

Typical Presentation of Erdheim-Chester Disease: A Case Report

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Abstract

Erdheim-Chester disease (ECD) is a rare type of non-Langerhans cell histiocytosis. The clinical presentation may range from an indolent focal disease to a life threatening organ failure. ECD may virtually affect any organ system, most commonly skeleton, kidneys, cardiovascular system, central nervous system. The typical histological findings consist in xanthogranulomatous or xanthomatous infiltration by foamy histiocytes, with immunohistochemistry positive for CD68 and CD163 and negative for CD1a.

We present the case of a patient with a history of central insipid diabetes and asbestos exposure who was hospitalized for dyspnoea associated with pleural effusion, with radiological findings of a typical multi-organ involvement (hairy kidneys, coated aorta, Symmetrical osteosclerosis of the middle-distal third of long bones, pericardial and pleural thickening) with the histological findings confirming the diagnosis of ECD.

Keywords: Erdheim-Chester; Histiocytosis; Pleural Thickening; Foamy Histiocytes

Introduction

Erdheim-Chester disease (ECD) is a rare type of non-Langerhans cell histiocytosis. Up to now, about 1500 cases have been reported worldwide [1]. The etiology of the disease is unknown. It mainly affects males between 40 and 60 years of age. It is assumed that ECD originates from a deregulation of the Th1 response, given the low levels of IL-4 and high INF- α , IL-7 and IL-12 [2]. Recently, BRAF^{V600E} mutation has been observed in more than a half of ECD patients, with new implications for therapeutic options [3].

The clinical presentation is variable as it may range from an indolent focal disease to a life-threatening organ failure. [4] ECD may virtually affect any organ system. The most frequently involved site is the skeleton (96% of ECD patients), often associated with bone pain. A pathognomonic finding is bilateral cortical sclerosis involving the diaphyseal regions, typically observed on radiographs, associated with an abnormally strong labeling on ^{99m}Tc bone scintigraphy. Cardiovascular involvement is frequent too (75% of cases), mostly presenting as pericardial infiltration, periaortic sheathing (“coated aorta”) and myocardial infiltration [5]. Central nervous system involvement appears in 51% of ECD cases, with central diabetes insipidus being the most common finding [6]. Pulmonary involvement (43% of cases) can lead to an interstitial lung disease or pleural effusion. ECD-associated involvement of the retroperitoneal space is reported in 68% of the patients, most of which asymptomatic, and infiltration of the perirenal fat produces a typical “hairy kidneys” appearance on CT scan images [7].

Histologically, xanthogranulomatous or xanthomatous infiltration of the tissue by foamy histiocytes can be detected, with immunohistochemistry (IHC) positive for CD68 and CD163 and negative for CD1a [8].

The prognosis of the disease is poor. At present, the treatment of first choice is interferon alpha [9] (IFN- α), with an average 5-year survival of 68%. Infliximab was successfully used in patients with cardiovascular involvement [10] and, in cases of BRAF^{V600E} mutation, vemurafenib can be used with positive effects on retroperitoneal fibrosis [11].

Case Presentation

We present the case of a 56-year-old man, with working exposure to asbestos for about 30 years. He was affected by

hypertension and central insipid diabetes, known since 2012, on therapy with desmopressin.

During 2018 he was hospitalized in the Pneumology Department for left pleural effusion treated with diagnostic-therapeutic thoracoscopy. Histological examination of the pleural samples highlighted only inflammatory and reactive aspects.

In November 2019 he was hospitalized in the Thoracic Surgery department for bilateral pleural thickening, major on the left, with elevated glucose metabolism assessed by PET-FDG. During hospitalization multiple left pleural biopsies were performed, documenting a chronic pachypleuritis, in absence of neoplastic cells. Immunohistochemical analysis was positive for calretinin, CK5-6, WT1, EMA, BerEP4, CEAP and HBME1.

