CLINICAL VIGNETTE

Langerhans Cell Histiocytosis – A Rare Cause of Diabetes Insipidus in an Adult

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Case Presentation

A 40-year-old female without significant past medical history presented to the emergency department with worsening confusion. The initial history was obtained from her boyfriend, who stated the patient was in her usual state of health until 2 months prior when she gradually became more confused. Her confusion manifested itself as the patient believing she was in her home country of Peru. She had decreased appetite and lost 13kg over 2 months. Her boyfriend noticed she had developed galactorrhea, polydipsia, polyuria, and cold intolerance. Her last menstrual period was at age 36 after delivery of her third child. Prior to 2 months ago, she was fully functional and worked as a chef. She was not taking any medications, nor supplements. She denied illicit drug, tobacco, and alcohol use.

Her vital signs were remarkable for low blood pressure of 79/65 mmHg. After receiving 6 liters of normal saline, the blood pressure improved to 102/65 mmHg. Heart rate was 100. Her BMI was 20.8 kg/m2. Physical exam was notable for orientation only to person. She perseverated on asking for her children and parents who lived in Peru. She did not follow commands on the rest of her neurological exam. Her initial labs showed elevated sodium of 148 meq/L (135-145 meq/L), serum osmolality 381mmol/kg (275 to 295 mmol/kg)), somatostatin 39 pg/ml (90-260 pg/ml), prolactin 166 ng/ml (less than 25 ng/mL) and diluted prolactin 130 ng/ml (2.8-29.2 ng/mL), LH<0.1 IU/L (women, follicular phase of menstrual cycle: 1.37 to 9 IU/L; women, midcycle peak: (6.17 to 17.2 IU/L), FSH 1.9 mIU/ml (1.5 to 12.4 mIU/mL), TSH 1.27 mIU/l (0.5 to 5.0 mIU/L), Free T4 0.83 ng/dl (0.9 to 2.3 ng/dL), ACTH 34 pg/ml (10 to 60 pg/mL), cortisol 10 mcg/dl at 8am (6 to 23 mcg/dl.), after stimulation her cortisol was 32 mcg/dl(>18 mcg/dl). Hcg negative. Her repeat sodium level was 160 meq/L.

The head computed tomography (CT) revealed a 2.7 x 2.3cm hyperdense lesion largely within the suprasellar cistern. Magnetic resonance imaging (MRI) of the brain showed a 2.2cm x 2.5cm mass centered on the hypothalamus. There was compression of the third ventricle and large amount of edema associated with this mass extending into bilateral thalami and right lateral pons. Furthermore, a lytic lesion on the right frontal calvarium measured 0.7cm x 0.9cm. CT chest and CT abdomen/pelvis did not show any abnormal findings. Lumbar puncture was negative for infection and malignancy. Patient was diagnosed with panhypopituitarism and central diabetes insipidus (DI). Dexamethasone (for the brain edema), Levothyroxine (treating her central hypothyroidism), DDAVP and IV dextrose were also given to the patient.

The patient underwent biopsy of the lesions of the hypothalamus and skull. Her hypothalamus pathology showed mild gliosis and a few perivascular reactive cells with no evidence of neoplasm. CD1a, an antigen typically found on Langerhans cells, was negative. The cranial lesion revealed trabeculae and an atypical infiltrate composed of lymphocytes, histiocytes, eosinophils and Langerhans cells *with groove*. The Langerhans cells were positive for S-100 and CD 68 (focal) and negative for CD1a, CD45, HMB45, PAX and EMA pankeratinl. Morphological and immunophenotypically findings are most consistent with Langerhans cells histiocytosis (LCH), despite CD1a being negative. Interestingly, repeat pathology exam showed a *positive* CD1a.

