Primary Biliary Cirrhosis – Autoimmune Hepatitis Overlap Syndrome Associated with Dermatomyositis, Autoimmune Thyroiditis and Antiphospholipid Syndrome

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ABSTRACT

Autoimmune liver diseases may be associated with extrahepatic autoimmune pathology. We report the case of a 52-year old woman who initially presented to the gastroenterology department for extreme fatigue, pale stools, dark urine and pruritus. Laboratory tests showed significant cholestasis and elevation of aminotransferase levels. Immunological tests revealed positive antinuclear (ANA=1:320) and antimitochondrial antibodies (AMA=1:40) with negative anti-smooth muscle and liver kidney microsomal type 1 antibodies. The biopsy was compatible with overlap syndrome type 1. The patient was commenced on immunosuppressive therapy according to standard of care (azathioprine 50mg, ursodeoxycholic acid and prednisone 0.5mg/kg), with moderate biochemical improvement. She subsequently developed proximal symmetrical weakness and cutaneous involvement and was diagnosed with biopsy-proven dermatomyositis. The immunosuppressive regimen was intensified to 150 mg azathioprine. At the three-month follow-up, her symptoms subsided and aminotransferases and muscle enzymes normalized. Upon further investigation the patient was diagnosed with autoimmune thyroiditis and antiphospholipid syndrome. To our knowledge, this is the first case of primary biliary cirrhosis – autoimmune hepatitis overlap syndrome associated with dermatomyositis, autoimmune thyroiditis and antiphospholipid syndrome.

Key words: autoimmune hepatitis – primary biliary cirrhosis – inflammatory myopathies – autoimmune thyroid disease – antiphospholipid syndrome.

INTRODUCTION

Autoimmune liver diseases comprise several pathological entities including autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis and overlap syndromes. Primary biliary cirrhosis is a progressive cholestatic liver disease characterized by destruction of small and medium bile ducts that may cause intrahepatic cholestasis and subsequent liver cell destruction, eventually cirrhosis [1]. Autoimmune hepatitis is a generally unresolved inflammation of the liver, characterized by specific histologic abnormalities (e.g. interface hepatitis, central portal bridging necrosis), clinical and laboratory findings (abnormal aminotransferases, elevated total serum globulin or IgG, seropositivity for antinuclear, ANA, anti-smooth muscle, ASMA or anti liver kidney microsomal-1, LKM-1) and exclusion of other etiological factors (viral or toxic) [2]. When clinical, biochemical, serological and histological features are common for both PBC and AIH, the term „overlap syndrome” is most appropriate.

Inflammatory myopathies are autoimmune inflammatory disorders characterized by the development of symmetrical, proximal muscle weakness. Levels of serum muscle enzymes such as creatine kinase (CK), lactate dehydrogenase...
(LDH), aminotransferases are usually elevated. High levels of aminotransferases and LDH, without assessment of creatine kinase (CK), are often misdiagnosed as hepatic diseases [3]. Conversely, concomitant elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and LDH along with the CK in patients with polymyositis, PM/dermatomyositis, DM may be considered to be due to myopathy itself, even in the case of coexistence with liver injury [3].

Autoimmune liver diseases are sometimes associated with autoimmune thyroid disease and connective tissue diseases such as systemic sclerosis or Sjögren's syndrome. Associations with DM are exceptional. We report a case of PBC-AIH overlap syndrome associated with DM, autoimmune thyroiditis and antiphospholipid syndrome.

