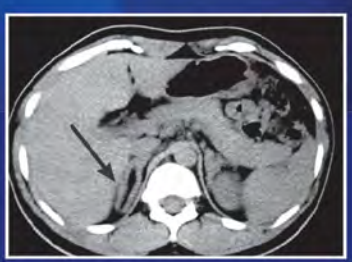
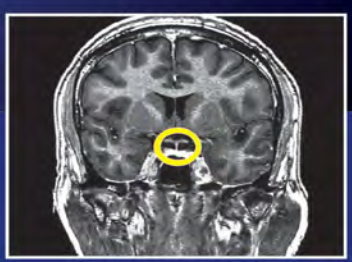
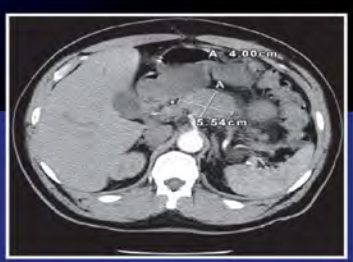
# Case Compendium in Endocrinology


*Editor*
**Romesh Khardori**

*Associate Editors*
**Sarita Bajaj**
**Smita Gupta**

# Contents

CHAPTER

# 4

# Vanishing Pituitary Tumor

*Vinay Dipali, Vageesh Ayyar S*

## CASE PRESENTATION

A 32-year-old male was referred to endocrine service for evaluation and further management of pituitary mass. He presented with acute history of headache, recurrent vomiting, easy fatigability, and diffuse aches, and pains. He also complained of nausea, reduced appetite, and loss of libido, polyuria, and polydipsia. He had no comorbidities and no significant past history except for one episode of febrile illness 2 weeks prior to the presentation that subsided spontaneously. No history of hospitalization in the past. General physical and systemic examination was normal with no localizing signs.

## DIFFERENTIAL DIAGNOSIS

In a patient with known lesion in sellar/suprasellar region and constellation of symptoms described above, following considerations are important to plan diagnostic approach as well as immediate management:

- Pituitary adenoma/infiltrative disorder/inflammatory lesion/infectious process
- Pituitary apoplexy
- Hypopituitarism
  - Hypogonadism
  - Hypoadrenalism
- Diabetes insipidus.

## INVESTIGATIONS

- Fasting blood glucose: 84 mg/dL (normal: 75–100 mg/dL)
- Hemoglobin: 14.1 g%
- White blood cell count: 8,110 (normal differential count)
- Differential count: Normal
- Erythrocyte sedimentation rate: 16 mm in first hour
- Serum creatinine: 0.7 mg/dL
- Serum sodium: 142 mmol/L
- Serum potassium: 4.2 mmol/L
- Liver function studies: Normal
- Routine urinalysis: Normal
- Workup for fever: Normal
- 24-hour fluid intake/output: 6 L/5.5 L
- Morning (8 AM) plasma cortisol: 0.8 ng/dL (normal: 7–20 µg/dL)
- Thyroid-stimulating hormone (TSH): 0.09 µU/mL (normal: 0.2–4.5 µU/mL)
- Free thyroxine (FT4): 0.6 ng/dL (normal: 0.8–2.1 ng/dL)
- Total plasma testosterone: <1 ng/mL (normal: 350–1,050 ng/dL)
- Follicle stimulating hormone: 0.9 mIU/mL
- Luteinizing hormone: <0.1 IU/mL
- Prolactin: 28.2 ng/mL (normal: 3–18 ng/mL)
- Imaging studies
    - Magnetic resonance imaging (MRI) of pituitary: Well-defined homogenously enhancing lesion, not separately visualized from the pituitary gland, causing expansion of sella with suprasellar extension and abutting the optic chiasm (Fig. 4.1).

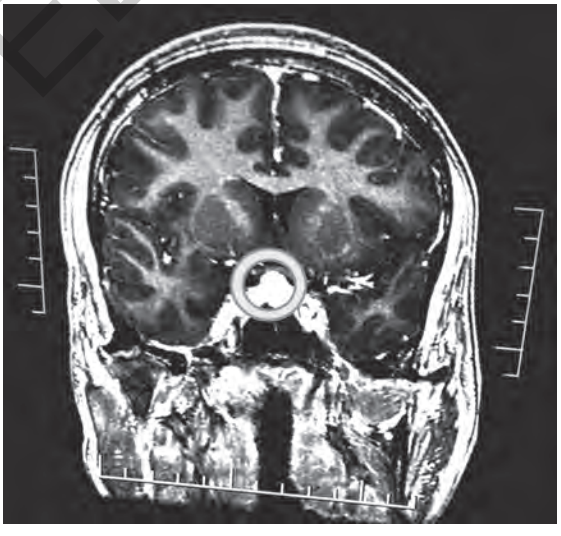


**Figure 4.1:** Post contrast MRI at diagnosis. Note the thickened stalk and homogenously enhancing pituitary

## DIAGNOSIS

Combined pituitary hormone deficiency with diabetes insipidus: lymphocytic hypophysitis.