Discussion

LCH is a rare neoplastic histiocytic disorder that occurs in pediatric as well as adult populations. It is considerably more common in children than in adults.[1] The exact incidence is unknown, but it is estimated as high as 5 cases per million children and 1 to 2 cases per million adults.[2] The incidence appears to be higher in male and caucasian populations.[2]

The exact pathophysiology of LCH is unknown. LCH is a clonal disorder of malignant myeloid cells that cause granulomatous deposits occurring at multiple sites within the body. The BRAF mutation is present in more than half the cases. The BRAF gene provides instruction for making a protein that is normally switched on and off in response to signals that control cell growth and developments. Somatic mutation caused the BRAF protein to be continuously on and cause the development of LCH by allowing the Langerhans cells to grow and divide uncontrollably.[3]

Changes in other genes such as the MAP2K gene (20% of the cases), and other more uncommon genes have also been identified in the Langerhans cells of some people with this condition. Some researchers believe that additional factors, such as viral infections and environmental toxins, may also influence the development of this complex disorder.[3] Known risk factors for LCH are family history of thyroid disease and a personal history of smoking (particularly for lung focal LCH).[4]

LCH can have variable involvements between patients. It can present at a single site or at multiple sites within one organ. It may also present in multiple organ systems simultaneously, or sequentially.[5] Patients who present with single organ system LCH can be of any age, and do not need to have systemic symptoms such as weight loss or fever. The bone, skin, lungs, pituitary (anterior and posterior), central nerve system (CNS), and lymphatic system are the most often affected organs.[5] On particular LCH may involve the CNS in 5 to 10% of the cases, presenting as DI with symptoms of neurodegeneration including ataxia, cognitive dysfunction, and proptosis.[5] Multiple system LCH can involve two or more organ system and it is important to identify those with involvement of critical organs such as CNS, lung, bone marrow, liver and spleen.[5]

More generally, adults with LCH present with skin rash, tumors of the cranium or mandible, dyspnea or tachypnea, polydipsia or polyuria, bone pain, weight loss, fever, gingival hypertrophy, ataxia, and memory impairment.[6,7] DI is the most frequent endocrine abnormality associated with LCH. It typically presents with polyuria, nocturia, and/or polydipsia. Patients who present with DI may have deficiencies of other pituitary hormones, ultimately leading to hypogonadism, growth failure, impaired glucose tolerance/diabetes mellitus, and thyroid enlargement.[5] DI can occur prior to (4 percent), concomitantly with (18%), or subsequent to the diagnosis of LCH.[8,9] In patients with apparent "isolated" DI, LCH is often diagnosed at a later date. In a series of children and adults with LCH presenting as isolated DI, 42 of 44 patients with DI had involvement of other organ systems: bone (68%), skin (57%), lung (39%), and lymph nodes (18%).[10]

Diagnosis of LCH starts with a thoroughly complete history and exam. Laboratory testing includes complete blood count and differential, prothrombin time and activated partial thromboplastin time, serum chemistries, pituitary hormones, osmolality, urine osmolality and urine sodium.[5] Other diagnostic tests depend on the organs involved. For instance, if lungs are involved, a pulmonary function test or bronchoalveolar lavage is useful. If lesions are found, biopsy of a lytic bone lesion, brain or skin is preferred. Patient may need bone marrow biopsy. Brain MRI with contrast is the image of choice to visualize CNS lesions including the 'posterior pituitary bright spot', which may be a sign of presence or when absent, the depletion of antidiuretic hormone stores.[5,11] CT/MRI abdomen can assess involvement of liver or spleen.

An effective treatment of LCH can reduce the risk for the development of DI. Treatment will depend on the site of involvement and may include radiation, surgery, or systemic therapy. Among patients treated with vinblastine and prednisone for six months, approximately 25 percent were diagnosed with pituitary involvement within 10 years of LCH diagnosis; but this declined to 12 percent in patients who completed six months of continuation therapy.[5] Patients with symptomatic diabetes insipidus should be treated with IV hydration and DDAVP, and have their electrolytes monitored closely. Patients are at risk for treatment-related toxicity, secondary cancers, and the myriad of endocrine complications.[12] Endocrinopathies may persist, despite effective treatment of pituitary involvement.[5] Positron emission tomography (PET) is preferred for response assessment, but CT, MRI, or clinical assessment can be used when PET is not available or appropriate (eg, brain lesions).[12] Treatment of relapsed/refractory LCH is individualized according to timing of relapse, sites of disease, performance status, and previous treatment.

In summary, LCH is a rare condition and can be very challenging to diagnose. It should be suspected in patients of any age with unexplained symptoms of any organ – bone, skin, lungs or CNS, including the pituitary gland. Likewise, due to the variability of the signs and symptoms, the diagnosis, prognosis, treatment, and clinical course can vary widely. When in doubt or if the abacus of suspicion does not lend itself to a diagnosis, think about Langerhans cell histiocytosis.

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