CASE REPORT

Erdheim-Chester syndrome, presenting as hypogonadotropic hypogonadism and diabetes insipidus

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ABSTRACT. Erdheim-Chester syndrome is a rare multisystem disease in which progressive xanthogranulomatous infiltration of several tissues are seen. Knee and leg pain are the most common symptoms and bilateral symmetric sclerosis of metaphyseal region of long bones of the lower extremity is typical. Histologically, it resembles Langerhans cell histiocytosis (LCH). However, it is still a matter of discussion whether Erdheim-Chester syndrome is a distinct entity or a type of LCH. The present case is a 46-yr-old man, that presented with signs and symptoms of diabetes insipidus and hypogonadotropic hypogonadism simultaneously. X-rays and bone scintigraphy showed typical and pathogonomic findings of Erdheim-Chester syndrome. Bone biopsy and immunohistochemical staining strongly support the diagnosis of non- Langerhans cell histiocytosis.

(J. Endocrinol. Invest. *25:* 727-729, 2002)

INTRODUCTION

Diabetes insipidus (DI) and gonadotropin insufficiency are 2 of the clinical manifestations in Erdheim-Chester syndrome (EC). Other components of this rare multisystem syndrome include arthralgia, symmetric sclerosis of long bones, periocular xanthogranuloma, nephrotic syndrome, and pulmonary fibrosis (1, 2).

The purpose of this study is to describe the first case of Erdheim–Chester syndrome diagnosed in Tehran, presenting with central DI, hypogonadotropic hypogonadism in the presence of normal PRL level and intact thyroid and adrenal axes.

CASE DESCRIPTION

On April 1999, a 46-yr-old man was referred to the Endocrine clinic because of polyuria, nocturia and polydypsia. There was also a history of significant weight loss, decreased libido and impotence. Physical examination revealed bilateral xanthelasma, mild gynecomastia, normal size testicles and normal secondary sexual characteristics. Hyposthenuria, mild normocytic normochromic anemia, elevated erythrocite sedimentation rate (ESR) (125 mm/hr), and normoglycemia were detected. Lipid profiles were normal. Water deprivation test proved central DI. Thyroid function tests were normal (T_4=6.1 µg/dl, T_3=183 ng/dl, TSH=0.97 mU/l, RT_3U=28.5%) and PRL level was 14.7 ng/ml. T, FSH and LH levels were 0.3 ng/ml, 0.9 and 4.4 IU/l respectively. Fasting serum F was 18.6 µg/dl and basal GH level was 1.3 ng/ml. We did not perform TRH and GnRH tests. Results of endocrine profile is shown in Table 1. MRI of pituitary and hypothalamic area were reported normal.

Marked symptomatic improvement in respect of polyuria, nocturia and polydypsia occurred after desmopressin (DDAVP) was prescribed. During follow-up the patient developed vague generalized bone pain and easy fatigability. Calcium, phosphorus, ALP, Ig electrophoresis and skull X-ray were normal but ESR remained elevated and mild anemia persisted. Serum iron and total iron binding capacity (TIBC) were normal. Bone-marrow aspiration and biopsy revealed no pathologic changes.

During the following 8 months, progressive weight loss and fatigability continued and bone pain was more pronounced especially in the lower extremities and hips. Bilateral flank pain developed somewhat later. X-rays showed a thickening of diaphyses and metaphyses of both femural bones in distal portions and both proximal parts of tibias, plus

Key words: Diabetes insipidus, Erdheim-Chester syndrome, histiocytosis, hypogonadism, hypothalamus, pituitary.

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Accepted February 26, 2002.

Table 1 - *Results of serum concentrations of various hormones in patient with Erdheim-Chester syndrome.*

