Mixed Connective Tissue Disease Associated with Autoimmune Hepatitis and Pulmonary Fibrosis

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For Editorial see page 725

Mixed connective tissue disease (MCTD) is a chronic autoimmune disease, characterized by Raynaud's phenomenon, swollen hands, polyarthritis, sclerodactyly, polymyositis, esophageal dysmotility, pulmonary hypertension, and interstitial lung disease (ILD), along with high levels of anti-U1RNP antibodies. MCTD can affect almost every organ, with different frequencies. With regard to solid organ involvement, the coexistence of MCTD with autoimmune hepatitis (AIH) is uncommon [1]. To the best of our knowledge the association between MCTD and AIH, complicated with interstitial lung disease (ILD), has not been described previously.

PATIENT DESCRIPTION

A 36 year old Caucasian female diagnosed with MCTD in 1979 had recurrent arthritis of the metacarpophalangeal and proximal interphalangeal joints, Raynaud's phenomenon, alopecia, purpura, myositis and sclerodactyly. There was no thrombotic event in the patient's history. The serum level of anti-U1RNP was high (28 U/ml, normal < 5 U/ml). Serum samples were negative for antibodies to ds-DNA, Sm, SSB, and SSA. Anticardiolipin antibodies were negative for immunoglobulin A and M, while anti-beta-2 glycoprotein-1 IgG antibody was elevated at 30.5 U/ml (normal 0–14.6 U/ml). Polyclonal hypergammaglobulinemia (IgG 21.42 g/L, normal 7–16) was detected. The levels of serum IgA and IgM were normal (IgA 3.92 g/L, normal 0.7–4.0; and IgM 1.66 g/L, normal 0.4–2.3). No monoclonal component was found with serum electrophoresis. Electrolytes, liver, renal function and urinary tests were also normal. No hepatitis B surface or core antibodies, hepatitis A or C antibodies, or antibodies against cytomegalovirus (CMV) or Epstein-Barr virus (EBV) were detected in the patient's serum. MCTD was diagnosed according to the criteria by Alarcon-Segovia [2]. Intermittently, nonsteroidal anti-inflammatory drugs and low dose methylprednisolone were started (4–6 mg daily), and the patient was followed regularly every 4 months.

Subsequently, she presented with periodic dyspnea and a slightly dry cough. The pulmonary function test and chest X-ray did not show abnormalities. Bronchodilators were administered and her complaints resolved. In 2000 elevated levels of transaminese and cholestatic enzymes were detected without clinical symptoms: alanine transaminase 97 U/L, aspartate aminotransferase 117 U/L, alkaline phosphatase 118 U/L, and gamma-glutamyltransferase 95 U/L. Physical examination did not show hepatomegaly or abdominal tenderness. The patient had no history of jaundice, exposure to toxins, blood transfusions, or alcohol or intravenous drug abuse. Erythrocyte sedimentation rate was 70 mm/hour, blood counts were normal, serum IgG was 17.14 g/L. Total bilirubin, albumin, serum copper, thyroid function tests and C-reactive protein were normal. Viral serology for hepatitis B and C virus (HBV, HCV), CMV and EBV were negative. Antinuclear antibodies were positive, showing a speckled pattern. The patient was positive to antibodies against U1RNP, Ro (SSA), La (SSB) and smooth muscle by enzyme-linked immunosorbent assay. Circulating immune complex levels were markedly elevated. Abdominal ultrasonograpy and bile culture test were negative.

In February 2001 percutaneous liver biopsy showed flared portal tracts, periportal piecemeal necrosis with lobular activity, and infiltration of lymphocytes and plasma cells in the portal tracts without involvement of the bile ducts. AIH type 1 was diagnosed, based on the criteria of the International Autoimmune Hepatitis Group [3]. The patient was treated with azathioprine (100 mg/day) and methylprednisolone (48 mg/day). Liver enzyme levels began to normalize 4 weeks after treatment began. The round opacities also decreased and chest X-ray showed bibasilar fibrosis. Following stepwise dose reduction of corticosteroids, liver enzymes were within the normal range during the subsequent 7 years. At the same time, chest X-ray indicated pulmonary fibrosis in the lower lobes of the lungs, and chest computed tomography showed bilateral basilar pulmonary fibrosis and a round opacity in the upper left lobe of the lungs. Bronchofiberoscopy indicated bronchial dyskinesis. Lung biopsy showed intense mononuclear cell infiltration of the

submucosa, rupturing the epithelium. The submucosal layer was markedly expanded by an increase in the number of smooth muscle cells, where islands of smooth muscle cells were present in a disorganized fashion. There was no sign of malignancy. On the grounds of MCTD, pneumonitis appeared which progressed to mild pulmonary fibrosis. After 21 years of MCTD diagnosis the patient developed AIH.

COMMENT

Generally, liver enzyme abnormalities are relatively common among patients with systemic autoimmune diseases, where hepatic injury from hepatotoxic drugs, coincidental viral hepatitis, is a common etiologic factor. Previously, AIH associated with MCTD, showing HLA-DR4 association, was only described in a few cases in the literature.

AIH can be associated with diffuse interstitial pneumonitis, mediated by anti-smooth muscle antibodies (aSMA) or an immuncomplex-mediated mechanism. The increase in smooth muscle thickness is due primarily to the presence of the aSMA, which can provoke local inflammation, leading to subsequent reactive proliferation. [4]. In our patient, azathioprine, administered for AIH, also effectively ameliorated the symptoms of ILD. In chronic fibrotic lung disorders, the proliferation of smooth muscle cells has been shown, probably derived from myofibroblasts in the interstitium, which produce collagen and other matrix proteins, proteases, growth factors and cytokines, affecting alveolar epithelial structures [4,5]. Thus they are able to perpetuate fibrotic processes [5].

Patients with MCTD associated with AIH usually respond well to steroid therapy in combination with azathioprine. In our patient, serum transaminase levels began to decline after 2 weeks of steroid and azathioprine therapy and normalized in 5 months.

In MCTD, the presence of aSMA, indicating AIH, may induce myomatosous lesions and smooth muscle hypertrophy in the lungs, which may eventually lead to pulmonary fibrosis. The proper and early diagnosis and assessment of solid organ involvement is pivotal to initiate appropriate and effective therapy in MCTD patients and decelerate pathogenetic processes and organ damage.

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