Autoimmune cholangitis – a clinical case
Ana Rita Cardoso, Cristina Gonçalves

Abstract
The authors present the case of a previously healthy, asymptomatic 45 year old female patient, who was referred to the Internal Medicine service for study of elevated hepatic enzyme levels (alkaline phosphatase, gamma-glutamyl transferase and amino transferases) diagnosed in routine laboratory tests. The patient did not present any alterations in the objective examination and further study revealed negative antimitochondrial and antinuclear antibodies, and positive anti-smooth muscle antibodies. Liver biopsy revealed bile duct lesion, supporting a diagnosis of autoimmune cholangitis. A brief review is given on this pathology, which is still controversial.

Key words: Autoimmune cholangitis, primary biliary cirrhosis, autoimmune hepatitis, antimitochondrial antibodies, anti-smooth muscle antibodies, alkaline phosphatase, gamma-glutamyl transferase

INTRODUCTION
Primary biliary cirrhosis (PBC) is a presumed autoimmune pathology, affecting mainly middle-age women, and is caused by the granulomatous destruction of the interlobular bile ducts, leading to progressive ductopenia. It is characterized by a cholestatic enzyme pattern, increase in IgM, presence of antimitochondrial antibodies (AMA) detected by immunofluorescence in a titer > 1:40 or presence of AMA-M2 (specific to PBC and detected by ELISA or Immunoblot), and lesion of the intra-hepatic bile ducts, with their destruction or scarcity.1,2 Currently, most cases of PBC are diagnosed during the asymptomatic phase of the disease, during investigation of alterations in hepatic exams detected in routine analyses, or in the study of a concomitant pathology.2

In 1987, Brunner and Klinge described, for the first time, the condition of three women with immunocholangitis with signs and symptoms similar to PBC, but with negative AMA and positive antinuclear antibodies (ANA), who presented good response to immunosuppression therapy.3

In fact, differential diagnosis between PBC and autoimmune hepatitis (AIH) is not always easy,4,5 and patients can often be included in one of the two pathologies, since in certain cholestatic hepatic diseases (such as PBC or primary sclerosing cholangitis), certain clinical, biochemical or serological characteristics may be observed which suggest the presence of AIH.6 This problem led to the creation of a scoring system for diagnosis of AIH,7 but discussion on the group of patients within this threshold zone has been rife, and is far from reaching a solution.

CLINICAL CASE
45-year-old female Caucasian patient, a housewife, married and residing in Ferreira do Zêzere. Patient was referred to consultation in the Internal Medicine Outpatient Department of Tomar Hospital in September 2006, to clarify alterations in hepatic exams found in routine analyses: alkaline phosphatase (AP) 401 U/L (N: 38-126 U/L), gamma-glutamyl transferase (γ-GT) 241 U/L (N: 7-64 U/L), glutamic-oxaloacetic transaminase (GOT) 56 U/L (N: 15-41 U/L) and glutamic-pyruvic transaminase (GPT) 71 U/L (N:17-63 U/L).

The patient was asymptomatic, with known pathological history. In the family history of one case of Hashimoto’s Thyroiditis, in a sister, is highlighted. During objective examination, the patient was alert, apyretic, anicteric, and without edema or any other skin or mucosa alterations. Weight 55 Kg (habitual weight, corresponding to BMI 22 Kg/m²). BP 112/79 mmHg, regular heart beat 70 bpm and cardiopulmonary exams without alterations. Abdominal examination did not reveal any collateral circulation, hepatosplenomegaly, or ascites, and palpation was painless. The rest of the objective examination was normal.

The complementary exams carried out for the stu-
The patient started therapy with ursodeoxycholic acid in the same month, with regression of analytical alterations after three months, continuing the follow-up with the Outpatient Department, without symptoms. The last analytical evaluation (October 2009) showed parameters still within the normal levels.

**DISCUSSION**

Patients who present histological alterations suggesting PBC, but who are AMA negative and present positive anti-smooth muscle autoantibodies or ANA, have been referred to in literature under various terms, including “BPC-AIH overlap syndrome”, “autoimmune cholangiopathy”, or “autoimmune cholangitis”.6 The lack of consensus in the use of these terms makes it difficult to define criteria for diagnosis, or to compare studies and characterize, classify and define the natural history of this pathology.

The term “overlap syndromes” has been used to describe syndromes that present various biochemical, serological and histological alterations of the principal autoimmune hepatobiliary diseases (AIH, PBC and primary sclerosing cholangitis) with a tendency to evolve into cirrhosis and hepatic insufficiency. It is still not clear whether these syndromes are distinct clinical entities or merely variants or transitory forms of the principal hepatopathies (Table 1).1

The term “autoimmune cholangitis” (AIC) has been used to describe a syndrome with many characteristics in common with PBC, including prevalence among women, enzymatic patterns of cholestasis, lesions of the bile duct, and progressive evolution to
hepatic fibrosis and cirrhosis. By definition, these patients are AMA negative and frequently ANA or ASMA positive. The IgG fraction has a higher likelihood of being increased than the IgM and the histology is similar to that found in PBC, with marked lymphocytic infiltrate and immunologic destruction of the bile ducts. Granulomas are also frequent.

