Neuroendocrinology Letters Volume 39 No. 1 2018
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

Lymphocytic hypophysitis associated with Behcet's disease: A case report and review of the literature

Tingting Tao [1], Ziyi Zhang [1], Hong Li [1]

1 Department of Endocrinology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China

Correspondence to: Hong Li, Department of Endocrinology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, 7th Floor,Tower I, 3 East Qingchun Road, Hangzhou, ZJ 571, China.
TEL/FAX: +86 571 86090073; E-MAIL: srrshnfm@zju.edu.cn

Submitted: 2017-12-04 Accepted: 2018-02-18 Published online: 2018-04-23

Key words: **Lymphocytic hypophysitis; Behcet's disease; MR imaging signs; Pathergy test; Steroid administration**

Neuroendocrinol Lett 2018; **39**(1):43–48 **PMID:** 29803206 NEL390118A08

Abstract

Lymphocytic hypophysitis (LH) is a rare inflammatory disorder involving the pituitary gland, often with other autoimmune diseases combined. The coexistence of LH and Behçet's disease (BD) is a rare combination and only one case was reported in the previous literatures. A 50-year-old man was admitted into Sir Run Run Shaw Hospital presented with frontal headache and fatigue which had lasted for four months. Endocrinological inspection indicated anterior pituitary dysfunction. Magnetic resonance imaging (MRI) revealed homogeneous pituitary enlargement and thickened pituitary stalk. Administration of glucocorticoids could effectively relieve headache and reduced pituitary mass volume. Oral aphthosis, skin lesions and positive pathergy tests were recognized later, which were characteristic features of BD. Although the diagnosis of BD is mainly dependent on clinical manifestations, PT is still a useful diagnostic tool 0f high specificityfor BD. And this male patient was diagnosed with both LH and BD afterwards. Then he was treated with cyclophosphamide and medium doses of methylprednisolone and remained in good conditions at the follow-up. LH and BD might share a common underlying autoimmune pathogenesis. The presentation of endocrinologic disturbances such as anterior pituitary dysfunction with typical features of skin lesions should prompt further investigation of possible comorbid autoimmune disease involving multiple organ systems. Early diagnosis and close monitoring are vitally important to ensure a stable endocrinologic status.

CASE STUDY

BACKGROUND

Primary hypophysitis is a rare autoimmune disease, characterized by an inflammatory process confined to pituitary gland without a well identifiable etiological agent. Based on histopathologic classification, the most common form of this disease is lymphocytic hypophysitis (LH; 71.8%), followed by granulomatous hypophysitis (18.6%) and xanthomatous hypophysitis (3.3%), whereas IgG4-related hypophysitis and necrotizing hypophysitis are rare (Caturegli & Iwama, 2013). LH can also be associated with other autoimmune diseases, such as Hashimoto thyroiditis, Graves disease, systemic lupus erythematosus, Sjogren syndrome, autoimmune polyglandular syndrome (APS) and type 1 diabetes. The coexistence of LH and Behçet's disease (BD) is a rare combination and was described only once in the previous literatures (Sánchez Sobrino *et al.* 2009). BD is considered to be an autoimmune disease involving multisystem, including mucocutaneous, articular, ocular, central nervous, cardiovascular, respiratory and gastrointestinal systems (Davatchi *et al.* 2010). The clinical manifestations of BD include oral aphthosis, genital aphthosis, skin lesions and ophthalmological involvement (Davatchi *et al.* 2010a; Davatchi *et al.* 2010b). However, BD can also present with atypical symptoms such as arthralgia, abdominal pain and anorexia, which may lead to delayed diagnosis.

Here we described a case of LH associated with BD, and discussed recent progress and limitations in the diagnosis and treatment of LH. Although there is still controversies involving the coexistence of LH and BD, it can be a very rare autoimmune disease and have multisystem complications. Written informed consent was obtained from the patient.

