

NOTE

A Case of Autoimmune Hypophysitis Associated with Asymptomatic Primary Biliary Cirrhosis

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Abstract. We report a 61-year old male patient with panhypopituitarism complicated with asymptomatic primary biliary cirrhosis (PBC). T1-weighted magnetic resonance imaging demonstrated high intensity of the anterior pituitary gland. There was no mass lesion or enlargement of the pituitary gland or the stalk. Immunoblot analysis of the patient's sera with rat pituitary antigens revealed a band with a molecular size of 22 kD. Anti-M₂ mitochondrial antibody has been consistently positive for five years. Liver biopsy revealed portal hepatitis with periportal infiltration of the inflammatory cells. This is the first case report of autoimmune hypophysitis complicated with asymptomatic PBC.

Key words: Anti-pituitary antibody, Anti-mitochondrial antibody, Asymptomatic primary biliary cirrhosis, Hypopituitarism

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IT HAS been reported that autoimmune hypophysitis was often complicated with other autoimmune diseases such as chronic thyroiditis [1]. It is also known that a variety of organ-specific autoantibodies are detected in the sera of patients with autoimmune hypophysitis. There have been several cases with positive anti-mitochondrial antibody [2, 3], but its pathophysiological significance has not been elucidated. Anti-mitochondrial antibody is highly specific for primary biliary cirrhosis (PBC). Especially anti-M₂ mitochondrial antibodies are most often found in patients with clinical PBC [4, 5]. In this paper, we report an elderly male patient with autoimmune hypophysitis associated with asymptomatic PBC which was ascertained by the liver biopsy.

Case Report

A 56-year old man was admitted to a hospital after an episode of palpitation, cold sweating and weakness five years earlier. Hypotension and hypoglycemia were relieved by treatment with hydrocortisone, and the patient was transferred to our hospital for further examination.

On physical examination, his blood pressure was 90/68 mmHg, and pulse rate was 64/min, regular. The visual field and the acuity were normal. Goiter was not palpable. Axillary and pubic hair distributions were normal.

Hematological and biochemical laboratory data showed no remarkable abnormalities except mild anemia (Hb: 11.8 g/dl). Serum electrolyte and transaminoferase levels were within normal limits. Endocrinological tests revealed impaired secretion of ACTH, GH, PRL and gonadotropins (Table 1, Fig. 1). Diabetes insipidus was not present. Serum anti-mitochondrial antibody was positive at a

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dilution of 1:160 by immunofluorescence. Serum IgM and IgG anti-M₂ mitochondrial antibodies were 700 U/ml and 368 U/ml, respectively as

Table 1. Laboratory findings on admission

Endocrine		Aldosterone	3.8 ng/dl
GH	<0.3 ng/ml	urine 17OHCS	0.6 mg/day
urine GH	3.3 pg/mgCr	urine 17KS	1.8 mg/day
IGF-I	27 ng/ml	Immunology	
PRL	2.4 ng/ml	C3	51 mg/dl
ADH	1.1 pg/ml	C4	41.9 mg/dl
TSH	6.5 µU/ml	CH50	34.5 U/ml
T3	120 ng/dl	IgG	1149 mg/dl
T4	6.6 µg/dl	IgM	166 mg/dl
Free T4	0.8 ng/dl	IgA	277 mg/dl
LH	3.2 mIU/ml	AMA	× 160
FSH	3.1 mIU/ml	anti-M ₂ IgM	700 U/ml
Testosterone	328 ng/dl	anti-M ₂ IgG	368 U/ml
ACTH	11 pg/ml	TGHA	< × 100
Cortisol	0.37 µg/dl	MCHA	< × 100

17OHCS, 17-hydroxycorticosteroids; 17KS, 17-ketosteroids; AMA, anti-mitochondrial antibody; anti-M₂, M₂ type of AMA; TGHA, anti-thyroglobulin antibody; MCHA, anti-microsomal antibody.

determined by enzyme immunoassay [6]. Anti-pituitary antibody was examined by immunoblot analysis as previously described by Yabe *et al.* [7]. As shown in Fig. 2, a major band was identified at 22 kD. A minor band also was seen at 49 kD, presumably due to anti-M₂ mitochondrial antibody.

T1-weighted image of magnetic resonance imaging (MRI) demonstrated a heterogenous high intensity in the anterior lobe of the pituitary gland. The posterior lobe and the stalk were normal (Fig. 3).

This patient has been treated with hydrocortisone for five years. During the treatment, daily excretion of urinary 17-OHCS remained within the normal range, and neither clinical signs nor laboratory findings indicated adrenal insufficiency. Serum transaminiferase levels remained within normal limits. Serum IgM (1256 U/ml) and IgG (605 U/ml) anti-M₂ mitochondrial antibodies were consistently high.