AIC and PBC have been discussed as separate entities or as variants of a same disease, which differ only in their autoantibody patterns. More recent studies have shown that most AIC patients present positivity in a repeat test with recombinant antigens, which detects antibodies targeting the E2 human fraction of the 2-oxo acid dehydrogenase complex (AMA-M2), and other published works reveal additional serological associations between the two pathologies.

Thus, in reality, and considering that in these cases clinical evolution and response to therapy are more similar to PBC than to IAH, some authors do not accept the overlap concept, considering the syndrome as AMA-negative PBC.

The ideal treatment for this pathology is also undefined. Although in some studies it has shown resistance to the ursodeoxycholic acid (UDCA), in some other studies biochemical regression was evident, being unclear whether or not it is accompanied by blocking of the necro-inflammatory process and delay of the evolution of the disease. In other series, response to treatment with UDCA (13-15mg/Kg/day) and the result of the liver transplant in terminal hepatic disease showed similarity with the response in PBC, another data suggesting that most of these patients suffer from true PBC, thereby putting into question the value of the association of corticotherapy in these cases.

Although the use of corticosteroids has resulted in the description of clinical and biochemical regression and no histological regression, in other series, this therapy alone has not shown significant results. It was suggested that the combination UDCA/corticosteroid might have synergic effects, since it was associated with clinical regression and improvement of analytical patterns in a series of patients with incomplete biochemical and histological response to with the isolated use of one of the drugs. After seven years, the association of UDCA and immunosuppressants proved to be more effective in the regression or stabilization of the histological alterations.

Thus, and in spite of the somewhat contradictory and controversial published results, some authors recommend starting the treatment of these cases with UDCA, associating corticosteroids (low dose prednisolone) if there is no biochemical response. Immunosuppressants such as azathioprine or cyclosporin A should be considered for individuals who are resistant to corticosteroids. Alternatively, an initial essay with corticotherapy was proposed, corticosteroids
being replaced by UDCA if there is no improvement in analytical patterns; UDCA can also be associated with the treatment of patients who do not respond to corticosteroids.16

It is also worth highlighting the family history of another autoimmune disease, in this case an endocrinopathy – Hashimoto’s thyroiditis, in the patient’s sister. A family association of hepatopathies with other autoimmune diseases has been reported,25 however, the development of these pathologies is based on the complex interaction between genetic and environmental factors. In recent years, the role of the CTLA-4 gene in the development of these diseases has been studied.26,27 This gene codifies a co-stimulant molecule expressed on the surface of activated T lymphocytes, playing a fundamental role in its activation after the presentation of antigens. Although this activation mechanism is not yet completely clear, recent studies have associated the CTLA-4 gene with the development of endocrinopathies and other autoimmune diseases such as primary biliary cirrhosis and multiple sclerosis, which explains the association of these pathologies in patients from the same family.

**CONCLUSION**

Autoimmune cholangitis is not a well-defined disease or condition, and there is still some controversy surrounding it. It is necessary to develop further basic investigation to unveil the etiopathogenic process of the duct lesion of PBC and the other autoimmune hepatobiliary pathologies.

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**TABLE I**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Autoimmune hepatitis</th>
<th>Primary biliary cirrhosis</th>
<th>Primary sclerosing cholangitis</th>
<th>Autoimmune cholangitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio ♀ : ♂</td>
<td>4:1</td>
<td>9:1</td>
<td>1:2</td>
<td>9:1</td>
</tr>
<tr>
<td>Predominant serum alterations in hepatic tests</td>
<td>GOT and GPT</td>
<td>AP and γ-GT</td>
<td>AP and γ-GT</td>
<td>AP and γ-GT</td>
</tr>
<tr>
<td>Increase in immunoglobulin</td>
<td>IgG</td>
<td>IgM</td>
<td>IgG and IgM</td>
<td>IgM</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>ANA, ASMA, anti-LKM and SLA, pANCA</td>
<td>AMA, AMA-M2</td>
<td>pANCA</td>
<td>ANA, ASMA</td>
</tr>
<tr>
<td>HLA Association</td>
<td>A3, B8, DR3, DR4</td>
<td>DR8</td>
<td>DR52</td>
<td>B8, DR3, DR4</td>
</tr>
<tr>
<td>Histology</td>
<td>Lymphocytic hepatitis with piecemeal type necrosis</td>
<td>Lesion and destruction of bile duct</td>
<td>Fibrosing lesion of bile duct</td>
<td>Lesion and destruction of bile duct</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Score AIH&gt;15</td>
<td>AMA-M2 Cholestatic serum pattern Compatible histology</td>
<td>Stenosis/bile duct dilatation Cholestatic serum pattern pANCA Inflammatory intestinal disease</td>
<td>Cholestatic serum pattern AMA-neg. ANA/ASMA positive Histology Compatible with PBC</td>
</tr>
<tr>
<td>First line therapy</td>
<td>Corticosteroids and azathioprine</td>
<td>UDCA</td>
<td>UDCA</td>
<td>UDCA</td>
</tr>
</tbody>
</table>


Adapted from Beurs U. Hepatic overlap syndromes. J Hepatol 2005; 42 (suppl 1):S93-S99
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References