Relevant Imaging Presentation of Erdheim-Chester Disease

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DOI: 10.22374/cjgim.v13i2.236

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Submitted: November 7, 2017; Accepted: January 2, 2018. Published: June 25, 2018.

Abstract

Erdheim-Chester disease (ECD) is a rare non-Langerhans multisystemic histiocytosis. This disorder is characterized by CD68+/CD1a⁻ foamy histiocytic infiltration of tissues, especially bones, retroperitoneum, heart, lung and brain. Clinical manifestations may range from asymptomatic bone lesions to multiorgan symptoms. Bone pain in lower extremities is the most common symptom. Typical imaging findings include symmetric diaphyseal osteosclerosis of long bones, periaortic sheathing (“coated aorta”) and retroperitoneal infiltration (“hairy kidney”). Lung and brain radiological abnormalities may also be seen. BRAF-V600E mutation is present in almost half of this population. Vemurafenib, a mutated BRAF inhibitor, is a promising treatment for patients with this mutation. We present the case of a 60-year-old man who arrived with a pathological right humerus fracture, initially thought to be tuberculous in nature. ECD was considered after imaging.

RÉSUMÉ

La maladie d'Erdheim-Chester (ECD) est une histiocytose multisystémique rare non langerhansienne. Ce trouble est caractérisé par une infiltration histiocytaire CD68+/CD1a⁻ mousseuse des tissus, en particulier des os, du rétropéritoine, du cœur, du poumon et du cerveau. Les manifestations cliniques peuvent aller de lésions osseuses asymptomatiques à des symptômes multiorganiques. La douleur osseuse dans les membres inférieurs est le symptôme le plus commun. Les résultats d'imagerie typiques incluent une ostéosclérose diaphysaire symétrique des os longs, un gainage péri-aortique (« aorte enduite ») et une infiltration rétro-péritonéale (« rein poilu »). Des anomalies radiologiques du poumon et du cerveau peuvent également être observées. La mutation BRAF-V600E est présente dans près de la moitié de cette population. Le vemurafénib, un inhibiteur de BRAF muté, est un traitement prometteur pour les patients atteints de cette mutation. Nous présentons le cas d'un homme de 60 ans qui est arrivé avec une fracture pathologique de l'humérus droit, initialement considérée comme tuberculeuse. L'ECD a été considérée après l'imagerie.

Erdheim-Chester disease (ECD) is a non-Langerhans histiocytosis, with 600 known cases to date.¹ First described in 1930 by Jakob Erdheim and William Chester, this disease is characterized by the infiltration of tissues with foamy histiocytes, typically CD68+/

CD1a⁻, unlike Langerhans cell histiocytosis, which is CD68+/CD1a⁺.^{2,3} The etiology of this condition is unclear.^{2,4,5} This multisystem disorder can lead to a variety of clinical manifestations, such as bone pain, exophthalmos, diabetes insipidus, cerebellar

syndromes and xanthelasma, particularly in men between 50 and 70 years old. However, patients with ECD may be completely asymptomatic.^{2,4,5} Symmetric diaphyseal osteosclerosis of long bones especially in lower extremities, periaortic thickening (called “coated aorta” when infiltration involves the thoracoabdominal aorta) and retroperitoneal infiltration with appearance of “hairy kidney” are typical imaging findings of ECD.^{2,4,6,7} Interlobular septal thickening and ground-glass/centrilobular opacities in lung computed tomography (CT) may also be observed, as well as pericardial effusion and myocardial infiltration. Cerebellar or brainstem lesions, dural-based lesions and brain parenchymal lesions also be identified.^{2,4,6–8} Biopsy is needed for diagnosis, and will reveal the typical foamy histiocytic infiltration of tissues, as well as BRAF-V600E mutation in 54% of ECD patients.^{1–3,9} This mutation is useful for selecting appropriate therapy. Vemurafenib might be more effective than interferon α and other treatment modalities in ECD for BRAF mutations. Further evidence is needed.^{10,11}

