CASE REPORT

# Lymphocytic hypophysitis with dacryoadenitis in a male patient: non-invasive diagnosis and high-dose methylprednisolone pulse therapy

**Zhaohui Lu, Jian Li, Jianming Ba, Guoqing Yang, Jingtao Dou, Yiming Mu, Juming Lu**
Department of Endocrinology, Chinese PLA General Hospital, Beijing 100853, P. R. China

*Correspondence to:* Juming Lu, MD.
Dept. of Endocrinology, Chinese PLA General Hospital,
Beijing 100853, P. R. China.
PHONE: +86-10-66939881; FAX: +86-10-68168631; E-MAIL: lujm@medmail.com.cn

*Submitted: 2009-11-02 Accepted: 2009-12-08 Published online: 2009-12-25*

*Key words:* **lymphocytic hypophysitis; dacryoadenitis; pituitary hypofunction; diabetes insipidus; glucocorticoid**

Neuroendocrinol Lett 2009; **30**(6):700–704 **PMID:** 20038929 NEL300609A01 

## Abstract

**OBJECTIVE:** Lymphocytic hypophysitis (LH) is a rare autoimmune disorder associated with lymphocytic cell infiltration of the pituitary. It is often detected in patients with other autoimmune systemic diseases such as Hashimoto's thyroiditis, epinephritis, megaloblastic anemia, and Langerhans cell histiocytosis. Pituitary biopsy and invasive histopathological examination provide the most reliable evidence for LH diagnosis. However, because glucocorticoids are extensively used for the treatment of disease, pathological diagnosis is not always necessary. Here, we report a rare case of a male patient (50 y) with LH associated with dacryoadenitis that was successfully treated with high-dose of methylprednisolone.

**RESULTS:** The patient had a history of swollen lacrimal glands for two years. In addition, magnetic resonance imaging (MRI) showed a markedly thickened infundibular stem and an indiscernible signal in the posterior lobe of the pituitary. Biopsy of the lacrimal glands revealed reactive hyperplasia of the lymphoid tissue. After a high-dose of methylprednisolone pulse treatment (HDMPT), lacrimal gland swelling and infundibular stem thickness were reduced, and adenopituitary function improved within a short time period.

**CONCLUSIONS:** Although association of LH with dacryoadenitis is a rare, it can be effectively managed with HDMPT. In addition, response to HDMPT can avoid the more invasive diagnostic procedures, including surgical intervention and pituitary biopsies.

**Abbreviations :**

| | |
|---|---|
| ACTH | - adrenocorticotropic hormone |
| ANCA | - anti-neutrophil cytoplasmic antibody |
| CNS | - central nervous system |
| CRP | - C-reactive protein |
| DAF | - decay accelerating factor |
| ESR | - erythrocyte sedimentation rate |
| FSH | - follicle stimulating hormone |
| FT3 | - free triiodothyronine |
| FT4 | - free thyroxine |
| GH | - growth hormone |
| GnRH | - gonadotropin-releasing hormone |
| HDMPT | - high-dose methylprednisolone pulse treatement |
| LAH | - lymphocytic adenohypophysitis |
| LH | - lymphocytic hypophysitis |
| LHRH | - luteinizing hormone-releasing hormone |
| LINH | - infundibulo-neurohypophysitis |
| LIPH | - infundibuolo-panhypophysitis |
| MRI | - magnetic resonance imaging |
| PRL | - prolactin |
| RF | - rheumatoid factor |
| T | - testosterone |
| TGAb | - thyroglobulin antibody |
| TPOAb | - thyroid peroxidase antibody |
| TSH | - thyroid stimulating hormone |
| UFC | - urinary free cortisol |

## INTRODUCTION

Lymphocytic hypophysitis (LH) is an autoimmune endocrine disease (Pestell *et al.* 1990; Crock, 1998). It is often detected in women during late pregnancy or within the early postpartum period, and only 10–15% of LH patients are male (Beressi *et al.* 1999). Clinical symptoms include anterior hypopituitarism and diabetes insipidus. In most patients, enlarged pituitaries and thickened pituitary stalks can be visualized upon magnetic resonance imaging (MRI).

