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CASE

A case of lymphocytic panhypophysitis (LPH) during pregnancy

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Abstract A 37-year-old pregnant woman developed continuous headache in the 10th week of pregnancy, followed by bilateral visual field defect and general malaise in the 24th week. The brain magnetic resonance imaging showed a pituitary mass. In laboratory examination, plasma concentration of free thyroxine, thyroid stimulating hormone (TSH), cortisol, and adrenocorticotropic hormone (ACTH) was low. General malaise vanished shortly after the replacement therapy of glucocorticoid and thyroid hormone, but partial central diabetes insipidus (CDI) appeared, which could be treated with desmopressin acetate (DDAVP). The visual field defect having enlarged, transsphenoidal surgery was performed in the 31st week of pregnancy. Adenohypophysis could be resected, and it showed infiltration of mature lymphocytes. After the surgery, the visual defect had improved, but hormone replacement was still necessary. She delivered a baby in the 38th week without any trouble. Provocative tests after delivery revealed a low response in TSH, prolactin (PRL), and follicle stimulating hormone (FSH). Hormone replacement and DDAVP administration was necessary in the same doses after delivery. The diagnosis was lymphocytic panhypophysitis (LPH). In the case of pregnant woman, LPH should be included in the differential diagnosis of pituitary mass for the fetomaternal safety.

Keywords Hypopituitarism · Diabetes insipidus · Lymphocytic panhypophysitis · Pregnancy · Pituitary tumor · Hormone replacement therapy · Transsphenoidal surgery

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Introduction

Lymphocytic hypophysitis (LH) was first described in 1962 by Goudie et al. [1] in a 22-year-old woman about an year after delivery presenting with vomiting and diarrhea. In 1967, Levine reported that allergic adenohypophysitis could be produced in rats [2]. Thereafter, many cases with LH have been reported, indicating that LH is not a rare disease [3, 4]. Originally, LH was considered to be confined only to adenohypophysis [3], and the term of LH has been used interchangeably with that of lymphocytic adenohypophysitis (LAH). On the other hand, Imura et al. [5] proposed that another type of LH involves only infundibular stem, and neurohypophysis is a cause of central diabetes insipidus (CDI), and called lymphocytic infundibuloneurohypophysitis (LINH). Finally, several cases of LH affecting both adenohypophysis and neurohypophysis were reported [6, 7, 8]. We proposed the term "lymphocytic panhypophysitis (LPH)" for such cases [9]. The term has been broadly accepted [10], but its entity and pathogenesis remain to be elucidated. Epidemiologically, LAH

shows a strong relationship with pregnancy, especially in the last month of pregnancy or in the first two months after delivery, but LINH and LPH are usually considered not be related to pregnancy [10]. Furthermore, there have been few evidences that autoimmune mechanism may affect both anterior and posterior lobes of the pituitary simultaneously.

Here, we report a case of a 37-year-old pregnant woman with LPH, which developed as headache in the 10th week of pregnancy and visual field defect in the 24th week.

Case report

A 37-year-old woman in the 28th week of pregnancy was referred to our hospital because of bitemporal quadrantanopia and general malaise. The patient had neither remarkable past medical history nor family history. In the 10th week of pregnancy, she suddenly developed continuous headache. Headache gradually disappeared within two months. She felt, however, bilateral blurred vision and general malaise around the 24th week of pregnancy. She visited a nearby neurosurgery clinic, where pituitary mass was detected by brain magnetic resonance imaging (MRI). The patient was referred to our hospital for further examination and treatment.

On admission, she complained of slight fatigue, but vital signs were completely normal. She had a visual field defect in bitemporal upper quadrants. The results of physical examination were otherwise normal including fetal development.

The brain MRI showed homogenous swelling of whole pituitary gland. This pituitary mass compressed sellar floor into sphenoid sinus, and suprasellar extension was also pointed out. The mass had a clear periphery and demonstrated homogenous signal, approximately isointense to gray matter both on T1 and T2-weighted images. The size of hyperintense area of neurohypophysis on T1-weighted image was a little smaller than that of normal (Fig. 1). From these findings, pituitary adenoma or lymphocytic hypophysitis (LH) was suspected.