CASE PRESENTATION

A 50-year-old man was admitted into Sir Run Run Shaw Hospital on June 13th 2012 presented with frontal headache and fatigue which had lasted for four months. Three months before the admission, he was referred to the local hospital because of severe dull headache and laboratory tests as well as brain magnetic resonance imaging (MRI) were obtained. The brain MRI revealed a homogeneous pituitary enlargement. Laboratory tests showed low levels of serum cortisol and luteinizing hormone (LH) (Table 1). Then the patient received methylprednisolone 12mg daily in local hospital and headache was relieved rapidly. However, the patient stopped taking methylprednisolone after 20 days' treatment considering the side effects of glucocorticoids and developed progressive headache afterwards. Besides, he had suffered recurrent mouth sores for over 4 years. On admission, the patient's vital signs were as follows: temperature, 37.7°C; pulse, 55 beats/min; blood pressure, 108/62 mmHg. Physical examinations revealed erythematous maculopapular on the back and neck, others were unremarkable.

Tab. 1. Serial endocrine values of the patient

	ACTH (ng/L)	Cortisol (μg/dL)	TSH (mIU/L)	FT3 (pg/mL)	FT4 (IU/L)	LH (IU/L)	FSH (ng/dL)	GH (ng/mL)	PRL (μg/L)	Testosterone (μg/L)
2012.5.4 (before the admission)	10.3→	0.64↓	-	-	-	1.1↓	3.3→	1.86→	10.9→	-
2012.7.13 (the day of admission)	<1.0↓	0.3↓	0.31↓	2.08→	0.8→	1.06↓	3.67→	1.86→	13.85↑	0.13↓
2013.1.8 (3 months after discharge)	<1.0↓	1.08↓	0.35→	2.84→	1.10→	3.84→	5.29→	-	7.52↓	2.54→

ACTH, Adrenocorticotropic hormone; TSH, Thyroid-stimulating hormone; FT3, Free tri-iodothyronine; FT4, Free thyroxine; LH, Luteinizing hormone; FSH, Follicle-stimulating hormone; GH, Growth hormone; PRL, Prolactin.
→ indicates within the normal ranges; ↓ indicates lower than normal limits; ↑ indicates higher than normal limits.
Bar means unevaluated.

Endocrinological examinations demonstrated low levels of aderenocorticotropic hormone (ACTH), cortisol, gonadotropin, testosterone and thyroid-stimulating hormone (TSH) (Table 1). Serum immunoglobulin G4 (IgG4) was within the normal range. Erythrocyte sedimentation rate (ESR) was 50 mm/hr. Complete blood count was and urine specific gravity were normal. Fluid deprivation test wasn't carried out because polydipsia and polyuria hadn't been noticed in the course. Chest X-ray was unremarkable. Pituitary MRI revealed a symmetrically enlarged and homogeneously enhancing pituitary gland, along with a thickened, but not deviated pituitary stalk (Fig. 1A, B), which strongly suggested the diagnosis of LH. Taking the MR imaging features,

