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Primary CNS Lymphoma with Bilateral Symmetric Hypothalamic Lesions Presenting with Panhypopituitarism and Diabetes Insipidus

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Abstract

We present an unusual case of primary CNS lymphoma presenting with bilateral symmetric hypothalamic lesions causing diabetes insipidus and hypopituitarism. A 50 year old male presented initially with mental status changes, polyuria and polydipsia. The patient was determined to have diabetes insipidus (DI) and significant anterior pituitary deficiencies resulting in symptomatic pleural and pericardial effusions. Brain MRI with contrast demonstrated bilateral enhancement of his hypothalamus extending to the optic tract. The extensive diagnostic workup that ensued on his initial presentation was non-diagnostic as he had no obvious site of involvement that was easily accessible to biopsy. With close follow-up, the patient had rapid radiographic progression of his disease to his cerebral hemispheres. He therefore underwent brain biopsy and was diagnosed with primary CNS large B cell lymphoma. Chemotherapy has resulted in disease remission with resolution of MRI findings, but the patient has not had resolution of the hypopituitarism or DI. This case highlights the unique diagnostic challenge of patients with isolated hypothalamic lesions.

Keywords

Primary CNS lymphoma; hypopituitarism; hypothalamus; diabetes insipidus

Introduction

Lesions in the hypothalamic-pituitary region often present with neurological symptoms secondary to mass effect, hormonal excess/deficiencies or as an incidental radiographic finding [1]. The underlying pathology of lesions specific to the hypothalamus overlaps with what is seen in pituitary disease; causes include developmental, infectious, infiltrative and malignant pathologies [1]. Infectious/infiltrative lesions in the hypothalamic-pituitary region leading to panhypopituitarism and often diabetes insipidus (DI) include tuberculosis, sarcoidosis and Langerhans' cell histiocytosis. In each of these diseases, there are often other affected sites providing safer options for diagnostic biopsy. However, there are reported cases of each of these diseases being isolated to the central nervous system (CNS)

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[2,3]. While malignancies, especially if metastatic, often have obvious other affected sites, primary malignancies in the hypothalamic-pituitary region do occur. These include gliomas, meningiomas, germinomas, and primary CNS lymphomas.

Primary CNS lymphomas are rare cancers, comprising about 3% of all brain primary tumors, and are most commonly associated with immunodeficiency [4]. The incidence is about 0.5 per 100,000 patient-years [4]. On presentation isolated lesions are commonly seen in the frontal lobes, periventricular white matter, or the corpus callosum. Cases of primary CNS lymphomas isolated to the hypothalamic-pituitary region have been rarely reported [5–9]. Distinguishing isolated malignant lesions from infectious, inflammatory, or primary malignancy in the hypothalamic-pituitary region presents a unique challenge. In this report, we present an unusual case in whom a primary CNS lymphoma presented with DI and anterior pituitary deficiencies from isolated lesions in the hypothalamus.

Case history

A 50 year old male with a history of resolved Bell's palsy in 2005 first presented to another hospital with an acute episode of chest pain. An investigation for acute coronary syndrome as well as pulmonary embolus was negative but during the evaluation he developed severe confusion, hallucinations and paranoia and was noted to be tremulous. Concern for meningitis prompted a lumbar puncture, which revealed no bacterial meningitis.

He was transferred to our hospital's Neurology Service for concern of encephalitis. The Endocrine Service was called two days later after a documented urine output over 24 hours of 10 liters. He was found to have a serum sodium of 154 mEq/L, serum osmolality of 300 mosm/kg, urine osmolality of 59 mosm/kg, and urine sodium of 16 mEq/L, findings consistent with DI. On questioning, the patient described polydipsia and polyuria for the past few months. His wife noted that for the past month the patient also was having episodes of difficulty speaking which included garbled and slurred speech and periodic disorientation. There was no history of travel; however he lives in a wooded area with daily mosquito exposure. He had a distant history over 20 years ago of both heavy alcohol use and intravenous drug use. Initial testing showed panhypopituitarism (Table 1) in addition to the DI. Brain MRI showed hypothalamic infiltrative lesions (Figure 1A) that included the optic tracts with minimal white matter involvement. Testing for HIV, hepatitis B and C were negative. Lumbar puncture was negative for elevated angiotensin converting enzyme, VDRL screen for syphilis, and cryptococcal antigen. Polymerase chain reactions of the CSF for Lyme disease, tuberculosis, Epstein-barr (EBV), varicella-zoster, cytomegalovirus, tropheryma whipplei, and human herpes-6 were all negative. CSF viral and fungal cultures as well as cytology were also unremarkable. Flow cytometry of the cerebrospinal fluid showed a very small population of kappa-restricted B cells.