Case Report

We report a case of a 60-year-old man who was admitted to the Internal Medicine department for pathological fracture of the right humerus. A CT-scan of the arm raised the suspicion of tubercular disease. The patient presented with a short history of severe pain in the right arm without obvious trauma. Over a period of 3 weeks, he had been aware of a mild discomfort in this arm: he attributed this to the use of crutches since his hip surgery 4 months previously. He had no other symptoms. He was admitted under Family Medicine, and underwent testing. Radiography of the right arm revealed a pathological fracture of the humerus and a heterogenic appearance of the diaphysis was

noted (Figure 1). The left hip demonstrated similar diaphyseal anomaly, as well as a 4 cm lytic lesion (Figure 2). In order to exclude a neoplasia, a CT-scan C+ and a scintigraphy were performed. The preliminary scan report raised the possibility of active tuberculosis: the patient was transferred to Internal Medicine and cared for in a negative pressure room.

This patient’s relevant medical history includes left and right hip replacements (in 2014 and 2016 respectively), polyarteritis nodosa at a young age and opioid dependence. He was taking a total of 190 mg of oxycodone per day. He also had 80 mg of testosterone per day on his drug profile for an unknown reason.

The patient had no other symptoms, or findings, of note. Laboratory tests revealed an anemia (hemoglobin 85 to 105g/L, MCV 79.8fL, relative reticulocytes 0.011, iron 6 μ mol/L, ferritin 204 μ g/L, transferrin 1.46g/L, transferrin saturation 0.16), but normal values for leucocytes and platelets. No bone marrow biopsy was performed. His glomerular filtration rate was 60mL/min, compared to 86 mL/min two years earlier (calculated with Cockcroft-Gault equation). Sodium levels were normal. Inflammatory markers were above the normal range (C-reactive protein 40.73 mg/L, ESR 71mm/hour). Ziehl-Neelsen stain was negative in bronchoalveolar lavage (BAL) and Mycobacterium Tuberculosis PCR and culture were negative in blood, urine and BAL.

The CT-scan and the scintigraphy showed multiple abnormalities. In addition to the right humerus fracture seen on X-ray, CT

Figure 1. Right humerus pathological fracture.

Figure 2. Lytic lesion and heterogenic aspect of the left hip.

images showed a bone heterogeneity and lytic lesions, as well as a pathological fracture of sacrum. Retroperitoneal infiltration was seen, along with bilateral hydronephrosis (Figure 3). Within the lungs, diffuse and bilateral centrilobular emphysema and pleuroparenchymal apical opacities were seen. Scintigraphy was partially performed, since the patient refused the 2nd part of the test. This early phase study suggested symmetrical accumulation in long bones of both legs and in sacrum alae (Figure 4).

Metastatic X-ray series also showed the heterogenic aspect of both femurs and humeri. Head CT and echocardiography were normal. PET scan showed diffuse sclerosis of the peripheral bone marrow, consistent with ECD.

In order to confirm the diagnosis, a histopathologic review of the right femoral head (removed 4 months earlier when he had hi joint surgery) was requested. Note that pathology report at the time showed severe arthrosis and chronic inflammation with foamy histiocytes attributed to avascular necrosis of femoral head. This review revealed foamy histiocytes CD68+/CD163+/CD1a-, confirming the diagnosis of ECD. Foamy histiocytes were also identified in bronchoalveolar lavage, but immunohistochemistry was not completed. BRAF V600E mutation was positive in the right hip specimen, and Touton giant cells were also seen. Note that PCR for BRAF V600E mutation was negative in blood.

As the BRAF V600E mutation was present, the hematology/oncology team suggested treatment with vemurafenib 960 mg q12h orally. His arm fracture was managed conservatively since the patient refused surgery.

