Autoimmune hepatitis and systemic sclerosis: a new overlap syndrome?

I. Marie, H. Levesque, J. L. Tranvouez1, A. François2, G. Riachi3, N. Cailleux and H. Courtois

Department of Internal Medicine, Centre Hospitalier Universitaire de Rouen-Boisguillaume, 76031 Rouen Cedex, 1Department of Gastroenterology, Centre Hospitalier Universitaire du Havre, 76083 Le Havre Cedex, 2Department of Cytology and Pathology, Centre Hospitalier Universitaire de Rouen, 76031 Rouen Cedex and 3Department of Gastroenterology, Centre Hospitalier Universitaire de Rouen, 76031 Rouen Cedex, France

Abstract

Objective. We report the cases of two patients with the complete CREST variant (calcinosi...es of systemic sclerosis (SSc) who developed autoimmune hepatitis.

Results. Our findings suggest that autoimmune hepatitis can be considered to be one of the liver manifestations associated with SSc. Our data also indicate that, because liver involvement may precede skin manifestations, evaluation for SSc is appropriate when autoimmune hepatitis is noted, and that the evaluation should include clinical examination, testing for antinuclear antibodies (especially for anticientromere antibodies) and nailfold capillaroscopy.

Conclusions. From a practical point of view, our two cases emphasize that suspicion of autoimmune hepatitis in SSc patients presenting with cytolitic hepatitis will help to achieve both accurate diagnosis and optimal management.

Key words: Systemic sclerosis, CREST syndrome, Autoimmune hepatitis.

Autoimmune hepatitis is an uncommon disorder that is characterized by both biochemical abnormalities and histological liver damage [1–3], i.e. (i) blood hypergammaglobulinaemia with a selective increase in IgG concentration; (ii) serum autoantibodies, i.e. typically antinuclear antibodies, antibodies to smooth muscle, actin, liver–kidney microsome type 1 (anti-LKM1) and antibodies to asialoglycoprotein receptor, soluble liver antigen, liver-pancreas antibody (anti-LP), liver cytosol type 1 (anti-LC1) or perinuclear-staining antineutrophil cytoplasmic antibodies; (iii) interface hepatitis, with piecemeal necrosis and periportal lymphocytolamocytic inflammatory infiltrates on histological examination of liver biopsy specimens; and (iv) the absence of evidence of concomitant viral hepatitis (i.e. negative serology for cytomegalovirus, Epstein–Barr virus, herpes simplex virus, hepatitis B surface antigen, antibodies to hepatitis B core antigen, hepatitis C virus and hepatitis A virus). Autoimmune hepatitis has been reported in patients with various diseases, including insulin-dependent diabetes, vitiligo, glomerulonephritis and autoimmune haemolytic anaemia [3, 4]. However, autoimmune hepatitis related to connective tissue disorders has been described as occurring rarely, for example during the course of systemic lupus erythematosus, Sjögren’s syndrome and mixed connective tissue diseases [5]. We observed two cases of particular interest, in which the patients with the complete CREST variant (calcinosi, Raynaud’s phenomenon, oesophageal dysmotility, sclerodactyly, telangectasia) of systemic sclerosis (SSc) developed autoimmune hepatitis.

