

Case Report

Primary lymphoma of the pituitary stalk presenting as diabetes insipidus and visual deterioration: a case report and literature review

Dongyi Yang¹, Xingyao Bu¹, Zhaoyue Yan¹, Xue Cheng², Tao Wu³

¹Department of Neurosurgery, Zhengzhou University People's Hospital, Zhengzhou, China; ²Department of Respiratory Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China; ³Department of Encephalopathy, The First Affiliated Hospital of Henan University of TCM, Zhengzhou, China

Received April 19, 2017; Accepted August 24, 2017; Epub October 15, 2018; Published October 30, 2018

Abstract: Objective: This report aims to present an unusual case of primary lymphoma of the pituitary stalk, and provide more evidences and treatment approaches for this rare disease. Case presentation: A 66-year-old female presents as headache, dizziness, polyuria, polydipsia and visual deterioration. Brain MRI revealed isolated pituitary stalk thickening (>5 mm) without pituitary mass, but with intense and homogeneous enhancement. Serological test for HIV antibodies was negative. Water deprivation test and vasopressin test confirmed central diabetes insipidus. The patient underwent right pterional craniotomy to resect the mass. The infiltrating lymphoid cells stained virtually positive for terminal deoxynucleotidyl transferase (TdT), CD20 (B-cell marker), CD79a, LCA, CD43 and CD99; while CD3 (T-cell markers), cytokeratin (CK), epithelial membrane antigen (EMA), CD5, CD23, S-100 protein, nuclear transcription factor (NF), and chromogranin A (CgA) were negative. Proliferation index by Ki-67 was greater than 70%. A definitive diagnosis of primary B-cell lymphoblastic lymphoma was made. Conclusion: This case shows that it is a necessary to be vigilant to endocrine and metabolic manifestations in patients with malignant central nervous system (CNS) involvement. Primary CNS lymphoma (PCNSL) should be considered as a potential cause of sellar mass.

Keywords: Lymphoma, pituitary stalk, diabetes insipidus, visual deterioration

Introduction

Cerebral lymphoma is a malignant lymphocytic neoplasm that was once considered a rare neoplasm, and the incidence of CNS lymphoma has increased significantly in recent decades [1]. Primary B-cell lymphoblastic lymphoma is a rare extranodal subtype of non-Hodgkin's lymphoma. This lymphoma of the pituitary stalk is relatively rare, while malignant brain tumor accounts for 0.7-1.5% of all non-Hodgkin's lymphomas (NHL) and 1-3% of all primary intracranial neoplasms [2]. It has no pathognomonic clinical and imaging features, and a diagnosis before surgery is uncommon. Individuals with acquired immune deficiency syndrome (AIDS) have a substantially higher risk for developing this condition. This report aims to describe a case of primary B-cell lymphoblastic lymphoma leading to pituitary infundibular stalk enlargement, and provide more evidence about its presentation.

Case presentation

A 66-year-old woman presented with gradual but developed blurred vision and progressive diminution of vision in both eyes for the past seven months, with off and on dizziness. Four months earlier before she visited a hospital, the acute onset of intermittent headache without vomiting presented. She developed polyuria and polydipsia for the past two months. The patient had no symptoms of anterior pituitary hormone deficiency at the time of admission. It did not make sense to any of the prescribed medications in her clinical history.

Physical examination revealed a poor mental state. Furthermore, no palpable lymph node was discovered, and there was no hepatosplenomegaly. Ophthalmic examination revealed reduced visual acuity in both eyes and bitemporal hemianopia. The specific gravity of urine was less than 1.010. In addition, water depriva-

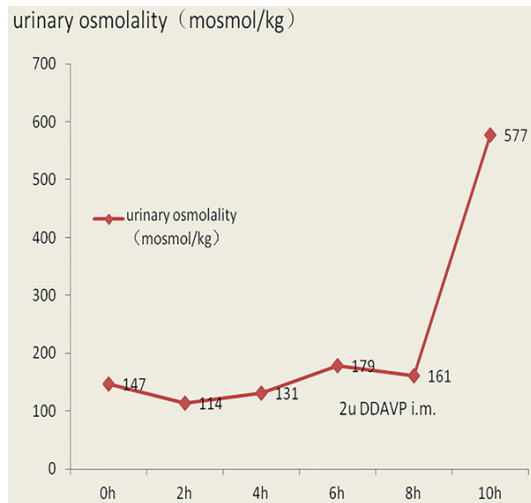


Figure 1. The Water deprivation test and vasopressin test was started at 7 a.m. Every two hours urine specific gravity and urinary osmolality were determined. After 8 h, 2 u DDAVP were injected i.m. and 2 hours later urinary osmolality was measured. The osmolality of the urine sample was increased from 161 mmol/kg to 577 mmol/kg.

