Pediatr Radiol (2015) 45:1870–1873
DOI 10.1007/s00247-015-3409-6

CASE REPORT

Isolated thymic Langerhans cell histiocytosis discovered on F-18 fluorodeoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT)

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Received: 2 April 2015 / Revised: 16 April 2015 / Accepted: 2 June 2015 / Published online: 9 July 2015

Abstract The thymic infiltration in young patients with multisystemic Langerhans cell histiocytosis and its radiologic features are well known. However, isolated thymic disease has seldom been reported in the literature. We report the case of a 10-month-old child admitted for fever of unknown origin. Whole-body F-18 fluorodeoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT) was performed to identify a focus of infection. It demonstrated an unusual aspect of the thymus, which led to further investigation and revealed isolated infiltration of the thymus by Langerhans cell histiocytosis. The patient was treated accordingly and is now disease free. As evaluation of Langerhans cell histiocytosis patients with F-18 FDG PET/CT is becoming more frequent, it is important to be aware of the scintigraphical characteristics of thymic Langerhans cell histiocytosis.

Keywords Child · F-18 fluorodeoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT) · Langerhans cell histiocytosis · Thymus · Ultrasound

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Introduction

Radiologic features of thymic infiltration in multisystemic Langerhans cell histiocytosis have been reported previously. However, isolated thymic Langerhans cell histiocytosis disease is extremely rare and its appearance on F-18 fluorodeoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT), to the best of our knowledge, has yet to be described.

Case report

A 10-month-old boy was transferred to our tertiary care institution for further evaluation of persistent fever of unknown origin and altered general condition. At admission, blood tests showed increased C-reactive protein, with a value of 157 mg/L (normal: 0.0–6.0 mg/L). Leukocytes counts were 13.3×10^9/L (normal: $6.0–17.0\times10^9$/L). Microcytic anemia (hemoglobin=84 g/L; normal: 105–135 g/L; mean corpuscular volume: 66.1 fL; normal: 70–86 fL) and hypoalbuminemia (24 g/L; normal: 30–49 g/L) were also demonstrated. Adenovirus came back positive in the blood by polymerase chain reaction (268 co/ml: detection threshold >200 co/mL) and in the nasopharyngeal and stool specimens by culture. Physical examination and abdominal US were unremarkable. As the boy remained feverish and with persistent inflammatory parameters, a F-18 FDG PET/CT scan was ordered to rule out an occult neoplasm or infectious process. The whole-body F-18 FDG PET was obtained 60 min after intravenous injection of 70 MBq of F-18 FDG. Concomitant CT without contrast (22mAs, 120 kVP, dose length product 138.2 mGy·cm) was performed for attenuation correction and anatomical localization. No sedation was needed. The F-18 FDG PET/CT showed an enlarged, multilobulated, heterogeneous thymus (Fig. 1)

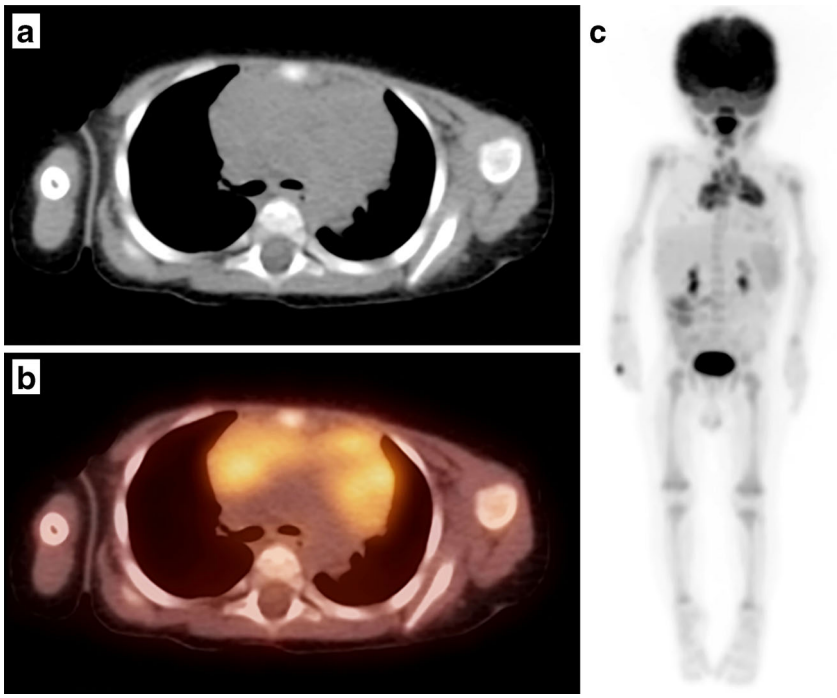

Fig. 1 CT images of a 10-month-old boy admitted for fever of unknown origin. **a** Axial image from F-18 fluorodeoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT) demonstrates an enlarged multilobulated thymus. **b** Axial fused PET/CT image shows increased F-18 FDG uptake of the thymus (maximum standardized uptake value [SUV-max]=4.0) with hypoactive regions. **c** Maximal intensity projection (MIP) rendition shows no additional abnormalities