LH was first described in 1962 by Goudie and Pinkerton (Goudie and Pinkerton, 1962). Since then, more than 400 cases have been reported; among 145 cases, 30% of the patients had other systemic autoimmune diseases such as Hashimoto's thyroiditis, epinephritis, megaloblastic anemia, Langerhans cell histiocytosis (Beressi *et al.* 1999). However, association of LH with dacryoadenitis rarely happens: only two cases have been reported in young female patients (Joussen *et al.* 1999; Lidove *et al.* 2004).

Pituitary biopsy and invasive histopathological examination are the most reliable diagnostic methods. However, because symptoms rapidly improve in response to glucocorticoid therapy, a positive response to glucocorticoid therapy is often used as anecdotal evidence of LH, thereby circumventing the requirement for more invasive histopathological procedures (Kristof *et al.* 1999; Yamagami *et al.* 2003; Reda, 2007).

Here, we report one case of LH associated with acryoadenitis. To the best of our knowledge, this is the first report of a male patient afflicted with this disease combination. Shortly after a high-dose methylprednisolone pulse therapy (HDMPT), marked shrinkage of the lacrimal gland and the pituitary stalk was observed. While one recurrence of lacrimal gland swelling was documented upon discontinuation of the therapy, improvement of pituitary function continued. After a second, short-term round of HDMPT, lacrimal gland swelling was rapidly relieved, and no further recurrence was observed.

**Tab. 1.** Serum LH, FSH, ACTH, and GH levels after LHRH and insulin stimulation.

| | Time (min) | | | | |
|---|---|---|---|---|---|
| | **0** | **30** | **60** | **90** | **120** |
| Glucose (mmol/L) | 4.40 | 1.89 | 2.04 | 3.49 | |
| LH (IU/L) | 0.09 | 0.32 | 0.37 | | 0.39 |
| FSH (IU/L) | 1.02 | 0.72 | 2.4 | | 1.99 |
| GH (μg/L) | < 0.5 | 1.3 | 1.6 | 1.4 | 1.0 |
| ACTH (pmol/L) | 7.6 | 5.2 | 18.9 | 17.8 | |

## PATIENTS AND METHODS

*Case report*

A male patient (50 years) experienced abnormal thirst and polydipsia/polyuria for three months and was hospitalized in October 2004. In 2002, the patient had noticed left eyelid swelling, which later affected both eyelids, as well as general fatigue, but did not seek medical attention for these symptoms. He was treated with cefoperazone sodium (2.0 g/d) and dexamethasone (6 mg/d) for bronchial asthma three months ago in July 2004. Regression of both the asthma and lacrimal gland swelling was noted the following day. However, he later developed abnormal thirst, polydipsia, and polyuria; his daily urine output was 9 L/d later on. After discontinuation of dexamethasone, urine volume decreased to 4–5 L/d, but swelling of the lacrimal gland returned. Since the beginning of 2004, the patient had experienced decreased libido, weight loss, nausea without vomiting, and visual impairment. Otherwise, the patient had no previous medical history or family history. After admission to the hospital, physical examination revealed that all vital signs were normal. The patient had bilateral swelling of the lacrimal gland, skin erythema without fever or tenderness, mild subconjunctiva congestion, edema, and a small amount of white secretion. Fundus oculi, eyesight and other physical parameters were all normal. All procedures were in accordance with our institutional protocols and the most recent Declaration of Helsinki.

