Lymphocytic panhypophysitis in a young man with involvement of the cavernous sinus and clivus

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Abstract Lymphocytic hypophysitis is an unusual inflammatory lesion that is caused by autoimmune destruction of the pituitary gland. We report a case of 42-year-old man who presented with a 6-month history of severe headache, blurred vision in the right eye, hearing loss, polyuria, polydipsia, and impotence. Medical history showed that he and his mother had osteopetrosis. The results of the physical examination and laboratory tests showed that secondary hypothyroidism, hypogonadism, and hypocortisolism had developed. Central diabetes insipidus was diagnosed by water deprivation test. MRI of the sella showed pituitary enlargement with symmetrical suprasellar expansion, compression of the chiasma, thickened infundibulum, and involvement of both bilateral cavernous sinuses and clivus. Hormonal substitution with hydrocortisone, levothyroxine, and DDAVP resulted in rapid improvement of all symptoms and signs. Transsphenoidal biopsy was diagnostic of lymphocytic hypophysitis. In spite of extensive literature reviewing, we have not been aware of any case of lymphocytic hypophysitis with clivus involvement. The present case represents a variant of lymphocytic hypophysitis which has progressed to involve bilateral cavernous sinuses and the clivus.

Keywords Lymphocytic hypophysitis · Diabetes insipidus · Cavernous sinus · Clivus · Osteopetrosis

Introduction

Lymphocytic hypophysitis (LH) is a rare autoimmune inflammatory disease of the pituitary gland. LH may present with several clinical forms such as adenohypophysitis (LAH), infundibulo-neurohypophysitis (LINH) or both (panhypophysitis, LPH). The natural history of LH remains poorly understood [1]. It more commonly affects women during pregnancy or shortly after delivery. About 15% of reported cases occurred in men [2]. Its clinical presentation and radiological findings may mimic pituitary adenoma. The common radiological features of the LH include symmetric and homogeneously enhanced pituitary mass after gadolinium, and thickened infundibulum on MRI [3]. The clinical presentation commonly includes headache, visual field abnormalities and hypopituitarism [4–7]. A definitive diagnosis, however, requires histological verification. The defining pathological feature of LH is the infiltration of the pituitary gland by lymphocytes [1]. We describe an unusual case with LH who presented with hypopituitarism and diabetes insipidus but the condition progressed to involve bilateral cavernous sinuses and clivus.

Case report

A 42-year-old man presented with a 6-month history of frontal progressive headache and 4-month history of polyuria, polydipsia, nausea, emesis, decreased libido,
and impotence. He had also complained of blurred vision in his right eye 4 months ago that resolved spontaneously in a few weeks. He had left eye blindness due to a previous traffic accident. At the same accident he had lost his left arm and proximal phalanx of his right hand. He and his mother had osteopetrosis but there was no family history of any other endocrine or autoimmune diseases. On physical examination, the patient was pale. Blood pressure was 90/65 mmHg and pulse was regular at 88 beats/min. There were no motor or sensory neurological deficits. Fundoscopic examination and perimetry of his right eye were normal. The full blood count displayed slightly reduced hemoglobin value of 11.8 g/l. Serum electrolytes were normal. The erythrocyte sedimentation rate was slightly elevated at 39 mm/h. Serum angiotensin converting enzyme concentration (ACE) was 21 U/l (N, 5-30). Chest X-ray and computerized tomography (CT) of the thorax revealed no abnormality.

Endocrinological evaluation showed secondary hypothyroidism [free T4 9.8 pmol/l (N, 12-22), TSH 1.11 µIU/ml (N, 0.27-4.2)], secondary hypogonadism [FSH 1.3 mIU/l (N, 1.5-12.4), LH 0.1 mIU/l (N, 1.7-8.6), testosterone 0.02 ng/ml (N, 0.27-2)], hypocortisolemia [basal cortisol 5.3 µg/dl (N, 5-25)], and mild hyperprolactinaemia [PRL 58 ng/ml (N, 4.1-18)]. IGF-1 level was 161 ng/ml (N, 101-303). Plasma osmolality was 341 mOsm/l (N, 285-293), urinary osmolality was 75 mOsm/l (N, 300-900). A water deprivation test provided evidence for central diabetes insipidus. Thyroid autoantibodies (anti-TPO and anti-tg antibodies) were negative.