Endocrinological examinations were performed. Plasma concentration of free thyroxine (T4; 0.51 ng/dl, normal range; 0.7–1.48), thyroid stimulating hormone (TSH; 0.01 μIU/ml, normal range: 0.35–4.94), and cortisol (2.6 μg/ml, normal range; 4.5–21.1) were significantly low, and that of adrenocorticotropic hormone (ACTH; 8.9 pg/ml, normal range; 9–52) was slightly below the normal range. Low value of urinary 17-hydroxycorticosteroids (17-OHCS; 1.3 mg/day, normal range; 2.2–7.3) also showed deficiency of cortisol. Plasma prolactin (PRL), growth hormone (GH), luteinizing hormone (LH), and follicle stimulating hormone (FSH) level were normal (Table 1).

Replacement of glucocorticoid (hydrocortisone; 10 mg/day, p.o.) followed by thyroid hormone (levothyroxine sodium; 25 μg/day, p.o.) was started, resulting in prompt resolution of general malaise. Five days after the replacement therapy, the patient developed polyuria up to 6,000 ml a day. Urinary osmolarity was significantly lower (79 mOsm/kg) than that of plasma (278 mOsm/kg), and plasma antidiuretic hormone (ADH) secretion was within the normal limit (0.7 pg/ml, normal range; 0.3–3.5). These findings indicated the presence of partial central diabetes insipidus (CDI). After nasal administration of desmopressin acetate (DDAVP; 10 μg/day), the amount of urine was rapidly decreased to the normal level.

The brain MRI, a week after the replacement therapy, showed no significant change in the pituitary size and the visual field defect had rather enlarged. In order to make final diagnosis and to achieve decompression of pituitary gland, transsphenoidal surgery was performed in the 31st week of pregnancy. The visual field was improved shortly after the surgery, and the pituitary mass size was reduced on MRI. Postoperatively, hormone replacement therapy with hydrocortisone, levothyroxine, and intranasal DDAVP was still necessary at the same dose. Laboratory data after surgery are shown in Table 1.

The resected specimen revealed diffuse infiltration of mainly mature lymphocytes and strongly destroyed adenohypophysis (Fig. 2). Only a small amount of PRL and

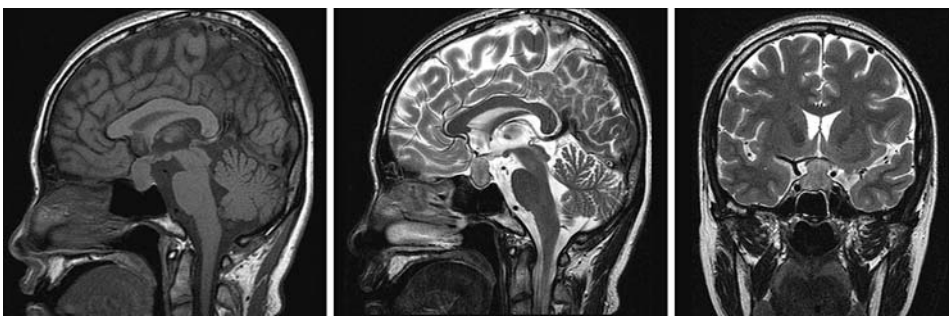

Fig. 1 Brain MRI on admission (T1-weighted sagittal, T2-weighted sagittal, and T2-weighted coronal section from the left). It showed homogenous swelling of whole pituitary gland, compression of sellar floor into sphenoid sinus, and suprasellar extension

Table 1 Laboratory data on admission, 10 days after surgery, and 8 days after delivery

