CASE STUDIES

A rare presentation of hypopituitarism in hepatic overlap syndrome of autoimmune hepatitis and autoimmune cholangitis

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Abstract

Autoimmune cholangitis is the antimitochondrial antibody-negative autoimmune hepatopathy with clinical and histological features similar to that of primary biliary cirrhosis. Autoimmune cholangitis has a predominant cholestatic phase. However, transaminasemia might be dominant in certain patients, indicating associated autoimmune hepatitis. Such an autoimmune hepatopathy has been termed as hepatic overlap syndrome. Due to the autoimmune nature of the disease, associated diseases of other organs have been reported. We report a case of an adult female with a very rare presentation of hepatic overlap syndrome of autoimmune cholangitis and autoimmune hepatitis associated with hypopituitarism.

Keywords: Autoimmune hepatitis, autoimmune cholangitis, overlap syndrome, hypopituitarism

Introduction

Autoimmune cholangitis (AIC) is an antimitochondrial antibody (AMA)-negative primary biliary cirrhosis (PBC) having a clinical constellation of chronic cholestasis and histological changes of chronic nonsuppurative cholangitis.[1] In patients with presentation of AIC with hepatitic biochemical derangement, a diagnosis of hepatic overlap syndrome between AIC and autoimmune hepatitis (AIH) needs to be considered.[2] Single cases of this rare overlap syndrome have been reported in literature.[2] We report a case of an overlap syndrome between autoimmune hepatitis and autoimmune cholangitis, and its association with hypopituitarism.

Case report

A 46-year-old postmenopausal female presented with a history of jaundice and pruritis for 2 years, and hyperpigmentation and fatigue for 6 months. On clinical examination, she had icterus, generalized hyperpigmentation over the body and hepatosplenomegaly. Her biochemical parameters were as follows: aspartate transaminase (AST)- 229 U/L (normal, N<40 U/L), alanine transaminase (ALT)- 294 U/L (N <40 U/L), alkaline phosphatase (ALP)- 875 U/L (N <141 U/L), and total serum bilirubin- 28.0 mg/dl (direct- 13.5 mg/dL and indirect- 14.5 mg/dL). Ultrasound examination did not show any evidence of biliary obstruction in the common bile duct and intrahepatic biliary radicles. Contrast-enhanced computed tomography, MRI and magnetic resonance cholangiopancreatography of abdomen were normal and did not reveal any dilatation of bile ducts.

Viral markers namely HIV, HBsAg, anti-HCV, IgM anti-HAV, and IgM anti-HEV were negative. Antinuclear antibodies (ANA) were positive in a homogenous staining pattern at a titre of 1:100. Anti-smooth muscle antibodies (ASMA), anti-liver-kidney microsome antibodies (anti-LKM), anti-soluble liver antigen (anti-SLA), perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) and AMA were negative. Serum iron, ferritin and ceruloplasmin levels were normal. Serum IgM levels were raised (295 mg/dL; N=40-230 mg/dL), while serum IgG levels were normal (986 mg/dL; N=700-1600 mg/dL). Liver biopsy findings revealed lymphoplasmacytic infiltration of portal triad, portal fibrosis, parenchymal necrosis, features of bile stasis and paucity of bile ductules within the portal areas with no evidence of granulomas.

The clinical profile, biochemical parameters (raised ALP and GGT), serological markers (negative AMA with raised IgM levels) and liver biopsy findings were suggestive of the diagnosis of AMA-negative primary biliary cirrhosis, i.e. autoimmune cholangitis.[3] Since the patient had markedly elevated liver enzymes (AST/ALT), which is not a feature of autoimmune cholangitis, a possibility of autoimmune hepatitis overlapping with autoimmune cholangitis was considered. Based on the scoring system for autoimmune hepatitis, the diagnosis was concluded as 'overlap syndrome' between AIC and AIH ('probable' AIH with a score of 14).[4] Patient was treated with combination of prednisolone (0.5 mg/kg/day) and azathioprine (50 mg/day) along with ursodeoxycholic acid (UDCA) 15 mg/kg/day.