Examination of the cerebrospinal fluid (CSF) revealed a slightly increased protein concentration of 471 mg/l (N, 150-450). ACE and ß-HCG of CSF were normal. Cytology of CSF showed increase in inflammatory cells. There was no immunoreactivity of S-100 protein and CD1a in antigenic analysis of CSF. Serological investigations for toxoplasma, HIV, tuberculosis, and syphilis were all negative. CSF cultures (including mycobacterial cultures) were negative, too.

Basal magnetic resonance imaging (MRI) showed a large intrasellar mass with a triangular shape, an enlarged pituitary stalk, and involvements of the bilateral cavernous sinuses and the clivus. Homogenous enhancement was observed after gadolinium injection with loss of the hyperintense signal of the neurohypophysis (Fig. 1a and b). Hormonal substitution with hydrocortisone, levothyroxin, and desmopressin acetate resulted in rapid improvement of all symptoms and signs. Three weeks later, MRI demonstrated significant regression of the lesion surrounding the optic chiasma, but the infiltration at the cavernous sinuses, the pituitary, and the clivus did not change significantly (Fig. 2a and b). Further regression of the pituitary lesion was observed on MRI 5 months later (Fig. 3). At the end of 1 year of follow-up, MRI showed that the infiltration at the optic chiasma was relieved, and pituitary was normal size but there was no significant regression around the cavernous sinuses and clivus (Fig. 4a and b). Despite radiologic resolution of the pituitary lesion, there was no improvement of the diabetes insipidus and hypopituitarism.

A definitive diagnosis, however, required transsphenoidal biopsy. His headache was dramatically relieved after transsphenoidal biopsy. Histology showed lymphocytic hypophysitis (Figs. 5, 6a and b). Immunohistochemical analysis showed lymphocytic infiltration of mixed T and B cell phenotype (Fig. 6a). Positivity for both light chains kappa and lambda demonstrated a polyclonal infiltration (Fig. 6b).

Discussion

Lymphocytic hypophysitis (LH) is an inflammatory disorder of the pituitary gland that is being recognized with increasing frequency. Among the subgroups of LH, LAH more commonly affects young women, LINH appears to affect both sexes equally, and LPH is slightly more common in women in the literature [1]. LH has a female predilection and frequently affects young women during late pregnancy or in the post-partum period; however, many cases have been reported also in men [2, 8–10]. In our case, inflammation was not only localized to the adenohypophysis but also involved the neurohypophysial system, the cavernous sinus and clivus. To our knowledge very few cases of LH with cavernous sinus involvement have been reported [3, 9, 11–14]. Moreover, up to our knowledge involvement of clivus by LH has not been reported in the literature previously.

Although the natural history of LH remains poorly understood, several studies suggested an autoimmune cause. Autoantibodies against pituitary cells were detected in some patients’ sera, and approximately 30% of patients were found to have other organ specific autoimmune diseases such as Hashimoto’s thyroiditis, adrenalitis or pernicious anemia, [10, 15, 16]. In this case, thyroid autoantibodies were negative, and there was no evidence of other autoimmune diseases.