Liver biopsy was performed to evaluate the liver histology and revealed portal hepatitis with periportal infiltration of inflammatory cells (Fig.

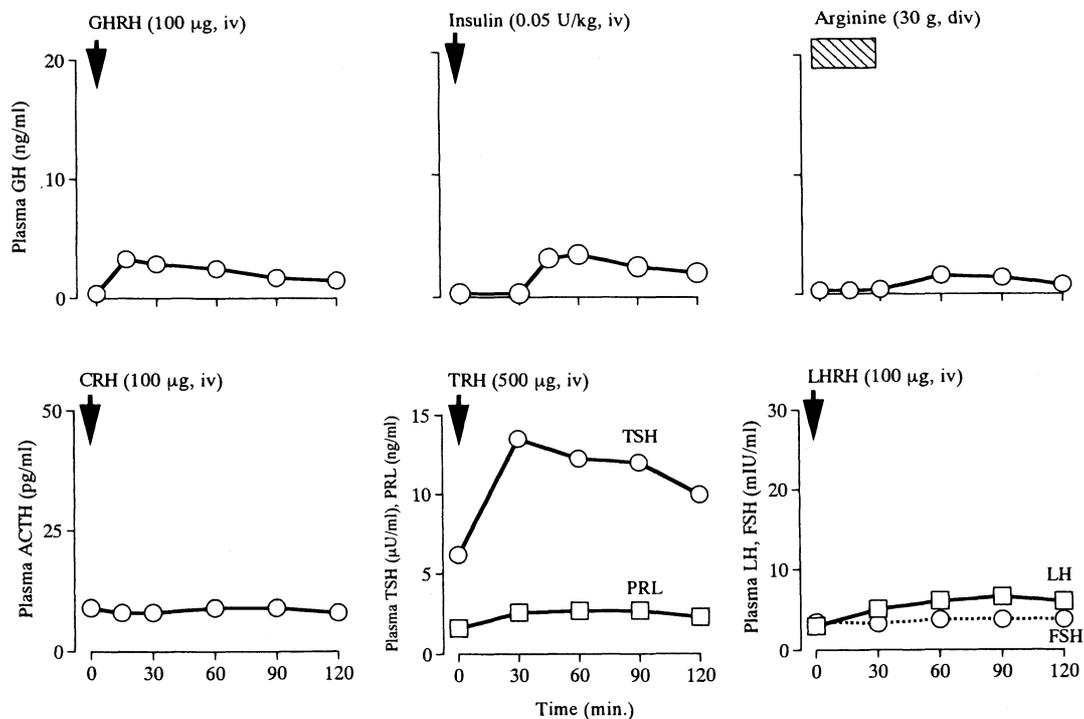


Fig. 1. Endocrinological provocative tests. Upper pannels; plasma GH responses to GHRH, insulin-induced hypoglycemia and arginine. Lower pannels; plasma ACTH, TSH and prolactin, and gonadotropin response to CRH, TRH and LHRH, respectively.

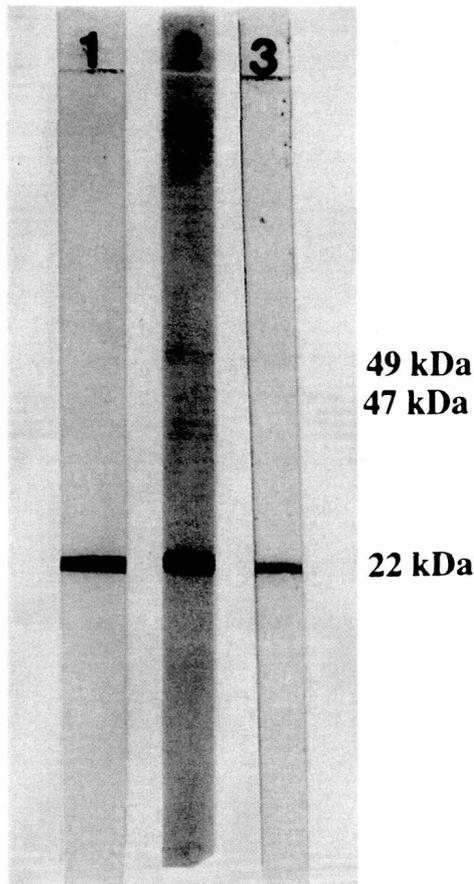


Fig. 2. Immunoblot analysis of the patient's sera with rat pituitary antigens. Rat pituitary antigens were electrophoresed in polyacrylamide gel, transferred to a PVDF membrane, and were reacted with the patient's serum (dilution; 1: 101), followed by the avidin biotin peroxidase complex method. Lane 1: positive control serum, Lane 2: patient's serum (February 1992), Lane 3: patient's serum (January 1996).