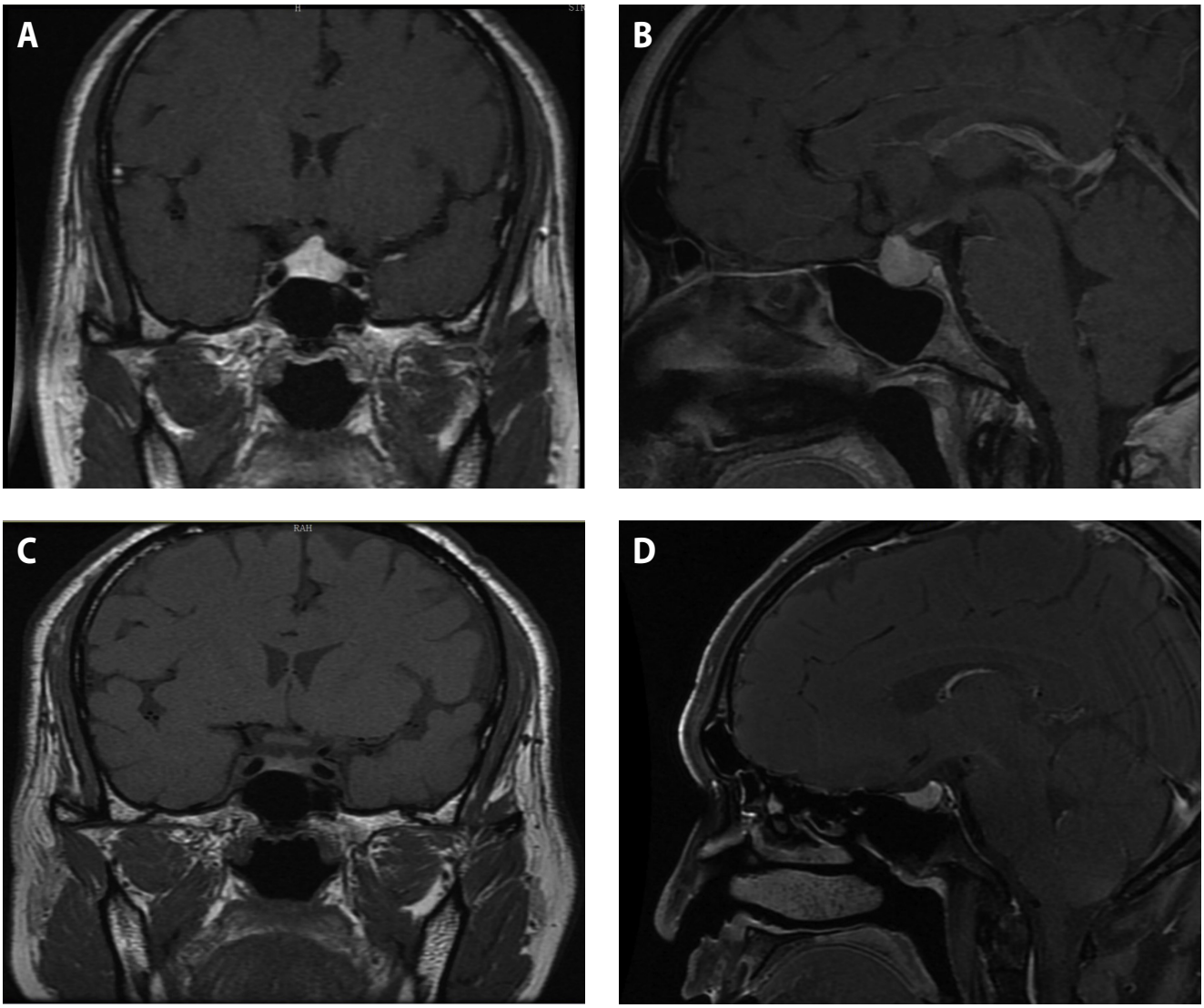

Fig. 1. Gadolinium-enhanced coronal and sagittal T1-weighted MR images of the patient. **(A)** A perfectly symmetrically enlarged and homogeneously enhancing gland. **(B)** Grossly enlarged and avidly enhancing pituitary stalk. **(C,D)** showing significant reduced volume of the lesion.

laboratory tests and epidemiological features into consideration, LH was considered. Although granulomatous hypophysitis could also present as infiltration of this region, however, it was extremely rare and mostly diagnosed in postmortem specimens. After the diagnosis of LH, treatment with supplements of pulse dose steroid was introduced to decompress the pituitary mass, using intravenous drip of methylprednisolone 500 mg initially for 3 days, followed by 300 mg for 3 days and 100 mg for 3 days. Frontal headache was relieved after 9 days of administration. Then, methylprednisolone was changed to 32mg taken orally once daily. 13 days after the steroid therapy, follow-up MRI reexamination demonstrated pituitary with normal size (Fig. 1C, D), which further supported the diagnosis of LH. The patient was discharged with 32 mg methylprednisolone taken orally once daily and adequate gonadal hormone replacement therapy. Then the dose of methylprednisolone was tapered gradually to 8 mg once daily in a follow-up period of over 2 months. The patient remained in good condition in the meantime and underwent endocrinological examinations three months after discharge which indicated that the pituitary function had improved (Table 1).

