

Primary Biliary Cirrhosis Associated with Graves' Disease in a Male Patient

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Abstract

Primary biliary cirrhosis (PBC), which predominantly affects women, has been associated with various autoimmune diseases. Although hypothyroidism accompanying PBC is well documented, the concomitance of PBC and hyperthyroidism is rare. Herein, we report the case of a 62-year-old man who was diagnosed with PBC several years after the development of Graves' disease. This is the first case of a male patient developing PBC with Graves' disease. Both serum alanine aminotransferase levels and serum thyroid hormone levels were normalized after the administration of thiamazole for Graves' disease. However, the cholestatic liver enzyme abnormalities continued, indicating that the PBC was actualized by the administration of thiamazole. After starting ursodeoxycholic acid treatment, cholestatic liver enzyme abnormalities improved. Taken together, when a cholestatic pattern of liver enzymes is observed during follow-up for Graves' disease, an association between Graves' disease and PBC should be considered as a differential diagnosis.

Key words: primary biliary cirrhosis, Graves' disease, autoimmunity

Introduction

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease with destruction of the small hepatic bile ducts, followed by progressive fibrosis and ultimately cirrhosis [1]. PBC is more common in women than in men, and its etiology is attributed to a combination of genetic predisposition and environmental factors [2, 3]. There are certain autoimmune diseases that occur often in PBC, including Sjögren's syndrome, rheumatoid arthritis, and autoimmune thyroid disease [4]. Autoimmune thyroid disease related to PBC is frequently seen in Hashimoto's thyroiditis and hypothyroidism [5]. However, only a few female patients with PBC and Graves' disease have been reported in the literature, and PBC associated with Graves' disease in a male patient has not been reported previously. Herein, we report on a male patient who was diagnosed with PBC several years after the development of Graves' disease and was effectively treated with ursodeoxycholic acid.

Case Report

In January 2009, a 62-year-old Japanese man was initially diagnosed with Graves' disease, with symptoms of weight loss of 5 kg in two months, tremors, sweating, a large goiter, exophthalmos, and diplopia. He also had hypertension (150/84 mmHg) and tachycardia (80 beats/min). Thyroid function tests revealed low serum thyroid stimulating hormone (TSH) (<0.01 $\mu\text{U/ml}$, range 0.35–4.94), high free T4 (2.58 ng/dl, range 0.70–1.48), and high free T3 (14.02 pg/ml, range 1.71–3.71). TSH receptor antibody positivity was 33.8%, suggesting Graves' disease. Other laboratory analyses, including a complete blood count and serum chemistry, showed no abnormalities except for a slight elevation of alanine aminotransferase (ALT) at 36 U/l (range 5–35), of

alkaline phosphatase (ALP) at 347 U/l (112–334), and of gamma-glutamyl transferase (GGT) at 86 U/l (8–65). A measurement of antimitochondrial antibodies was not performed at that time. After the administration of thiamazole (15 mg/day), the patient's symptoms were alleviated, followed by the normalization of thyroid function tests. Despite the normalization of serum thyroid hormone levels and ALT levels, a persistent slight elevation in the GGT level, ranging between 102 and 258 U/l, was observed during the follow-up period for Graves' disease. Serum ALP was also sometimes elevated, ranging between 291 and 426 U/l.

In August 2013, the patient was referred to our office because of elevated serum liver enzymes on a laboratory examination. He had also been feeling tired and fatigued. The laboratory findings showed a total bilirubin level of 1.0 mg/dl (range 0.2–1.2), an ALP level of 499 U/l (range 112–334), a GGT level of 224 U/l (range 8–65), an aspartate aminotransferase (AST) level of 39 U/l (range 8–40), and an ALT level of 54 U/l (range 5–35). Antimitochondrial antibodies were positive at a titer of 1:160, and M2 type antimitochondrial antibodies were 105.4 U/ml. Serum immunoglobulin M (IgM) was 292 mg/dl (range 35–220). Serum immunoglobulin A and immunoglobulin G levels were in the normal range. At that time, serum thyroid hormone levels were all normal. Abdominal ultrasonography and magnetic resonance imaging did not reveal any evidence of biliary dilatation or any other diseases. The histological findings were compatible with PBC at an early stage (Scheuer Stage I). Specifically, mixed inflammatory infiltrates were seen in the enlarged portal area, and the stratified epithelium of the interlobular bile duct was infiltrated with lymphocytes (Fig. 1). Human leukocyte antigen (HLA) typing was positive for DRB1*08:02, assessed using the polymerase chain reaction-reverse sequence specific oligonucleotide (PCR-rSSO)

method. The patient was diagnosed with PBC according to the clinical criteria and pathological findings, and treatment with ursodeoxycholic acid (600 mg/day) was initiated. The patient's clinical course is presented in Fig. 2. Six months after starting the ursodeoxycholic acid treatment, his ALP, GGT, and IgM serum levels had decreased to 308 U/l, 72 U/l, and 139 mg/dl, respectively.