*Laboratory studies*

The urine had low specific gravity (1.001–1.005) and low urine osmolality (146–147 mOsm/L), and blood osmolality was 293–298 mOsm/L. Except obvious dyslipidemia (cholesterol 7.82 mmol/L and triglycerides 12.91 mmol/L), conventional hematological parameters were within a normal range. Results of inflammation and immunological examinations, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, were normal. Levels of rheumatoid factor (RF) and T cell subsets (CD3, CD4, and CD8) were within normal ranges (data not shown). Immunoprotein electrophoresis as well as anti-nuclear, anti-double strand (ds)-DNA, anti-Smith (Sm), anti-Sjogren's syndrome (SS) A, anti-SSB, and anti-neutrophil cytoplasmic (ANCA) antibodies were all negative. As shown in Table 1, baseline and luteinizing hormone-releasing hormone (LHRH) and insulin–stimulated hormone levels revealed secondary gonadal hypofunction (luteinizing hormone [LH]: 0.08 IU/L, normal level [N] 1.5–9.3; follicle stimulating hormone [FSH]: 0.85 IU/L, N 1.4–18.1; and testosterone [T]: 0.47 nmol/L, N 8.4–28.7), hypoadrenocorticism (adrenocorticotropic hormone [ACTH] 8:00 am: 11.4 pmol/L, N<10.12, cortisol [F] 8:00 am: 463.8 nmol/L, N 198.7–797.5; and urinary free cortisol [UFC]: 76.7 nmol/24 h, N 78.6–589.6), and hypothyroidism (free triiodothyronine [FT3]: 4.30 pmol/L,

N 2.76–6.30; free thyroxine [FT4]:12.27 pmol/L, N 10.42–24.32; and thyroid stimulating hormone [TSH]: 0.36 mU/L, N 0.35–5.50). The patient's prolactin (PRL) level was slightly higher at 25.07 ug/L, (N 2.1–17.7) and growth hormone (GH) was <0.5 ug/L. The presence of thyroid autoantibodies such as thyroglobulin antibody (TGAb) and thyroid peroxidase antibody (TPOAb) and thyroid stimulating hormone (TSH) receptor antibody (TRAb) were negative. In addition, Schirmer's test was negative. Upon admission, the water deprivation-vasopressin revealed central diabetes insipidus.

*Radiological and pathological analysis*

Pituitary MRI showed bilateral exophthalmos and increased bilateral lacrimal gland size with a relatively uniform signal. In addition, while the extraocular muscles appeared and anterior pituitary was normal, obvious pituitary stalk thickening was detected. Upon gadolinium contrast-enhanced MRI, thickening of the pituitary stalk became more obvious; and the nodular enhancement area (6 × 9 mm) appeared uniform with a clear border.

*Histological analysis*

Histological (HE, original magnification ×200) analysis of the left lacrimal gland biopsy revealed non-specific, chronic lacrimal inflammation with reactive lymphoid hyperplasia (RH) in fatty tissues (Figure 1).

The lacrimal gland biopsy confirmed non-specific chronical lacrimal gland inflammation. The patient also responded well to glucocorticoid treatment. Based on these results, the patient was clinically diagnosed with lymphocytic dacryoadenitis. In addition, pituitary stalk thickening and a normal anterior pituitary were observed with MRI. Pituitary hypofunction, mainly manifested as secondary gonadal hypofunction complicated with diabetes insipidus, was also detected. Taken together, these studies suggested the patient had LH. Successful treatment of clinically suspect LH without pathological evidence with HDMPT has been reported (Kristof *et al.* 1999; Yamagami *et al.* 2003; Reda, 2007). Furthermore, a rapid response to HDMPT supports the diagnosis of LH. Thus, HDMPT serves as both a therapy and a diagnostic method.