After being followed up for 16 months, the patient suffered abdominal distension, sickness, vomit, decreased defecation and fever. He had stopped taking methylprednisolone for about three months before this admission. Upper endoscopy revealed fungal esophagitis, bulboduodenal inflammation and stenosis (Fig. 2A, B).

Although the fever was effectively controlled with anti-inflammatory therapy, the patient still suffered disease progression and upper endoscopy suggested partial obstruction of pylorus. Gastrojejunostomy was performed to alleviate abdominal discomfort. Pathologic

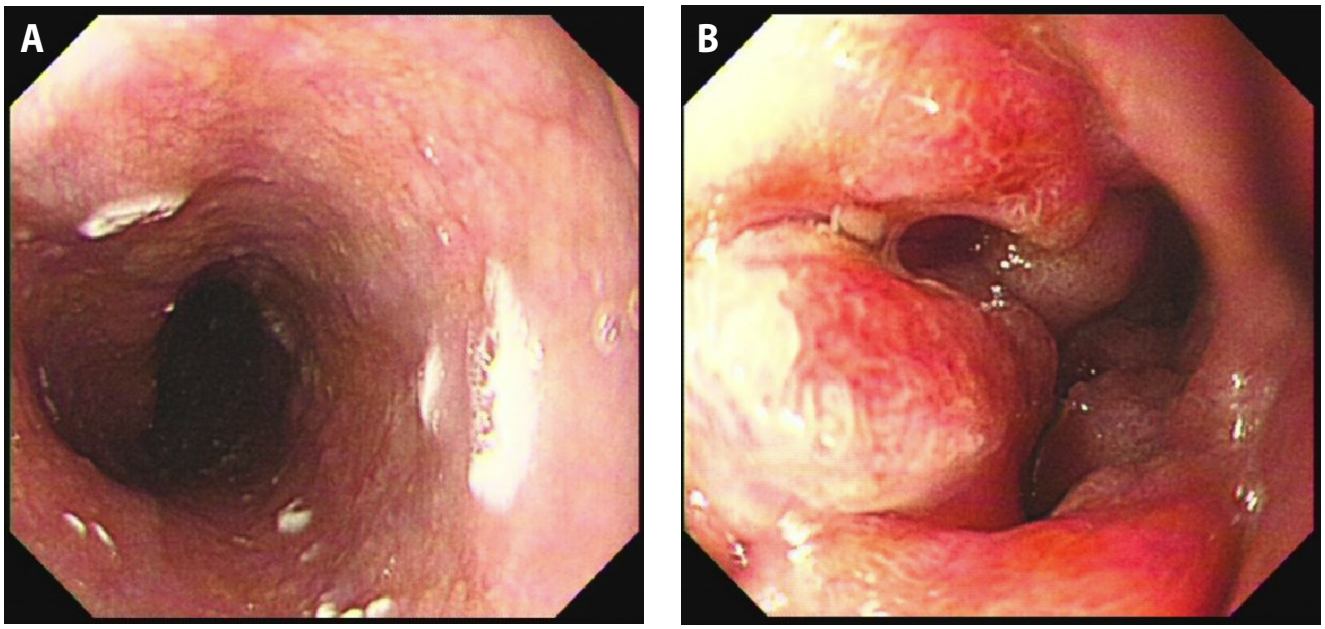

Fig. 2. Gastroscope images of the patient. **(A)** fungal esophagitis. **(B)** bulboduodenal inflammation and stenosis

examination of duodenal bulb showed massive infiltration of lymphocytes, plasma cells and neutrophils in the interstitial tissue as well as granulation tissue proliferation. The patient received hydrocortisone 25 mg once daily and was followed up as outpatient at our clinic.

