

Erdheim-Chester disease, A fatal xanthelasma-like lesion

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ABSTRACT:

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Erdheim-Chester disease is a rare, non-Langerhans histiocytosis characterized by chronic histiocytic infiltration of multiple organs. There are fewer than five hundred cases reported. Our case presented with headache, diplopia and knee pain. He had a year of progressively periorbital xanthelasma-like lesion as a presenting dermatologic manifestation.

Key words: Erdheim-Chester disease, histiocytosis, xanthelasma-like lesion

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Our case

A 52-year-old Thai man had 1-year history of asymptomatic yellowish plaques on bilateral periorbital regions. His both eyes progressively became exophthalmos which was more prominent on the right side. One month prior to the admission, he had headache, diplopia and knee pain. Computerized tomography (CT) of brain found several intracranial masses causing proptosis of both eyes. Retroperitoneal soft tissue masses were also observed from CT abdomen. Roentgenographic examination of both knees showed sclerotic lesions on proximal tibia. Physical examination revealed bilateral nontender yellowish plaques on both periorbital regions (Figure 1,2). Other physical examination including oral cavity were normal. A 4-mm punch biopsy taken from right lower eyelid revealed diffuse infiltration in the whole dermis which was composed of predominantly foamy histiocytes with clear cell boundaries and numerous Touton-type giant histiocytes. (Figure 3). Immunohistochemistry staining demonstrated positive CD68 and CD163, whereas CD1a, S100 and Langerin were negative. (Figure 4). His genetic testing showed a BRAF codon 600 mutation. A retroperitoneum biopsy also revealed atypical histiocytic proliferation. From clinical and histopathological features, the patient was diagnosed with Erdheim-Chester disease.



Figure 1 and, 2 Bilateral periorbital infiltrative yellowish plaques with chemosis on the right eye.

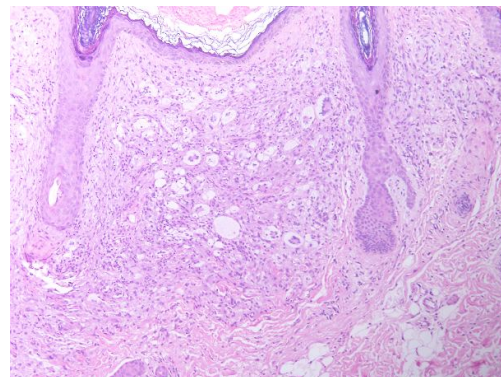


Figure 3 Diffuse infiltration in whole dermis with predominantly foamy histiocytes and Touton-type giant histiocytes. (Hematoxylin-eosin staining, x10)

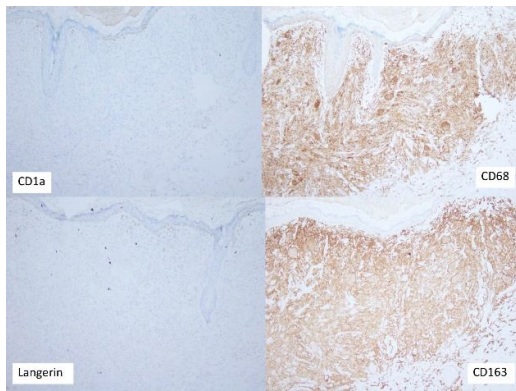


Figure 4 Immunohistochemistry staining demonstrated positive staining of CD68 and CD163 of tumor cells, whereas CD1a, Langerin were negative.

Discussion

Erdheim-Chester disease (ECD) is a rare, non-Langerhans cell histiocytosis originally described as "Lipid Granulomatosis" in 1930 by Jakob Erdheim and William Chester. The clinical manifestations are caused by the infiltration of lipid-laden histiocytes with foamy or eosinophilic cytoplasm in various organs including skin, lungs, bones, kidneys, retro-orbital and periorbital tissues, pituitary-hypothalamic axis, heart, great vessels, breasts, skeletal muscles, central nervous system, sinonasal mucosa and retroperitoneum¹. Individuals affected by this disease are typically adults between their fifth and seventh decades of life with slightly male predominance². The etiology of the disease is unknown and considered to be non-genetic and not associated with an infectious agent³. Recent detection of a

mutation in the BRAFV600E proto-oncogene in most of patients suggests clonal nature of the disease¹.

Clinical manifestations of ECD are variable including bone pain, diabetes insipidus, neurological and constitutional symptoms, although retroperitoneal, cutaneous, cardiovascular and pulmonary involvements have also been reported¹. The most common presenting symptom of ECD is bone pain. Skeletal involvement occurs in upto 95%. Bilateral cortical sclerosis involving the diaphyseal regions, are considered pathognomonic. Other common physical signs are bilateral exophthalmos due to histiocytic infiltration producing a xanthogranulomatous tissue deposit, diabetes insipidus from pituitary-hypothalamic axis involvement, and fever⁴. Cutaneous involvement is seen around 27% of patients, most commonly presented with xanthoma-like papules and periorbital xanthelasma-like skin lesions². Although periorbital lesion in ECD is quite similar to xanthelasma palpebrarum, the lesions in ECD tend to be more diffuse and also extending to other areas of the face. Moreover, xanthelasma-like lesions can be observed in other subtypes of adult orbital xanthogranulomatous disease that includes adult-onset xanthogranuloma, adult-onset asthma and periocular xanthogranuloma, necrobiotic xanthogranuloma and Erdheim-Chester disease. The orbital lesions of the first 3

diseases, tends to involve the anterior orbit including the eyelids, whereas intraconal and diffuse lesions are also affected in ECD. The presence of systemic involvement is helpful for the differential diagnosis of these diseases⁵.

The diagnosis of ECD is based on clinical suspicion and pathologic findings. A biopsy is usually obtained from bone, skin, retro-orbital or retroperitoneal soft tissue. The pathology consists of accumulation of foamy or clean histiocytes, Touton giant cells, variable amounts of fibrosis and lymphoplasmacytic infiltration arranged in lymphangitis pattern. Immunohistochemical staining shows histiocytes that express three common macrophage surface markers, namely CD14, CD68 and CD163. In addition, the cells express factor XIIIa (a tissue transglutaminase) and fascin (an actin-binding protein), both of which are typical of interstitial and interdigitating dendritic cells. These histiocytes generally lack all markers of Langerhans cells such as S100, CD1a, and langerin⁶.

Various treatments have been administered to ECD patients. Interferon alpha provides the best management strategy, with sustainable stabilization of the disease⁷. Another promising pharmaceutical agent is the BRAF inhibitor vemurafenib, which recently exhibited dramatic efficacy in the treatment of three ECD patients whose histiocytes were positive for the V600E BRAF mutation⁸.

The prognosis of ECD has been reported as poor, with 43% of patients alive after average follow-up of 32 months⁴. Recent reports of survival of patients uniformly treated with interferon therapy described an overall 5-year survival of 68%⁷. The response to treatment was highest in the cutaneous foci of the disease, followed by CNS, pituitary, lungs and heart⁹.

Our patient has been diagnosed as Erdheim-Chester disease. He had been treated with pegylated interferon alpha 180 micrograms weekly for three weeks. Unfortunately, he had upper urinary tract infection and died from septic shock.

In summary, we report a case of Erdheim-Chester disease who presented with xanthelasma-like lesion. Since this rare disease has high mortality rate, poor prognosis and usually undiagnosed at the beginning, the presence of xanthelasma-like lesion with normolipid and bone pain might contribute to an increased awareness of the disease, leading to the early diagnosis and management.

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