

A new role for fluorine-18-fluorodeoxyglucose positron-emission tomography/computed tomography in Erdheim-Chester disease

ABSTRACT

Erdheim-Chester disease (ECD) is a rare form of non-Langerhans cell histiocytosis, with multisystem manifestation such as bone pain, being the most common presenting symptom, cardiovascular or central nervous system involvement, interstitial lung disease, skin and orbital lesions, adrenal enlargement, retroperitoneal fibrosis and renal impairment as well fever, and weight loss. The disease is challenging to diagnose due to its rarity and mimicry of other infiltrative processes. Technetium-99 m bone scintigraphy showing pathological bone activity in the long bones is highly suggestive of ECD. However, not all patients have bone complaints. Till now, fluorine-18-fluorodeoxyglucose positron-emission tomography/computed tomography (¹⁸F-FDG PET/CT) was especially used after histological diagnosis to determine disease activity and extent, as well as the evaluation of treatment response. With this case, we suggest an additional role for ¹⁸F-FDG PET/CT earlier on in the diagnosis workup as follows: detecting a possible biopsy site to establish the diagnosis of ECD especially in a clinical context without bone pain.

Keywords: Erdheim-Chester disease, non-Langerhans cell histiocytosis, normal bone scintigraphy, subcutaneous nodule

INTRODUCTION

Erdheim-Chester disease (ECD) is a rare form of non-Langerhans cell histiocytosis and manifests itself most commonly in skeletal structures; however, it can also involve other organs. Diagnosing ECD is challenging especially in the absence of bone complaints or pathological uptake on bone scintigraphy. Positron-emission tomography/computed tomography (PET/CT) currently plays a role in determining disease activity and extent, and to evaluate treatment response. With this case, we highlight the additional utility of fluorine-18-fluorodeoxyglucose PET/CT (¹⁸F-FDG PET/CT) to establish the diagnosis of ECD when bones are not involved.

CASE REPORT

A 74-year-old female with a prior history of breast neoplasia and atrial fibrillation presented with dyspnea, chest pain, and pericardial effusion for which steroid treatment already was

initiated. Blood testing showed a C-reactive protein (CRP) level of 120 mg/L. Antinuclear and rheumatoid factors were negative. Chest radiography showed a small bilateral pleural effusion. The pleuropericarditis was labeled as viral and steroids were continued.

Two months later, cough and dyspnea reappeared, and CRP remained elevated (141 mg/L). She also presented a subcutaneous nodule on the left buttock that recently had

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become bigger and more painful. ¹⁸F-FDG PET/CT scan, to determine the inflammatory focus and evaluate the lungs and the subcutaneous sacral nodule, showed intense hypermetabolism at the ascending aorta, between the 11th and 12th rib and in the retrosacral region [Figure 1].

Repeated autoimmune tests, syphilis, Lyme borreliosis, bartonellosis, brucellosis, and Q-fever serological tests were all negative. Immunoglobulin G4 level was normal. Microbiological culture of the sacral abscess was sterile, and histopathology was noncontributive. Technetium-99 m methylene diphosphonate (^{99m}Tc-MDP) bone scintigraphy did not show any pathologic uptake.

A biopsy of the hypermetabolic intercostal nodule detected on PET/CT was performed. Histopathology revealed a xanthogranulomatous infiltration, CD68+ CD1a-S100, compatible with a non-Langerhans histiocytosis. No BRAF mutation could be withheld.

Interferon (IFN)-alpha therapy was started after a negative BRAF-mutation retest, with rapid disappearance of symptoms and normalization of CRP-levels.

DISCUSSION

ECD is a rare entity which occurs most commonly in middle-aged patients, equally distributed between the two sexes.^[1,2] The disease is characterized by xanthomatous or granulomatous tissue infiltration by non-Langerhans histiocytes. The immunohistologic characteristics are used to distinguish from Langerhans cell histiocytosis as follows: in ECD, histiocytes stain positive for CD68 and negative for CD1a, staining for S-100 is negative in 80%.^[3]

