Autoimmune cholangitis – a clinical case

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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, born 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/cm^2). 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-

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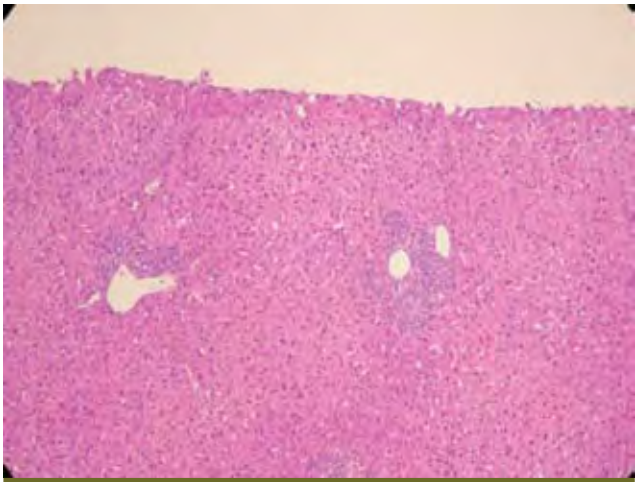
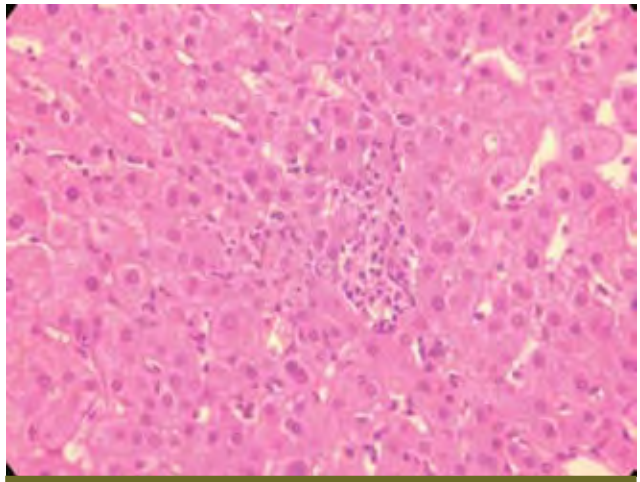


20 x enlargement. Hematoxylin-eosin staining (H&E.). Expanded portal spaces with preservation of the limiting lamina.

FIG. 1



40 x enlargement. H&E staining . Evident Kupffer cell activation.

FIG. 2

dy include: complete blood count and prothrombin time tests without any alterations and a sedimentation rate of 29 mm on the first hour. Serum levels of bilirubin, glucose, urea, creatinine, albumin, cholesterol, triglycerides, ferritin, α1-antitrypsin and ceruloplasmin, and the urinary levels of copper, were within the normal parameters. Serum immunoelectrophoresis revealed polyclonal hypergammaglobulinemia and the level of C-reactive protein was 3.6 mg/dL (N: <1.0 mg/dL). Abdominal ultrasonography did not show alterations. Serologies for hepatitis A, B and C and HIV and antinuclear antibodies, antineutrophil cytoplasmic antibodies (ANCA), anti-liver/kidney microsomal (LKM) antibodies, anti-soluble liver antigen (SLA) antibodies, anti-mitochondrial and anti-M2 antibodies were negative. The anti-smooth muscle autoantibodies were positive with a 1/320 titre. Endoscopic retrograde cholangiopancreatography (ERCP) did not reveal any irregularities of the biliary tract that would suggest sclerosing cholangitis. The patient was submitted to liver biopsy in October 2006, which revealed mononuclear inflammatory infiltrate in the portal spaces, with bile duct lesion *(Fig. 1, 2, 3 and 4)* and histological alterations which, together with the antibody patterns, led to a diagnosis of Autoimmune Cholangitis.

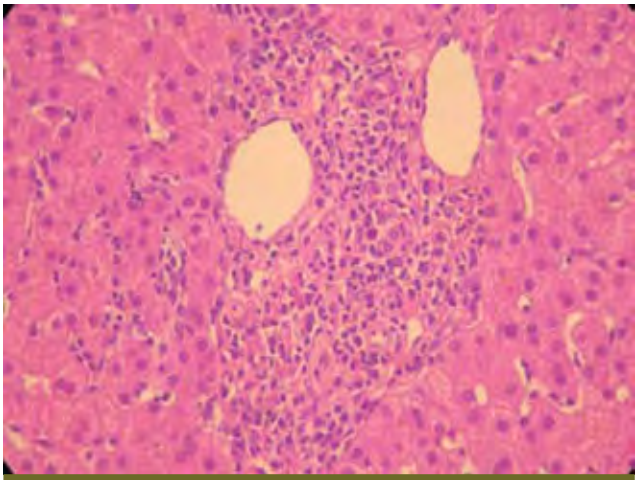
The patient started therapy with ursodeoxycholic acid in the same month, with regression of analytical alterations after three months, continuing the follow-up with the Outpatient Department, without symptoms. The last analytical evaluation (October 2009) showed parameters still within the normal levels.