Discussion

In this report, we describe a male patient who presented with PBC associated with Graves' disease. The PBC was diagnosed by liver histology, the presence of antimitochondrial antibodies, increased IgM levels, and elevated ALP and GGT levels. After starting ursodeoxycholic acid treatment, the liver abnormalities improved. This result indicates that ursodeoxycholic acid is also useful in cases of PBC associated with Graves' disease. Five previous case reports were identified in the English literature using MEDLINE. There are some previous reports about PBC patients who had evidence of hyperthyroidism not in the form of Graves' disease [6, 7]. We excluded those cases in this review because the terms "Graves' disease" and "hyperthyroidism" are not synonymous. Although Graves' disease is the most common cause of hyperthyroidism, a variety of nosological subtypes with different etiologies can cause this condition [8]. Table 1 shows the clinical features of the five relevant cases and the present one. In a prospective study of 361 PBC patients, Floreani et al. reported on seven patients with PBC associated with Graves' disease, although detailed information about those patients was not shown [4]. The five reported cases were all females. Three of the five patients were diagnosed with Graves' disease before the diagnosis of PBC. There seemed to be no relationship between the time of onset of PBC and Graves'

disease. Two cases suffered from concomitant autoimmune diseases. It has been reported that the onset of hyperthyroidism can cause liver abnormalities in PBC patients [6, 13]. However, the onset of hyperthyroidism itself did not seem to have any impact on the severity or clinical course of PBC in other case reports, as far as appropriate treatment.

In our case, liver test abnormalities, including in GGT and ALP levels, had already been found at the time of the diagnosis of Graves' disease. The presence of liver test abnormalities in the setting of hyperthyroidism has been reported [14]. The mechanisms of liver injury in the setting of hyperthyroidism are categorized into three groups: liver abnormalities due to hyperthyroidism alone, liver damage related to heart failure and hyperthyroidism, and liver disease. It is apparent that the functions of the thyroid and the liver are intertwined, thus causing difficulty in the differential diagnosis. In our case, cholestatic liver enzyme abnormalities continued in spite of the normalization of serum thyroid hormone levels. However, the serum ALT level normalized after the administration of thiamazole, indicating that the hepatic enzyme abnormalities in this case might have been caused by hyperthyroidism due to Graves' disease per se. We expect that the PBC in this patient was actualized by the administration of thiamazole for Graves' disease.

A serious limitation of this case report is the lack of measurement of antimitochondrial antibodies at the time of the Graves' disease diagnosis, so we cannot verify whether the patient had PBC at that time. The scarcity of men with PBC might be implicated in the delay of the diagnosis in this case. Additionally, the patient's symptom of fatigue, which is one of the main and common symptoms in both PBC and Graves' disease, may cause difficulty with the clinical work-up. Routine examinations, including

measurements of antimitochondrial antibodies and serum IgM, should be done to assess the possible relationship between PBC and Graves' disease in cases of concomitant cholestatic liver enzyme abnormalities and hyperthyroidism. Since some cases of PBC and Graves' disease may still remain unrecognized, further reports are required to determine the frequency of concomitant PBC and Graves' disease.

As mentioned earlier, PBC is a disease that predominantly affects women, with the female-to-male ratio ranging from 9:1 to 22:1 [15, 16]. The underlying reasons for the low incidence of men with PBC are largely unknown. Clinically, it seems there are some differences in PBC patients between the sexes, with females tending to present with pruritus more often than males, and with males at a higher risk of developing gastrointestinal bleeding and hepatocellular carcinoma [17, 18]. It is noteworthy that males are less likely to suffer concomitant autoimmune disease than females [4, 18]. The present patient had no other autoimmune diseases, such as Sjögren's syndrome or rheumatoid arthritis, which are commonly associated with PBC.

PBC and Grave's disease are etiologically complex conditions thought to result from interactions between multiple genetic and environmental factors. Single nucleotide polymorphisms (SNPs) in cytotoxic T lymphocyte antigen-4 (CTLA-4), which negatively regulates T cell function, have been implicated in the genetic risk for both PBC and Graves' disease [19, 20]. Genetic variants in HLA genes have also been associated with the majority of autoimmune diseases. In our case, HLA typing was positive for DRB1*08:02. It has been reported that the DRB1*08:03 allele (not DRB*08:02) and the DRB*08:03-DQB1*06:01 haplotype are associated with PBC in Japanese patients [21]. We suppose that common immunoregulatory mechanisms may be involved in the etiology of PBC and Graves' disease, and further studies are needed

to evaluate genetic predispositions between these two diseases.

In conclusion, although PBC associated with Graves' disease is rare among men, it should be considered as a differential diagnosis in patients with cholestatic liver enzyme abnormalities in the presence of underlying Graves' disease.

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Figure legends

Fig. 1 (a) A dense lymphoid infiltrate is observed in the portal tract, which shows bile duct loss (original magnification 120×). (b) A bile duct is surrounded by inflammatory cells. The stratified epithelium of the bile duct (arrow) is infiltrated with lymphocytes (arrowhead) (original magnification 400×). (c) The typical infiltrate is composed of small lymphocytes, some plasma cells, and a few eosinophils. Arrows indicate the eosinophils (original magnification 400×). (d) Masson's trichrome staining shows an enlarged portal area with fibrosis (original magnification 120×).