In July 2020 he was admitted to our department of Internal Medicine for the recent onset of dyspnea after habitual physical activity (climbing a flight of stairs) and weight loss of about 20 kg in the previous 4 months.

At the entrance vital signs were normal and he was afebrile. Physical examination was unremarkable, except for reduced vesicular breath sounds on the left and the presence of periorbital xanthelasma.

Blood exams showed neutrophilic leukocytosis (WBC $10.51 \times 10^9/L$, normal value $<10.0 \times 10^9/L$, neutrophils 78.0%) mild normocytic anemia (Hb 12.9 g/dL, normal value 13.5- 17.2 g/dL; MCV 77 fL, normal value 80-99 fL), high platelets ($522 \times 10^9/L$, normal value $160-370 \times 10^9/L$), RCP 7.64 mg/dL (normal value < 0.50 mg/dL), low total proteins 6.3 g/dL (normal value 6.6-8.3 g/dL).

ECG showed sinus rhythm with QTc elongation (492 ms, normal value 300-440 ms).

Pharyngo-tonsillar swab for SARS-CoV-2 infection was negative.

Chest X-ray showed interstitial thickening of lung, ilio-perilary congestion and bilateral pleural effusion major on the left. The findings were investigated with contrast enhanced CT of chest and abdomen, which documented the presence of solid tissue infiltrating both pleurae, mediastinal fatty tissue and pericardium, perirenal fascia and perihepatic area, and surrounding the aortic arch, the proximal tract of the epiaortic vessels.



Figure 1: Venous contrast enhanced phase CT scan showing the periaortic sheathing (coated aorta)



Figure 2: Venous contrast enhanced phase CT scan showing the perirenal fat infiltration (hairy kidneys)

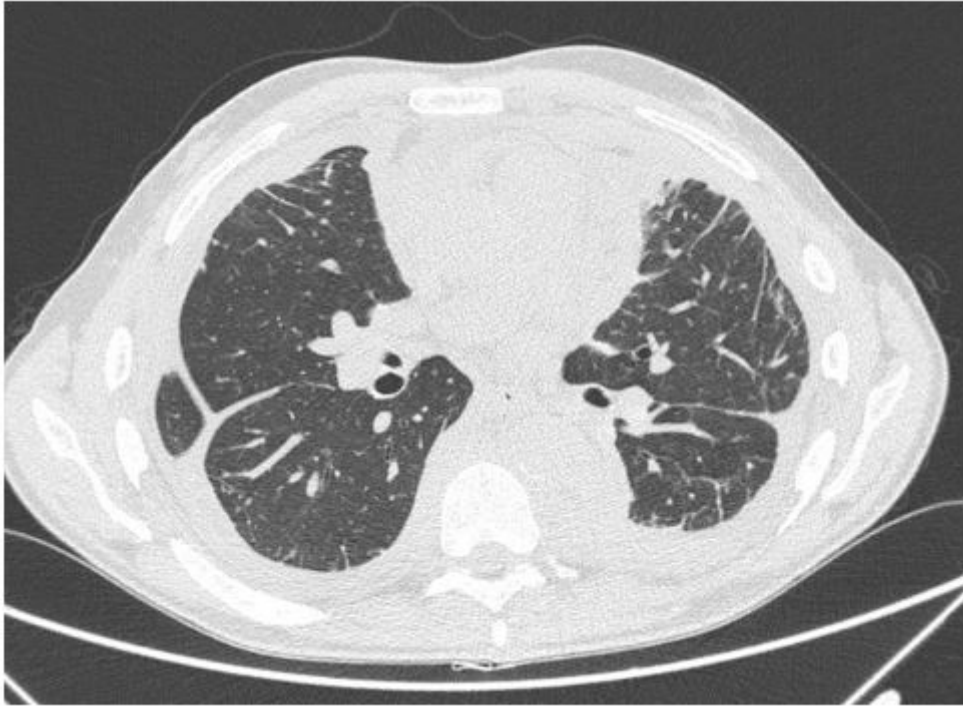


Figure 3: Thoracic HRCT scan showing lung involvement and the pleural sheath

We excluded IgG4-related disease, due to the normal levels of IgG4 on serum and on old histological samples. On suspicion of a multisystem disease, such as Erdheim-Chester dis-

ease, we performed bilateral thigh and leg X-rays, reporting symmetrical osteosclerosis of the middle-distal third of both femurs and the middle-distal third of both tibiae.