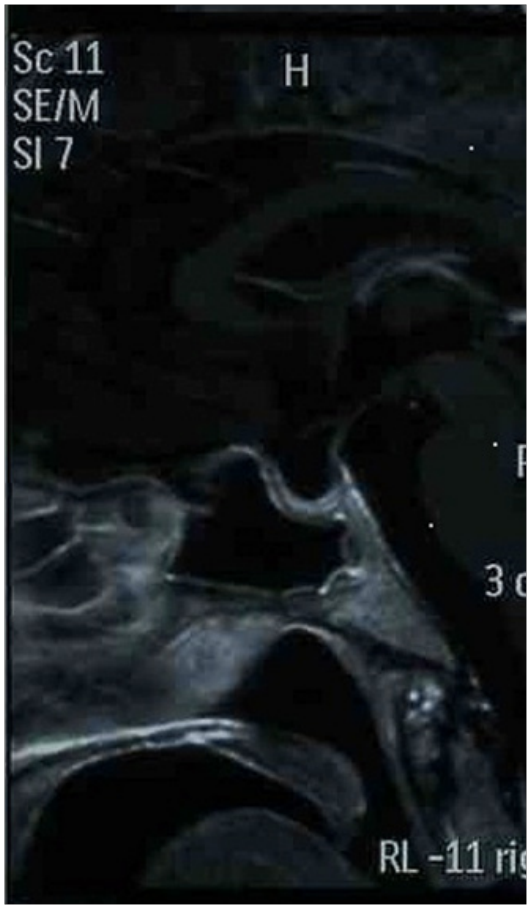
The patient was found to have decreased free T3, free T4, TSH, LH and FSH, and GH levels. Prolactin levels were normal. Serum cortisol levels (morning 9 a.m.) of >500 nmol/L ruled out ACTH deficiency.[5, 6] [free T3: 1.90 pg/mL (N=2.30-4.20 pg/mL), free T4: 0.56 ng/dL (N=0.89-1.76 ng/dL), TSH: 0.83 uIU/mL (N=0.35-5.50 uIU/mL), LH: 0.13 mIU/mL (N=15.9-54.0 mIU/mL for postmenopausal women), FSH: 1.08 mIU/mL (N=23-116 mIU/mL for postmenopausal women), GH: 0.23 ng/mL (N=0.50-17 ng/mL), prolactin: 11.50 ng/mL (N=1.80-20.30 ng/mL), serum cortisol (morning 9 am): 579.9 nmol/L]

The values of hormonal assays were suggestive of hypopituitarism. MRI of brain revealed empty sella with an atrophied pituitary gland (Fig. 1).

Based on all the clinical evidence and lab investigations, the final diagnosis was concluded as a rare case of an overlap syndrome between autoimmune hepatitis and autoimmune cholangitis associated with hypopituitarism.

Discussion

AIC has common clinical features as that of PBC, but has negative AMA and positive antinuclear antibodies (ANA), with or without smooth muscle antibodies (SMA).[3] It was first reported as immunocholangitis in 1987, since then it became a matter of discussion whether PBC and AIC are separate entities or variants of a single disease with differing pattern of associated autoantibodies.[2] AIC has also been discussed as a variant of AIH, a hybrid of PBC



and AIH, and a result of consecutive occurrence of PBC and AIH.[2] Studies indicate that majority of AIC patients suffer from true PBC, since most of these patients have been found to be positive by a new AMA-M2 recombinant assay that detects autoantibodies directed against human E2 members of the 2-oxo acid dehydrogenase complex family. PDC-E2 immunoreactivity has been expressed on apical membranes in most patients with AIC.[7, 8]

Thus, AIC is used for clinical assessment of patients who are defined by (i) ANA and/or SMA seropositivity and/or hypergammaglobulinemia; (ii) absence of AMA by immunofluorescence; (iii) biochemical and/or histological features of cholestatic and hepatocellular injury; (iv) exclusion of chronic viral, metabolic or toxic liver disease (as in the current case).[2]

AIC is distinguished from AIH based on lower serum levels of AST and higher serum levels of ALP.[4] In the present case, there was marked rise in transaminase activity, suggestive of associated hepatitis i.e. AIH. The combination of AIC and AIH has been termed as hepatic overlap syndrome, which may represent various combined forms of classical autoimmune hepatopathies: AIH, PBC and PSC. Such overlap syndromes are ill defined and are characterized by evidence of different autoimmune hepatopathies. Moreover, standard diagnostic criteria are lacking.[4]

AIC-AIH hepatic overlap syndrome is gradually progressive and may require liver transplantation.[4] No controlled trials have been performed due to the paucity of cases. UDCA, oral steroids and azathioprine therapies have shown response. In patients achieving remission, a maintenance dose of UDCA is recommended. In patients showing incomplete response to UDCA, the treatment combinations involving systemic corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, chlorambucil, penicillamine, colchicine, silymarin and benzofibrate have shown a benefit in terms of improving biochemical markers, decreasing the intensity of pruritis, improving liver histology, reducing the incidence of major complications of cirrhosis and delaying the need for liver transplantation.

The hypopituitarism, noted in the present case, may be due to autoimmune/lymphocytic hypophysitis. Lymphocytic hypophysitis has been previously reported to be associated with primary biliary cirrhosis.[9] MRI brain in this case, however, revealed empty sella which could be the final outcome of lymphocytic hypophysitis.[10, 11] Many biopsy-proven cases of lymphocytic hypophysitis (showing enlarged pituitary and enhancement with gadolinium contrast at the time of diagnosis) when followed over months to years have later revealed an empty sella on MRI brain.[10, 12] This may be due to infiltration of the pituitary with lymphocytes along with plasma cells and macrophages causing atrophy of the acini of pituitary cells.[10] Hence, hypopituitarism in this case could be secondary to lymphocytic hypophysitis.

The present case highlights a rare hepatic overlap syndrome of autoimmune cholangitis and autoimmune hepatitis complicated by hypopituitarism.

Competing interests
The authors declare that they have no competing interests.

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