The clinical presentation of LH has usually been with frontal headache, nausea, emesis and visual symptoms arising from involvement of the suprasellar optic pathways and hypopituitarism with mild hyperprolactinemia [4–7, 17, 18]. This patient was also
complaining of headache, nausea, emesis, and the symptoms of hypopituitarism in addition to diabetes insipidus. Although the principal site of involvement was considered to be the adenohypophysis, a small number of patients had clinical evidence of diabetes insipidus [6, 9, 15, 19]. LH is often misdiagnosed as pituitary adenoma [5, 7, 20–22]. Pituitary MRI is suggestive of a pituitary mass with evidence of suprasellar extension in many cases [7]. In LINH the MR imaging may demonstrate a thickened pituitary stalk or enlarged neurohypophysis [3]. There may also be a loss of the hyperintense signal of the normal neurohypophysis on contrast enhanced T1-weighted images. The anterior pituitary is spared, which distinguishes this condition from LAH radiologically. However homogeneity and symmetry of the pituitary mass, the lack of erosive changes of the sella floor, intense enhancement after gadolinium and the involvement of dura matter are important clues in differentiation of LAH from a typical pituitary adenoma [3, 20]. Some researchers have reported extensions of LH to the posterior lobe or infundibulum, to the cavernous sinuses or the carotid arteries [3, 9–12, 20]. In our case, the sella MR imaging showed thickened pituitary stalk with dural thickening in bilateral cavernous sinuses and the clivus. In the literature, we could not find any other report about involvement of clivus by LH, but extrapituitary involvement of the subarachnoid space, sphenoid sinus,
clivus or cavernous sinus can be seen in invasive pituitary adenomas as well [13, 23, 24].

The presence of diabetes insipidus at the presentation almost completely rules out the pituitary adenoma and raises suspicion of infiltrative or inflammatory diseases such as hemochromatosis, sarcoidosis, infectious diseases like tuberculosis and fungal infections, vascular compromise, metastatic tumors including lymphomas, leukemias, breast cancer, and lung cancer [12]. In our case endocrinologic evaluation demonstrated hypopituitarism, mild hyperprolactinemia and diabetes insipidus. Further laboratory investigations and cerebrospinal fluid (CSF) analysis, chest X-ray, computerized tomography of the thorax and abdomen did not give any evidence for the above mentioned conditions in the differential diagnosis. Because of its low prevalence in males, LH has not often been included in the differential diagnosis of pituitary mass lesions in male patients. So, definitive diagnosis required transsphenoidal biopsy. Histopathological examination showed lymphoplasmacytic infiltration and areas of fibrosis. Morphological appearance and the reticulin-pattern excluded pituitary adenoma. Immunohistochemical examination revealed polyclonal mixed B (CD20 positive) and T cell (CD3 positive) infiltration with immunostaining for \( \kappa \) and \( \lambda \) light chains. A plasmacytoma was excluded by the polyclonality of plasma cells, and lymphoma was unlikely since it should be associated with atypical cells and the CNS lymphomas nearly always consisted of the B cell type. Tuberculosis, sarcoidosis, and Wegener granulomatosis were all excluded because there were no well-defined granulomas, giant cells or vasculitic features. Langerhans histiocytosis was also excluded because stains for S100 protein and CD1a were negative. Therefore, a diagnosis of LH was established.

Treatment of LH is symptomatic, and replacement therapy of the deficient hormones is essential in the management of patients. Progressive and permanent hypopituitarism or spontaneous recovery have been reported [10]. Surgical removal of the infiltrative pituitary has been used to treat some patients who present with symptoms of sellar compression [25–27]. Headaches and visual deficits resolve promptly by achieving decompression of the sellar mass with endonasal transphenoidal surgery [25–27]. However, surgical intervention may result in further deterioration of pituitary gland functions; so, a frozen section should be performed to confirm the diagnosis and to avoid further aggressive resection. Patients presenting with hypopituitarism, diabetes insipidus or hyperprolactinemia rarely benefit from surgery because the defects are secondary to diffuse lymphocytic hypophysitis rather than to compression of the normal parenchyma that surrounds the pituitary mass. In our case headache, nausea, and emesis were dramatically relieved after biopsy of the pituitary lesion due to partial decompression. While some authors suggested a therapeutic trial with supraphysiological doses of...
glucocorticoids, others have reported lack of response to steroids [3, 21, 22, 28, 29]. More recently other immunosuppressive drugs such as azothiopirine and methotrexate have been used in cases of LINH with good results [10, 12]. The optimum management of this disease is still unclear, but a conservative (non-operative) approach is often advocated. Our patient was discharged with replacement therapy.

In conclusion, the presented patient is unusual because of the long clinical history, the patient’s male sex, and the involvement of both cavernous sinuses and clivus with panhypophysitis.

References