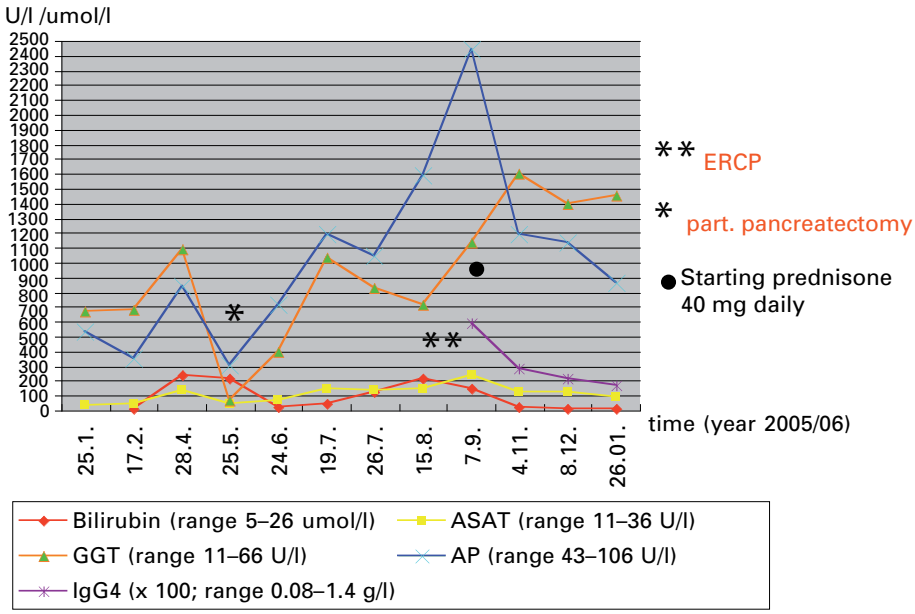
Abbreviations

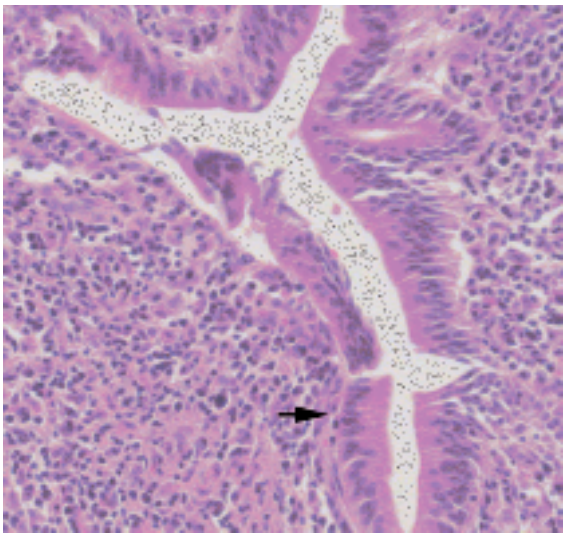
AIP	=	autoimmune pancreatitis
ANA	=	anti nucleoid antibodies
ASAT	=	aspartat aminotransferase
AP	=	alkaline phosphatase
CA 19-9	=	cancer antigen 19-9
CA I/II	=	carbonic anhydrase 1 and 2
CEA	=	carcinogenic embryonal antigen
CT	=	computed tomography
ERCP	=	Endoscopic Retrograde Cholangio Pancreaticogram
EUS	=	Endoscopic ultrasonography
GGT	=	gamma glutamintransferase
IgG4	=	immunoglobulin G4
PSC	=	primary sclerosing cholangitis

No financial support declared.

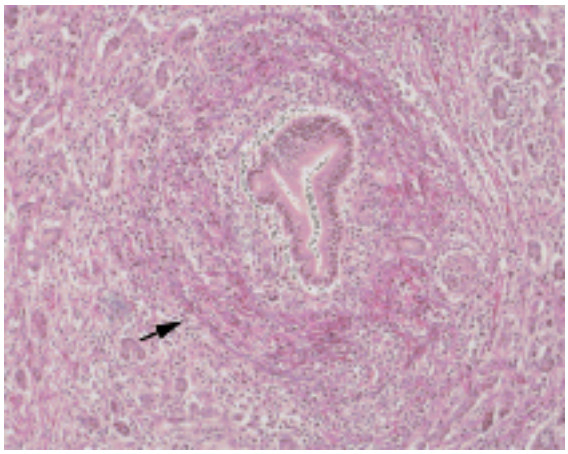
Figure 1

Fluctuations of the laboratory parameters.