4). No granulomatous lesion or inflammatory destruction of bile ducts was found. These findings correspond to the portal stage of PBC according to morphologic staging described by Ludwig *et al.* [8].

Discussion

Autoimmune hypophysitis is characterized by lymphocytic infiltration into the pituitary gland [2, 3] and by the presence of anti-pituitary antibody in the serum [7, 9, 10]. In the present case, the detection of anti-pituitary antibody by a

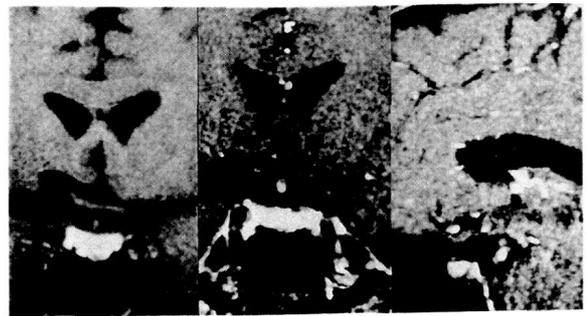


Fig. 3. T1-weighted MRI images. Left: coronal, plain. Middle: coronal, gadolinium (Gd) enhancement. Right: sagittal, Gd enhancement. Note the high intensity in the anterior pituitary gland. No enlargement of the pituitary gland or the stalk was found.

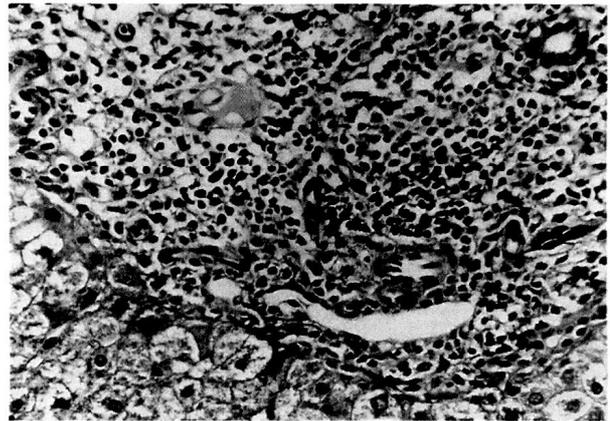


Fig. 4. Histology of the liver ($\times 400$) shows periportal infiltration of inflammatory cells. No granuloma or destruction of bile ducts was found.

conventional immunofluorescence method was interfered by an anti-mitochondrial antibody, but immunoblotting with antigens of rat pituitary gland revealed an antibody to the antigen with a molecular size of 22 kD.

Anti-M₂ mitochondrial antibody was consistently positive in the present case. Nine types of anti-mitochondrial antibody (M₁-M₉) have been described. Among them, anti-M₂ mitochondrial antibody is the most specific for PBC [4, 5]. There have been several case reports of autoimmune endocrine diseases associated with positive anti-mitochondrial antibodies. Perros *et al.* [11] reported two patients with Graves' disease in whom

anti-mitochondrial antibody was detected. In these patients, anti-M₂ mitochondrial antibody was negative and there was no liver dysfunction. A few autoimmune hypophysitis patients with positive anti-mitochondrial antibody have been described [2, 3], but no detailed information on antibody subtypes, liver function or histology is available.

Portal hepatitis with periportal inflammation was demonstrated in the liver biopsy in the present case. Neither granuloma nor nonsuppurative destructive cholangitis was noted. According to the morphological staging by Ludwig *et al.* [8], these findings correspond to portal stage of PBC. Anti-M₂ mitochondrial antibody of the IgM type is generally found in patients with asymptomatic PBC, and seroconversion from IgM to IgG antibody often indicates progression of the disease [5, 6]. In our patient, no clinical liver dysfunction has been found during the clinical course for five years. This might be related to the fact that IgM anti-M₂ mitochondrial antibody has been positive without seroconversion to IgG type. Although

asymptomatic PBC patients usually have a favorable prognosis, it sometimes takes more than ten years for the asymptomatic PBC to develop into the stages of advanced histologic lesions and clinical liver dysfunctions [12].

In summary, we report an old male case of lymphocytic hypophysitis complicated with asymptomatic PBC. Anti-pituitary antibody and anti-mitochondrial antibody were demonstrated in the serum. Histopathological examination of the liver demonstrated portal hepatitis with periportal inflammation. These findings suggest that anti-M₂ mitochondrial antibody might have pathophysiological significance in this patient with autoimmune hypophysitis in the development of PBC.

Acknowledgments

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