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CASE REPORT | LIVER

Overlap Syndrome and Myasthenia Gravis: An Uncommon Association With Unusual Features

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ABSTRACT

The author presents a rare case of overlap syndrome associated with myasthenia gravis in the absence of acetylcholine receptor antibody and thymoma. Various liver autoantibodies developed at different times later in the disease course and myasthenia occurred 5 years after the diagnosis of liver disease. The importance of repeating antibody panel later in the disease course for proper diagnosis and timely treatment is highlighted. The exact mechanism of the development of myasthenia gravis in autoimmune liver disease also needs investigation for the possibility of new drug development that might be beneficial to both.

INTRODUCTION

Myasthenia gravis (MG) may occur in association with many other autoimmune diseases, but an association with autoimmune liver disease is rare. There are 14 such cases reported to date in the English medical literature, in which MG was associated with any of autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), or primary sclerosing cholangitis.[1–14] The association with the overlap syndrome has been reported once.[15]

CASE REPORT

A 49-year-old man, nonsmoker and teetotaler, presented for the first time in 2012 with increasing pigmentation of the skin over the forehead, chest and upper extremities for the past 1 year, associated with generalized itching that caused sleep disturbance. Liver function tests (LFTs) revealed bilirubin 5.4 mg/dL, direct bilirubin 4.8 mg/dL, albumin 4 g/dL, globulin 4.8 g/dL, aspartate aminotransferase 52 IU/L, alanine aminotransferase 63 IU/L, alkaline phosphatase 234 IU/L, and gamma glutamyl transferase 267 IU/L. Hemogram included hemoglobin 12.4 g/L, total leukocyte count 8,600/mm^3, and platelet 2.2 $\times$ 10^5/mm^3. Serum immunoglobulins were IgG 1,980 mg/dL, IgA 297 mg/dL, and IgM 133 mg/dL. Antibody panel showed positivity for antinuclear antibody (ANA titer 1:80, speckled pattern), but negative anti-smooth muscle antibody, anti-mitochondrial antibody-M2, anti-liver kidney microsome 1 antibody, anti-SLA/soluble liver pancreas antigen/actin antibody, and antineutrophil cytoplasmic antibody (p & c). He was also diagnosed with diabetes (fasting/postprandial blood glucose 200/214 mg/dL) with triglyceride 366 mg/dL, cholesterol 267 mg/dL, and normal serum iron, total iron-binding capacity, ferritin, vitamin B12, folic acid, and thyroid function tests. HBsAg/Anti-HCV/HIV tests were negative with normal serum ceruloplasmin and alpha-fetoprotein level. Upper gastrointestinal endoscopy revealed small (grade 1) esophageal varices and mild portal hypertensive gastropathy. A liver biopsy revealed a lymphocytic destructive cholangitis with mild peri-portal fibrosis. He was administered high-dose ursodeoxycholic acid (1,200 mg/d) without steroid because of predominant biliary involvement on LFT and liver biopsy, which did not sooth his itching. He also received nateglinide (120 mg tid), long-acting propranolol (40 mg od), atorvastatin (10 mg/d), and calcium (500 mg bid). Atorvastatin in lower dose was prescribed for the high serum cholesterol and triglycerides because fibrates/niacin had to be avoided in view of his liver disease.

In the period from 2013 to 2017, he was treated in a number of liver hospitals where the investigations were repeated. He became positive for anti-mitochondrial antibody-M2 and anti-liver kidney microsome antibody since 2014, and his ANA titer increased to 1:320 in 2017. His serial LFT showed aspartate aminotransferase/alanine aminotransferase 1.5–2 times normal (5–40 IU/L), alkaline

