Lymphocytic Hypophysitis with a Long Latent Period Before Development of a Pituitary Mass

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ABSTRACT: Background: Lymphocytic hypophysitis is an autoimmune condition that commonly presents in women of childbearing age as hypopituitarism and a sellar mass. Case report: A 66-year-old woman presented with anterior pituitary dysfunction. Computed tomography imaging revealed a small hypodensity that was not felt to be the cause of the pituitary dysfunction. Eight years later, her vision rapidly deteriorated and MRI showed a pituitary mass lesion causing optic chiasm compression. Histological examination of the partially resected gland revealed evidence of lymphocytic hypophysitis. Conclusion: Our patient is an example of the variable presentation and course of lymphocytic hypophysitis. Such a long latent period between the initial presentation of adenohypophysial hypofunction and optic chiasm compression due to an enlarging pituitary mass has not been reported.

RÉSUMÉ: Période de latence prolongée avant l’apparition d’une masse pituitaire dans l’hypophysite lymphocytaire. Introduction: L’hypophysite lymphocytaire est une maladie auto-immune qui survient habituellement chez des femmes en âge de procréer et dont la présentation est celle d’un hypopituitarisme et d’une masse sellaire. Cas clinique: Une femme âgée de 66 ans a consulté pour une dysfonction de l’hypophyse antérieure. Huit ans plus tard, sa vision s’est détériorée rapidement et l’IRM a montré une masse pituitaire comprimant le chiasma optique. L’examen histologique de la glande partiellement résecée a montré qu’il s’agissait d’une hypophysite lymphocytaire. Conclusion: Notre patiente est un exemple de la variabilité dans la présentation clinique et dans l’évolution de l’hypophysite lymphocytaire. Il s’agit de la première publication rapportant un cas où la période de latence entre l’apparition de la symptomatologie de l’hypophysite lymphocytaire et celle de la compression du chiasma optique due à une masse pituitaire expansive a été aussi longue.


Lymphocytic hypophysitis is an uncommon condition, with a natural history that is not well-known. Patients usually present with chiasmal compression and varying degrees of pituitary dysfunction. We report a case of lymphocytic hypophysitis that initially presented as partial hypopituitarism. Eight years later, the patient developed symptoms of chiasmal compression.

CASE REPORT

A 66-year-old woman presented eight-and-a-half years previously with bilateral leg edema and was found to have a free thyroxine level of 6 pmol/L (reference range 11-23). Despite an inappropriately normal thyroid stimulating hormone (TSH) and negative anti-microsomal antibodies she was diagnosed with primary hypothyroidism and treated with L-thyroxine. No other investigations were done. Four years later, she presented with a three-day history of vomiting and generalized weakness. She had no headaches, visual complaints, abdominal symptoms, polyuria, polydipsia or nocturia. There was no previous history of postpartum hemorrhage. She was unable to lactate after each of her two deliveries, but had normal menses until a hysterectomy at age 48 for dysfunctional uterine bleeding. Her ovaries were not removed. She had significant hyponatremia (sodium 116 mmol/L) that responded partially to hydration with normal saline. Urine sodium was 36 mmol/L, serum urea 1.8 mmol/L (reference range 2.5 - 7.0), follicle stimulating hormone (FSH) 1 IU/L, and morning serum cortisol 65 nmol/L (reference range 165 – 628). There was no hyperpigmentation, hypotension or hyperkalemia. Serum calcium, parathyroid hormone and anti-adrenal antibodies were negative.

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She was diagnosed with hypopituitarism and treated with hydrocortisone. This resulted in normalization of serum sodium and resolution of her symptoms. A contrast-enhanced CT scan of the head and sella turcica showed a normal sized pituitary with a 6 x 4 mm hypodense area, minimal convexity of the overlying diaphragma sellae and contralateral shift of the infundibular stalk. A repeat scan done 14 months later showed no change.

During regular biannual follow-up she was clinically well on replacement doses of hydrocortisone and L-thyroxine. Four and one half years later she presented with a two-month history of progressive bilateral decrease in vision. On examination she had a dense bitemporal visual field loss. Lab investigations revealed: TSH < 0.01 mU/L (reference range, 0.25-5.50), free T4 13 pmol/L (reference range, 11-23), PSH < 1 IU/L, LH < 1 IU/L, prolactin 11, adrenocorticotropic hormone (ACTH) < 2.2 pmol/L. A gadolinium-enhanced MRI showed a heterogeneously enhancing sellar mass extending 1.7 cm above the sella. The mass had a figure of eight appearance and bowed the optic chiasm.

She underwent a transsphenoidal partial removal of the pituitary mass. The tissue was extremely fibrous and relatively avascular. Histopathology of the lesion showed multiple fragments of sclerotic connective tissue (Figure A) with remnants of anterior pituitary showing a mixed infiltrate of lymphocytes, plasma cells and macrophages (Figure B). The lymphocytes showed no atypia. Anterior pituitary cells were hardly recognizable, but a synaptophysin stain (Figure C) and pituitary hormone stains showed islands of remaining endocrine cells. Additional stains for acid-fast bacilli, fungi and bacteria were negative. The final pathologic diagnosis was lymphocytic hypophysitis. Her visual fields improved and remained stable at five months after surgery.