but no other abnormal findings. Diagnosis was atypical thymic stimulation with the possibility of underlying congenital immune deficiency. At that time, neoplastic infiltration seemed less likely. Subsequent US of the thorax revealed findings highly suggestive of Langerhans cell histiocytosis (Fig. 2) where the cystic lesions corresponded to the hypoactive regions on F-18 FDG PET/CT. Chest radiographs at admission (Fig. 3) were reported to be within normal limits, the thymus size being unremarkable for the age of the patient. On the subsequent thoracic CT (Fig. 4), the thymus was also multilobulated but only slightly heterogeneous. Thymic Langerhans cell histiocytosis was confirmed with an open biopsy with positive Hematoxylin Phloxin Saffron staining and CD1a positivity (Fig. 5). There was no evidence of necrosis in the specimen, but presence of microabscesses was noted.

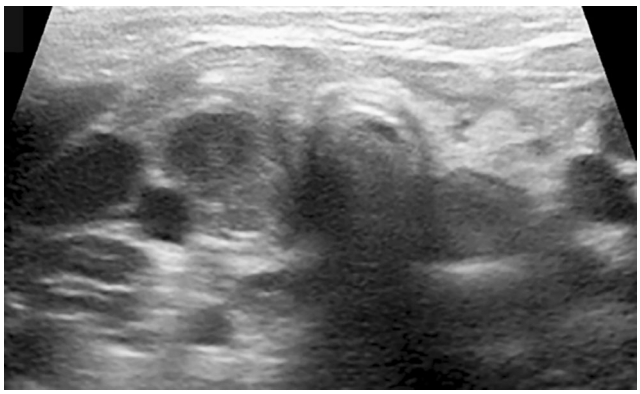

Fig. 2 Ultrasound image shows a heterogeneous and infiltrated thymus with multiple cysts

Additional staging, including brain MRI, skeletal survey, CT scan of the upper abdomen and bilateral bone marrow aspiration/biopsy, was negative. The boy's isolated thymic disease was considered the precursor of potential subsequent multisystemic Langerhans cell histiocytosis and he was treated according to Langerhans cell histiocytosis-III trial [1]. Complete remission, with no visualization of the thymus, was demonstrated on follow-up F-18 FDG PET/CT (Fig. 4) at the end of induction treatment (week 6).

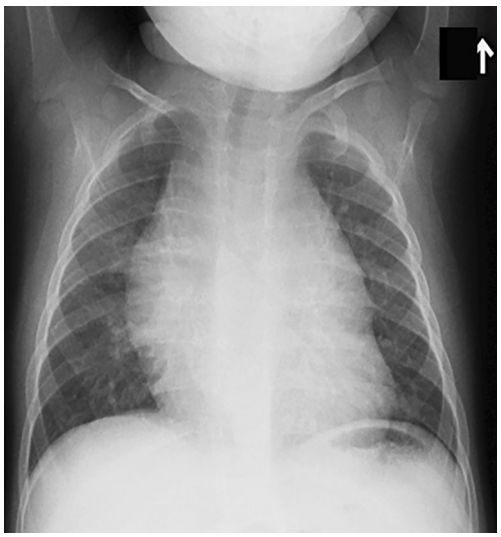

Fig. 3 Prominence of the thymus on the chest radiograph was considered normal considering the young age of the patient. The study was otherwise unremarkable

