Erdheim-Chester disease: a multisystem disease case illustration with rare manifestations and treatment challenges.

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Abstract

Erdheim-Chester disease is a rare multisystemic disease. A 50-year-old woman, presented with a recurrent pain and swelling of the left knee. Bone scintigraphy showed increased tracer uptake of peripheral skeleton. The computed tomography showed tissular infiltration in the retroperitoneum, around the vessels. Immunohistochemistry showed CD68 (+) and CD1a (-).

Title page

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Introduction:

Erdheim-Chester disease (ECD) is a rare multisystemic disease of undetermined origin, clinically characterized by multi organ involvement, affecting primarily middle-aged adults (1) preponderantly males. Histologically ECD is characterized by the presence of foamy-macrophages in a fibrotic inflammatory stroma. Histiocytes test positive for CD 68 and CD163 but negative for CD1a. Molecular testing for BRAF and MAPK-ERK pathway mutations has opened the doors for targeted therapies.

The clinical spectrum of ECD is wide and includes frequently bone lesions, cardiovascular manifestations, retroperitoneum and kidney involvement, endocrine manifestations, central nervous system, respiratory involvement and dermatologic lesions. Genital organs and digestif tract involvement are rare (2).

We herein report the case of a patient illustrating the muti-organ manifestations of ECD with rare manifestations such as breast and liver lesions.

Case report:

A 50-year-old woman with a history of hypothyroidism, presented with a recurrent pain and swelling of the left knee and the right breast. Physical examination found high blood pressure, normal cardiac auscultation and a normal EKG. Pulmonary auscultation found fine crackles in both lower lobes with no history of cough or breathlessness. The abdomen examination found hepatomegaly. No enlarged peripheral lymph nodes neither thyroid nodules were found. She had xanthelasma of the right upper eyelid, an erythematous plaque of the inferior medial quadrant of the left breast with no nodules or mass.

Standard radiography of the knee showed an osteolytic and heterogenous lesion of the proximal tibia and fibula metaphyses. Bone scintigraphy showed increased tracer uptake of the humeri diaphysis, both iliac bones, distal femora extremity and tibias (figure 1a,1b,1c). Echography of thyroid glands showed pseudo-nodular heterogenous lesions. The computed tomography (CT) showed a small pericardial effusion and a moderate encapsulated right pleural thickening and effusion associated to a bilateral and diffuse septal thickening and a micronodule in the apical segment of the upper right pulmonary lobe. It also showed an infiltrative process of subcutaneous tissues of the breasts, tissular infiltration in the retroperitoneum, tissue thickening around the aorta from its thoracic portion to the sub-renal portion along with tissue infiltration of the inferior vena cava and the kidney pedicules and peri-renal fascia thickening and ureteral dilation. The CT also showed hepatomegaly (Figure 2a,2b,2c). Mammography was normal. Pulmonary function tests found a mixed pattern (forced vital capacity: 47%) with reversible obstruction.

During the disease course the patient had an ischemic stroke in the territory of the middle cerebral artery confirmed by magnetic resonance imaging (MRI) that showed no other abnormalities, the cardiac echography showed a small pericardial effusion and no atrioventricular mass. Our patient had no central nervous system neither ocular involvement as demonstrated by cerebral MRI imaging.

The biopsy of the retroperitoneum tissue thickening showed fibrosis with inflammatory infiltrate including foamy macrophages along with Touton giant cells. Pleural biopsy found fibrotic pachypleuritis. Immunohistochemistry was positive for CD68 and negative for CD1a and PS100 (Figure 3a, 3b, 3c).

The clinical presentation and the histopathologic aspects corroborated the diagnosis of ECD.

Because of the multi-organ involvement, the patient received a treatment regimen of prednisone at the dose of 1mg/kg/day with infusion of infliximab 5m/kg/ 6 weeks associated to 15 mg per week of methotrexate.

The follow up was mainly by clinical assessment and a PET-CT is intended within 6 months of treatment.

Discussion:

First described in 1930 by William Chester and Jakob Erdheim (3), ECD is now considered a clonal hematopoietic disorder (4). It makes part of the "L" group along with Langerhans histiocytosis according to the Histiocyte Society classification (5), both sharing genetic mutations and they may even coexist (6). The molecular alterations underpinning the disease such as recurrent mutations activating kinases of the mitogen-activated protein kinase (MAPK) are now more understood (7).

Histological diagnosis requires the presence of xanthogranulomatous lesions typically characterized by foamy histiocytes in a background of inflammatory stroma with an immunochemical characteristic of CD68 positivity and CD1a negativity. The multisystem infiltrate makes variable histological aspects depending on the organ (4).

