A Case of CREST Syndrome with Rapidly Progressive Liver Damage

Hiroyuki Yabe, Kenji Noma, Norio Tada, Seibu Mochizuki and Makoto Nagano

A patient with CREST syndrome (calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) who had severe jaundice (total bilirubin 29.1 mg/dl) and rapidly progressive liver damage is reported. The liver damage findings matched the criteria of autoimmune chronic active hepatitis (CAH). There have been no prior reports of a case of CREST syndrome with autoimmune CAH in Japan. Anticentromere antibody (ACA) was detected in the serum; ACA seemed to be related to the pathogenesis of these two diseases.

Key words: autoimmune chronic active hepatitis, anticentromere antibody

Introduction

Anticentromere antibody (ACA) is an autoantibody which was discovered by Moroi et al (1) in 1980. They reported that ACA is frequently detected in the serum of patients with CREST syndrome (calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia), which is a limited type of scleroderma. Since then, the presence of ACA has been tested in patients with autoimmune diseases, and it has become clear that ACA is sometimes present in the serum of patients with other autoimmune diseases. Primary biliary cirrhosis (PBC) has the second highest incidence of serous ACA following CREST syndrome (2), and thus a relationship between ACA and the pathogenesis of autoimmune liver diseases containing PBC has been proposed (2–4).

We report a patient with CREST syndrome who had rapidly progressive liver damage.

Case Report

A 51-yr-old Japanese woman began to suffer from anorexia and general fatigue in August 1988, and Raynaud's phenomenon started to appear frequently in the following month. Jaundice was recognized and rapidly progressed 1 month later, accompanied by persistent putty-colored stools and chills. She visited our hospital and was immediately admitted on December 22, 1988. She had a past history of blood transfusion 25 yr ago, but neither liver damage nor jaundice was experienced. She had no habitual drug or alcohol use. She was a housekeeper and she had no experience of overseas travel. In addition, she had been aware of the existence of telangiectasia on her chest for 5 yr.

On admission, her consciousness was alert and severe jaundice was noted in the bulbar conjunctiva and skin. Multiple telangiectasia were present on the upper part of the chest (Fig. 1) and on her back. Sclerodactyly was noted on every finger (Fig. 2), with superficial ulcers on the fingertips. There were no vascular spider lesions or palmar erythema. Her heart sounds and breath sounds were clear. The liver was palpable 3 cm below the costal arch in the right midclavicular line; it was slightly blunt, elastic-hard, and tender. The spleen was not palpable and no ascites was detected.

Results of the laboratory examination are listed in Tables 1 and 2. Briefly, the erythrocyte sedimentation rate (ESR) was 14 mm/h, thrombo test (TT) 34%, heparin test (HPT) 47%, and antithrombin III (AT III) 39.9%. The serum levels of total bilirubin (T.Bil), direct bilirubin (D.Bil), GOT, GPT, and cholinesterase (Ch-E) were 29.1 mg/dl, 16.9 mg/dl, 453 mU/ml, 295 mU/ml, and 3.34 IU/ml, respectively. Increases in biliary enzymes were mild and the serum ammonia level was normal. In the serological study, the serum levels of IgG, IgA, and
IgM were 2,005, 335, and 390 mg/dl, respectively. There was no serological evidence of hepatitis B or C infection. Serum anti-nuclear antibody (ANA) was positive (640× centromere pattern); no anti-mitochondrial antibodies and no LE cells were detected.

Chest X-ray findings and electrocardiograms were normal and the spirogram and arterial blood gas analysis showed no abnormalities. An X-ray of the arm showed subcutaneous calcinosis; and X-ray examination of the esophagus showed distal aperistalsis (Fig. 3). Sclerodermatous skin was found on a biopsy specimen of a finger. Hence the diagnosis of CREST syndrome was made. An abdominal computed axial tomography scan disclosed mild hepatosplenomegaly with no intrahepatic or extrahepatic mass lesions or ascites.