Case reports

Patient 1

A 67-yr-old woman was diagnosed with complete CREST variant of SSc in 1990. The cutaneous impairment of the CREST syndrome was characterized by limited cutaneous sclerosis associated with telangectasias, pitting scars and cutis calcinosis. Systemic manifestations of CREST syndrome included: (i) Raynaud’s phenomenon; (ii) oesophageal involvement, characterized by both the absence of peristalsis in the lower two-thirds of the esophageal body and low pressure in the lower oesophageal sphincter; and (iii) interstitial lung disease, i.e. mild bibasilar pulmonary shadowing on computed...
tomography (CT) and both decreased vital capacity and
diffusing capacity of carbon monoxide on pulmonary
function tests (92 and 68% of predicted values re-
spectively). Autoantibody screening tests were positive for
antinuclear antibodies (1: 600) and anticitromere anti-
body. She received treatment with combined diltiazem
and cismanide. In April 1997, the patient presented with
mild pain involving the right hypochondrium area.
General physical examination was otherwise normal.
Liver tests revealed alanine aminotransferase (GPT)
240 U/l (normal range 3–21), aspartate aminotrans-
ferase (GOT) 223 U/l (normal range 3–26), γ-glut-
amyldtransferase (GGT) 510 U/l (normal range 5–25),
alkaline phosphatase 250 U/l (normal range 73–207) and
total bilirubin 5 U/l (normal range 2–18). Other routine
laboratory investigations were normal, notably pro-
thrombin time (90%). Blood electrophoresis revealed total
protein 76 g/l, albumin 38 g/l, polycylic gammapathy
with increased IgG (21 g/l; normal range 6.75–12.65).
Abdominal ultrasound examination was normal. Viral
serologies (cytomegalovirus, Epstein–Barr virus, herpes
simplex virus, hepatitis B surface antigen, antibodies
to hepatitis B core antigen, hepatitis C virus, hepatitis A
virus, human immunodeficiency virus) were negative.
Autoantibody screening was positive for antinuclear
antibodies (1: 1000) and antinitromere antibody, and
negative for cryoglobulinaemia, antimitochondrial and
anti-smooth muscle antibodies, anti-LKM1 antibodies,
anticardiolipin and antiphospholipid antibodies and
lupus-like anticoagulant. Liver biopsy specimens dem-
strated damage consistent with chronic active auto-
imune hepatitis, i.e. portal inflammatory infiltrates,
composed of both lymphocytes and plasma cells,
associated with piecemeal necrosis; lobular necrosis,
porto-portal bridging fibrosis and cirrhotic nodules were
absent. The diagnosis of autoimmune hepatitis in
a patient with CREST syndrome was made. The patient
was treated with oral steroid therapy, at an initial
dose of 0.7 mg/kg daily (i.e. prednisone 40 mg per
day), which resulted in complete resolution of abdominal
pain and marked improvement of liver test abnormalities.
In December 1999, when the patient was taking pred-
nisone 9 mg daily, there were no abdominal symptoms,
and liver tests showed GPT 22 U/l, GOT 14 U/l, GGT
37 U/l, alkaline phosphatase 128 U/l and total bilirubin
3 U/l.

Patient 2
A 48-yr-old woman had a 10-yr history of Raynaud’s
phenomenon. In February 1999, the patient was
admitted for dysphagia that had been developing for
1 month. Physical examination revealed limited
cutaneous sclerosis and telangiectasias, and was other-
wise normal. Autoantibody screening was positive for
antinuclear antibodies (1: 1000) and anticitromere anti-
body. Nailfold capillaroscopy showed organic
microangiopathy with enlarged capillary loops. Gastro-
scopy was normal, and revealed no evidence of
oesophagitis. Oesophageal manometry demonstrated
low pressure in the lower oesophageal sphincter and
an absence of peristalsis in the lower two-thirds of
the oesophageal body. Investigations, including pulmonary
CT scanning and function tests and salivary gland
histology, were within normal limits. CREST syndrome
was diagnosed. Laboratory findings were abnormal for
GPT (175 U/l), GOT (147 U/l), GGT (250 U/l) and
alkaline phosphatase (245 U/l). Blood electrophoresis
revealed polyclonal gammapathy, with increased IgG at
35 g/l. Abdominal ultrasound examination was normal.
Viral serologies (cytomegalovirus, Epstein–Barr virus,
herpes simplex virus, hepatitis B and C, human immuno-
deficiency virus) were negative. Liver biopsy specimens
revealed damage consistent with chronic active auto-
imune hepatitis. Autoantibody screening was negative
for antimitochondrial and anti-smooth muscle anti-
bodies, anti-LKM1 antibodies, antiphospholipid antibodies,
cryoglobulinaemia and antineutrophil cytoplasmic anti-
bodies. The diagnosis was autoimmune hepatitis in a
patient with CREST syndrome. The patient was treated
with combined diltiazem and cismanide. Prednisone
was started concomitantly at 0.5 mg/kg daily (i.e.
35 mg/day), in association with azathioprine, and this
treatment resulted in the complete disappearance of liver
test abnormalities. In March 2000, when the patient
was taking both prednisone 15 mg daily and azathi-
oprime, there were no abdominal symptoms and liver
tests showed GPT 25 U/l, GOT 18 U/l, GGT 27 U/l and
alkaline phosphatase 77 U/l.