After 6 months follow-up, the patient stayed asymptomatic. He developed a rash after four months of treatment, but it resolved without any intervention. Anemia stayed similar (hemoglobin 97 g/L, MCV 84fL, relative reticulocytes 0.024, iron 3µmol/L,

ferritin 239 µg/L, transferrin 1.61 g/L, transferrin saturation 0.07) and glomerular filtration dropped to 49 mL/min after 3 weeks but then stabilized to his base value (58 mL/min). Scintigraphy performed after 2 months of treatment remained unchanged. PET scan was selected as control imaging at 6 months because it has been shown to be the best marker of disease activity and a choice investigation modality during follow-up.^{2,4,6} It revealed a near-normal metabolism of bone structures, a fracture to his right scapula and a right hypermetabolic pleural effusion with hilar ganglions slightly hypermetabolic. These new findings were asymptomatic and the fracture was managed conservatively. Thoracentesis could not be performed since the pleural effusion was too small. A control PET scan is planned after a 12 months follow-up. Note that the patient was not always compliant with treatment even though he did not developed any side effects.

Discussion

ECD is a rare multisystemic disease which can be a diagnosis challenge. Imaging studies were helpful in this case. According to Célia Autunes et al.⁴, symmetric osteosclerosis of long bones together with perirenal disease or aortic perivascular thickening is almost pathognomonic of ECD. Our patient met some of these criteria: only the aortic infiltration was missing. As a result, the diagnostic probability was high even before tissue analysis. Pulmonary abnormalities found on both CT and bronchoalveolar lavage are non-specific,^{4,8} but consistent with the diagnosis.

It should be noted that bilateral symmetrical osteosclerosis of long bones is present in 74% of patients¹, but “coated aorta” and “hairy kidney” are less frequent (6% and 16% respectively¹).

Bone pain is common in ECD.^{1,3-6,8,10} Our patient had pain associated with a humeral fracture but did not report any other

Figure 3. Retroperitoneal infiltration and hydronephrosis at CT-scan.

Figure 4. Symmetrical accumulation in long bones of both legs at scintigraphy.

discomforts despite widespread pathology. This may be due to the high dose of opioid analgesic he was taking. Cough and dyspnea are sometimes associated with ECD^{1,5,8} when there is lung involvement: our patient didn't have pulmonary involvement. He was also free of neurological symptoms, which are present in 25 to 50% of cases¹ in the literature.

Histopathologic review confirmed the diagnosis, and the BRAF-V600E mutation was present in the pathologic specimen. Vemurafenib (a mutated BRAF inhibitor) shows promise in treatment, with more rapid results than interferon α .^{10,11} There is a body of evidence in the literature supporting treatment using interferon α ^{1-3,6,12}: we chose vemurafenib in the hope of higher efficacy.^{10,11} Severe cutaneous side effects can occur with BRAF inhibitor therapy, such as squamous cell carcinoma and vasculitis; interferon α may be better tolerated.^{11,13,14} Longitudinal follow-up is needed with this treatment. In Quebec, vemurafenib therapy costs 136,56\$CAD/day and is also used for metastatic melanoma.¹⁵

After 6 months of treatment, vemurafenib was well tolerated in our patient. Significant improvement was seen on PET scan, since bone metabolism has declined to a near-normal value. However, a pathological fracture to the right scapula and a pleural effusion appeared. Since our patient didn't manifest any symptoms, the age of the fracture is unknown. It might have happened before the clinical effect of vemurafenib occurred. Haroche et al.¹⁰ saw a significant improvement on clinical symptoms, CRP and pathological uptakes on PET scan within four months in their three patients. However, our patient was partially compliant to treatment, so there might have been a delay in efficacy. Pleural effusion could not be characterized since it could not be drained, so the cause remains unclear. PET scan control at 12 months might give more information on vemurafenib efficacy in our patient.

Conclusions

We present a 60-year-old man with a pathological fracture with imaging findings suggesting of ECD. There was a paucity of signs and symptoms, other than anemia. Indeed, clinical manifestations are protean and variable. Bone and retroperitoneal abnormalities were key findings for diagnosis in our patient. The mutated BRAF inhibitor vemurafenib may be a promising treatment for patients with BRAF-V600E mutation. However, definitive management guidelines are still evolving.

Conflict of Interests

None.

Consent Form

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

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