Systemic Sclerosis-Polymyositis Overlap Syndrome Associated with Autoimmune Hepatitis and Cerebral Vasculitis

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Abstract

Autoimmune hepatitis (AIH) is a chronic disorder characterized by persistent hepatocellular inflammation and necrosis. AIH overlap syndromes with other autoimmune diseases have been reported, including connective tissue diseases (CTD). Reports of AIH in systemic sclerosis (SSc), however, are scarce and have been particularly described in the limited SSc subtype. We report a case of systemic sclerosis-polymyositis overlap syndrome that developed AIH and subsequently, cerebral vasculitis. To our knowledge, this is the first report of such a complex mosaic of autoimmunity. We also review the literature regarding scleroderma-related AIH.

Key words

Systemic sclerosis – scleroderma – autoimmune hepatitis – polymyositis – cerebral vasculitis.

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by fibrosis of the skin and internal organs, marked alterations in the microvasculature, and immunological abnormalities. Gastrointestinal involvement has been reported in as many as 90% of patients with SSc, yet the frequency of liver involvement remains low. Among autoimmune liver diseases, SSc has an established association with primary biliary cirrhosis (PBC) and the presence of anticentromere antibodies. Primary biliary cirrhosis is the leading cause of liver dysfunction in SSc (76.1%) [1], 20% of patients with SSc testing positive for PBC screen antibodies [2].

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The relation of autoimmune hepatitis (AIH) to SSc remains to be defined. There have been isolated reports of SSc with AIH [3-13] occurring in the course of the disease, as well as reports of localized scleroderma occurring during the course of AIH [14].

We hereby describe a case of SSc and silent polymyositis who developed AIH and, subsequently, cerebral vasculitis, with excellent response to immunosuppressive therapy.

Case report

A 53-year-old active nurse, diagnosed in 2007 with limited SSc, but no features of major organ involvement, presented in October 2010 in our department for the six-month regular follow-up. She had no complaints and the clinical examination revealed no particular abnormalities. Her laboratory tests however, disclosed increased erythrocyte sedimentation rate (44mm/h) and serum aminotransferase levels (ALAT=186UI/l, AST=138UI/), without cholestasis or elevated muscle enzymes level. The immunological report revealed positive anti-nuclear antibodies (ANA) (1:1280, speckled), with negative antibodies to mitochondrial, smooth muscle, liver-kidney microsome type 1 (LKM-1). The screening for viral hepatitis, Wilson disease, α1-antitripsin deficiency and dyslipidemia was negative, and she had no history of hepatotoxic medication or alcohol intake. She was referred to the gastroenterology unit, where the abdominal ultrasound showed hyperechoic mild hepatomegaly. A liver biopsy revealed piecemeal necrosis, plasma cell infiltration into the portal tract and liver lobes, and fibrosis (Fig. 1). The diagnosis of AIH was made and she was administred 0.5mg/kg/day prednisone and azathioprine.

Three weeks later the patient developed dysphagia due to severe esophageal candidiasis, and was started on antifungal agents, together with a reduction in the steroid dose. Despite therapy, her condition rapidly altered. Ten days later, the patient was admitted to the hospital for severe fatigue and proximal muscle weakness. She had lost weight and was dehydrated due to the persistence of the gastrointestinal complaints. Striking were the presence of cognitive dysfunction, confusion and anxiety disorder, as well as a