The clinical presentation of ERD is variable. Bone lesions are the most common affecting up to 95% of patients (1). Usually symptomatic of bone pain most frequently in the knees. It can reveal the disease, such is the case of our patient. Meta-diaphyseal osteosclerosis around the knees is pathognomonic (8). Plain radiographs may show cortical osteosclerotic lesions but the Technetium-99 bone scintigraphy is more sensitive revealing the increased radiotracer uptake in the distal metaphysis and diaphysis of femur, tibia and fibula. Pelvic bones involvement like in the case of our patient is less common as well as axial skeleton, skull, and ribs lesions.

Retroperitoneal fibrosis can be found in one third of ECD patients (9) with typically a perirenal infiltrate described as " hairy kidney", including encasement of renal pedicules and ureter that can, sometimes, be complicated of high blood pressure, hydronephrosis and renal failure. Retroperitoneal fibrosis is a common site of biopsy. Histologically it is characterized by abundant fibrosis with inflammatory infiltrate often mimicking IgG4-related disease (4). Our patient had retroperitoneal fibrosis with bilateral ureteral dilation with normal renal function.

Pan et al reported hepatomegaly as an unusual manifestation of ECD (10). Similarly, our patient had hepatomegaly among multisystem involvement and pathologic proof of ECD therefore other diagnosis such as lymphoma didn't seem quite probable since she also had a very good general state.

Villatoro-Villar et al reported tissue thickening sheathing the thoracic and abdominal aorta and its branches usually described on CT imaging as "coated aorta" in approximately 50% of patients (11). Arterial involvement includes as well aneurysms, ectasia and stenosis. Periarterial encasement of the aortic arch branch vessels has also been described with the left carotid being the most involved (11). In this case supra-aortic branches were infiltrated by atherosclerosis rather than soft tissular encasement causing thus the ischemic cerebral stroke.

In the case of our patient the perivascular infiltrate included the inferior vena cava which is rarely described (9).

Cardiac involvement in ECD include pericardial disease which is frequent (9), right atrium pseudotumor and myocardial infarction complicating coronary arteries stenosis (12). Our patient had pericardial effusion but no signs of coronary disease.

Pulmonary disease includes parenchymal and pleural involvement. When systematically screened by chest computed tomography parenchymal abnormalities reach up to 90% of patients and pleural involvement 63% (13) in some studies and 53% and 41%, respectively, in others (14). Interstitial lung disease including frequently septal thickening, solitary or multiple nodules, ground glass opacities and less commonly cysts (13). When systematically performed in patients with CT lesions, pulmonary function tests are usually abnormal with mostly diffusing- capacity defects (13). Mixed ventilation disorders such in our patient's case has been reported in 13% of patients in Wang et al study (13).

Cutaneous lesions in ECD are typically periorbital xanthelasma reported in around one third of patients in many series (9).

Breast involvement in ECD is rare and has been mentioned in few case reports (15) including breast lumps with axillary expansion sometimes, with variable mammographic findings and infiltration of the breast tissue and skin thickening on CT scans. Our patient had an erythematous and macular plaque on the left breast skin with no nodules and normal mammography but the scan revealed bilateral infiltrative lesions.

Treatment of ECD has drastically evolved since the better understanding of the molecular aspects of the disease. Various treatment regimens have been tried with some conventional therapies and recently targeted therapies. Goyal et al (8) summarized the different treatment protocols based on case reports, series and clinical trials. First line conventional therapy include Interferon alpha (IFN- α) and pegylated IFN-α with large series (16) demonstrating the favorable clinical efficacy and better survival rates even in severe cases. Cladribine and Anakinra efficacy have been cited in case reports and series with moderate responses (17) (18) . The use of second line conventional therapy demonstrated variable results and were particularly an interesting solution in case of no access to targeted therapies and low-burden disease. This latter, including , but not only, Tocilizumab (IL-6 receptor antagonist), Infliximab (anti TNF-α inhibitor) which results are controversial (19). Methotrexate that has a low clinical and radiologic response (20) however its use seems interesting in reducing infliximab immunogenicity. Due to the lack of targeted and conventional first line therapy in our country, narrowing down the treatment options, the management of our patient's disease was challenging. Considering the risk of progression and the altered quality of life we opted for a combined protocol including second line agents.

Targeted therapies like BRAF inhibitors (Vemurafenib, Dabrafenib) and MEK inhibitors (Cobimetinib, Trametinib) have promising results yet considerable risks and side effects.

More clinical trials, series and experience sharing are needed to improve the management of ECD patients and to provide consensus guidance.

Clinical response in our case is assessed by anamnesis and physical examination during follow-up and a PET-CT is intended to assess the radiological response after six months of treatment.

Conclusion:

This case illustrates the multi organ involvement and complications of ECD with a particularity of breast involvement, hepatomegaly and infiltration around the inferior vena cava. By reporting our challenging experience in treating ECD in a low-income country with limited access to novel therapies we aim to enlarge the data on the management of ECD in specific circumstances. Evolution and response will be communicated later.

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