## MANAGEMENT

Based on the clinical, biochemical, and MRI findings, a diagnosis of lymphocytic hypophysitis was made. Patient was started on replacement doses of thyroxine (1.6 µg/kg/day), hydrocortisone (12 mg/m$^2$/day) and testosterone (250 mg every 3 weeks, IM). Patient was asked to follow-up every month with hormonal assessment. We could see the recovery of pituitary function on follow-up, testosterone and thyroxine replacement were stopped and hydrocortisone dose was tapered and stopped. Patient is currently off all medications with a totally normal pituitary profile. He required replacement for a total duration of 6 months (including the time required for tapering). His repeat MRI showed a normal pituitary with no changes in signal intensities (Fig. 4.2). Patient will be asked to follow-up with periodic pituitary function assessment.

## DISCUSSION

Inflammatory involvement of pituitary gland (hypophysitis) is relatively uncommon and mimics pituitary adenoma clinically and radiologically. Treatment options for these two diagnoses vary and the two can be differentiated unequivocally only by tissue biopsy. Lymphocytic hypophysitis

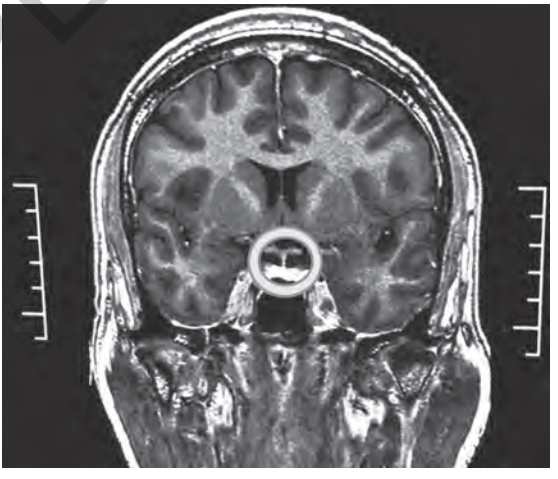


**Figure 4.2:** MRI at follow up visit. Note the resolution of mass and clear visualisation of the stalk

is an inflammatory disorder and presumed to have autoimmune basis. Autoimmune hypophysitis was first described in 1962 by Goudie and Pinkerton. They reported a 22-year-old woman, 14 months after her second child birth. She died 8 hours following appendectomy, presumably compounded by adrenal insufficiency. Her pituitary gland showed lymphocytic infiltration.

## Definition

Currently three forms of hypophysitis are recognized: lymphocytic hypophysitis, granulomatous hypophysitis, and xanthomatous hypophysitis. Each of these may develop de novo or secondary to a systemic process. Lymphocytic hypophysitis being relatively common has received the most attention. Idiopathic granulomatous hypophysitis was first described in 1908, while Xanthomatous hypophysitis was described first in 1998.

Lymphocytic hypophysitis is further subdivided based on affected anatomical target:

1. Lymphocytic adenohypophysitis (LAH) when only anterior pituitary is involved.
2. Lymphocytic infundibuloneurohypophysitis (LINH) when there is exclusive involvement of pituitary stalk and posterior pituitary.
3. Lymphocytic infundibulopanhypophysitis (LIPH) that has features of both anterior and posterior pituitary involvement.

## Epidemiology

Lymphocytic hypophysitis is a relatively rare disease with a reported incidence of 1 in 9 million individuals (<1% of unselected samples obtained at surgery). Majority of cases reported are females though significant proportion of men have been reported as well (23%). It is seen most often in the later stages of pregnancy or immediate postpartum period, and less often in the peripubertal and postmenopausal period. Mean age at diagnosis is around 35 years in females and 45 years in males. As opposed to lymphocytic hypophysitis, there is no predominant female predilection in granulomatous and xanthomatous types.