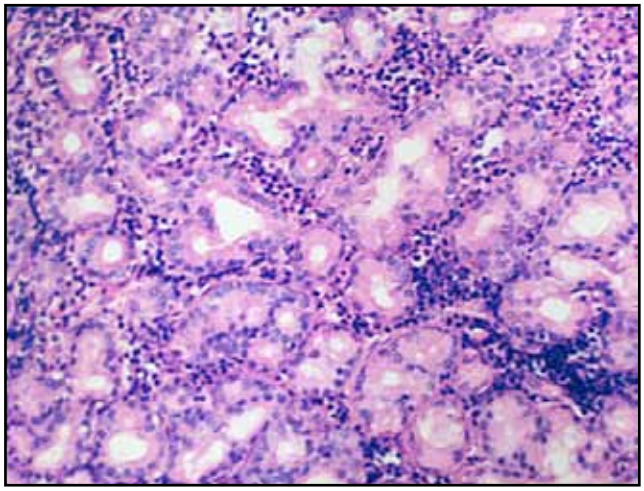

**Fig. 1.** Left lacrimal gland with lymphocytic infiltration (hematoxylin and eosin, magnification ×200 ).

*Therapy*

After obtaining the patient's written and informed consent, HDMPT was initiated on November 16, 2004. HDMPT consisted 800, 600, and 400 mg of intravenous methylprednisolone daily, followed by dose tapering from 80 to 20 mg over a 9 day period. Then, oral prednisone (20 mg daily) was administered for 2 weeks and then decreased by 5 mg every 2 weeks. When the dose was reduced to 10 mg, it was further reduced by 2.5 mg every 2 weeks. After the dose was administered at 5 mg for two weeks, the dose was reduced to 2.5 mg/ d until complete discontinuation. After one day of treatment, lacrimal gland swelling improved (Figure 2A and 2B); however, the urine volume increased to 9 L/d. After

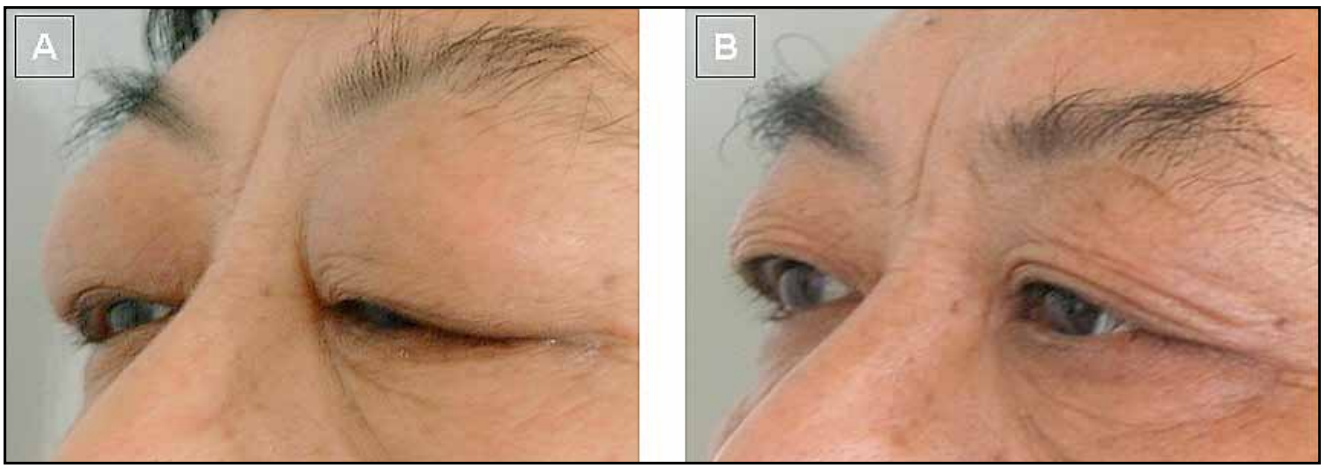


**Fig. 2.** Effects of methylprednisolone pulse therapy on lacrimal gland swelling. (A) Symmetrical swelling of the lacrimal glands before therapy. (B) Reversal of the swelling after one day of methylprednisolone pulse therapy (800 mg).