tion test and vasopressin test confirmed central diabetes insipidus (CDI) (**Figure 1** and **Table 1**). She also had electrolyte imbalance with hyponatremia and hypomagnesaemia. Furthermore, hematological parameters were within normal limits, and serological test for HIV antibodies was negative. Moreover, basal and stimulated hormone levels (prolactin, FSH, LH, thyrotropin, ACTH, and cortisol) were all within the normal range.

Chest radiography and abdominal ultrasound were normal. Further MRI of the sellar region revealed isolated pituitary infundibular stalk thickening (>5 mm) without pituitary mass, which was low intensity on T1 weighted images. The lesion exhibited homogeneous enhancement on gadolinium-enhanced T1-weighted images (**Figure 2**).

The patient underwent right pterional craniotomy to resect the mass. Confirmation of the tumor was obtained by pathological, immunohistochemical and molecular biology techniques (**Figure 3**). Histopathological examination of the surgical specimen revealed a diffuse proliferation of lymphocytes, which were predominantly intermediate in size with a round, oval, or convoluted nuclear shape with a scanty and faintly basophilic cytoplasm. The infiltrating lymphoid cells stained virtually positive for ter-

Table 1. Water deprivation test and vasopressin test

	UV (ml)	SG	Uosm (mOsm/l)
At diagnosis	9000	1.006	161
After water deprivation	8500	1.006	174
After injection of DDAVP	2300	1.017	577

UV, urine volume; SG, specific gravity; Uosm, urine osmotic pressure; DDAVP, vasopressin.

минаl deoxynucleotidyl transferase (TdT), CD20 (B-cell marker), CD79a, LCA, CD43 and CD99, according to the immunohistochemical staining results of the brain slices. Monoclonal antibodies CD3 (T-cell markers), CK, epithelial membrane antigen (EMA), CD5, CD23, S-100 protein, NF and CgA were negative. Proliferation index by Ki-67 was greater than 70%. Furthermore, *in situ* hybridization (ISH) results for Epstein-Barr virus-encoded RNA were negative. A definitive diagnosis of primary B-cell lymphoblastic lymphoma was made. Desmopressin (DDAVP, 0.1-0.2 mg twice per day) was given to control urine volume. After two weeks, the polydipsia disappeared, and DDAVP was gradually reduced to avoid withdrawal. The patient received a total of six courses of R-CHOP chemotherapy, including methotrexate intrathecal (15 mg) and radiation of the CNS (45 Gy). Visual acuity and visual field defects were markedly ameliorated. At present, the patient is regularly being followed-up.

Discussion

Primary central nervous system lymphoma (PCNSL) is almost always lethal, and is likely to derive from late germinal center lymphoid cells [2]. More than 98% of PCNSLs are of B-cell origin, and are predominantly sub-typed as diffuse large B-cell lymphoma based on our literature findings. Previous reports have demonstrated that this type of B-cell lymphoma typically develops in patients who are approximately over 50 years old, and is more common in men than in women [3].

Our patient was revealed isolated pituitary infundibular stalk thickening (>5 mm) without pituitary mass, associated with diabetes insipidus and chiasmal compression. Enlargement of the pituitary stalk by approximately 2.6 mm is considered pathologic [4]. Pituitary stalk thickens in the setting of diabetes insipidus,