However, after two years of the first admission, the patient was referred to our hospital again presented as recurrent fever and fatigue that had been lasting for one month. The patient had been continuously taking hydrocortisone 25 mg once daily after last admission. Four days before the referral, the patient received antibiotics in the local hospital which were of no use with the fever. Physical examinations on admission showed a painful oval oral ulcer, erythema nodosum on the back and neck, and an abdominal surgical scar of gastrojejunostomy . Laboratory tests only showed a slight decrease in serum cortisol and increases in C-reactive protein (CRP) and ESR. Brain MRI was unremarkable. Chest computerized tomography (CT) showed multiple nodules in the lungs and mediastina (Fig. 3A, B).

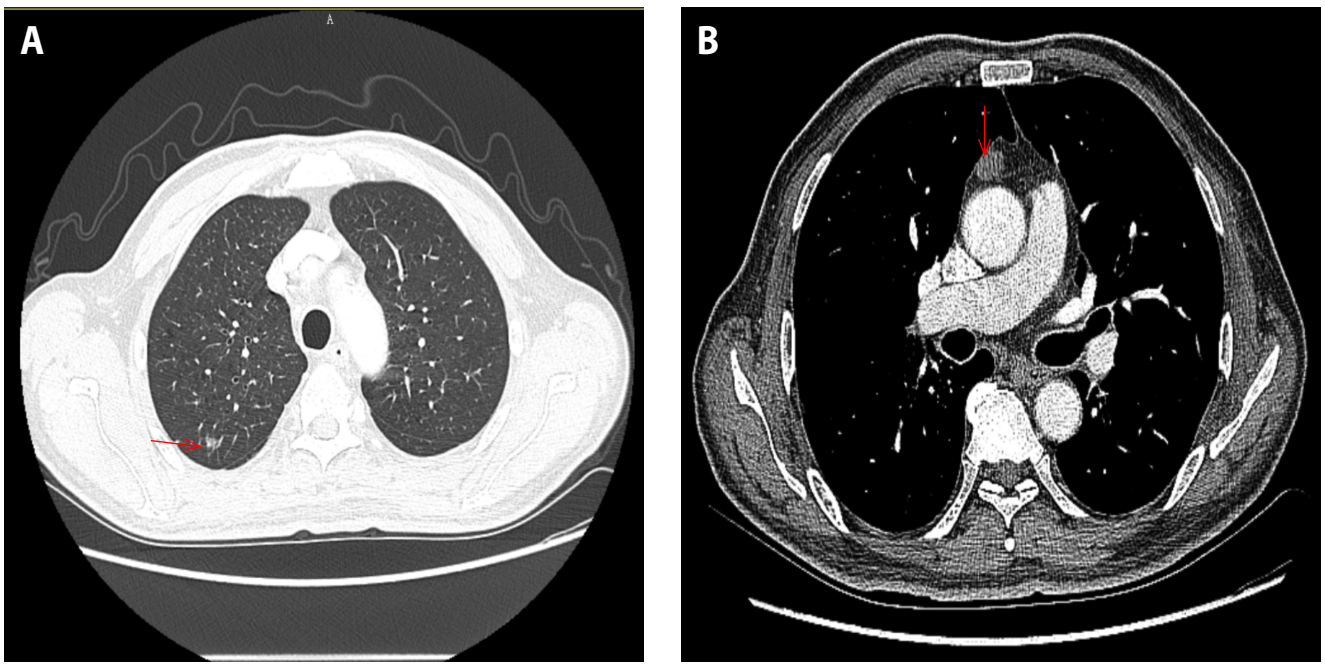

Fig. 3. A chest computerized tomography of the patient. **(A)** scobinations of in the lungs. **(B)** a scobination of in mediastina.