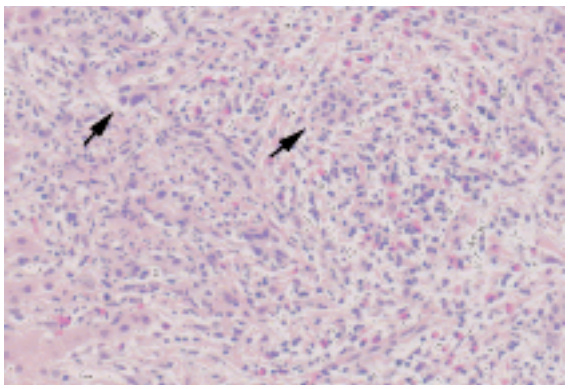




A



B



C

Figure 2

A: Histology of pancreas: Medium sized pancreatic duct surrounded by a dense inflamatory infiltrate composed of lymphocytes, plasmacells and some granulocytes. Single inflammatory cells infiltrate the duct epithelium (arrow). HE 20x
B: Pancreatic duct surrounded by fibrosis (arrow). 20x
C: liver biopsy: Portal space with severe inflammmatory infiltrate (lymphocytes, plasma cells, granulocytes), edema (cholestasis) with disruption of bile ducts (arrows) and neoductulation. 20x

Following surgery, the serum aminotransferases and cholestatic parameters reduced briefly, however a month later, increasing cholestatic parameters were noticed (figure 1). A subsequent ultrasonography and CT scan of the abdomen were done which showed mildly dilated intrahepatic bile ducts. Further ERCP displayed tapered peripheral intrahepatic ducts which in comparison with the previous ERCP images were suggestive of a rapidly progressive sclerosing cholangitis (figure 3). The liver biopsy confirmed this diagnosis (figure 2 C). Laboratory investigations also revealed elevated serum gammaglobulins (42.7%; [range 10–18%]), with markedly raised IgG levels (29.8 g/l [range 6.5–15 g/l]) of predominantly IgG4 type (5.94 g/l [range 0.08–1.40 g/l]; figure 1). The ANA-titre was elevated (1:640; [range 1:40]).

A final diagnosis of IgG4 positive autoimmune pancreatitis (AIP) with associated rapid progressive sclerosing cholangitis was made. Other investigations for AIP such as autoantibodies to carbonic anhydrase 1 and 2 (CA I/II) and lactoferrin were negative.

We commenced therapy with corticosteroids (prednisone 40 mg daily). 6 months later the patient was observed to have a good clinical response and was anicteric. Serum IgG4 levels fell down, but the cholestatic parameters remained high (figure 1).

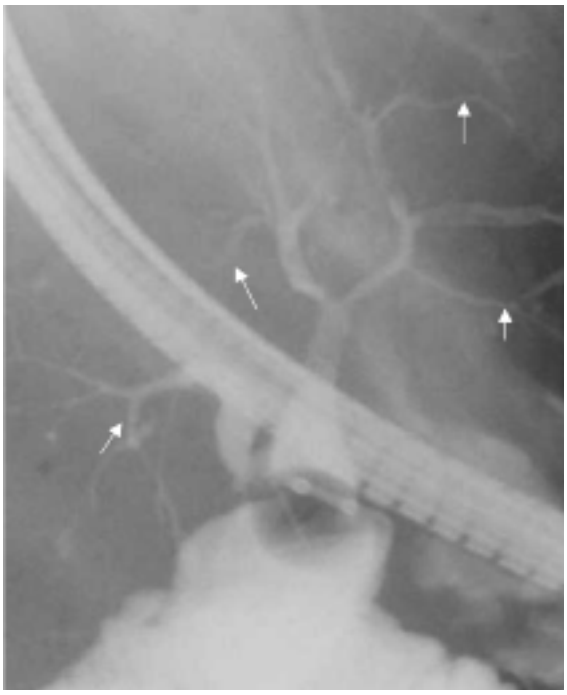


Figure 3

ERCP shows multiple irregular walls of bile ducts without any dominant stricture (arrows).

Discussion

Autoimmune pancreatitis (AIP) is a rare entity and a unique form of chronic pancreatitis. The cause of AIP is uncertain, but immunologic mechanisms appear likely, given the characteristic histologic findings of lymphoplasmacytic infiltration, prevalence of hypergammaglobulinaemia, autoantibodies, and response to steroids [5]. AIP has been described as a primary pancreatic disorder as well as in association with other diseases of autoimmune aetiology including sclerosing cholangitis, Sjögren's syndrome, rheumatoid arthritis, sarcoidosis [6].