Fig. 2 Clinical course of the patient. UDCA, ursodeoxycholic acid.

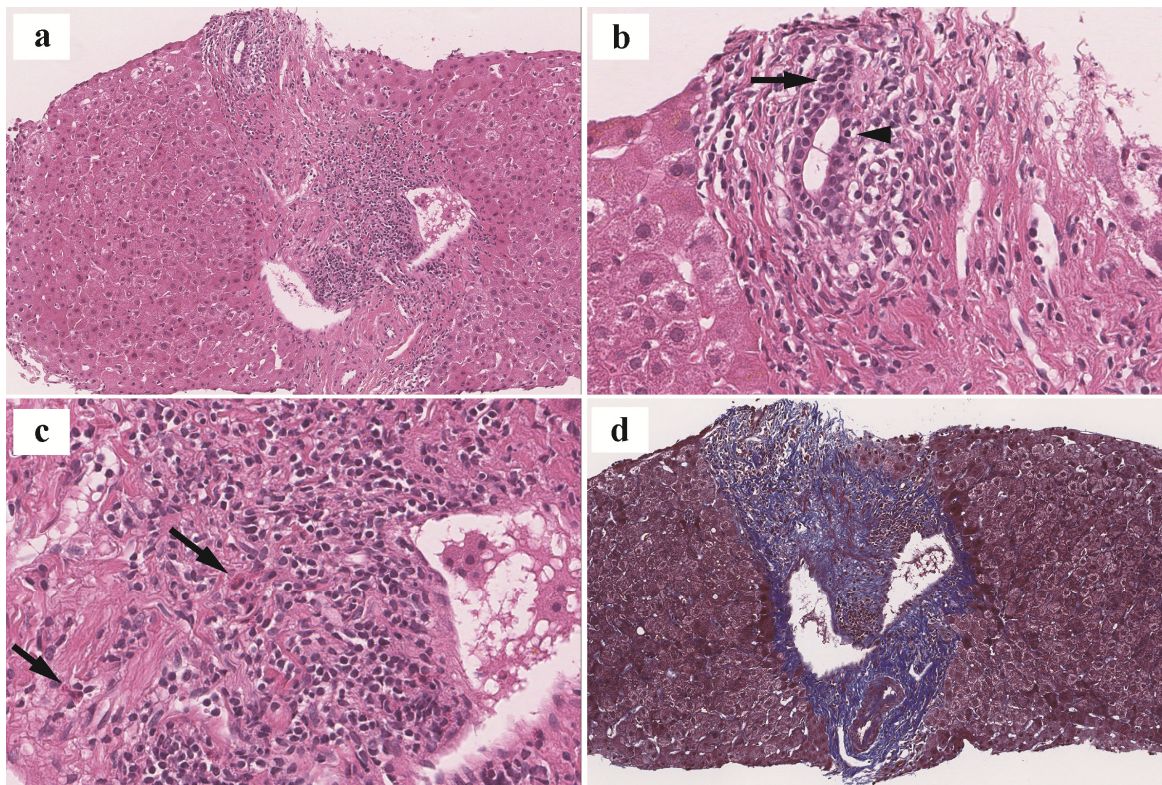


Fig.1

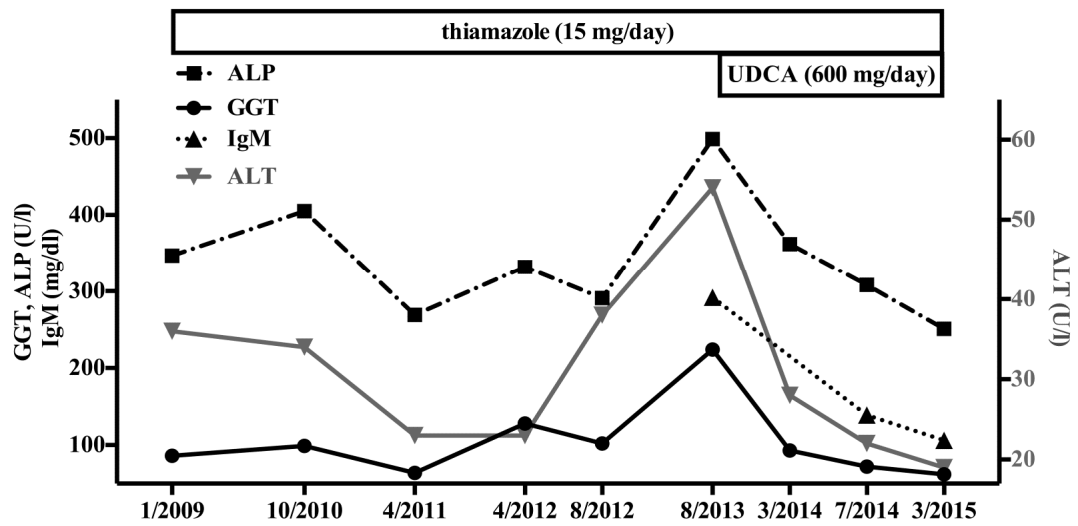


Fig.2