Pathologic examination of the pneumocentesis specimen demonstrated organized pneumonia. Bone marrow aspiration showed no evidence of malignant lymphoma.

Moreover, the following tests were negative: the tuberculosis test, blood culture, haematozoon test, Treponema pallidum hemagglutination test, antinuclear antibodies, rheumatoid factor, anti-single-stranded and anti-double-stranded DNA antibodies. Based on the clinical manifestation, organized pneumonia and previous histological examination of duodenal bulb, BD was considered. Then pathergy test (PT), a diagnostic tool for BD, was performed and the result was positive. According to the International Criteria for Behcet's Disease (ICBD) (Davatchi *et al.* **2010a?**), the patient was diagnosed with both LH and BD. Subsequently, the patient received intravenous infusion of cyclophosphamide 400mg once, along with methylprednisolone 60mg once daily followed by a tapering dose. After 10 days of treatment, the fever was relieved and the levels of CRP and ESR were within the normal range. At follow-up, the patient remained in good condition while being treated with 600 mg of cyclophosphamide monthly and 12 mg of methylprednisolone daily. Unfortunately, four years after the first adminstraton the patient suffered an unexpected death and his families refused to perform autopsy.

DISCUSSION

We herein described a 50-year-old male patient who developed LH accompanied by BD. He firstly suffered severe frontal headache, followed by various clinical manifestations involving almost all body systems. His endocrinological disturbances, MRI features and dramatic response to glucocorticoids were supportive of the diagnosis of LH. However, gastrointestinal manifestations and prolonged fever required further investigation. According to the International Criteria for Behcet's Disease (ICBD), our patient was diagnosed as BD in view of oral aphthosis, skin lesions and positive pathergy test. Subsequent response to treatment was consistent with the diagnosis of LH combined with BD.

LH is a rare inflammatory disorder of the pituitary gland. LH, which is the main form of primary hypophysitis, was morphologically classified into adenohypophysitis (LAH), infundibuloneurohypophysitis (LINH) and panhypophysitis (LPH) (Caturegli *et al.* 2005). LAH, which is suggested to have an association with autoimmune diseases and pregnancy, affects the anterior lobe of pituitary and leads to hypopituitarism and space-occupying effect (Honegger *et al.* 1997). LINH is characterized by posterior pituitary dysfunction presenting as polyuria and polydipsia (Oiso *et al.* 2013). LPH shares the both characteristics. Although LAH is common among women, especially in the last semester of pregnancy and in the post-partum period, cases involving non-pregnancy women are increasing in the recent years (Caturegli *et al.* 2008). Our patient suffered headache and his endocrinological examination showed hypopituitarism. Moreover, polydipsia and polyuria hadn't been noticed in the course. He was classified into LAH.

LH was firstly reported by Goudie and Pinkerton in 1962 (Goudie *et al.* 1962), and the diagnosis of which is always challenging, as it has complicated clinical manifestations and individual variations (Caturegli P *et al.* 2008). Pituitary biopsy is still the gold standard for diagnosing LH, however, it's difficult to perform and receive consent from the patients. The combination of endocrinological assessment and MRI has promoted tremendous advances not only in diagnostic accuracy but also in distinguishing hypophysitis from other types of lesions, especially from pituitary adenomas (Gutenberg *et al.* 2009). MRI, as a noninvasive method, contributes to the diagnosis and differential diagnosis of LH. Gutemberg et al. (Gutenberg A *et al.* 2009) proposed a new radiologic score to distinguish LH from nonfunctioning pituitary adenoma. The authors summarized eight features to distinguish pituitary tumor from hypophysitis: age, pregnancy, pituitary mass volume and symmetry, signal intensity, signal intensity homogeneity after gadolinium, posterior pituitary bright spot presence, stalk size and mucosal swelling. A score greater than or equal to 1 prompts diagnosis of adenoma, whereas a score less than 1 suggests diagnosis of LH (Gutenberg A *et al.* 2009). The score of our patient was -6, which highly suggested the diagnosis of LH. Searching for antipituitary antibodies (APA) may contribute the diagnosis of LH. However, there are still controversies concerning clinical interpretation and testing techniques of APA, therefore APA is still not fully considered as a diagnostic tool for hypophysitis (Caturegli *et al.* 2008).