Primary B-cell lymphoblastic lymphoma of pituitary stalk

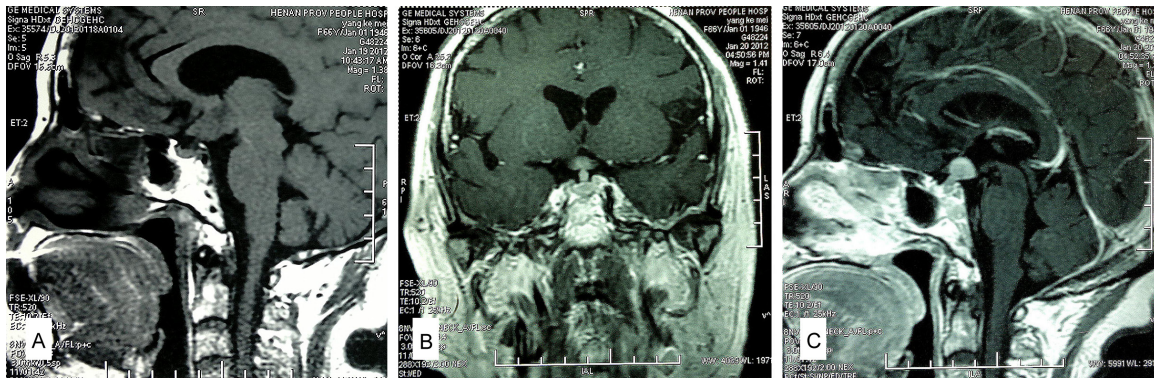


Figure 2. MRI images showing a mass located in the upper pituitary infundibular stalk. Sagittal view of the pituitary stalk showing hypointense on T1 weighted image (A). Coronal (B) and sagittal (C) contrast T1 weighted images show nodular enlargement and thickening of the pituitary stalk with homogeneous enhancement.

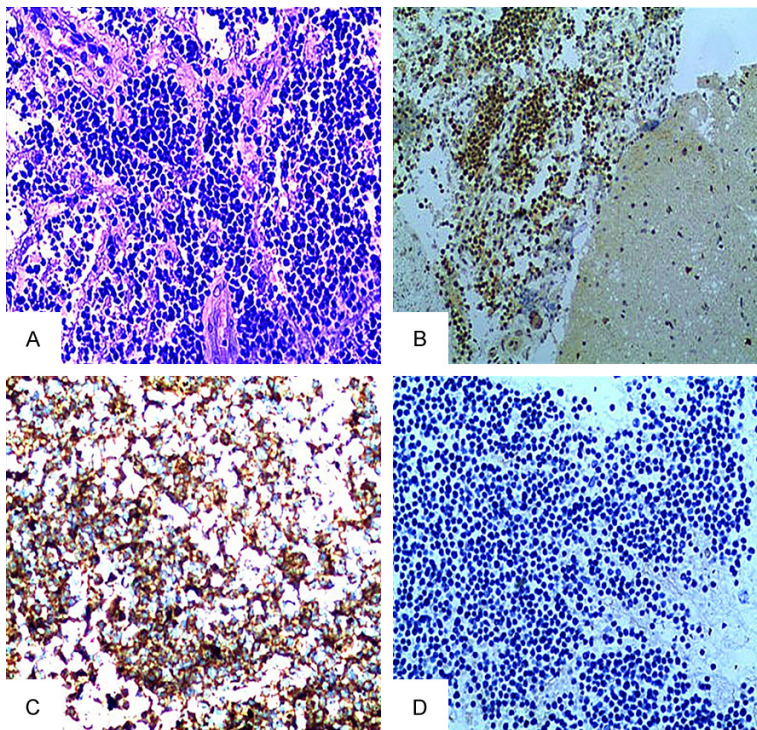


Figure 3. Histopathological examination demonstrated a diffuse infiltrate of lymphoma (A, H&E $\times 20$). Immunohistochemical studies showed that neoplastic lymphocytes are positive for TDT (B, $\times 100$), CD20 (C, $\times 200$). The lymphoma cells revealed negative for EBER by FISH (D, $\times 10$).

and is more likely to have a neoplastic etiology [5]. Water deprivation and DDAVP tests were performed to ensure a correct diagnosis.

The patient may present with a variety of clinical presentations related to the mass effect of the lesion, such as headache, cranial nerve palsies and visual deterioration [6, 7]. Neurological findings with headache or visual field defects

have been described in 55% of patients with PPL [8-10] and 41% of pan-hypophysitis cases [3]. Differential diagnosis of the sellar mass involving the pituitary stalk includes cystic lesions (craniopharyngioma, Rathke's cleft cyst), primary tumors (pituitary adenoma, meningioma, germ cell tumor) and infectious or autoimmune inflammatory processes (lymphocytic hypophysitis, sarcoidosis and histiocytoses) [11]. In addition, metastatic or hematologic malignancies may also infiltrate the hypothalamic-pituitary system, all of which have been generally thought to be indistinguishable by clinical presentation alone. Symptoms of PCNSL arising in the infundibulum can easily be confused with diseases that affect the pituitary stalk and/or neurohypophysis preoperatively.