marked increase in the number and size of telangiectasia lesions. Laboratory and immunological investigations showed: leukopenia (2600/mm^3), thrombocytopenia (82,000/mm^3), aminotransferase elevation (ALT=123, AST=52), increased lactate dehydrogenase (1558U/l) and creatine phosphokinase levels (298IU/l), as well as high titers of serum globulin, positive ANA, positive anticentromere antibodies and negative anti-dsDNA and antiphospholipid antibodies. A broad septic screen was positive for candida albicans and candida kefir cultures from the buccal smear, but with negative blood cultures. Additional investigations showed small pericardial effusion on echocardiography and exudative alveolitis with incipient fibrosis on pulmonary CT. A muscle biopsy was performed and was consistent with mostly chronic damage, but also active lesions of myositis (Fig. 2). The brain MRI revealed small hyperintense T2-weighted focal lesions, localized bilaterally in the fronto-parietal white mass, suggestive for cerebral vasculitis/vasculopathy. The patient was diagnosed with additional myositis and cerebral vasculitis. Treatment with pulse methylprednisolone and cyclophosphamide was initiated, while simultaneously continuing the antifungal therapy. The evolution within the three following months was spectacular, with a recovery of the muscle strength, cognitive status and anxiety disorder, as well as normalization of muscle and liver enzymes and of blood cells.

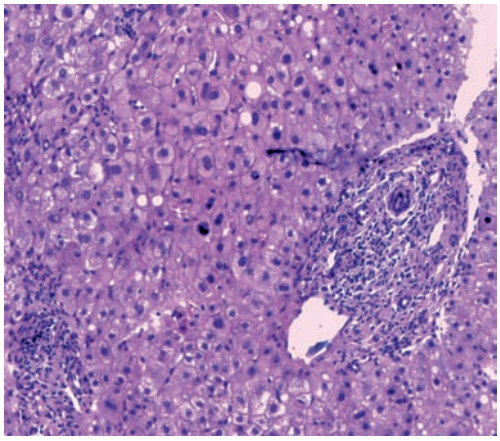

Fig 1. Automimmune hepatitis on frozen section. Infiltration of the portal tact and liver lobes (H&E 10x).

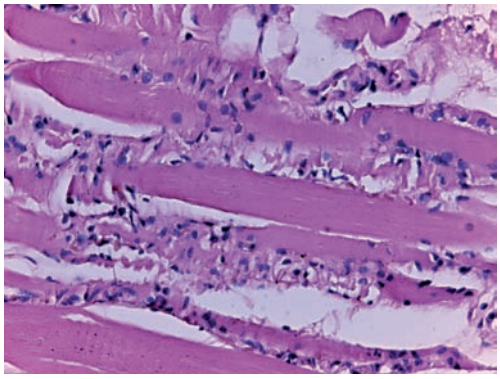

Fig 2. Polymyositis on frozen section. Extensive myophagocytation with vacuolation (H&E 40x).

Discussion

Autoimmune hepatitis is a chronic disorder characterized by persistent hepatocellular necrosis and inflammation. Overlapping syndromes have been described in both hepatic and extrahepatic autoimmune diseases. The AIH-PBC overlap syndrome is the most common hepatic overlap syndrome, documented to affect around 10% of patients with AIH or PBC [15]. Regarding extrahepatic autoimmune diseases, AIH has been associated with autoimmune thrombocytopenia or thyroiditis [3, 16, 17]. Yet, while AIH shares clinical and immunological similarities with connective tissue diseases, reports of AIH related to CTD have been scarce. Autoimmune hepatitis has been observed in relation to systemic lupus erythematosus (SLE) - accounting for 13% of the cases with liver abnormalities [18], to Sjögren's syndrome and mixed connective tissue disease, but very rarely to SSc.

We found eleven case reports of AIH associated to scleroderma, out of which three cases had AIH-PBC overlap syndrome [3-5]. Limited SSc (9/11), particularly the CREST subtype [6-10], was the most frequent type of scleroderma reported; one patient had diffuse SSc [12], and one patient had scleroderma-polymyositis overlap syndrome [13]. With one exception [5], all patients developed AIH in the course of SSc.

The reports are represented in Table I. Among the AIH subtypes, type 1 with ANA positivity was the most common, all patients having positive ANAs. Anticentromere antibodies were present in all cases, with one exception [3]. Anti-mitochondrial antibodies were positive in all patients with AIH-PBC overlap syndrome and in one patient without histological features suggestive for PBC, but with cholestasis [12]. With regard to therapy, prednisone and azathioprine was the treatment of choice, with good response. Despite the potential risk for renal crisis in scleroderma during steroid therapy, no cases were reported.