	Normal range	On admission	10 days after surgery	8 days after delivery
GOT(AST)	8–40 U/l	24	10	14
GPT(ALT)	4–44 U/l	17	6	17
LDH	230–460 U/l	262	279	188
ALP	75–234 U/l	119	169	259
Total protein	6.5–8.0 g/dl	5.3 L	5.9 L	5.9 L
CK	36–188 U/l	33 L	14 L	51
Glucose	70–109 mg/dl	72	101	78
BUN	8.0–20.0 mg/dl	5.3 L	6.2 L	9.0
Creatinine	0.4–1.1 mg/dl	0.43	0.38 L	0.52
Sodium	136–147 mEq/l	138	135 L	140
Potassium	3.6–5.0 mEq/L	3.7	3.5 L	4.1
Chlorine	98–108 mEq/l	105	100	105
C reactive protein	<0.3 mg/dl	0.47 H	0.64 H	0.89 H
Red blood cell count	$376–500 \times 10^4/\mu l$	355 L	368 L	388
Hemoglobin	11.3–15.2 g/dl	11.9	11.2 L	11.0 L
Hematocrit	33.4–44.9%	33.3 L	32.6 L	32.9 L
Platelet count	$13–36.9 \times 10^4/\mu l$	19.1	22.9	29.8
White blood cell count	$35–91 \times 10^4/\mu l$	70	87	86
Urine osmolarity	100–1300 mOsm/kg	397	376	357
Plasma osmolarity	275–290 mOsm/kg	271 L	268 L	282
Estradiol	6–29 ng/ml	11.16	6.20	
Progesterone	345–390 ng/ml	122.3	152.9	
Free T4	0.7–1.48 ng/dl	0.51 L	0.77	
T3	0.58–1.59 ng/ml	1.28	0.85	
TSH	0.35–4.94 μIU/ml	0.01 L	<0.01 L	
LH	<0.2 mIU/ml	<0.07	<0.07	
FSH	<1.0 mIU/ml	0.3	0.7	
Cortisol	4.5–21.1 μg/dl	2.6 L	3.7 L	
Urine cortisol (24 h)	26–187 μg/day	25.6 L	249.5 H	123.7
PRL	3.01–18.6 ng/ml	10.9	9.6	
ADH	0.3–3.5 pg/ml	1.1	0.8	0.6
Urine 17-KS (24 h)	2.4–11 mg/day	5.3	7.6	3.8
Urine 17-OHCS (24 h)	2.2–7.3 mg/day	1.3 L	7.4 H	12.1 H
IGF-I	73–311 ng/ml	77	136	
ACTH	9–52 pg/ml	8.9	7.0 L	
GH	0.28–1.64 ng/ml	0.31	0.10 L	

Abbreviations: H or L: higher or lower value than the normal range for a pregnant female in our hospital, T3: triiodothyronine, LH: luteinizing hormone, FSH: follicle stimulating hormone, 17-KS: 17-ketosterids, IGF-I: insulin-like growth factor-I

ACTH were detected on immunohistochemical staining. Infiltrating lymphocytes included both T and B cells, which were positive for CD3 and L26, respectively. Posterior lobe specimen could not be obtained.

About seven weeks after surgery, she delivered a healthy baby by cesarean section in the 38th week without any trouble. Intravenous hydrocortisone (100 mg/day) was administered until three days after delivery, with bolus injection (100 mg) just after the expulsion of placenta, and was reduced to 50 mg, another two days after that. Uterine contraction was good after delivery, but breast feeding was not possible. Laboratory data after delivery are shown in Table 1.

Provocation test of adenohypophysial functions with corticotropin releasing hormone (CRH), growth hormone releasing factor (GRF), gonadotropin releasing hormone (GnRH), and thyrotropin releasing hormone (TRH) was performed. The result was normal response in cortisol, ACTH, GH, and LH, but low response in TSH, PRL, and FSH (Table 2).

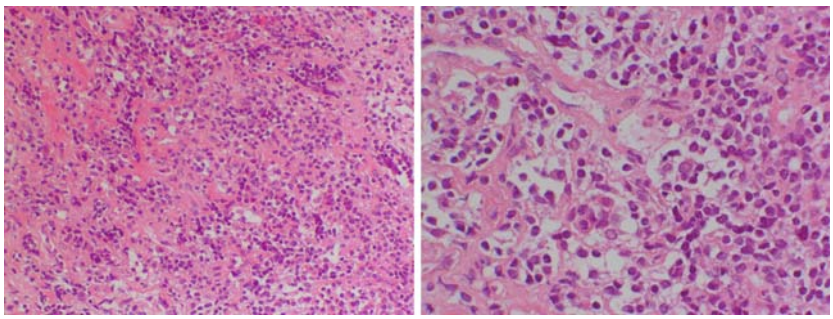

Fig. 2 The pathology of the resected specimen (hematoxylin and eosin (HE) staining). It showed diffuse infiltration of mainly mature lymphocytes and strongly destroyed adenohypophysis

