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Case Report

Can diabetes insipidus be used as a marker for multisystemic and progressive disease in Langerhans cell histiocytosis?

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ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare disease with an yearly incidence of 9 cases per a million in children and 1 - 2 cases per a million adults. 68.6% of LCH presented with multisystem involvement. A 40-year-old woman who admitted to endocrinology outpatient clinic with the symptoms of polyuria, polydipsia and headache was diagnosed with diabetes insipidus (DI). Desmopressin treatment was initiated but six months after therapy, re-evaluation reveals progression in hypophyseal mass. Thoracoscopic biopsy shows LCH with multisystemic involvement. She did not respond clinically to systemic chemotherapy and external radiotherapy and died due to pneumonia.

LCH should be taken into consideration in patients diagnosed with DI. DI is almost always the hallmark of hypothalamic pituitary axis involvement and sign of multi-systemic involvement.

KEYWORDS: diabetes insipidus, Langerhans cell histiocytosis, multisystemic disease

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare disease in childhood and adulthood which is a part of diseases caused by infiltration of Langerhans Cells across multiple organs, such as the lungs, bones, skin, pituitary gland, and lymph nodes[1]. Yearly incidence is 3 - 5 cases per million between 1 and 3 years of age[2] and 9 cases per a million in children[3]. LCH is rarer in adults with an yearly incidence of 1 - 2 cases per a million[4,5].

Exact pathogenesis of LCH is still not defined but identified tumor-associated mutation (BRAFV600E) indicating that LCH is more a neoplastic disease rather than a reactive disorder, although it exhibits a strong inflammatory component[6,7]. Presence of Birbeck granules in electron microscopy or S100/ CD1a positivity in immunohistochemical staining confirms the diagnosis of LCH[7].

The International LCH Study of the Histiocyte Society categorized LCH into localized (single-system disease) and disseminated forms (multisystem disease)[8]. According to International Histiocyte Society Registry from January 2000 to June 2001, 68.6% of LCH presented with multisystem involvement[9].

The most commonly involved organs are lungs (58.4%) and bones (57.3%). Local pain (34%), weight loss (11%), and fever (10%) are the most common symptoms at presentation[9]. The most common endocrine manifestation of LCH in adults is Diabetes insipidus (DI, 29.6%)[9].

CASE REPORT

A 40-year-old woman admitted to endocrinology outpatient clinic with the symptoms of polyuria, polydipsia and headache. In the initial examinations, there was no feature except for hypo-osmolar urine in routine tests. No hormonal insufficiency was detected in anterior pituitary function tests. Thirst test was compatible with DI without anterior hypophysis failure. Magnetic resonance imaging (MRI) of the hypophysis shows an area of approximately 4x4 mm focal thickening with contrast enhancement at the distal portion of the infundibular stalk (Figure 1). Chest-x-ray was considered as normal. She was followed-up under desmopressin treatment for six months.

She was re-evaluated with the symptoms such as lethargy, diplopia, menstrual irregularity, headache and forgetfulness. Control hypophysis MRI shows heterogeneous, contrast enhanced, 18x15 mm nodular thickness that extends through hypothalamus (Figure 2). Hormonal evaluation reveals that her PRL levels was elevated to 92 ng/mL, cortisol response to ACTH stimulation test was normal with 33 mcg/dL highest value of cortisol response and she had secondary hypogonadism. Serum Angiotensin converting enzyme, 24 hours' urine calcium excretion, complete blood count, erythrocyte sedimentation rate, ferritin, progesterone, alpha-feto protein, beta-HCG levels were within normal limits.

High resolution computed tomography scanning of the lungs shows multiple, irregularly shaped cystic lesions at the posterior and upper lobes of both lungs, posterior reticulonodular opacities and multiple lymph nodes with max 20 mm diameter at the right paratracheal, pre-carinal region (Figure 3). PET-scan for differential diagnosis of lymphoma reveals increased osteoblastic activity at the 6th, 8th and 9th right ribs and in the central part of the left femoral shaft (Figure 4). Bone marrow biopsy was reported as normocellular. Biopsy through thoracoscopic surgery revealed pulmonary Langerhans cell histiocytosis on histopathologic examination with positive CD68, S100 and CD1a staining. No complication was observed during and after the procedure. The thickness progressed to 2.5 cm diameter in control MRI during these diagnostic processes which lasts within 6 months (figure 5).

External radiotherapy and six-cycle of chemotherapy (vinblastine + prednisolone) was planned. In the follow-up, panhypopituitarism was well established and replacement therapy with levothyroxine and prednisolone was added in addition to desmopressin treatment. However, she did not respond clinically to systemic chemotherapy and external radiotherapy and she died due to pneumonia developed several times.