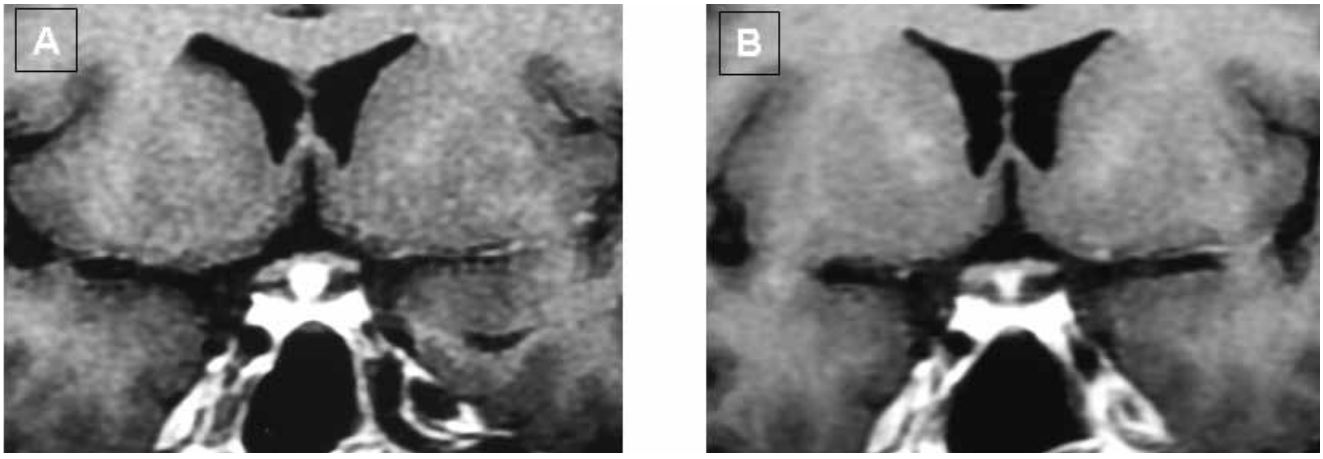


**Fig. 3.** Effects of methylprednisolone pulse therapy on pituitary stalk thickness. (**A**) MRI revealed obvious thickening in pituitary stalk before therapy. (**B**) After 2 weeks methylprednisolone pulse therapy, pituitary stock thickness was reduced.

treatment with the antidiuretic hormone, Minirin (Desmopressin acetate, DDAVP, 0.05–0.1 mg), urine volume decreased.

Two weeks after HDMPT, obvious shrinkage of the pituitary stalk was seen on the routine MRI, indicating that the therapy was effective (Figure 3A and 3B). The amount of daily urinary excretion reduced from 9 to 3 L/d. After discontinuation of prednisone in March 2005, the patient experienced one incident of lacrimal gland swelling recurrence, but no thirst, polyuria, and polydipsia. Further shrinkage of the pituitary stalk was observed in a subsequent MRI in April 2005 (data not shown). To treat the relapse of dacryoadenitis, the patient received a short round of HDMPT (600 mg/ daily for 3 d), which resulted in improvement of the lacrimal gland swelling. The glucocorticoid replacement treatment was then discontinued without further recurrence.

## DISCUSSION

LH is typically found in women in late pregnancy or within the postpartum period; only 10–15% of LH patients are male (Beressi *et al.* 1999; Duran Martinez *et al.* 2001). Its clinical presentation, including headache, decreased visual acuity, visual field defect, and anterior hypopituitarism, closely resembles pituitary ademona. In men, sexual impotence and decreased libido are the most common symptoms (Beressi *et al.* 1999). Upon pathological examination, both B and T lymphocytes can be detected within most pituitary infiltrates (Joussen *et al.* 1999).

Based on the location of the lymphocyte infiltration, LH may be classified as lymphocytic adenohypophysitis (LAH), lymphocytic infundibulo-neurohypophysitis (LINH), or lymphocytic infundibulo-panhypophysitis (LIPH) (Molitch and Gillam, 2007). LAH is the most common form of LH. In LINH, diabetes insipidus is often present along with increased PRL secretion while the anterior pituitary remains unaffected (Molitch and Gillam, 2007). LIDP is the rarest form of LH, affecting both the anterior and posterior pituitary.