Figure 4: X-rays showing symmetrical cortical osteosclerosis of long bones

Further haematochemical tests were performed, documenting increased IL-6 (31.3 pg/mL, normal value < 6.4 pg/mL), slight increase in CD4+/CD8+ ratio (3.73, normal value 1.00-2.70). Blood levels of TNF alpha, IL-8, IL 12p70, IL-1 Beta, IL-10 were normal.

Finally, percutaneous CT-guided needle biopsy of the perirenal tissue was performed. Histological examination of the

sample and IHC documented the presence of fibrous tissue with infiltration of foamy histiocytes containing lipids, with weak positive staining for S-100 and reactive for CD68, consistent with the diagnosis of ECD. IHC showed BRAF cytoplasm reactivity of uncertain significance.

Molecular analysis showed BRAF p.Val600Glu (V600E) genetic variant.

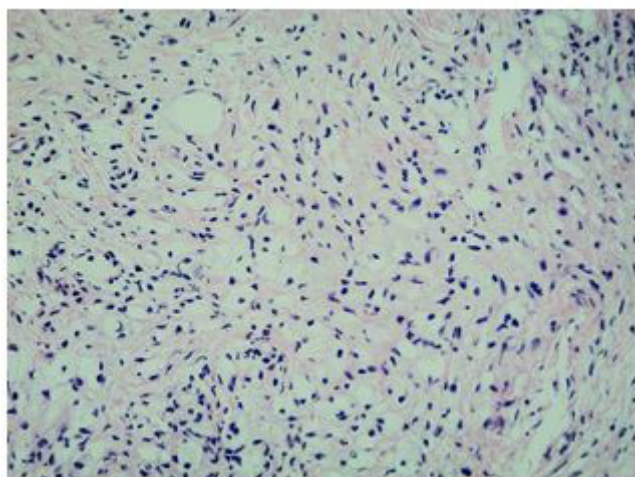


Figure 5: Biopsy specimen of perirenal adipose tissue stained with hematoxylin and eosin

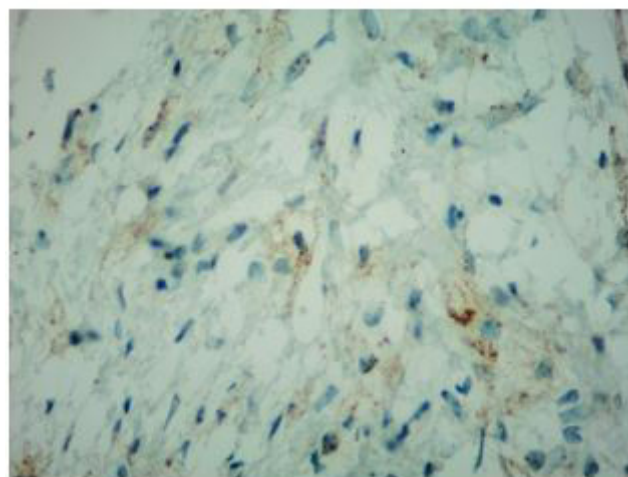


Figure 6: Immunohistochemical examination of a biopsy specimen of perirenal adipose tissue showing rare S100 positive cells