BD is currently considered as vasculitis disease, but also an autoimmune disease (Davatchi F *et al.* 2010). According to ICBD, the patient presented as oral ulcer, skin manifestations and positive PT, which suggested a score of four points and could be diagnosed as BD. Although the diagnosis of BD is mainly dependent on clinical manifestations, PT is still a useful diagnostic tool for BD which is also easy to perform. Although the sensitivity of PT has declined in recent years, it still has high specificity (Davatchi *et al.* 2011). When multiple systems are involved during the clinical process of LH, PT should be considered to exclude the diagnosis of BD, especially in the patient with recurrent oral ulcer. our patient was diagnosed as BD in view of oral aphthosis, skin lesions and positive pathergy test. In the course the presentation of oral ulcer, skin lesion with abdominal discomfort hadn't been noticed, which led a diagnosis delay of BD.

For LH patients, therapeutic strategies are different during the acute and chronic phase. During acute phase of LH, treatment is aimed at reducing the pituitary volume and preventing adrenal crisis (Leung *et al.* 2004).

High doses of glucocorticoid treatment is essential for LH patients with acute adrenal insufficiency (Caturegli *et al.* 2008). Intravenous drips of pulse dose of corticosteriod leads to rapid relief of neurological symptoms and was more favourable in cases with short standing disease. Glucocorticoid pulse therapy and prolonged low-dose corticosteroid administration have been proposed as first-choice conservative treatments, capable of shrinking the pituitary mass and recovering pituitary function (Kristof *et al.* 1999). However, it also lead to a high recurrence rate. Surgery should be considered when the patient suffers severe compression symptoms, however, it cannot prevent the recurrence. Immunosuppressive drugs and irradiation have also been reported to relieve symptoms, particularly in corticosteroid-resistant cases. During chronic phase of LH, clinical management is mainly aimed at maintaining adequate hormone levels with appropriate replacement therapy (Fukuoka, 2004). Follow-up studies showed that pituitary hormone axis recovery was seen in 41.67% of cases (55.5% for cortisol and 41.67% for gonadotropin), and long-term hormone replacement treatment was required in 73% of hypophysitis cases (Fukuoka, 2004). Our patient suffered from severe headache and his cortisol levels was extremely low. High doses of methylpredonisolone (followed by a tapering dose) soon relieved his symptoms, reduced pituitary volume and avoid adrenal crisis. In our patient, endocrinological examination 6 months after the start of steroid therapy revealed normalization of response of TSH and testosterone levels to provocative testing. We believe that the improvement of pituitary function in this patient can be attributed to successful steroid therapy. BD patients with neurological, cardiac or pulmonary involvements need aggressive treatment with cytotoxic drugs and medium to high doses of steroids (Davatchi *et al.* **2010b?**). Our patient had gastrointestinal manifestations and pulmonary involvements, which might be life-threatening. Therefore, he was treated with cyclophosphamide and medium doses of methylprednisolone and remained in good conditions at the follow-up. During the first admission, we payed too much attention to the symptoms of LH and ignored the presentation of oral ulcer, skin lesion with abdominal discomfort, which led to a diagnosis delay. And early diagnosis may help to maintain the stable endocrinologic status. Autopsy was also required to figure out his unexpected death.