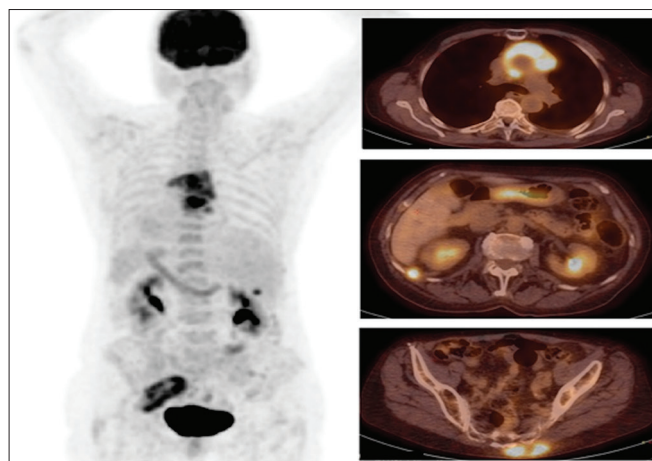


Figure 1: Fluorine-18-fluorodeoxyglucose positron-emission tomography/computed tomography showing intense hypermetabolism at the ascending aorta (SUV_{max} 12), intercostal nodule posterolateral on the right (SUV_{max} 8), and the retrosacral region (SUV_{max} 10)

Pathogenesis is poorly understood. Studies have shown histiocyte recruitment and accumulation in the tissues by cytokines and chemokines.^[4] The BRAFV600E mutation has been identified in approximately 50% of ECD cases.^[5] BRAF plays a role in the signaling pathway leading to enhanced cell proliferation and survival. Hence, there are both clonal proliferations associated with the BRAFV600E mutation and nonclonal tissue accumulation of histiocytes due to systemic proinflammatory cytokines and chemokines.^[3]

Treatment should be initiated in all patients. IFN-alpha and pegylated IFN-alpha are the first-line choices for prolonged treatment, where the latter has lesser side effects. In ECD patients carrying the BRAF mutation, the use of BRAF inhibitors such as vemurafenib may be an alternative to IFN-alpha. Given the potential therapeutic implication of BRAFV600E mutations, retesting in case of a negative result is encouraged.^[6]

ECD is a true multisystem disease with manifestations not only in diverse organs such as in bones, cardiovascular or central nervous system, lungs, skin, eyes, adrenal glands, and kidneys but also systemic symptoms such as fever and weight loss.^[2,7] The clinical course of ECD is largely dependent on disease extent and distribution, and symptoms can range from asymptomatic bone lesions to a multisystem, life-threatening form with poor prognosis.^[1-3]

Bone pain is the most common presenting symptom of ECD. Long bone uptake due to cortical osteosclerosis on ^{99m}Tc-MDP bone scintigraphy is a highly suggestive sign.^[3,8] Our patient, however, did not have bone pain and bone scintigraphy showed no pathological uptake.

Cardiac involvement with ECD is seen in the majority of patients, leading to important morbidity and mortality. Most frequently, there is involvement of the circumferential periaortic sheathing and pericard, as seen in our patient.^[9]

Pulmonary involvement of the lung parenchyma and/or pleura occurs in 25%–50% of patients. It can be asymptomatic or manifests as dyspnea and cough.^[1] Our patient's pleuropericarditis and periaortitis were probably a manifestation of ECD; however, this was not confirmed by histopathology.

Cutaneous manifestation is relatively uncommon (around 20%). There is a broad clinical spectrum of cutaneous lesions, with xanthelasma-like lesions most frequently seen. Interestingly, ECD patients with xanthelasma-like lesions are more likely to have the BRAFV600E mutation. Our patient, however, had an atypical skin manifestation and was BRAFV600E negative.^[7]

Diagnosing ECD is challenging due to its rarity and mimicry of other infiltrative processes. Diagnosis is based on histopathologic evaluation of involved tissue within the clinical context. Bone scintigraphy is useful to show skeletal involvement and to exclude other causes of bone pain,^[8] however, not all patients-like ours-have bone involvement. ¹⁸F-FDG PET/CT is frequently performed after the diagnosis to determine disease activity and extent.^[3] It had also proven useful to evaluate treatment response and to monitor disease activity.^[9] Moreover, PET/CT is valuable in the follow-up during treatment with BRAF inhibitors.^[3,6] A recent retrospective French study stated a superiority of bone scintigraphy in the initial evaluation, and a comparable performance of PET/CT with regard to conventional morphological examinations.^[10] However, our case illustrates the superiority of PET/CT to bone scintigraphy at baseline in establishing the diagnosis of ECD. Thus, even without classic bone symptoms or a negative bone scintigraphy, a possible diagnosis of ECD should be borne in mind.

In conclusion, ECD is a rare, multisystem histiocytic disorder requiring a multidisciplinary approach in the diagnostic workup, treatment, and follow-up. Biopsy showing characteristic immunohistological features is essential to establish the diagnosis. Till now, PET/CT was typically used after diagnosis to determine disease activity and extent, and for treatment response evaluation. With this case, we suggest an additional role for ¹⁸F-FDG PET/CT in ECD, earlier on in the workup paradigm as follows: detecting a possible biopsy site and thereby guiding the diagnosis, especially in a clinical context without bone pain.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published

and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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