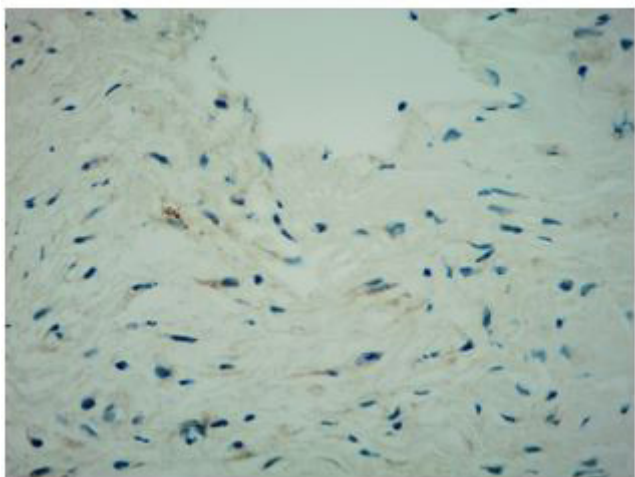


Figure 7: Immunohistochemical examination of perirenal adipose tissue biopsy specimen showing reactive BRAF ^{V600E} with fine cytoplasmic granules

In order to evaluate intracranial and orbital involvement, gadolinium MRI of the brain was performed, showing a short pituitary peduncle. The neurohypophysis was not visible and there was no sign of orbital involvement.

Cardiac and mediastinal involvement was investigated by cardiac MRI, which showed elevated T1 myocardial values, suggestive for infiltrative/storage disease. A solid tissue diffusely

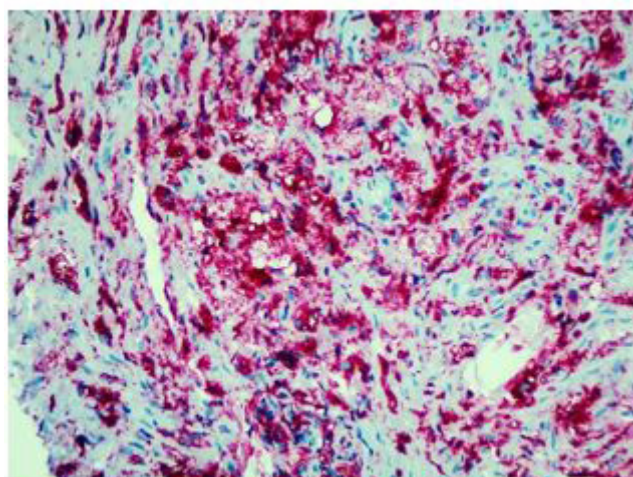


Figure 8: Immunohistochemical examination on a biopsy specimen of perirenal adipose tissue showing positivity for CD68

infiltrated pericardium, especially in the right posterolateral position, and the atrioventricular right sulcus.

Also a bone scintigraphy was performed, revealing hyperfixation in all long bones (femours, tibias, radius, clavículas), corresponding to the osteostructural osteoaddensing alterations described at X-rays.

The patient was referred to a Rare Diseases Centre (San Raffaele Hospital in Milan) and, due to the presence of BRAF^{V600E} genetic variant, a therapy with Vemurafenib and Anakinra was started, with rapid improvement of dyspnoea.

Discussion

Erdheim-Chester disease is a rare disease. The clinical presentation may range from an indolent focal disease to a life threatening organ failure and it may virtually affect any organ system, therefore the diagnosis is very difficult.

In our patient occupational exposure to asbestos was an important confounding factor. Pleural lesions have guided the main clinical suspicions for years, leading primarily to exclude the diagnosis of mesothelioma.

In fact, the imaging examinations performed during the last hospitalization showed a multiorgan involvement, including coated aorta, hairy kidney, long bone thickening lesions, that lead us to consider a systemic disease. All that findings were consistent with the diagnosis of ECD, which was further corroborated by the histological finding of foamy histiocytes containing lipids reactive for CD68.

Conclusion

ECD is a rare disease with multi-organ involvement. The aim of this report is to raise awareness of this clinical condition, in order to recognize it, achieve an early diagnosis and start a targeted treatment, improving patients' quality of life.

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