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Erdheim-chester disease: Case report with testes involvement and review of literature

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Introduction

Histiocytosis is a group of rare diseases characterized by abnormal accumulation of macrophages, dendritic cells or monocyte-derived cells in different tissues causing various clinical findings.[1] ECD is a rare, non-familial, non-Langerhans cell histiocytosis of unknown etiology with characteristic radiological and histological features, which was firstly described by Jakob Erdheim and William Chester in 1930.[2] There have been up to 700 cases reported to date. Recently ECD has been recognised as an inflammatory myeloid neoplasia associated with oncogenic mutations of kinase signaling pathway including BRAF, NRAS, KRAS, MAP2K1, and PIK3CA in histiocytes.[3] The recent studies have demonstrated BRAFV600E mutations in more than 50% cases. It is characterized by excessive proliferation of CD68-positive and CD1a-negative foamy histiocytes and lipid-laden macrophages in different organs and tissues. The most relevant characteristics of ECD are described in Table 1. The prognosis depends on the extent and distribution of the disease, ranging from asymptomatic bone lesions to life-threatening forms.[4] Respiratory distress, extensive pulmonary fibrosis and cardiac failure are the most common cause of death.[4] We described here the case of a 53 year old caucasian man who presented with hypogonadism and diabetes insipidus, having a rare organ involvement of testes (see Fig. 1).

Case report

A 53 year old man presented to our outpatients clinic with diabetes insipidus and hypogonadism with 3 months history of progressive polyuria, polydipsia, loss of lipido and headache. On physical examination, there were bilateral gynecomastia and very hard testis. Cardiovascular and pulmonary examinations were normal. His vital signs were normal. Laboratory investigation pointed to hypergonadotropic hypogonadism, subclinical hypothyroidism along with normal results of lactate dehydrogenase, alpha fetoprotein and human chorionic gonadotrophin. Scrotal magnetic resonance imaging showed fibrosis, pituitary magnetic resonance imaging showed a 0.6 cm thickened pituitary stalk, and loss of signal intensity in neurohypophysis. Neurosarcoidosis and IgG4 related diseases are important diseases in the differential diagnosis. These disease were excluded as serum IgG4 and ACE levels were normal. All laboratory results of our patient are shown in Table 2. He showed no sign of fever. The patient was diagnosed with central diabetes insipidus and was treated with nasal spray of desmopressin once daily which normalized serum sodium and urinary density. TSH was elevated and thyroid antibodies were positive. Levothyroxine replacement therapy was begun for the chronic lymphocytic thyroiditis. Computed tomography scan of the abdomen showed bilateral parenchymal heterogenity, bilateral hydronephrosis, soft tissue infiltration surrounding the abdominal aorta and both kidneys.

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Table 1
Characteristics of Erdheim-Chester disease.

Definition	Multisystemic non-Langerhans histiocytosis of unknown origin
Population	Middle-aged patients, slight male predominance, the median age of diagnosis is 55 years (in fifth decade) with few cases reported in children
Pathophysiology/ Histology	Shows polyclonal proliferation of histiocytes associated with abnormal Th1 immune response. The recent studies have suggested a clonal origin by demonstrating BRAFV600E mutations in more than 50% cases. Xanthogranulomatosis or polymorphic granuloma with foamy/lipid laden histiocytes with immunoreactivity to CD68, but negative for CD1a
Most common findings	Any tissue or organ can be affected, bone is most frequently affected (>90%), at least one soft tissue component is seen in more than 50% of patients, symtomatic or asymtomatic, bilateral, symmetric cortical osteosclerosis of the diaphyseal and metaphyseal regions of the long bones Retroperitoneal involvement, assosciated with renal failure and/or renovascular hypertension Peri-aortic infiltration (coated aorta) Hairy kidneys Central nervous system involvement (diabetes insispitus, panhypopituitarism, headache, ataxia) Orbital, exophthalmos, diplopia, visual impairment Pulmonary involvement Pericardial involvement cardiac tamponade, cardiac failure, myocardial infarction Skin, xanthelasma, xanthoma
Diagnostic criteria	Foamy histiocyte infiltration and fibrosis or xanthogranulomatosis, with positive CD68 and negative CD1a

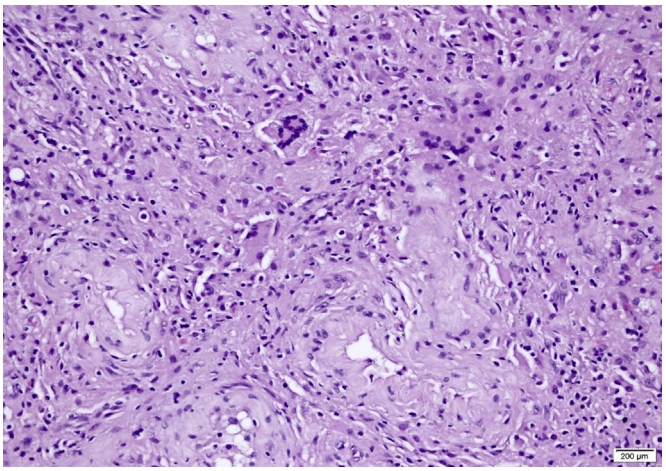

Fig. 1. Testis biopsy showed xanthogranulomatous infiltrate, mainly composed by foamy histiocytes accompanied by fibrosis with multinuclear touton-like giant cell.