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phosphatase 1.5–3 times normal (30–129 IU/L), and gamma glutamyl transferase 4–7 times normal (up to 60 IU/L). Biliary enzymes were more severely deranged than hepatocellular enzymes. After initial drop to 1.4 mg/dL in 2014, his bilirubin again rose to baseline levels (ie, 5.4 mg/dL), and there was serial drop in hemoglobin to 9.3 g/L, platelet count to $1.1 \times 10^5/mm^3$, and albumin to 2.6 g/dL with persistently high IgG level till 2017. Multiple ultrasonographies and triple-phase computed tomography (CT) scan of the abdomen revealed cirrhotic liver with collaterals and periportal and peripancreatic lymphadenopathy (thought to be a part of his autoimmune liver disease), but with normal pancreas. Hepatic venous pressure gradient on 2 occasions were 4 mm Hg and 6 mm Hg, and varices remained grade 1 until 2017. He continued to receive ursodeoxycholic acid, but propranolol and nateglinide were changed to carvedilol (3.125 mg/d) and short-acting insulin injections, respectively, with stoppage of atorvastatin since 2015 after lipid levels normalized.

In 2016, he gradually developed proximal muscle weakness of all 4 limbs with unilateral ptosis, which increased especially in the evenings (without dysphagia or cranial neuropathy). Reflexes were brisk without any sensory or autonomic abnormality. An electromyogram/nerve conduction velocity study showed pattern consistent with MG along with raised serum choline esterase level and positive Tensilon test. He was administered tab pyridostigmine (60 mg qid), which improved his muscle power to normal level. Acetylcholine receptor antibody (anti-AchR) was negative and a computed tomography scan of thorax did not reveal any thymoma or lung abnormality. In addition, he also developed psoriasis. Throughout his disease course, he did not have any incidence of hepatic encephalopathy and continued with his activities of daily living and office job normally. In 2017, ascites appeared for the first time (within 6 years of disease onset), and until the last follow-up, he is on liver transplant wait list although still continuing to work normally with medicines.

DISCUSSION

The present case shows that different autoantibodies related to autoimmune liver disease may not be present initially but develop at variable times later in the course of the disease. Hence, antibody panel should be repeated at later intervals for proper diagnosis and appropriate timely therapy. Our patient had definite overlap syndrome according to the recent criteria, unlike other case reports.[1,10,15–19] If steroids were given at the initial diagnosis in our case in 2012 (based on high IgG and ANA positivity in lower titer), it could have slowed disease progression.

In the previously reported cases, any one of AIH, PBC, or primary sclerosing cholangitis (clinically and/or histologically predominant) was associated with MG, both were usually diagnosed simultaneously but the liver disease could occur later (especially acute AIH) and responded poorly to treatment.[1–14] All (except 1) were positive for AChR antibody, and all (except 2) had thymoma.[3,8] The unique feature in our case was the development of 2 autoimmune diseases such as MG 5 years after the diagnosis of overlap syndrome in the absence of anti-AChR and thymoma along with psoriasis. In the only other similar report of later development of MG, it also occurred 5 years after diagnosis of PBC without thymoma but with positive anti-AChR. In the only other similar report of overlap syndrome associated with MG, both antiAChR and thymoma were present.[8,15] The thymus plays an important role in the growth and differentiation of T lymphocytes and its disorder can cause a spectrum of autoimmune diseases due to disturbance in cell-mediated immunity including synthesis of anti-AChR leading to MG. In our case, possibly anti-AChR was negative because MG occurred in the absence of thymoma. It is also possible that subclinical thymic disease was present or that anti-AChR might develop later. There is also evidence that injection of serum antibodies from patients of PBC in mice decrease the number of receptors at skeletal muscle neuromuscular junction.[20] Its clinical significance and mechanism in humans needs investigation, especially in patients like ours who are negative for both thymoma and anti-AChR. The other differential diagnosis of Eaton Lambert syndrome, botulism, and thyroid disorders were primarily excluded by dramatic response of neurologic symptoms to pyridostigmine in addition to the presence of normal deep tendon reflexes, gradual onset of symptoms unrelated to food intake, normal thyroid function tests, and findings on electromyogram/nerve conduction velocity study.

As in the other cases, the course of liver disease was relentlessly progressive in our patient leading to decompensation over 6 years. We did not use steroids or immunosuppressives, the prescription of which is a therapeutic dilemma in such patients' therapeutic approach.

DISCLOSURES

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