This is the first report of an association between diffuse SSc, polymyositis, cerebral vasculitis and AIH. The diagnosis of AIH was established on the basis of positive ANAs, increased levels of serum globulin and histological findings after exclusion of viral hepatitis, alcohol or drug toxicity.

One particularity of this case was the progressive deterioration of the clinical course. Shortly after the start of steroids and azathioprine, a severe gastro-esophageal candidiasis was diagnosed. Furthermore, the patient's condition rapidly worsened. The underlying scleroderma became highly active: a subclinical pre-existing polymyositis (chronic lesions described at biopsy) became clinically and biologically active, active interstitial lung disease and pericardial effusion were present, as well as a spectacular increase in the number and size of telangiectasias. Simultaneously, the patient developed a neuropsychiatric syndrome in the context of cerebral vasculitis, as reflected by the hyperintense T2-weighted lesions on MRI.

Regarding the cause of this particular evolution of our

Table I. Immunological features of patients with systemic sclerosis and autoimmune hepatitis

Author (Ref)	Autoimmune liver disease	CDT	ANA	ACA	SMA	LKM	AMA	HGG	Anti-dsDNA
Toyoda et al [3]	HAI-PBC	lSSc	+	NK	NK	NK	+	+	+
West et al [5]	HAI-PBC	lSSc	-	+	NK	NK	NK	NK	NK
Efe et al [4]	HAI-PBC	lSSc	+	+	-	+	+	NK	NK
Rodrigues et al [12]	HAI	dSSc	NK	NK	-	-	+	NK	NK
Lis-Swiety et al [13]	HAI	SSc-PM	+	NK	+	-	-	NK	NK
Ishikawa et al [8]	HAI	lSSc	+	+	+	NK	-	+	NK
Yabe et al [9]	HAI	lSSc	-	-	NK	NK	-	+	NK
Marie et al [6]	HAI	lSSc	+	+	-	-	-	+	NK
Ngo Mandag et al [7]	HAI	lSSc	+	+	-	-	-	+	NK

CDT: connective tissue disease; ANA: antinuclear antibodies; ACA: anticentromere antibodies; SMA: anti-smooth muscle antibodies; LKM: anti-liver-kidney microsome-1 antibodies; AMA: antimitochondrial antibodies; HGG: hypergammaglobulinemia; HAI-PBC: autoimmune hepatitis-primary biliary cirrhosis overlap; lSSc: limited SSc; dSSc: diffuse SSc; SSc-PM: systemic sclerosis-polymyositis overlap syndrome; +: positive; -:negative; NK: not known (not done or not reported).

patient, one hypothesis is that the infection with candida augmented the autoimmune status and induced the cerebral vasculitis. Infectious agents are triggers and enhancers of connective tissue diseases: vasculitis, including cerebral vasculitis [19, 20] has been reported as a consequence of candidiasis. Another hypothesis is that the complex autoimmune disease was following its own course, and that the patient might have benefited from a more aggressive immunosuppression from the start.

Concerning the neuropsychiatric syndrome, our patient fulfilled four SLE classification criteria: ANA positivity, hematological disorder, serositis and neurological disorder. Nevertheless, the ANA positivity, pericarditis and cytopenias may have been present in the context of SSc. Autoimmune hepatitis and SLE also share clinical and immunological similarities, but cerebral vasculitis is not a feature. A differential diagnosis with steroid-induced psychosis was considered, but the symptoms did not withdraw after lowering the steroid dose. Finally, the diagnosis of cerebral vasculitis, regardless of context, was supported by the remission under cyclophosphamide.

Conclusion

Overlap syndromes aggravate the clinical course of the disease and raise treatment controversies. Scleroderma-AIH is a rare overlap syndrome, predominantly associated with the limited subtype of SSc, yet not to be disregarded as a feature of gastrointestinal involvement in patients with diffuse SSc. Patients with SSc and persistent elevation of liver enzymes of no other underlying cause should be screened for AIH.

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