**CASE REPORT**

A 52-year-old woman with a history of PBC-AIH overlap syndrome was referred to the dermatologist for a papulo-pustular rash and Raynaud's phenomenon. Six months prior to admission, she presented to the gastroenterology department because of extreme fatigue, pale stools, dark urine and pruritus. Laboratory tests were remarkable for significant elevations of alkaline phosphatase (AP=1,998 UI/l), γ-glutamyl transpeptidase (GGT=499 UI/l), and transaminases [ALT=5.4x upper normal limit, UNL, AST=5.1xUNL]. Immunological tests revealed positive ANA (1/320, nucleolar and speckled pattern) and AMA (1:40) with negative ASMA and LKM-1 antibodies. Immunoglobulin G levels were 2.5x UNL. A liver biopsy was compatible with PBC-AIH overlap syndrome, showing bile duct damage around the portal area, focal duct obliteration and interface hepatitis characterized by a lympho-plasmocytic infiltration located predominately around the perilobular areas (Fig. 1). The fibroscan test revealed heterogeneous fibrosis ranging from F2 to F4 (7.8 to 9.4kPa). Testing for hepatitis B and C as well as other infectious diseases was negative. The patient was commenced on ursodeoxycholic acid (UDCA) 16 mg/kg/day, prednisone 0.5 mg/kg/day and azathioprine 50 mg/day with moderate biochemical response; the treatment regimen was later continued with an increase of UDCA to 20 mg/kg.

Upon presentation, the patient's vital signs were normal. Cutaneous examination revealed symmetric facial heliotrope erythema involving the eyelids, telangiectasias and mild papulo-pustular skin eruption on the posterior upper trunk. The patient's medical history was notable for a 10-year duration of photosensitivity and Raynaud's phenomenon and a 4-month duration of symmetrical proximal myalgia and fatigue, raising the suspicion of associated dermatomyositis. Analysis for *Demodex folliculorum* was negative, decreasing the likelihood of an associated rosacea. Serum levels of CK and LDH were elevated (884mg/dl and 423mg/dl, respectively) and cholestasis (AP=362 UI/l, GGT=119 UI/l) as well as mild elevation of transaminases (AST=1.5xUNL, ALT=1.1xUNL) were also present.

The screening for autoimmune thyroiditis indicated increased anti-thyroperoxydase antibodies with unaffected thyroid function. The ultrasound of the thyroid gland revealed a heterogeneous echotexture with hypoechogenic micronodules that were surrounded by echogenic septations, suggestive of autoimmune thyroiditis. The electrocardiogram showed no signs of ischemia or conduction abnormalities.

A diagnosis of DM, acneiform eruption secondary to glucocorticoids and autoimmune thyroiditis was established. The patient was referred to the rheumatologist for further evaluation. A muscle biopsy of the left quadriceps showed inflammatory infiltrates associated with disruption of the muscle architecture and muscle fibre necrosis (Fig. 2), confirming the diagnosis. Ultrasound elastography revealed moderate elasticity in the median area of the right quadriceps muscles and reduced elasticity in the left proximal region of the quadriceps muscles - soft areas alternating with rigidity suggestive of myositis [4]. Additional immunological tests were remarkable for negative anti-Jo1 antibodies and positive lupus anticoagulant (LA). An associated diagnosis of antiphospholipid syndrome was established based on a history of repetitive deep vein thrombosis, a pregnancy loss in the 2nd trimester and two positive tests for LA. Accordingly, immunosuppressive treatment was intensified to prednisone 0.5 mg/kg, azathioprine 150 mg/day and topical cutaneous therapy. At the 3-month follow-up, the proximal muscle weakness remitted, the rash improved and the muscle enzymes and AP and GGT normalized.

**DISCUSSION**

Several concepts are encompassed under the umbrella of shared autoimmunity, including the presence of manifestations...
of different autoimmune diseases in the same patient [5]. This perspective also applies to autoimmune liver diseases, characterized by a high percentage of disease associations. Floreani et al. reported a 61.2% concurrence of PBC and extrahepatic autoimmune conditions [6], out of which up to 46.6% are represented by one or more connective tissue diseases [7]. Autoimmune thyroid disease has been observed in 23% of patients with PBC [8] and 18.3% of patients with PBC-AIH overlap syndrome [9].