The findings of a liver biopsy specimen were as follows (Fig. 4-a): Infiltrating inflammatory cells, mainly con-
Fig. 3. X-ray examination of the esophagus. Note the finding of the distal aperistalsis.

sisting of lymphocytes, were prominent in Glisson's sheath and extended into the parenchyma. In these areas there was a network of collagen fibers, and hepatocytes were focally degenerated. These hepatocytes were markedly swollen and hydropic, and acinar arrangements and cytolysis were found. Infiltrating lymphocytes were also seen around these degenerated hepatocytes. There were no findings of cholesis. These findings were consistent with the histologic features of autoimmune CAH proposed by Dienes et al (5). They reported that in 26 auto-immune CAH patients, plasma cells were conspicuous in only 4 patients and inflammatory infiltrates consisted mostly of lymphocytes.

Fig. 4. (a) Liver biopsy specimen before the prescription of prednisolone (Masson-trichrome, ×100). (b) Liver biopsy specimen after 4 months duration of prednisolone therapy (Masson-trichrome, ×100).

Figure 5 shows the clinical course. Despite supportive therapy (rest, sufficient nutrition, administration of glycyrrhizin, glucagon-insulin), liver function declined progressively, and TT and HPT fell to 21 and 30%,
respectively. Then treatment with 40 mg/day of prednisolone was started because autoimmune CAH was strongly suggested by the increase of immunoglobulin, the presence of autoantibody, the absence of habitual drug or alcohol use, the absence of hepatitis B or C markers, and an autoimmune CAH-compatible liver specimen. Consequently, the coagulative study and the serum level of T.Bil, transaminase, and immunoglobulin improved dramatically and there was a disappearance of the liver tenderness. Two months later, abnormal laboratory data were completely normalized. But the level of increased ACA did not change and the findings of sclerodactyly were consistent. A second liver biopsy was done after 4 months of prednisolone therapy (Fig. 4-b). The specimen showed excellent improvement compared with the first biopsy. Namely, cellular infiltration of Glisson's sheath and swelling of hepatic cells had disappeared and normalized. Limiting plates were preserved and slight pericellular fibrosis remained. Hence the effect of prednisolone was confirmed pathologically, and the diagnosis of autoimmune CAH was made.

Discussion

The liver damage of this case was thought to be autoimmune CAH. The grounds for diagnosis were as follows: a) the patient was a middle-aged woman, b) the presence of antinuclear antibody in the serum, c) a clinical course of over 6 months, d) a serous immunoglobulin level above 2.0 g/dl, e) the absence of HBs-Ag and HCV-Ab, f) no history of habitual drug or alcohol use, g) the findings of liver biopsy specimen were compatible with the histological features of autoimmune CAH proposed by Dienes et al (5), h) dramatic effect of prednisolone treatment. The negative data, such as the only slightly accelerated ESR, the relatively low level of serous IgG, and the absence of anti-smooth muscle antibody can not negate the diagnosis of autoimmune CAH. PBC was ruled out because the serous alkaline phosphatase and total cholesterol levels were not high, anti-mitochondrial antibody was absent, and histological findings of the liver biopsy specimen were not compatible with PBC.

She was also diagnosed as having CREST syndrome, because the 5 symptoms of CREST syndrome were fully satisfied and there were no systemic organic lesions, which are usually seen in the diffuse progressive type of scleroderma. ACA was detected in her serum. ACA was discovered by Moroi et al (1) in 1980 and its high incidence in the sera of CREST syndrome patients was also reported. Since then it has been reported that this autoantibody is present not only in the serum of CREST syndrome patients but also in other autoimmune diseases accompanied by PBC. Table 3 shows the incidence rate of ACA in the sera of CREST syndrome patients as well as in PBC and autoimmune CAH (1-4, 6-8). ACA is sometimes present in the serum of autoimmune CAH patients. PBC has been reported as a liver complication of CREST syndrome. The incidence rate of CREST syndrome in PBC patients ranges from 3 to 17% (6, 8, 9). Further, CREST syndrome very frequently complicates PBC patients who have ACA in their sera. Makinen et al (8) reported that almost all PBC patients who had ACA in their sera had some symptoms of CREST syndrome; Powell et al (9) reported similar results. For that reason, the relation between PBC and CREST syndrome has been regarded as significant.