**Discussion**

Lymphocytic hypophysitis is primarily a disease of young women, characterized by lymphocytic infiltration and destruction of the pituitary gland. Its pathogenesis has been attributed to autoimmunity, supported by the presence of circulating antipituitary antibodies in some patients. Depending on the stage of disease the pituitary may be enlarged secondary to inflammatory infiltration, or small and atrophic from destruction of pituitary tissue and replacement by fibrosis. Many patients present clinically with headaches and/or visual field impairment. Others present with features of hypopituitarism and coexisting pituitary masses of significant sizes at the time of presentation. Littie has been reported about the course of this condition after its diagnosis.

We describe a 66-year-old woman with lymphocytic hypophysitis, placing special emphasis on features that illustrate the highly variable natural history of this condition. Typically, the disease is seen most commonly in young women (mean age of 34.5 years) in late pregnancy or in the postpartum period, but it has been reported in postmenopausal women. There is a 30% coexistence with other autoimmune disorders, including Hashimoto’s thyroiditis, Graves’ disease, retroperitoneal fibrosis, parathyroiditis, pernicious anemia and idiopathic Addison’s. Our patient had no personal or family history of these associated conditions.

A unique aspect of our case is the long latent period between onset of hypopituitarism and development of optic chiasm compression. The initial manifestation of lymphocytic hypophysitis was likely hypothyroidism. The normal TSH in the setting of a low free thyroxine suggests that she had secondary rather than primary hypothyroidism. Four years later, she had findings of combined ACTH, thyroid and gonadotropin deficiencies, likely due to massive parenchymal destruction of adenohypophyseal cells. This unusual pattern of endocrine abnormalities may help distinguish lymphocytic hypophysitis from a tumor in a patient presenting with hypopituitarism. Tumors often cause a loss of growth hormone and gonadotropin first, followed by low levels of TSH and ACTH. In contrast,
lymphocytic hypophysitis frequently results in isolated ACTH deficiency or combined adrenal/thyroid deficiencies with normal gonadotropin and growth hormone secretion.\textsuperscript{2}

Our patient did not have evidence of posterior pituitary involvement. Previous distinctions have been made between lymphocytic hypophysitis and lymphocytic infundibulohypophysitis, based on whether the anterior or posterior pituitary is affected.\textsuperscript{3} However, some patients present with both anterior and posterior pituitary dysfunction\textsuperscript{4,5} and it may be appropriate to consider lymphocytic hypophysitis as a syndrome including disorders of both the anterior pituitary (lymphocytic adenohypophysitis) and the posterior pituitary (lymphocytic infundibuloneurohypophysitis).\textsuperscript{6}

Pituitary dysfunction with little or no pituitary abnormality on neuroimaging is often labeled as idiopathic hypopituitarism but may be another clue to the diagnosis of lymphocytic hypophysitis.\textsuperscript{2} Our patient presented with hypopituitarism, but had only a small pituitary lesion that would normally not be associated with pituitary hypofunction. Bevan et al\textsuperscript{7} reported a patient who presented with TSH and ACTH deficiencies, and in whom CT imaging showed no evidence of a sellar mass. Our case illustrates that in such a situation it is important to suspect a diagnosis of lymphocytic hypophysitis and perform serial imaging to detect an enlarging pituitary mass. Wild et al\textsuperscript{8} reported a patient with lymphocytic hypophysitis presenting with amenorrhea and hyperprolactinemia whose initial pituitary imaging was normal; repeat imaging done eight months later showed a sellar mass. Tubridy et al\textsuperscript{11} reported a patient with posterior, but not anterior, pituitary dysfunction and normal pituitary imaging, who developed compressive symptoms after a six-month latent period.

When the patient presented with hypopituitarism, MRI may have detected pituitary enlargement or revealed inflammatory changes that did not appear on CT imaging. Loss of the hyperintense "bright spot" signal of the posterior pituitary, thickening of the pituitary stalk, or enlargement of the posterior gland can be seen on MRI in patients with lymphocytic hypophysitis.\textsuperscript{1} During the patient’s latent period, it is not known how quickly pituitary enlargement occurred but there was no change in CT scan findings 14 months after the first scan was done. Weinmann et al\textsuperscript{10} reported that MRI changes of the pituitary stalk may present as long as three years after development of posterior pituitary dysfunction.

Lymphocytic hypophysitis may present with pituitary dysfunction with no or minimal enlargement of the pituitary. This patient highlights the fact that enlargement of the pituitary, causing chiasmatic compression, can occur after a quiescent period of eight or more years, and points out the importance of long-term radiologic monitoring of patients with idiopathic hypopituitarism.

REFERENCES