Table 2 Provocative test after delivery

	Plasma concentration				
	Before	30 min	60 min	90 min	120 min
Provocative test with CRH, GRF, LHRH					
GH (ng/ml)	0.7	5.6	4.7	2.4	0.9
LH (mIU/ml)	<0.07	0.62	0.30	0.26	0.09
FSH (mIU/ml)	1.31	1.71	1.79	1.94	2.00
Cortisol (μg/dl)	4.8	10.0	12.4	12.6	10.4
ACTH (pg/ml)	8.8	61	66	40	25
Provocative test with TRH					
TSH (μIU/ml)	<0.01	0.04	0.04	0.04	0.03
PRL (ng/ml)	4.4	4.5	4.6	4.3	4.3

The result was normal response in cortisol, ACTH, GH, and LH, but low response in TSH, PRL, and FSH

The patient was discharged ten days after delivery. She continued to be well controlled by oral administration of hydrocortisone (10 mg/day), levothyroxine (25 μg/day), and intranasal DDAVP (10 μg/day) at the same doses.

Discussion

We reported a case of a pregnant woman presenting with panhypopituitarism. Polyuria after the replacement therapy was believed to be so-called "masked DI" due to adrenal insufficiency [11, 12]. In CDI patients, the brain MRI often shows a diffuse thickening of pituitary stalk and the disappearance of T1 hyperintense area of neurohypophysis. This area is believed to represent secreting granules of ADH [5, 13]. In this case, there existed T1 hyperintense area, although it was smaller than the normal. This suggests that ADH secretion was partially reserved.

There are several possibilities to explain the pathogenesis of CDI in the present case. First, CDI in pregnancy can be caused by vasopressinase, a cystine aminopeptidase, secreted from placental tissue [14]. Intranasal DDAVP was needed even after delivery, suggesting that involvement of vasopressinase was unlikely. Second, swelling of adenohypophysis itself can cause CDI. In this case, CDI did not show any recovery even after transsphenoidal surgery, although decompression was successfully achieved with normalization of visual field. This suggested that CDI was not due to compression by the mass in adenohypophysis. Third, inflammation of infundibular stalk or neurohypophysis can cause CDI [5]. Lymphocytes may destruct the normal structure regarding ADH secretion. Other common causes of hypophysitis, such as granulomatous hypophysitis, xanthomatous hypophysitis, and adenoma [15] were excluded on pathological examination.

Taken together, it is plausible that the inflammation of both adenohypophysis and neurohypophysis occurred in the present case, and the diagnosis of LPH is reasonable. We failed, however, to demonstrate the infiltration of lymphocytes into neurohypophysis on pathological examination, as in most cases, reported to be LPH [8, 10]. Therefore, the exact pathogenetic mechanism of LPH still remains controversial [16].

Epidemiologically, the incidence of LH is significantly higher during pregnancy because of unknown causes [10, 17], and it was associated with sudden maternal death because of hypopituitarism until recently [18, 19]. Prompt diagnosis and treatment are necessary for the fetomaternal safety.

The treatment of LPH includes the hormone replacement and the surgery, the latter of which is necessary mainly for mass reduction. Glucocorticoids are effective as

hormone replacement therapy and high dose methylprednisolone pulse therapy is reported to reduce the mass of LH [10, 20]. According to one trial, 4 mg/day of dexamethasone was given for 5 days [21]. If the compression of the tumor effects on the surrounding structures, transsphenoidal surgery is the most common treatment [10]. In this patient, high dose of glucocorticoids was not administrated because hypercortisolism may induce prematurity and intrauterine growth retardation [22]. The visual defect as a result of mass compressive effect deteriorated, and the mass reduction surgery was performed. As for thyroid hormone, free thyroxine level during replacement therapy was just above the lower limit until delivery. More levothyroxine should be administrated in order to reduce the risk of gestational hypothyroidism, impaired intellectual and cognitive development, and fetal death [23].

Most of LPH patients are reported to require long term hormone replacement therapy, and a few of them become free from hormone replacement after mass reduction surgery [6]. In this case, the same dose of hormone replacement has been necessary until today, even after the mass reduction surgery and delivery.

In summary, we reported a case of LPH during pregnancy presenting with quadrantanopia, hypopituitarism, and partial CDI. Panhypopituitarism, lymphocyte infiltration in adenohypophysis, and low secretion of ADH was compatible with the diagnosis of LPH. We propose that LPH should be included in the differential diagnosis of pituitary mass in a case of panhypopituitarism and CDI.

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