The most widely recognised clinical presentation of AIP is mimicking pancreatic ductal adenocarcinoma [1]. Jaundice is a leading symptom, occurring in 40–81% of patients [1]. Abdominal pain, if present, is mild [7]. Weight loss may be significant. Diabetes mellitus, usually of recent onset, may be present in up to 50% of patients [1]. AIP is a benign finding seen in approximately 2.5% of patients who undergo pancreaticoduodenectomy for presumed pancreatic ductal adenocarcinoma as noted in our case [3, 4]. Early recognition confirmed by clinical, laboratory and histological parameters is desirable to prevent surgical intervention. More often history and radiological tests are not sufficiently sensitive to identify patients with AIP. While comparing AIP patients and those with pancreatic ductal carcinoma, there are no major differences in the occurrence of abdominal pain, weight loss, jaundice, raised carcinoembryonic antigen (CEA) or CA 19–9 levels at the time of presentation [4] which hinders a definite diagnosis.

IgG4 has been found to be an early elevated marker aiding in the diagnosis of AIP. Studies, especially from Japan, showed that elevated serum IgG4 levels strongly supported the diagnosis of AIP, demarcating from pancreatic cancer, alcohol-induced/idiopathic chronic pancreatitis, primary biliary cirrhosis and primary sclerosing cholangitis (PSC). Levels of serum IgG4 over 135 mg/dl had a sensitivity of 95% and specificity of 97%, distinguishing AIP from pancreatic cancer [2, 8]. Serum IgG4 levels have also been found to be useful for the follow-up therapy of AIP [2]. We noticed that in our patient declining IgG4 levels (figure 1) appeared to correlate with clinical and laboratory improvement. However, conflicting reports showing only 33% [9] and 62% of patients with AIP [10] questioned the validity of raised IgG4 levels and pointed out that markers such as serum IgG4 levels and CA II antibodies are not specific enough to differentiate AIP in patients with other pancreatic disorders [11].

Clinical response to steroid therapy, at least partially, has been reported. However, an optimal treatment regime is still undefined and a morphological response may take a number of weeks if not months [6, 12]. In several series involving small numbers of patients with AIP, treatment with prednisone at a dosage of 20 to 40 mg/day has resulted in clinical, radiologic and histologic improvement [2, 5]. In those patients following a partial pancreatic resection, the benefit of a steroid therapy remains unclear [5]. Some authors have noted spontaneous resolution without treatment [1, 5]. Measures to monitor treatment response includes assessment of symptoms, pancreatic exocrine and endocrine function, liver function tests, EUS with or without biopsy, CT [12] and IgG4 levels [2].

Additionally, we presented a rare association of AIP with progressive sclerosing cholangitis (single stricture of the common bile duct to peripheral pruning of the intrahepatic ducts) occurring within three months of onset of jaundice. This fulminant clinical expression of sclerosing cholangitis appears different from naive PSC and these patients seem to belong to a subset of AIP [13]. Histologically, the bile ducts are damaged by a dense transmural lymphoplasmacytic infiltrate, with many IgG4-positive plasma cells [13, 14]. Notably, biliary disease associated with AIP differs from PSC because the ductal abnormalities resolve with steroid therapy [15].

Conclusions

The diagnosis of autoimmune pancreatitis (AIP) is likely to be missed due to the general lack of specific symptoms, a clinical presentation that may mimic other disorders, mainly pancreatic ductal carcinoma, and the lack of specific imaging tests. An elevated serum IgG4 level is a helpful marker in the diagnosis and therapy of AIP. However, it is early to underscore its exact validity and specificity. Until further prospective studies defining the role of IgG4 as an early diagnostic marker come forth, histological evidence with characteristic lymphoplasmacytic infiltration of the pancreas will prove to be the gold standard [1, 5] Steroids are the milestone of therapy, but cannot be recommended if substantial doubt about malignancy exists. There is a rare association between AIP and rapid sclerosing cholangitis and one should think of this possibility, if a patient presents with the picture of cholangitis and a pancreatic mass.

AIP remains a challenging diagnosis based on a combination of clinical, radiologic, serologic, and histologic findings [1]. Emerging awareness and knowledge will shed more light in the management of these patients.

We acknowledge Dr Luigi Tornillo, Department of Pathology, University Hospital of Basel, for providing us the histological pictures.