CONCLUSION

We described a rare case of LH associated with BD. The coexistence of these two diseases suggested a common underlying autoimmune pathogenesis. The presentation of endocrinologic disturbances such as anterior pituitary dysfunction with typical features of skin lesions should prompt further investigation of possible comorbid autoimmune disease involving multiple systems. Most cases of LH can experience regression of the lesion with steroid administration. Cytotoxic drugs are recommended in BD patients who at risk of a potentially life-threatening condition. Early diagnosis and close monitoring are vitally important to ensure a stable endocrinologic status.

DISCLOSURES

All authors have no conflicts of interest or financial ties to disclosure.

AUTHOR CONTRIBUTIONS

T.T. drafted the article. T.T. and H.L. participated in the analysis and interpretation of data. H.L. treated the patient and critically revised the manuscript. H.L. and Z.Z. acted as consultant clinicians and assisted in writing the manuscript. All the authors read and approved the final version of the manuscript.

REFERENCES

1 Caturegli P, Iwama S (2013). From Japan with love: another tessera in the hypophysitis mosaic. J Clin Endocrinol Metab **98**: 1865–1868.
2 Caturegli P, Lupi I, Landek-Salgado M, Kimura H, Rose NR (2008). Pituitary autoimmunity: 30 years later. Autoimmun Rev **7**: 631–637.
3 Caturegli P, Newschaffer C, Olivi A, Pomper MG, Burger PC, Rose NR (2005). Autoimmune hypophysitis. Endocr Rev **26**: 599–614.
4 Davatchi F, Chams-Davatchi C, Ghodsi Z, Shahram F, Nadji A, Shams H et al (2011). Diagnostic value of pathergy test in Behcet's disease according to the change of incidence over the time [J]. Clinical rheumatology **30**(9): 1151–1155.
5 Davatchi F, Shahram F, Chams-Davatchi C, Shams H, Nadji A, Akhlaghi M, et al (2010a). Behcet's disease: from east to west. Clin Rheumatol **29**: 823–833.
6 Davatchi F, Shahram F, Chams-Davatchi C, Shams H, Nadji A, Akhlaghi M, et al (2010b). How to deal with Behcet's disease in the daily practice. Int J Rheum Dis **13**: 105–116.
7 Fukuoka H (2004). Hypophysitis. Endocrinol Metab Clin North Am **44**: 143–149.
8 Goudie EB, Pinkerton PH (1962). Anterior hypophysitis and Hashimoto's disease in a young woman. J Pathol Bacteriol **83**: 584–585.
9 Gutenberg A, Larsen J, Lupi I, Rohde V, Caturegli P (2009). A radiologic score to distinguish autoimmune hypophysitis from nonsecreting pituitary adenoma preoperatively. Am J Neuroradiol **30**: 1766–1772.
10 Honegger J, Fahlbusch R, Bornemann A, Hensen J, Buchfelder M, Müller M et al (1997). Lymphocytic and granulomatous hypophysitis: experience with nine cases. Neurosurgery **40**: 713–722; discussion 722–723.
11 Kristof RA, Van Roost D, Klingmüller D, Springer W, Schramm J (1999). Lymphocytic hypophysitis: non-invasive diagnosis and treatment by high dose methylprednisolone pulse therapy ? J Neurol Neurosurg Psychiatry **67**: 398–402.
12 Leung GK, Lopes MB, Thorner MO, Vance ML, Laws ER Jr (2004). Primary hypophysitis: a single-center experience in 16 cases. J Neurosurg **101**: 262–271.
13 Oiso Y, Robertson GL, Nørgaard JP, Juul KV (2013). Clinical review: treatment of neurohypophyseal diabetes insipidus. J Clin Endocrinol Metab **98**: 3958–3967.
14 Sánchez Sobrino P, Páramo Fernández C, Lamas Ferreiro JL, Manti?án Gil B, Palmeiro Carballeira R (2009). García-Mayor RV Enfermedad de Beh?et asociada a déficit de corticotropina [J]. Endocrinología y Nutrición **56**: 463–466 (In Spanish).