## Pathology

In lymphocytic hypophysitis, pituitary histopathology reveals diffuse inflammation with widespread infiltration by inflammatory cells comprising polymorphs, lymphocytes, plasma cells, histiocytes, and occasional eosinophils. Immunohistochemical staining reveals presence of both B (CD20 positive) and T (CD3 positive) cells admixed with macrophages

(CD 68 positive). In granulomatous hypophysitis, histiocytes and multinucleated giant cells and granulomas would be seen. In xanthomatous hypophysitis, cystic areas interspersed with foamy histiocytes are seen.

Although considered an autoimmune process (association with other autoimmune diseases, inflammatory/immune cell infiltration on histopathology), no specific antigen or antigens have been identified. Antibodies against pituitary and hypothalamic tissue, hormones secreted by the pituitary, transcription factors involved in pituitary development, and nonpituitary tissues (thyroid, testis) have been reported. Similar antibodies have been reported in certain individuals without evidence of hypophysitis. Thus, it is not recommended to include these antibodies in the formal evaluation of patients.

Progress in understanding of pathogenesis of hypophysitis was limited due to nonavailability of animal model. The development of mouse model should lead to better understanding. However, it is not always easy to translate mice studies to human biology. Recently increasing number of hypophysitis and hypothalamitis are being reported following introduction of cytotoxic T-lymphocyte antigen-4 (CTLA-4) blockers (ipilimumab) to treat malignant melanoma.

## Clinical Features

Symptoms/presentation in those with lymphocytic hypophysitis may be related in majority of the cases to mass effect from expanding pituitary gland and stalk (58%). Symptoms include headache, visual field defects and decreased visual acuity. Second common presentation relates to consequences arising from deficiency of anterior pituitary hormones (44%); ACTH deficiency being most predominant (32% of cases), followed by TSH deficiency (15%), and gonadotropin deficiency (14%). There are no precise data available on growth hormone deficiency. Third presentation relates to diabetes insipidus (31%) consequent to stalk involvement disrupting axonal transport of antidiuretic hormone from the hypothalamic nuclei to the posterior pituitary. Some patients present with symptoms of hyperprolactinemia (17–23%).

ACTH deficiency is earliest functional alteration reported in patients with lymphocytic hypophysitis.

## Diagnosis

Diagnosis requires high index of suspicion and thorough evaluation of clinical setting and risk factors. Evaluation requires full assessment of both anterior and posterior pituitary functions. Once biochemical evaluation is complete, imaging of sellar and suprasellar structures is necessary. Whereas

diabetes insipidus is very common in LIPH and LINH, it is less frequent with LAH. Females predominate in LAH while LIPH and LINH are seen more in men. Ultimately the distinctions rests on histopathology of tissue obtained at biopsy or surgery.

Immunophenotyping is not recommended since markers cited in literature are very nonspecific, and also do not segregate according to the region of pituitary affected.

## Imaging

Findings on MRI in patients with lymphocytic hypophysitis may overlap with those seen in patients with pituitary adenoma. Enlargement of the pituitary gland with thickening of infundibulum extending into suprasellar area is seen in almost 80% of cases. After contrast administration there is marked early and homogenous enhancement often involving the dura (*dural tail*). A strong and homogenous enhancement of the anterior pituitary, similar to the cavernous sinus, is more suggestive of an inflammatory infiltrative process such as lymphocytic hypophysitis rather than a macroadenoma. Macroadenomas enhance less or more slowly than the normal pituitary on dynamic MRI. Certain radiological features may help differentiate hypophysitis from an adenoma (Table 4.1). It should be noted that there may be lack of radiological abnormalities in a very small percentage of patients, and also abnormalities may evolve slowly after hormonal abnormalities have appeared.

Even when using modern MRI studies, approximately 40% of the cases are misdiagnosed preoperatively as pituitary adenomas. Hence, the gold standard for diagnosis of lymphocytic hypophysitis is the pituitary biopsy.

Lymphocytic hypophysitis may coexist with other pituitary lesions such as germinoma, pituitary apoplexy, and pituitary adenoma. These lesions may be encountered in associated systemic pathology such as Wegener's granulo-

**TABLE 4.1: Magnetic resonance imaging features: lymphocytic hypophysitis versus pituitary adenoma**

| Feature | Lymphocytic hypophysitis | Pituitary adenoma |
|---|---|---|
| Asymmetric mass | No | Yes |
| Intact sellar floor | Yes | ± |
| Suprasellar extension | Yes | ± |
| Stalk thickening | Yes | No |
| Stalk displacement | No | ± |
| Homogeneous enhancement | Yes | No |
| Loss of posterior pituitary bright spot | Yes | No |

matosis, Langerhans histiocytosis, lymphocytic thyroiditis, sarcoidosis, tuberculosis, and other bacterial, viral or fungal processes.