Computed tomography (CT) of his chest showed a large pericardial effusion and bilateral pleural effusions. Follow-up echocardiography revealed right ventricular diastolic collapse and a moderate to large size circumferential pericardial effusion with exudates consistent with tamponade. A pericardial biopsy was negative for bacteria or mycobacterium growth, and the stains for S-100 and CD1a (markers of Langerhans cell histiocytosis) were negative. Pleural fluid also had negative cytology and was transudative. Bone marrow and bladder biopsies were both negative. A metabolic bone scan was negative for any lytic lesions, but did indicate bilateral calcified hilar lymph nodes consistent with prior granulomatous disease. With supportive care, diuresis, and pituitary replacement his acute issues resolved and he was discharged on desmopressin, hydrocortisone and levothyroxine with careful follow-up. Brain MRI one month after presentation was essentially unchanged. However, three months after initial presentation, a repeat MRI showed interval progression of T2

signal abnormalities in both cerebral hemispheres, including the thalamus and right caudate (Figure 1B).

A frontal lobe brain biopsy demonstrated marked perivascular lymphocytic infiltration (Figure 2A). The lymphocytes were predominantly small, although some larger atypical cells with prominent nucleoli were also present. Within the surrounding brain parenchyma scattered atypical cells and reactive glial cells were noted. Immunostains for CD3 (T-cell marker) and CD20 (B-cell marker) were performed (Figure 2B). A subset of the perivascular cells and most of the infiltrating atypical cells stained positively for CD20. A diagnosis of large B-cell lymphoma was made (CD20+, CD3-, faintly positive CD45, EBV hybridization negative).

Positron emission tomography scan was negative for systemic lymphoma and there was no evidence of ocular lymphoma on slit lamp exam. He was treated with five cycles of high dose intravenous methotrexate (3.5 g/m²), procarbazine, vincristine, and rituximab and achieved a complete response. He deferred whole brain radiotherapy and subsequently received two cycles of cytarabine as consolidation therapy.

At his six month follow-up he is without clinical or radiographic evidence of disease recurrence (see Figure 1C). However, his hypopituitarism persists, requiring thyroid, testosterone, desmopressin and steroid replacement therapy.

Discussion

CNS lymphoma presenting with DI and hypopituitarism due to isolated hypothalamic involvement has been reported only once previously [9]. In our patient, the initial differential diagnosis was broad and included benign/malignant tumors, infiltrative lesions and infections. To determine the etiology of this patient's initial findings, pericardial effusion fluid evaluation and biopsy, lumbar puncture and CSF analysis, bone marrow biopsy, bladder biopsy and a metabolic bone survey were performed, but were unfortunately unrevealing. It was not until his disease had progressed to a more superficial localization within his brain and a brain biopsy was performed that his diagnosis was made, highlighting the diagnostic challenge of isolated hypothalamic pathology.

Considering the overall low incidence rate of primary CNS lymphoma and its usual presentation with more diffuse cerebral involvement, it must be low on the differential diagnosis list of isolated hypothalamic lesions, but should always be considered. One similar case report described a patient with diabetes insipidus and localized hypothalamic involvement [9] that required a more aggressive diagnostic approach including stereotactic biopsy of the hypothalamus. That case and the one presented here underline the challenges that can be faced with this unique presentation of a primary CNS lymphoma, and emphasize the need for vigilance and persistence in the diagnostic evaluation.

Conclusion

As the differential diagnosis of primary hypothalamic lesions is broad, this case highlights the diagnostic challenge that is faced when more superficial sites of biopsy are not accessible. This case provided a challenge of trying to diagnose a rare disease (CNS lymphoma) with an unusual initial site of presentation, and highlights the importance of close follow-up when a diagnostic dilemma occurs.

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Figure 1.

Figure 1A. Axial Flair MRI revealed enhancement in the hypothalamus and optic tract (see arrows).

Figure 1B. Axial Flair MRI revealed extension of the enhancement in the right cerebral region (see arrows).

Figure 1C. Axial Flair MRI revealed resolution of the enhancement in the hypothalamus and optic tract.

Figure 2.

Figure 2A. Brain-biopsy specimen (20X). A hematoxylin and eosin stain showed a marked perivascular lymphocytic infiltrate, with penetration into and through vessel walls. Within the surrounding brain scattered atypical lymphocytes and reactive glial cells were present. Figure 2B. Brain-biopsy specimen (20X). Immunohistochemical staining performed using pan-B-cell marker CD20 revealed the immunophenotype of the tumor cells. Staining for CD3, a T-cell marker, (not shown) revealed a smaller population of reactive lymphocytes.

Table 1

Endocrine laboratory values observed at initial consultation.

Component	Reference Range	
TESTOSTERONE	2–8 ng/ml	0.26
CORTISOL	µg/dL (4 am)	6.6
ACTH	6–46 pg/ml (4 am)	7.0
FREE T4	0.7–1.5 ng/dl	0.44
TSH	0.40–4.00 uIU/ml	1.76
IGF-1	94–252 ng/ml	60