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.

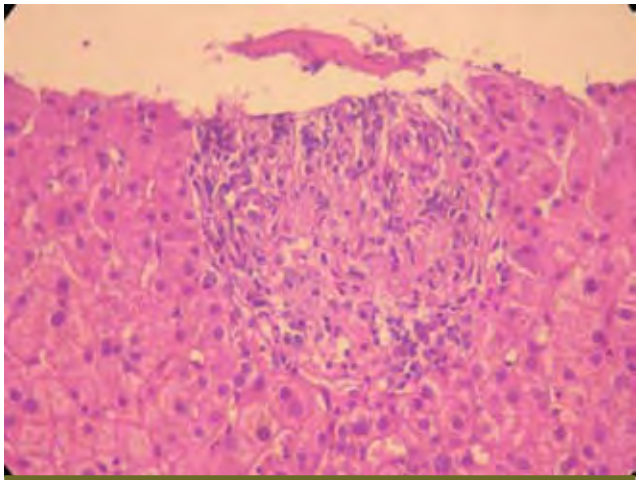
The term "overlap syndromes" has been used to describe syndromes that present various biochemical, serological and histological alterations of the principal autoimmune hepatobiliary diseases (AIH, PBC and primary sclerosing cholangitis) with a tendency to evolve into cirrhosis and hepatic insufficiency. 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



40 x enlargement. H&E staining. Portal spaces with predominantly lymphocytic infiltrate preserved in the limiting lamina.

FIG. 3



40 x enlargement. H&E staining. Portal granuloma.

FIG. 4

hepatic fibrosis and cirrhosis.[8] By definition, these patients are AMA negative and frequently ANA or ASMA positive.[1,2] The IgG fraction has a higher likelihood of being increased than the IgM[9,10] 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.[11,12,13]

AIC and PBC have been discussed as separate entities[9,10] or as variants of a same disease, which differ only in their autoantibody patterns.[1,12,14,15] 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)[16], and other published works reveal additional serological associations between the two pathologies.[11,17]

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.[1,6]

The ideal treatment for this pathology is also undefined. Although in some studies it has shown resistance to the ursodeoxycholic acid (UDCA),[18] 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.[19,20] 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.[1,21,22]

Although the use of corticosteroids has resulted in the description of clinical and biochemical regression and no histological regression,[14,18] in other series, this therapy alone has not shown significant results.[19,23]

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[(19)]. After seven years, the association of UDCA and immunosuppressants proved to be more effective in the regression or stabilization of the histological alterations.[24]

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

TABLE I

Clinical, biochemical, histological and cholangiographic characteristics of autoimmune hepatopathies

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

GOT - glutamic-oxaloacetic transaminase; GPT – glutamic-pyruvic transaminase; AP – alkaline phosphatase; γGT – gamma-glutamyl transferase; ANA – antinuclear antibodies; ASMA – anti-smooth muscle antibodies; LKM – anti-liver/kidney microsomal antibodies,SLA – anti-soluble liver antigen antibodies; ANCA – anti-neutrophil cytoplasmic antibodies; UDCA – ursodeoxycholic acid
Adapted from Beurs U. Hepatic overlap syndromes. J Hepatol 2005; 42 (suppl 1):S93-S99

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.[1,6]

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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References

1. Beuers U, Rust C. Overlap Syndromes. Semin Liver Dis. 2005; 25(3):311-320. www.medscape.com/viewarticle/512463

2. Heathcote J. JAASLD guidelines: Management of primary biliary cirrhosis. Hepatology 2000; 31:1005-1013.

3. Brunner G, Klinge O. A chronic destructive non-supurative cholangitis-like disease picture with antinuclear antibodies (immunocholangitis). Deutsch Med Wochenschr 1987; 112:1454-1458.

4. Datta D, Sherlock S, Scheuer P. Post-necrotic cirrhosis with chronic cholestasis. Gut 1963; 4:223-230.

5. Okuno T, Seto Y, Okanoue T, Takino T. Chronic active hepatitis with histological features of primary biliary cirrhosis. Dig Dis Sci 1987; 32:775-779.