A thickened pituitary stalk, loss of hyperintense in the posterior lobe, normal anterior lobe, normal serum ACTH and TSH levels, and slightly higher PRL levels indicated that the lesions were located in the posterior lobe and pituitary stalk. Because the patient also experienced secondary gonadal hypofunction, lymphocytic infiltration into the anterior lobe may have also occurred; LINH patients with anterior pituitary hypofunction have been reported (Hashimoto *et al.* 1997). Whereas GH and gonadotropin-releasing hormone (GnRH) secretion deficiency is a major symptom of LINH, secretion of ACTH is rarely affected (Takao *et al.* 2000). However, in the event of lymphocytic infiltration of the adenohypophysis and neurohypophysis, decreased ACTH secretion in addition to diabetes insipidus is expected. Taken together, we postulated that this patient had pituitary lesions that were consistent with LINH.

The etiology of LH is not well known; it is commonly considered an autoimmune disease; organ-specific autoantibodies are often detected in the serum of LH patients. In addition, LH is often accompanied with autoimmune diseases such as Hashimoto's thyroiditis, epinephritis, megaloblastic anemia, or Langerhans cell histiocytosis (Beressi *et al.* 1999); however, the patient reported here had no other autoimmune disease, and autoantibodies were not detected. Instead, lymphocytic infiltration of the lacrimal gland was observed. Because the lacrimal gland possesses immune function, lymphocytic infiltration may induce autoimmune inflammation.

The lacrimal gland function is largely regulated by the immune and endocrine signaling; it also contains a variety of lymphocytes as well as immunoactive components (Wicezorek *et al.* 1988). Its secretions also contain lysozyme, lactoferrin, apolipoprotein D, invertase, and decay accelerating factor (DAF) (Berta, 1982; Cocuzzi *et al.* 2001). Hypothalamic and pituitary neu-

roendocrine function directly affects the innervation of the lacrimal gland and modulates its immunoactivity. Although rare, the association between lacrimal gland inflammation and the nature of a pituitary lesion may be predicated based on the pathology of the lacrimal gland. However, the exact nature of this association remains unclear.

The most reliable clinical result for the diagnosis of LH are histopathological result, which require invasive surgery or pituitary biopsy. In this study, the patient was diagnosed with LH without the need for pituitary biopsy due to the following reasons: (1) only the presence of pituitary stalk thickening, normal anterior pituitary function, and homogenous pattern of enhancement and (2) immediate reduction in symptoms upon HDMPT. The reduction in pituitary stalk thickness in response to HDMPT further ruled out pituitary adenoma in which enhanced pituitary stalk thickness is often observed (Ozawa and Shishiba, 1993). Because surgery may result in irreversible damage, resulting in pituitary dysfunction, less invasive diagnostic measures are increasingly being sought. Indeed, many studies have indicated that under extensive monitoring of the condition, immediate response to glucocorticoid therapy can be used to diagnose highly suspect LH (Kristof *et al.* 1999; Yamagami *et al.* 2003; Reda, 2007).

Clinical management of LH falls within two categories: 1) surgical approach or 2) glucocorticoid therapy. Although the pituitary and central nervous system (CNS) symptoms can be relived shortly after surgery, permanent damage to pituitary function remains a major risk. In addition, surgical removal of the entire mass is nearly impossible in most cases (Beressi *et al.* 1999). Thus, the surgical approach should be avoided as much as possible for probable LH patients, and glucocorticoid therapy should be considered before undertaking more invasive procedures.

Although initiation of glucocorticoid therapy offers a non-invasive approach to LH treatment, there is disagreement on the treatment procedure and dosage. In addition, relapse of symptoms or recurrence of LH and/or other autoimmune diseases after dose reduction or therapy discontinuation remains a concern. In the current case, lacrimal gland swelling recurred shortly after dose reduction and discontinuation of the therapy, but pituitary shrinkage continued to improve. After a second round of HDMPT, relapse of the disease was not detected during the follow-up visit. In the two previously reported cases of LH with dacryoadenitis, lacrimal gland swelling improved within a few days after high-dose glucocorticoid treatment (intravenous methylprednisolone 100 mg and 80 mg daily) (Joussen *et al.* 1999; Lidove *et al.* 2004). Furthermore, no relapse was observed after dose reduction and discontinuation of the therapy. Although the reason for the difference in response to the treatment is not known, it is possibly related to the gender of the patients. However, long-term patient follow-up is necessary to monitor for LH recurrence.