Positron emission tomography revealed increased uptake in the distal ends of the bilateral femurs and tibias, on the perivascular region of the thoracic and abdominal aorta, bilateral testes, and perirenal region. Cerebrospinal fluid was obtained to determine the etiology of the stalk infiltration and the result was unremarkable. The testis was recommended as the optimal biopsy site. A biopsy was taken from the testis tissue. A diffuse infiltration by epitheloid cells with abundant foamy cytoplasm, multinucleated cells with the appearance of touton-type giant cells and patchy lymphoid infiltrate were found. The testicular tubules were atrophied and replaced by hyaline and collagenous material. On immunohistochemical staining, the cells were positive for CD68, and negative for CD1a. These findings supported the diagnosis of ECD. BRAF mutation was not detected in heavily infiltrated testis tissue. The treatment started with interferon-alfa injections subcutaneously at the doses of 3×10^6 units 3 times weekly.

Discussion

ECD may be asymptomatic or may present as a severe multisystemic disease with life-threatening manifestations. Now, ECD is considered as a clonal hematopoietic disorder with MAPK signaling pathway genetic alteration. The skeletal involvement is the most common initial presentation.[4] In our case there was an osteosclerotic lesion in the left distal femoral region and positron emission tomography images showed increased symmetric FDG

Table 2
Laboratory tests before and after the interferon alpha treatment.

	03.03.2017 (before)	27.05.2017 (after 3 months)	14.09.2017 (after 6 months)
FSH mIU/mL (1.5–12.4)	**12.8**		
LH mIU/mL (1.7–8.6)	**20.7**		
Total Testesteron ng/dL (280–800)	**48.9**	**55.9**	**65.4**
Free Testesteron pg/mL (7–22.7)	**2.14**		
Prolaktin ng/mL (4.0–15.2)	**30.7**		
Sodium mg/dL	**152**	139	
Creatinine mg/dL	**1.5**	**1.1**	
Urinary Density	**1002**	1008	
İdrar Osmolalitesi mosm/kg	**130**	410	
ACTH pg/mL	42		
Cortisol ug/dL	**11**	13.7	
Short ACTH stimulation test cortisol respond ug/dL	8-25-26		
TSH ulU/mL (0.3–4.2)	**6.47**	2.45	
FT4 ng/dL (0.8–1.7)	1.01	1.25	**0.61**
FT3 pg/mL	2.6		
Anti TPO IU/mL (<35)	**305**		
Anti TG IU/mL (<115)	**653**		
IGF-1 µg/L (55–248)	61.6	79.4	
Sedimentation mm/h (0–18)	**76**	**40**	**26**
CRP mg/L (<5)	**48.7**	**6.8**	

uptake in the distal ends of the femurs and the tibias which may be associated with skeletal involvement of the ECD. However the patient didn't have any bone pain. Approximately half of the cases of ECD present with extraskeletal manifestations. The most common cardiovascular manifestation is periaortic fibrosis that appears as a coated aorta.[4] In our patient, there was dense infiltration surrounding the abdominal aorta. Retroperitoneal involvement is also a common feature of ECD.[4] In our case, there was hairy kidney appearance due to symmetric and bilateral infiltration of the perirenal space and creatinin level was elevated and hydronephrosis was present. These were highly suggestive of the diagnosis. Testis infiltration is an unusual localization of ECD. A review of the literature revealed six cases of testis involvement. Two of them were reported in a series of 42 patients with ECD.[5] Our case was with testis and pituitary involvement. He was diagnosed with only testis biopsy. ECD can also involve the central nervous system. Our patient was initially presented with diabetes insipidus with thickening of the pituitary stalk, but we didn't obtain tissue specimen from the pituitary gland.

Because of the rarity of this disease, there is no consensus on the standard treatment for ECD.[3] Currently, IFN-alpha is preferred for the treatment and associated with improved survival.[4] Treatment should be continued indefinitely if tolerated. Treatment for ECD is now moving toward targeted therapy mostly due to the high percentage of proven BRAF V600E-positive cases. In our case, the BRAF mutation wasn't detected in heavily infiltrated testis tissue. In the recent report of Ozkaya et al. they also didn't find BRAF mutation however they detected MAP2K1 mutation in the testis of one patient.[5] IFN-alpha was started to our patient. CRP and ESR levels decreased but testesterone level didn't change.

Conclusion

The wide clinical spectrum and poor knowledge about this rare disease make its diagnosis diffucult, therefore clinical suspicion is an important factor in its diagnosis. Due to raising awareness of ECD, the number of new diagnoses is increasing dramatically. It is necessary to perform biopsies and immunohistochemical staining for a correct diagnosis. In BRAF mutation-harboring forms of ECD vemurafenib therapy can be used. Further research on large patient groups with long-term follow-up is needed to better understand and treat this disease.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eucr.2018.02.007.

Statement of ethics

Written consent of the patient was obtained for publication of this case report.

Declatarion of conflicting interests

The authors declared that they have no competing interests.

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