DISCUSSION

LCH is most often multisystemic and pituitary gland involvement is particularly frequent in adults[10]. Anterior pituitary dysfunction is found in nearly 20% of patients with LCH, and is almost always associated with DI[10]. In case of pituitary gland involvement, DI is the most common endocrine abnormality, occurring in 12% of children and 30% of adults with LCH [10]. In one of the largest series which included 274 adult patients with biopsy-proven LCH, DI exist in 81 of 188 (43.1%) patients with multisystemic involvement[9].

In a retrospective study recruited during a 50-year period with 314 LCH patients, 44 patients with pituitary-thalamic axis (HPA) LCH was observed and all of them had DI[11]. Kaltsas *et al*[12] followed-up 12 adult multisystemic LCH patients with HPA involvement for 20 years. While 8 of them developed some anterior pituitary hormonal deficiencies during the follow-up they all had DI which is considered as the earliest hormonal deficiency. Isoo *et al* reported 2 patients who had DI as the first noted abnormality[13]. Asano T *et al*[14] reported a patient in whom DI was the only HPA abnormality. There are several cases presented in the literature that had DI and APD at the time of LCH diagnosis[15,16]. APD occurred almost exclusively with DI in the series of seven cases [17]. Radojkovic *et al*[18] and Tabarin *et al*[19] reported a case that has pituitary LCH and hypothalamic LCH without any sign and symptoms of DI, respectively. In our case, patient diagnosed and treated with DI progressed rapidly as a multisystemic and progressive disease.

Established DI is generally permanent[9,10]. In a study evaluating the efficacy of chemotherapy in childhood LCH, preexisting central DI persisted after chemotherapy in 23 patients, with the exception of two cases of partial central DI in which the disappearance of pituitary stalk thickening was observed on MRI and desmopressin was no longer required (complete remission)[20]. This emphasizes the need for early intervention before DI is fully established. It is hypothesized that the pathogenesis of DI is related to autoantibodies against antidiuretic hormone or scarring/ infiltration of the HPA[21]. In autopsy series, granulomatous tissue has been determined on the pituitary gland and stalk which suggests HPA axis involvement leading to pituitary hormone deficiencies[22]. The progression of hypophyseal mass can also lead to APD as in our case.

APD is almost always seen in patients with multisystem disease. Arico *et al*[9] reported that while all patients with DI had multisystemic disease, 43.1% of multisystemic patients had DI. So, it is logical to extend diagnostic approach in LCH patients with DI.

DI may be the first clinical finding in LCH patients with systemic involvement. Kurtulmus *et al*[23] reported that seven of nine patients had DI initially and the other 2 cases developed DI within 3 years. Kaltsas *et al*[12] published that while, 4 of 12 LCH patients had DI initially, the remaining eight patients developed DI over the next 1–20 years (median: 2 years). These studies prove that DI can be used as a clue for investigation of multisystemic disease.

CONCLUSION

LCH should be taken into consideration in patients diagnosed with DI. DI is almost always the hallmark of HPA involvement and sign of multisystemic involvement. Since there are some cases with isolated DI in LCH, it is usually associated with multisystemic and progressive disease in which early diagnosis and appropriate treatment can affect quality of life and can also prolong life expectancy.

Infiltrative diseases should be considered in the cases presenting with diabetes insipidus. Histiocytosis is a disease with poor prognosis; therefore, early diagnosis is important. It should be kept in mind that lung involvement, one of the typical sites of involvement, cannot be ruled out by x-ray alone.

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Figure 1: Magnetic resonance imaging (MRI) of the hypophysis shows an area of approximately 4x4 mm focal thickening with contrast enhancement at the distal portion of the infundibular stalk

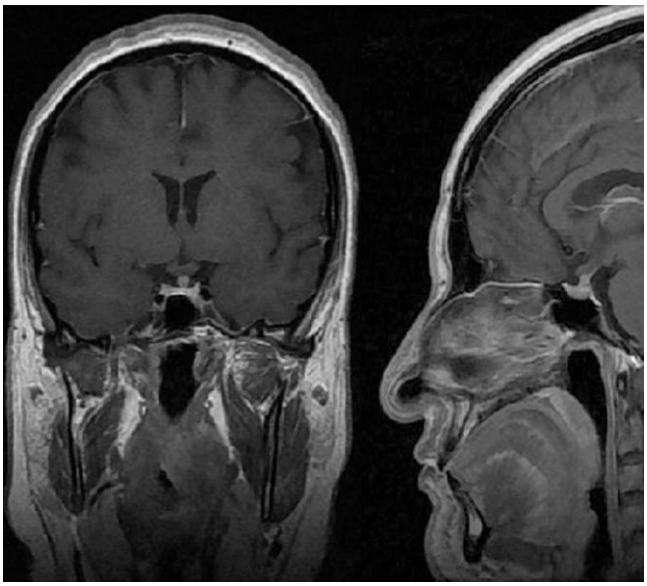

Figure 2: Control hypophysis MRI shows heterogeneous, contrast enhanced, 18x15 mm nodular thickness that extends through hypothalamus