Correspondence:
Dr Michael Christian Sulz
Department of Gastroenterology and Hepatology
University Hospital of Basel
Petersgraben 4
CH-4031 Basel
sulzm@uhbs.ch

References

1 Pearson RK, Longnecker DS, Chari ST, Smyrk TC, Okazaki K, Frulloni L, et al. Controversies in clinical pancreatology: autoimmune pancreatitis: does it exist? Pancreas 2003;27:1–13.
2 Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med 2001;344:732–8.
3 Abraham SC, Wilentz RE, Yeo CJ, Sohn TA, Cameron JL, Boitnott JK, et al. Pancreaticoduodenectomy (Whipple resections) in patients without malignancy: are they all chronic pancreatitis? Am J Surg Pathol 2003;27:110–20.
4 Hardacre JM, Iacobuzio-Donahue CA, Sohn TA, Abraham SC, Yeo CJ, Lillemoe KD, et al. Results of pancreaticoduodenectomy for lymphoplasmacytic sclerosing pancreatitis. Ann Surg 2003;237:853–8.
5 Lara LP, Chari ST. Autoimmune Pancreatitis. Current Gastroenterology Reports 2005;7:102(101–106).
6 Okazaki K, Chiba T. Autoimmune related pancreatitis. Gut 2002;51:1–4.
7 Yadav D, Notahara K, Smyrk TC, Clain JE, Pearson RK, Farnell MB, et al. Idiopathic tumefactive chronic pancreatitis: clinical profile, histology, and natural history after resection. Clin Gastroenterol Hepatol 2003;1:129–35.
8 Hirano K, Komatsu Y, Yamamoto N, Nakai Y, Sasahira N, Toda N, et al. Pancreatic mass lesions associated with raised concentration of IgG4. Am J Gastroenterol 2004;99:2038–40.
9 Farrell JJ, Garber J, Sahani D, Brugge WR. EUS findings in patients with autoimmune pancreatitis. Gastrointest Endosc 2004;60:927–36.
10 Kim K-p, Kim M-H, Song MH, Lee SS, Seo DW, Lee SK. Autoimmune chronic pancreatitis. Am J Gastroenterol 2004;99: 1605–16.
11 Aparisi L, Farre A, Gomez-Cambronero L, Martinez J, De Las Heras G, Corts J, et al. Antibodies to carbonic anhydrase and IgG4 levels in idiopathic chronic pancreatitis: relevance for diagnosis of autoimmune pancreatitis. Gut 2005;54:703–9.
12 Sutton R. Autoimmune pancreatitis – also a Western disease. Gut 2005;54:581–3.
13 Deshpande V, Mino-Kenudson M, Brugge W, Lauwers GY. Autoimmune pancreatitis. More than just a pancreatic disease? A contemporary review of its pathology. Arch Pathol Lab Med 2005;129:(1151):1148–54.
14 Zen Y, Harada K, Sasaki M, Sato Y, Tsuneyama K, Haratake J, et al. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis. Am J Surg Pathol 2004;28: 1193(1193–1203).
15 Ichimura T, Kondo S, Ambo Y, Hirano S, Ohmi M, Okushiba S, et al. Primary sclerosing cholangitis associated with autoimmune pancreatitis. Hepatogastroenterology 2002;49:1221–4.

Swiss
Medical Weekly

Official journal of
the Swiss Society of Infectious disease
the Swiss Society of Internal Medicine
the Swiss Respiratory Society

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)

- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses

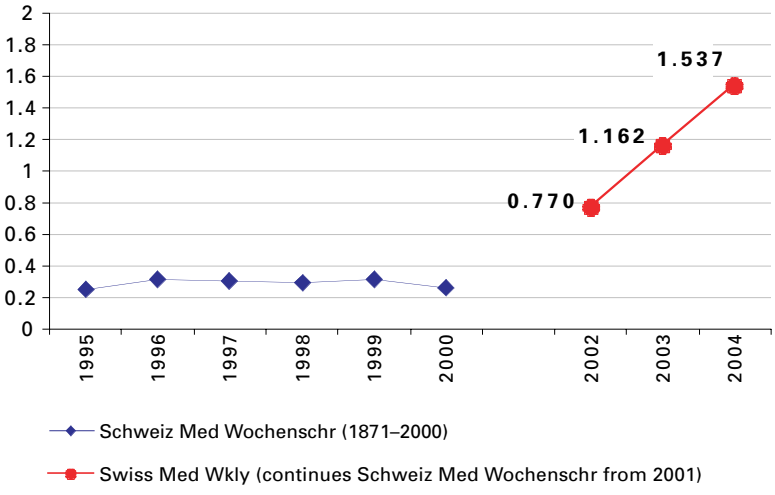
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly



EMH FMH Schwabe
Editores Medicorum Helveticorum

All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnsburgerstrasse 8
CH-4132 Muttenz

Manuscripts: submission@smw.ch
Letters to the editor: letters@smw.ch
Editorial Board: red@smw.ch
Internet: http://www.smw.ch