Hormone	Serum level
T (ng/ml)	0.3
LH (IU/l)	4.4
FSH (IU/l)	0.9
TSH (mU/l)	0.97
T_4 (µg/dl)	6.1
T_3 (ng/dl)	183
RT_3U (%)	28.5
FT_4I	1.74
IGF-I (µg/l)	308
GH (ng/ml)	1.3
F (µg/dl)	18.6
PRL (ng/ml)	14.7

sclerotic changes of these areas. Bone scintigraphy showed increased uptake in the mentioned areas. Abdominal sonography showed bilateral enlarged kidneys with increased parenchymal thickness and indistinct cortico-medullary junction. Bone biopsy from distal femur showed fibro-collagenous and fatty tissue infiltrated by clusters of foamy histiocytes with central vesicular nucleus and abundant vacuolated cytoplasm, some touton-shaped giant cells, small aggregation of histiocytic like cells with eosinophilic cytoplasm and ovoid-grooved nuclei. Immunohistochemical staining of the bone biopsy showed leukocyte common antigen (LCA) in most mononuclear and histiocytoid cells. CD.15 was positive in 10% and C.D.3 in 30% of mononuclear cells. S100 was negative in the histiocytic cells. Unfortunately CD 68 was not available. Pulmonary function tests and echocardiography were both normal. The patient developed severe upper gastrointestinal bleeding on prednisolone and inedomethacin, so they were discontinued. Azathioprine 5 mg daily and vinblastin every 2 weeks, were started. The patient has received 20 courses of vinblastin ever since and there is marked symptomatic improvement of his bone pain and disability. He still needs DDAVP and T enanthate injections.

DISCUSSION

Erdheim-Chester syndrome is a rare multisystem disease in which a progressive xanthogranulomatous infiltration of several tissues is seen (1, 2). Sixty-two patients have been reported in the literature until today. Histologically, it resembles Langerhans cell histiocytosis (LCH), and it is still a matter of discussion whether EC syndrome is a distinct entity or a type of LCH (3). Langerhans cells stain with S-100 protein stain, but non-Langerhans cell histiocytes do not stain for S-100 protein (4). Some studies suggest that EC syndrome is a monoclonal lesion consistent with neoplastic disorder (5).

Knee and leg pain are the most common symptoms and bilateral, symmetric sclerosis of metaphyseal region of long bones of the lower extremity is typical (1, 6, 7). Other clinical manifestations reported in the literature include bilateral periocular xanthogranuloma (8), nephrotic syndrome (9), progressive dyspnea due to extensive pulmonary fibrosis (10), DI (1, 11), and gonadotropin insufficiency (11). Clinical presentations and progression are quite variable in the reported cases in the literature, ranging from isolated organ involvement to a widely disseminated disorder.

Central DI is characterized by polyuria and polydypsia due to a deficiency of arginine vasopressin. Differential diagnosis of DI is large, and many patients with a diagnosis of DI and a normal hypothalamic-pituitary CT or MRI are diagnosed as having idiopathic DI (4). In many normal subjects, the posterior pituitary is hyperdense on saggital T_1-weighted MRI. The absence of this finding serves as a non-specific indicator of central DI (12, 13). The finding of a thickened infundibulum or pituitary stalk, suggests the presence of an infiltrative disease (13, 14). However, the pituitary may remain hyperintense in 6% and pituitary stalk may be normal in 46% of the patients with central DI on initial MRI (13). In patients with Langerhans-cell histiocytosis and DI the risk of anterior pituitary hormone abnormality is independent of the size of the pituitary stalk even though the size of anterior pituitary on last MRI study remains normal in 75% (13). However, loss of pituitary hyperintensity and thickening of the stalk may be shown during follow-up MRI.

The present case presented with simultaneous signs and symptoms of DI and hypogonadotropic hypogonadism; some of the common etiologies of central DI, such as head injury, brain surgery or brain tumor can be readily excluded in our patient. However, tuberculosis, lymphoma metastatic cancer, Wegener granulomatosis and histiocytosis can also cause central DI (15). The lack of lung involvement, the absence of lymphadenopathy, the unremarkable bone marrow and normal urine sediment argue against any of these processes in this patient. During follow-up, progressive weight loss and disabling bone pain developed. X-rays and bone scintigraphy showed typical and pathogno-

nomic findings of EC syndrome including bilateral symmetrical thickening and sclerosis of methaphysial regions of long bones of lower extremities. Bone biopsy and immunohistochemical staining strongly support the diagnosis of non-Langerhans cell histiocytosis (S-100 - negative histiocytic cells). In conclusion, the clinical presentation, characteristic radiological and histological findings, and the evidence against other disorders led us to the diagnosis of Erdheim-Chester syndrome in this patient.

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