Discussion
SSc is a systemic inflammatory disorder affecting
the skin and other organs, especially the gastrointestinal
tract [6–10]. Although the prevalence of oesophageal
and anorectal impairment in patients with SSc has
been reported to be as high as 90% [6–11], liver
involvement is considered to be rare in SSc, usually
arising during the course of the disease [6, 8, 10–14].
Abu-Shakra et al. [12] noted that only four of 262 SSc
patients (1.5%) had chronic liver disease. In a post-
mortem series of 57 SSc patients, D’Angelo et al. [14]
found histological liver damage in 8.8% of cases.

Primary biliary cirrhosis is the liver disorder that is
the most frequently encountered in SSc patients
[6, 8, 10, 11, 15–26]. It is a chronic progressive
cholestatic disease characterized by the destruction of
intrahepatic bile ducts and inflammation within the
portal tracts, leading to cirrhosis [20]. Larger [27]
observed that the prevalence of primary biliary cirrhosis
was as high as 51.2% in SSc patients (22 of 43 patients)
with liver dysfunction. On the other hand, many authors
demonstrated that clinical manifestations of SSc were
common in primary biliary cirrhosis, occurring in as
many as 3–18% of patients [17, 18, 28]; the majority of
these patients, with both SSc and primary biliary cirrho-
sis, had anticitromere antibody. In a series of 83 patients
with primary biliary cirrhosis [17], 17% of patients
had concomitant SSc (two with CREST syndrome
and 12 with limited cutaneous SSC). Culp et al. [18] noted that 20 of 113 patients with primary biliary cirrhosis (18%) had clinical evidence of SSC and variants (eight with CREST syndrome, three with SSC and nine with Raynaud’s phenomenon). Interestingly, primary biliary cirrhosis may be more frequent in SSC patients with anticientromere antibody than in those without it (15.8 vs 9%), but the role of anticientromere antibody in the genesis of liver damage remains unclear in SSC [29].

Nodular regenerative hyperplasia of the liver has been reported in association with SSC relatively uncommonly [11, 30-33]. It is defined histologically by nodules of hyperplastic hepatocytes within the liver (without disturbance of the architectural framework, fibrosis or hepatocyte necrosis), and may be responsible for dramatic complications related to portal hypertension in SSC patients [30-33]. As few authors [21] have found both histological damage of nodular regenerative hyperplasia of the liver and primary biliary cirrhosis in patients with CREST syndrome, nodular regenerative hyperplasia of the liver may represent an early histological stage of primary biliary cirrhosis.

Finally, a few isolated observations of SSC patients presenting with additional liver manifestations have been described: (i) idiopathic portal hypertension [22, 34, 35]; (ii) spontaneous rupture of the liver [22]; (iii) massive infarction of the liver [36] (the authors postulated that underlying histological sclerosis of the splanchic vessels, with large swollen, loosely arranged endothelial cells, was probably the factor that precipitated vasospasm, responsible for the massive necrosis of the liver); and (iv) hepatic duct obstruction related to vasculitis [22].