6. Bonis P, Krawitt E. Definition and treatment of variants of autoimmune hepatitis. UptoDate 15.1. www.UptoDate.com

7. Czaja A, Freese D. Diagnosis and treatment of autoimmune hepatitis. Hepatology 2002; 36:147-497.

8. Heathcote J. Autoimmune cholangitis. Gut 1997; 10:440-442.

9. Michieletti P, Wanless I, Katz A et al. Antimitochondrial antibody negative primary biliary cirrhosis: a distinct syndrome of autoimmune cholangitis. Gut 1994; 35:260-265.

10. Taylor S, Dean P, Riely. Primary autoimmune cholangitis. An alternative to antimitochondrial antibody-negative primary biliary cirrhosis. Am J Surg Pathol 1994; 18:91-99.

11. Ohana M, Okasaki K, Hajiro K, Uchida K. Antilactoferrin antibodies in autoimmune liver diseases. Am J Gastroenterol 1998; 93:1334-1339.

12. Kinoshita H, Omagari K, Whittinngham S et al. Autoimmune cholangitis and primary biliary cirrhosis – an autoimmune enigma. Liver 1999; 19:122-128.

13. Gordon S, Quatrociocchi-Longe T, Khan B et al. Antibodies to carbonic anhydrase in patients with immune cholangiopathies. Gastroenterology 1995; 108:1808-1809.

14. Goodman ZD, McNally P, Davis D, Ishak K. Autoimmune cholangitis: a variant of primary biliary cirrhosis. Clinicopathologic and serologic correlations in 200 cases. Dig Dis Sci 1995; 40:1232-1242.

15. Omagari K, Ikuno N, Matsuo I et al. Autoimmune cholangitis syndrome with a bias towards primary biliary cirrhosis. Pathology 1996, 28:255-258.

16. Miyakawa H, Tanaka A, Kikuchi K et al. Detection of antimitochondrial autoantibodies in immunofluorescent AMA-negative patients with primary biliary cirrhosis using recombinant autoantigens. Hepatology 2001; 34:243-248.

17. Ikuno N, Scealy M, Davies J et al. A comparative study of antibody expressions in primary biliary cirrhosis and autoimmune cholangitis using phage display. Hepatology 2001; 34: 478-486.

18. Ben-Ari Z, Dhillon A, Sherlock S. Autoimmune cholangiopathy: part of the spectrum of autoimmune chronic active hepatitis. Hepatology 1993; 18:10-15.

19. Chazouillères O, Wendum D, Serfaty L et al. Primary biliary cirrhosis-autoimmune hepatitis overlap syndrome: clinical features and response to therapy. Hepatology 1998; 28:296-301.

20. Czaja A, Carpenter H, Santrach P, Moore S. Autoimmune cholangitis within the spectrum of autoimmune liver disease. Hepatology 2000. 31:1231-1238.

21. Kim W, Poterusha J, Jorgensen R et al. Does antimitochondrial antibody status affect response to treatment in patients with primary biliary cirrhosis? Outcomes of ursodeoxycholic acid therapy and liver transplantation. Hepatology 1997; 26:22-26.

22. Joshi S, Couch-Dudek K, Wanless I et al. Primary biliary cirrhosis with additional features of autoimmune hepatitis: response to therapy with ursodeoxycholic acid. Hepatology 2002; 35:409-413.

23. Terracciano L, Patzina R, Lehman F et al. A spectrum of histophatologic findings in autoimmune liver disease. Am J Clin Pathol 2000; 114 (5):705-711.

24. Chazouillères O, Wendum D, Serfaty L et al. Long term outcome and response to therapy of primary biliary cirrhosis-autoimmune hepatitis overlap syndrome. J Hepatol 2006; 44:400-406.

25. Findor J, Sorda J, Daruich J, Manero E. Familial Association in Autoimmune Liver Disease. Medicina 2002; 62: 241-244.

26. Juran B, Atkinson E, Schlicht E, Fridley B, Lazaridis K. Primary Biliary Cirrhosis is Associated With a Genetic Variant in the 3' Flanking Region of the CTLA4 Gene. Gastroenterology 2008; 135(4); 1200-1206.

27. Vaidya B, Pearce. The Emerging Role of the CLTA-4 Gene in Autoimmune Endocrinopathies. European Journal of Endocrinology 2004; 150: 619-626.