The imaging manifestations of our patient revealed isolated pituitary stalk thickening (>5 mm) without pituitary mass. The lesions were hypointense on T1 and hypo-to isointense on T2, with intense and homogeneous contrast enhancement on MRI. The presence of a thick pituitary stalk and diabetes insipidus was an argument against pituitary adenoma [12], and the absence of a cystic lesion discarded the

possibility of a craniopharyngioma or Rathke's cleft cyst. It has been reported in lymphocytic infundibulo neurohypophysitis, which reveals loss of the normal high-intensity signal of the posterior on MRI scans [13]. It was suggested that MRI scanning is a fairly sensitive neuroimaging technique for diagnosing PCNSL preoperatively [12, 14]. However, none of these suggestive abnormalities is specific for the diagnosis of PCNSL. Based solely on imaging findings, it is easily misdiagnosed as pituitary tumors or meningiomas. Due to the nature of anatomical structures, the presence of CDI is usually an important feature of this condition [3, 15]. Tumor cells revealed invasive growth, morphological atypia and were multi-mitotic. These characteristics confirmed the lesions as malignant tumors, which could help to distinguish these tumors from pituitary adenomas and other benign lesions. Metastatic carcinoma that spreads to the posterior pituitary and/or pituitary stalk is one of the common causes of CDI in people with breast cancer or lung cancer [16]. In 14%-20% of adult patients presenting with spontaneous diabetes insipidus, the disease is caused by a metastatic pituitary tumor. Imaging of the pituitary often reveals a thickened hypophysial stalk and an "empty sella" phenomenon [17]. Hence, it should be excluded in patients with normal chest films.

For PCNSL, the definitive diagnostic test is the examination of the tumor material for pathology and histology [18]. The diagnostic criteria include morphological features and phenotypes. In this case, histopathology analysis revealed the typical architectural and cytological features of non-Hodgkin lymphomas. Lymphoma cells were stained positively for CD20, CD79a and LCA, but negatively for CD3 and EBV hybridization, which can be defined as B cells. Therefore, the possibility of inflammatory diseases and high-grade glioma can be excluded. In addition, Langerhans-cell histiocytoses were ruled out, because cells were negative with S100 [19]. One third of these patients have circulating antibodies to vasopressin-producing cells (Scherbaum and Bottazo, 1983). Positive of TDT is the evidence of metrococyte source. In addition, the increased proportion of lymphocytes in peripheral blood may prompt the disease. Increasing tumor cell and lymphocyte count can be detected in cerebrospinal fluid. PCR-based automated high-resolution

fragment analysis of rearranged immunoglobulin heavy-chain genes is a highly sensitive means for identifying clonal B-cell responses, which has important value for lymphoma diagnosis [20]. As to granulomatous diseases, in the absence of systemic involvement, osteolytic lesions made Langerhans's cell histiocytosis or sarcoidosis impossible.

This type of lymphoma is often extremely aggressive, and is associated with a high mortality rate. Therapeutic options for PCNSL consist of corticosteroid therapy, radiotherapy, chemotherapy and a combination of these treatment modalities [2, 21, 22]. Although the lymphoma is sensitive to chemoradiotherapy, outcome in patients with PCNSL is significantly worse than in patients with systemic non-Hodgkin's lymphoma.

Conclusion

For the case presented in this report, findings of the isolated and thickened pituitary stalk may be difficult to differentiate from other diseases. Lymphoma infiltration to the pituitary stalk should be considered pre-operatively, although the definitive diagnosis of PCNSL mainly depends on histologic findings. The patient with primary B-cell lymphoblastic lymphoma in this study presented a satisfying response to treatment at initial staging. However, one of the limitations of our case report is that long-term follow-up data are needed.

Acknowledgements

This work was supported by the Key Programs of Science and Technique Foundation of Henan Province (152102310136) and the Medical Science and Technique Foundation of Henan Province (201601016).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xingyao Bu, Department of Neurosurgery, Zhengzhou University People's Hospital, 7 Weft Five Street, Jinshui District, Zhengzhou 450003, China. Tel: +86 18538-297990; E-mail: buxingyao0923@163.com; Dr. Tao Wu, Department of Encephalopathy, The First Affiliated Hospital of Henan University of TCM, 19 Renmin Road, Jinshui District, Zhengzhou 450003,

China. Tel: +8613592127512; E-mail: wutao008-009@126.com

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