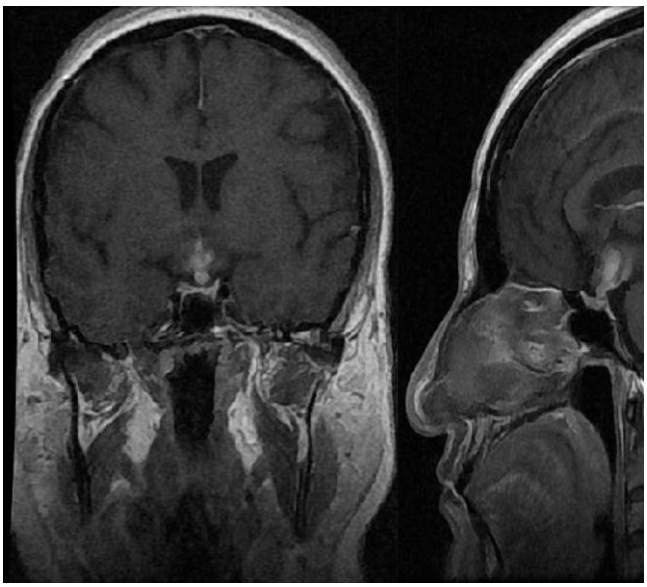

Figure 3: High resolution computed tomography scanning of the lungs shows multiple, irregularly shaped cystic lesions at the posterior and upper lobes of both lungs, posterior reticulonodular opacities and multiple lymph nodes with max 20 mm diameter at the right paratracheal, pre-carinal region

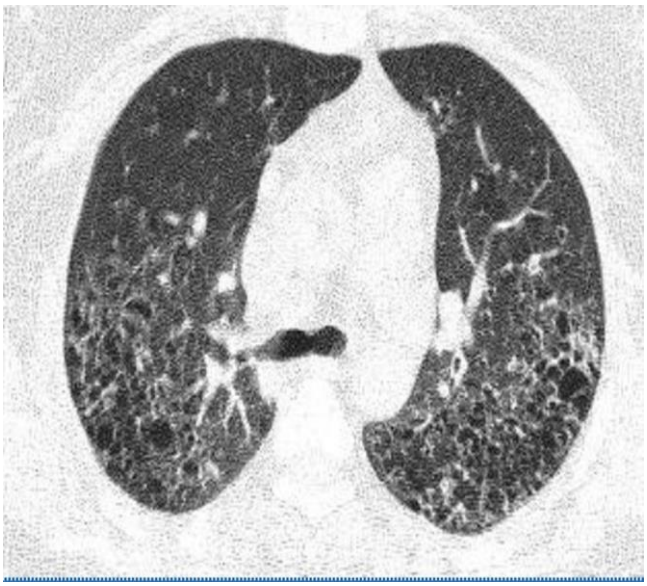

Figure 4: PET-scan for differential diagnosis of lymphoma reveals increased osteoblastic activity at the 6th, 8th and 9th right ribs and in the central part of the left femoral shaft

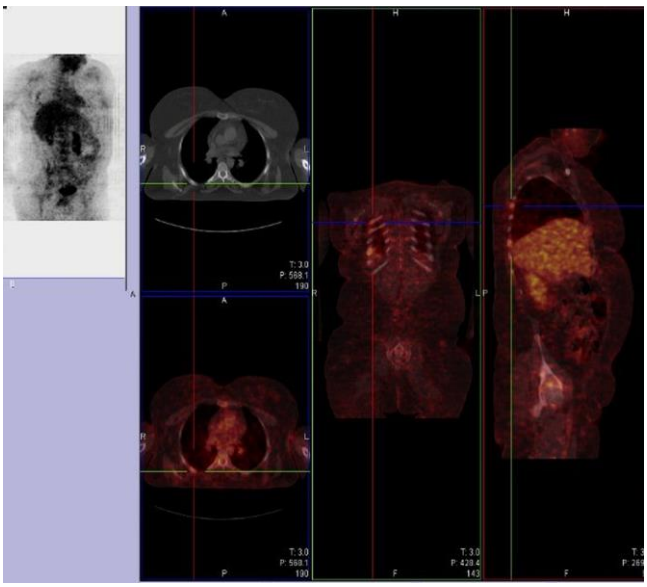

Figure 5: The thickness progressed to 2.5 cm diameter in control MRI during the diagnostic processes which lasts within 6 months