On the other hand, the association of autoimmune CAH and CREST syndrome is quite rare; there is only one report of a case of autoimmune CAH complicated by CREST syndrome with ACA (10). Although the complication of autoimmune CAH with CREST syndrome is rare, this association seemed to be important and meaningful, because ACA has been detected in some cases of autoimmune CAH. In the present case, Raynaud's phenomenon and the symptoms of liver damage appeared during the same period. This fact suggests that there is a relevance between the activity of these two diseases.

ACA is a specific antibody for the centromere region of chromosome and the centromere region seems to be important in the normal movement of chromosomes during mitosis. Chromosomal abnormalities in patients with scleroderma who had ACA in their sera were

Table 3. Incidence Rate of Serous ACA in CREST Syndrome, PBC, and Autoimmune CAH

<table>
<thead>
<tr>
<th></th>
<th>CREST syndrome</th>
<th>PBC</th>
<th>Autoimmune CAH</th>
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<tbody>
<tr>
<td>Moroi et al (1)</td>
<td>7/10 (70%)</td>
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</tr>
<tr>
<td>Powell et al (2)</td>
<td>194/343 (57%)</td>
<td>50/404 (12%)</td>
<td>---</td>
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<tr>
<td>Imai et al (3)</td>
<td>---</td>
<td>6/22 (27%)</td>
<td>2/16 (13%)*</td>
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<tr>
<td>Cassani et al (4)</td>
<td>---</td>
<td>8/83 (10%)</td>
<td>1/31 (3%)</td>
</tr>
<tr>
<td>Bernstein et al (6)</td>
<td>---</td>
<td>10/110 (9%)</td>
<td>0/80 (0%)**</td>
</tr>
<tr>
<td>Penner et al (7)</td>
<td>---</td>
<td>11/38 (29%)</td>
<td>0/30 (0%)</td>
</tr>
<tr>
<td>Makinen et al (8)</td>
<td>---</td>
<td>14/48 (29%)</td>
<td>1/30 (3%)</td>
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* Incidence rate of CAH including the autoimmune variety, ** incidence rate of lupoid hepatitis.
CREST Syndrome with Severe Liver Damage

detected by Fritzler and Ayer (11), but the reason why some patients with scleroderma have an antibody in their serum that reacts with specific chromosomal subjects is still unknown. Although it is now uncertain whether ACA plays a primary role in the pathogenesis of CREST syndrome and autoimmune CAH, it can be at least suggested that these two diseases occurred based on an immunological abnormality that revealed a positive ACA reaction. The titer of ACA did not decrease in correlation with the improvement of liver damage. This is an unusual pattern when compared with the titer of ANA, which usually diminishes with steroid treatment in patients with autoimmune CAH (12). However, a recent long-term study in patients with scleroderma has shown that the titer of ACA does not change conspicuously over time (13). Further, the severity of liver damage in our patient was marked when compared with the usual clinical course of autoimmune CAH. Recently, overt jaundice is no longer a frequent presenting syndrome, because this disease is detected earlier in its course in an increasing number of patients (12).

Meanwhile, Powell et al (9) reported that 91% of the cases of PBC complicated by CREST syndrome also had accompanying Sjögren syndrome. In the present case, the complication of the Sjögren syndrome was ruled out due to the lack of symptoms, the absence of SS-A and SS-B antibody, and the negative result of Schirmer’s test and salivary gland scintigraphy (99 m-Tc). We intend to follow this patient carefully, taking into consideration the possible occurrence of Sjögren syndrome or PBC in the future, because there have been many reported cases of autoimmune CAH complicated by Sjögren syndrome, and also some cases of the mixed type of CAH and PBC (14, 15).

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References