## MANAGEMENT

Although the transition is often from symptoms of mass effect to development of hypopituitarism, some cases may show spontaneous, partial, or full recovery. About 10% cases eventually develop the "empty sella syndrome." Death is rare, but reported in some cases and is possibly related to unattended glucocorticoid deficiency.

During the phase of hypopituitarism, patients will require hormone replacement hydrocortisone, thyroxine, and testosterone. In those with diabetes insipidus, 1-desamino-8-d-arginine vasopressin must be provided to avoid serious water and electrolyte disturbances. Up to 70% of cases require life-long hormone replacement. Periodic monitoring is necessary. Use of steroids remains controversial since resolution has not been uniformly reported, even when using high doses. Furthermore perils of chronic glucocorticoid replacement must be weighed when contemplating large dose steroids.

This case is remarkable for efficacy of glucocorticoids in mitigating hormone.

Deficits as well as resolution of sellar and supra sellar abnormalities noted on the MRI. It serves as a reminder that clinical judgment sometimes trumps trends in literature.

Surgery may be needed when the mass is rapidly increasing and leading to neurovascular compromise. Radiotherapy has been used in a small number of cases.

### KEY POINTS

- Lymphocytic hypophysitis is rare but increasingly recognized clinical entity
- It should be considered in the differential diagnosis of any nonsecretory pituitary mass, especially if presenting during pregnancy or postpartum
- Tissue histopathology (obtained at biopsy or surgery) remains the most definitive way of establishing the diagnosis
- Treatment is dictated by the clinical presentation
- Immunophenotyping is not helpful in diagnosis at the present state of art
- When hypopituitarism is suspected, it must be treated actively, and patient monitored periodically for any recovery. Amongst the hormone replacements, sex steroids are least necessary particularly when considering that acute sickness is often associated with reversible secondary hypogonadism.

## SUGGESTED READINGS


1. Falorni A, Minarelli V1, Bartoloni E, et al. Diagnosis and classification of autoimmune hypophysitis. Autoimmune Rev. 2014;13(4-5):412-6.
2. Hindocha A, Chudhary BR, Kearney T, et al. Lymphocytic Hypophysitis in males. Case Reports. J Clin Neurosci. 2013;20:743-5.
3. Howlett TA, Levy MJ, Robertson IJ, et al. How reliably can autoimmune hypophysitis be diagnosed without pituitary biopsy. Clin Endocrinol (Oxf). 2010;73:18-21.
4. Khare S, Jagtap VS, Budyal SR, et al. Primary (autoimmune) hypophysitis: a single centre experience. Printed online: Pituitary, December 28, 2013.
5. Ole-Petter R, Hamnvik, Anna R Laury, et al. Lymphocytic hypophysitis with diabetes insipidus in a young man. Nat Rev Endocrinol. 2010;6:464-70.
6. Torino F, Barnabei A, De Vecchis L, et al. Hypophysitis induced by monoclonal antibodies to cytotoxic T lymphocyte antigen 4: challenges from a new cause of rare disease. Oncologist. 2012;17:525-35.

# Case Compendium in Endocrinology

***Key Features***

- A comprehensive compendium of interesting cases on various topics in endocrinology
- Helps understand fundamentals of physiologic principles governing the endocrine system
- Written by experts who are well known for their academic inclination and capability
- Up-to-date reviews of current practice recommendations for management of endocrine disorders
- Easy-to-navigate format loaded with practical scientific information that is relevant and highly pertinent.

**Romesh Khardori** MD PhD FRCP(C) FACP
Professor of Medicine
Division of Endocrinology and Metabolism
Strelitz Center for Diabetes, Endocrine, and Metabolic Disorders
Department of Internal Medicine
Eastern Virginia Medical School
Norfolk, Virginia, USA

**Sarita Bajaj** MD DM
Consultant Endocrinologist
Director-Professor and Head
Department of Medicine
Moti Lal Nehru Medical College
Allahabad, Uttar Pradesh, India

**Smita Gupta** MD
Consultant Endocrinologist
Community Health Network
Indianapolis, Indiana, USA

**Available at all medical bookstores**
**or buy online at www.jaypeebrothers.com**

**JAYPEE BROTHERS**
**Medical Publishers (P) Ltd.**
**www.jaypeebrothers.com**

Join us on facebook.com/JaypeeMedicalPublishers

Shelving Recommendation
**ENDOCRINOLOGY**

ISBN 978-93-5152-643-8