In conclusion, we here reported a rare case of clinically suspected lymphocytic hypophysitis complicated with lymphocytic dacryoadenitis supported by pathological evidence that is effectively treated with HDMPT. In addition, response to the HDMPT suggested the association between lacrimal gland inflammation and the pituitary lesion. On the other hand, HDMPT offers not only a therapeutic approach, but also a non-invasive diagnostic tool for LH. Finally, although rare, lymphocytic infiltration can simultaneously cause dacryoadenitis and pituitary inflammation, even for middle-aged males.

REFERENCES


1 Beressi N, Beressi JP, Cohen R, Modigliani E (1999). Lymphocytic hypophysitis. A review of 145 cases. Ann Med Interne. **150**: 327–341.
2 Berta A (1982). A polyacrylamide-gel electrophoretic study of human tear proteins. Graefes Arch Clin Exp Ophthalmol. **219**: 95–99.
3 Cocuzzi E, Szczotka LB, Brodbeck WG, Bardenstein DS, Wei T, Medof ME (2001). Tears contain the complement regulator CD59 as well as decay-accelerating factor (DAF). Clin Exp Immunol. **123**: 188–95.
4 Crock PA (1998). Cytosolic autoantigens in lymphocytic hypophysitis. J Clin Endocrinol Metab. **83**: 609–618.
5 Duran Martnez M, Santonja C, Pavon de Paz I, Monereo Megias S (2001). Lymphocytic hypophysitis:report of an unusual case of a rare disorder. J Endocrinol Invest. **24**: 190–193.
6 Goudie RB, Pinkerton PH (1962). Anterior hypophysitis and Hashimoto's disease in a young woman. J Pathol Bacteriol. **83**: 584–585.
7 Hashimoto K, Takao T, Makino S (1997). Lymphocytic adenohypophysitis and lymphocytic infundibuloneurohypophysitis. Endocr J. **44**: 1–10.
8 Joussen AM, Sommer C, Flechtenmacher C, Voelcker HE (1999). Lymphocytic hypophysitis associated with dacryoadenitis: an autoimmunologically mediated syndrome. Arch Ophthalmol. **117**: 959–962.
9 Kristof RA, Van Roost D, Klingmuller 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.
10 Lidove O, Piette JC, Charlotte F, Cassoux N, Correas JM, Papo T (2004) Lymphocytic hypophysitis with lachrymal, salivary and thyroid gland involvement. Eur J Intern Med. **15**: 121–124.
11 Molitch ME, Gillam MP (2007). Lymphocytic hypophysitis. Horm Res. **68**: 145–150.
12 Ozawa Y, Shishiba Y (1993). Recovery from lymphocytic hypophysitis associated with painless thyroiditis: clinical implications of circulating antipituitary antibodies. Acta Endocrinol. **128**: 493–498.
13 Pestell RG, Best JD, Alford FP (1990). Lymphocytic hypophysitis. The clinical spectrum of disorder and evidence for an autoimmune pathogenesis. Clin Endocrinol (Oxf). **33**: 457–466.
14 Reda E (2007) Suspected lymphocytic hypophysitis in a man. NZMA. **120**: U2783.
15 Takao T, Asaba K, Tanaka H, Matsumoto R, Nanamiya W, Hashimoto K (2000). A case of lymphocytic infundibuloneurohypophysitis showing diabetes insipidus followed by anterior hypopituitarism associated with thrombasthenia. Endocr J. **47**: 285–291.
16 Wicezorek R, Jakobiec FA, Sacks EH, Knowles DM (1988). The immunoarchitecture of the normal human lacrimal gland: Relevancy for understanding pathologic conditions. Ophthalmology. **95**: 2100–2109.
17 Yamagami K, Yoshioka K, Sakai H, Fukumoto M, Yamakita T, Hosoi M, *et al.* (2003). Treatment of lymphocytic hypophysitis by high-dose methylprednisolone pulse therapy. Intern Med. **42**: 168–173.