However, the association of autoimmune liver diseases with myositis is rare. Among the two types of AIH, type 1 is more often associated with other autoimmune diseases, but only exceptionally with inflammatory myopathies. Indeed, among the 11 reported cases of autoimmune hepatitis associated with inflammatory myositis, AIH type 1 was more common, patients exhibiting more often ASMA and ANA antibodies [10-19] (Table I). Moreover, among inflammatory myopathies, PM is more commonly associated with AIH [17].

Primary biliary cirrhosis and inflammatory myopathies may also occur concomitantly. A recent study that evaluated 322 Chinese patients with PBC revealed a PBC-PM coexistence rate of 3.1% [7]. European-based studies demonstrated a much lower incidence, for instance, no cases were reported in a cohort of 160 PBC patients [8]. These discrepancies suggest a possible impact of geographical and probably genetic background. A possible explanation for the uncommon association of autoimmune liver diseases and myositis could be the different underlying pathophysiological mechanisms, such as cytotoxic CD8+ T lymphocytes in PM [20] and complex pathophysiologies in DM, such as humoral mechanisms, overactivation of the innate immune system (e.g. interferon associated pro-inflammatory pathways) and genetic alterations [21].

To our knowledge, this is the first reported case of PBC-AIH overlap syndrome associated with DM, autoimmune thyroiditis and antiphospholipid syndrome. This case is interesting not only due to the rare disease association, but also due to the response to therapy. The patient first presented with the PBC-AIH overlap syndrome for which treatment with UDCA, azathioprine 50 mg and prednisone was initiated with moderate response. After the diagnosis of DM was established, the immunosuppressive regimen was intensified to 150

<table>
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<tr>
<th>Author</th>
<th>Autoimmune liver disease</th>
<th>Inflammatory Myopathy</th>
<th>Associated autoimmune diseases</th>
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<tr>
<td>Bradley et al.</td>
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<td>PM</td>
<td>-</td>
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<td>PM</td>
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<td>AITP</td>
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<td>PM</td>
<td>ISSc</td>
<td>ISSc first, followed by PM-AIH</td>
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AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PM, polymyositis; DM, dermatomyositis; ANA, antinuclear antibodies; AMA, antimitochondrial antibodies; LKM-1, liver kidney-microsomal type 1 antibodies; ASMA, anti-smooth muscle; ISSc, limited systemic sclerosis; AITP, autoimmune thrombocytopenic purpura; NK, not known or not reported
mg azathioprine followed by normalization of both muscle enzymes and liver tests, thus indicating that patients with overlapping autoimmune liver disease may, in certain cases, benefit from higher doses of immunosuppressive therapy than the recommended standard of care.

Clinical features and biochemical hallmarks of autoimmune diseases, even though specific for certain pathologies, cross diagnostic criteria. Such is the case of PBC, where biochemical markers might be overlapping and misleading. For instance, Raynaud's phenomenon occurs in PBC, in inflammatory myopathies as well as in systemic sclerosis, a disease frequently associated with PBC [22]. Furthermore, high levels of AST, ALT and LDH, without assessment of CK may lead to a false diagnosis of a liver disease in a patient with PM. On the other hand, elevations of AST, ALT and LDH along with CK in myositis patients may be interpreted to be due to muscle injury and not liver involvement [3]. Therefore, in patients with PBC or especially AIH type 1, awareness of associated autoimmune diseases may lead to prompt diagnosis and better outcome. Active screening of extrahepatic associated conditions enabled us to raise awareness on thyroiditis and antiphospholipid syndrome.

**CONCLUSION**

In managing patients with autoimmune liver diseases, especially AIH type 1, clinicians should stay alert for the coexistence of associated autoimmune disease. Patients with autoimmune hepatitis and coexisting myositis, without a complete response to standard of care, may benefit from an intensified immunosuppressive regimen.

**Conflicts of interest:** No conflict to declare.

**Authors’ contribution:** C.P. and E.C. conceived this article, drafted and revised the paper in the light of the critical feedback from S.R. E.B., H.I. P., P.I. R. gathered, analysed and structured the data. All authors reviewed and approved the final version of the manuscript.

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**REFERENCES**