Our two unusual cases are reminiscent of those reported by Ishikawa et al. [37] and Yabe et al. [38], who described two Japanese patients with CREST syndrome and autoimmune hepatitis. Twenty-three patients with complete CREST variant were seen at the University of Rouen medical centre between 1990 and 1999. In our population, the prevalence of autoimmune hepatitis was therefore 8.7% (2/23) in this subgroup of SSC patients. In this instance, the diagnosis of autoimmune hepatitis was reasonably definite because our two Caucasian patients with CREST syndrome fulfilled all the diagnostic criteria of the International Autoimmune Hepatitis Group for autoimmune hepatitis [1, 2], i.e. (i) increased GGT and GPT levels with alkaline phosphatase levels less than three times the normal value; (ii) total γ-globulin or IgG levels more than 1.5 times the upper limit of normal; and (iii) high titres of antinuclear antibodies (> 1:80). Our patients were negative for anti-mitochondrial, anti-smooth muscle, anti-LKM1 and antineutrophil cytoplasmic antibodies [other liver autoantibodies associated with autoimmune hepatitis (i.e. antibodies to asialoglycoprotein receptor, soluble liver antigen, liver–pancreas and liver cytosol type) were not tested in either patient, as the detection of these antibodies is not yet available in our University hospital]; (iv) characteristic histological liver damage, i.e. interface or periportal hepatitis (histological evidence of damage associated with primary biliary cirrhosis was absent, which excluded primary biliary cirrhosis/autoimmune hepatitis overlap); (v) viral serologies (hepatitis A, B and C, cytomegalovirus, Epstein–Barr virus) were all negative; and (vi) there was no evidence for other causes of liver disorders. The patients had no history of alcohol abuse and they had not received drugs that can idiosyncratically cause hepatitis, including those that can mimic autoimmune hepatitis. Although diltiazem and cisapride have been shown to cause biochemical liver test abnormalities and even clinical hepatitis occasionally, they were clearly not implicated in Patient 2 because this therapy was instituted after the diagnosis of autoimmune hepatitis. Hepatotoxicity of both diltiazem and cisapride can also be excluded in Patient 1, as biochemical liver values returned to normal after the initiation of steroid therapy.

The pathological mechanisms of autoimmune hepatitis in our two patients with CREST syndrome remain unclear, which raises the question of whether the condition arose through a causal association (as part of a continuum) or by chance. However, autoimmune hepatitis may be due in part to dysfunction of both cell and humoral immunity related to SSC, as anticientromere antibody has been detected in 0–13% of patients with autoimmune hepatitis [28, 37, 38]. No definite conclusion can be drawn, and these findings warrant further investigation.

The treatment of autoimmune hepatitis is difficult in patients with SSC, as patients (mainly with diffuse cutaneous SSC) receiving more than 15 mg prednisone daily are at high risk of renal crisis related to their SSC [39]. Our two patients with CREST syndrome were followed very closely initially, and the outcome of their autoimmune hepatitis was favourable. Patient 1 had a disease course that was benign both clinically and biochemically with steroid therapy. Our findings are in accordance with those of other authors [37, 38], who described two SSC patients who showed improvement of autoimmune hepatitis with prednisone as a monotherapy. Patient 2 was successfully given combined therapy with prednisone and azathioprine. Neither of these patients developed complications related to steroid therapy.

We suggest that autoimmune hepatitis can be considered to be one of the liver manifestations associated with SSC. Autoimmune hepatitis occurred late in the course of SSC (at the 7-yr follow-up) in Patient 1, whereas the diagnoses of SSC and autoimmune hepatitis were concomitant in Patient 2. Our findings therefore indicate that, because liver involvement may precede skin manifestations, evaluation for SSC is appropriate when autoimmune hepatitis is noted, and this evaluation should include clinical examination, testing for antinuclear antibodies (especially for anticientromere antibodies) and nailfold capillaroscopy.
From a practical point of view, our data also emphasize that suspicion of autoimmune hepatitis in SSc patients presenting with cytolysis will help to achieve both accurate diagnosis and optimal management. Finally, physicians, particularly rheumatologists and internists, should be aware of the possibility of such liver damage in patients with SSc.

References