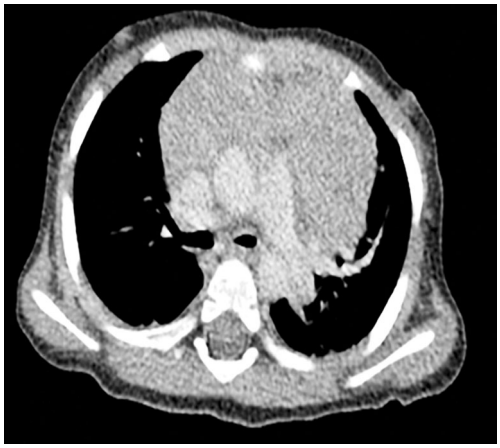

Fig. 4 Thymic anomalies were less obvious on CT

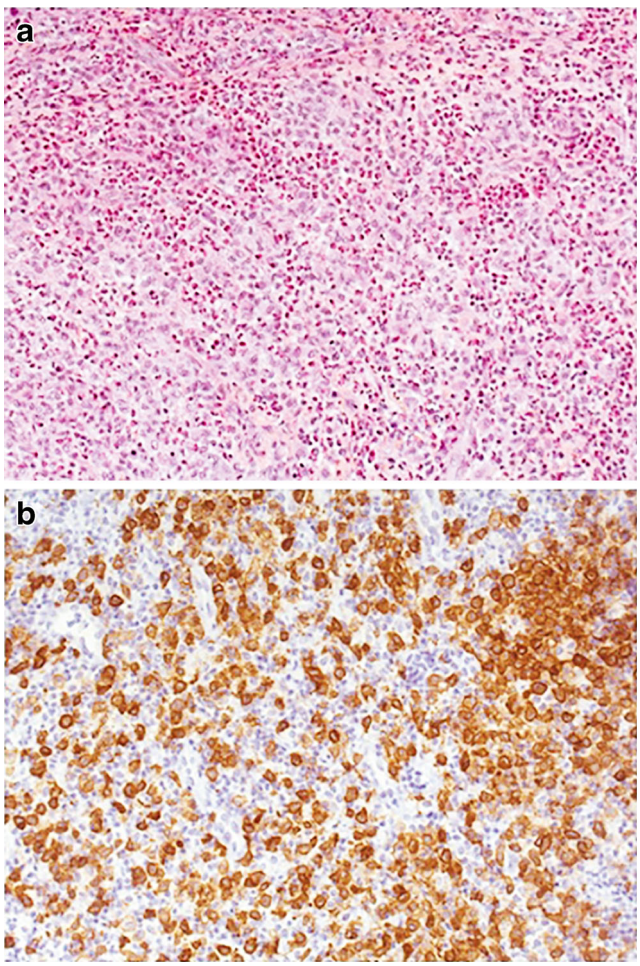

Fig. 5 Histology. **a** Hematoxylin Phloxin Saffron stain demonstrates extensive Langerhans cell infiltration. Magnification factor 200×. **b** Langerhans cell infiltration confirmed by positivity of CD1a. Magnification factor 200×

Discussion

Fever of unknown origin constitutes a diagnostic challenge in adults and in children. Following clinical history, physical examination, laboratory tests and basic imaging, one must decide the best algorithm to elucidate the cause of fever. The next step can be whole-body screening using MRI or F-18 FDG PET/CT before dedicated imaging or more aggressive investigations. Only a few series of children imaged with F-18 FDG for fever of unknown origin can be found in the literature. Jasper et al. [2] conducted a retrospective study in 69 children with unexplained inflammatory signs, including fever. F-18 FDG PET and PET/CT was useful in identifying the cause of inflammation focus in 23% of the children and excluding disease in 22%. Malignancies were found in 8% of their patients. Using our F-18 FDG PET/CT protocol, effective dose ranges from 5 to 8 mSv for PET and 3 to 5 mSv for CT. Whole-body MRI has the advantage of being radiation free, but standard protocols have yet to be defined and effectiveness in fever of unknown origin validated. Another limitation of MRI is the need for sedation in young patients. However, newer technology combining functional information of F-18 FDG and anatomical delineation of MRI may revolutionize the way infection and inflammation are imaged.

Langerhans cell histiocytosis remains an elusive disease of unclear etiology mostly found in children. The annual incidence is between 2.6 and 5.4 cases per million [1, 3]. Normal Langerhans cells are dendritic cells found in the skin and mucosa, acting as antigen-presenting immune cells in infections. They are similar to macrophages, contain large granules (Birbeck granules) and express Langerin (CD207). They are also normal components of lymph nodes and found in the medulla and corticomedullary junction of the thymus [4]. Langerhans cell histiocytosis is characterized by a clonal accumulation and proliferation of abnormal bone marrow-derived Langerhans cells. Langerhans cell histiocytosis infiltration consists not only of Langerhans cells but also of lymphocytes, eosinophils and normal histiocytes, all being F-18 FDG avid.

Lakatos et al. [5] reviewed data from the German Langerhans cell histiocytosis trials to document thymic involvement. Of the 1,264 patients, 18 (1.4%) were found to have thymic Langerhans cell histiocytosis and all patients had multisystemic Langerhans cell histiocytosis. This frequency was probably underestimated as thymus was not systematically evaluated in those trials or falsely reported as normal by conventional chest radiographs. On US and on CT, thymus was heterogeneous with some calcifications and hypoechogenic cysts, similarly to our patient. On MRI, the cysts were hypointense on T1 and hyperintense on T2. None of their patients had isolated thymic Langerhans cell histiocytosis [5].

Thymic enlargement in a young patient on chest radiographs may be misleading and considered normal. CT is not systematically used in Langerhans cell histiocytosis staging

[1]. In some patients with thymic Langerhans cell histiocytosis, findings may include contrast-enhanced septae and concomitant lung disease. We considered in our differential diagnosis the possibility of congenital immune deficiency. *Pneumocystis carinii* infections have been associated with cystic pulmonary and thymic lesions [3].

Langerhans cell histiocytosis limited to thymus is extremely rare. Only a small number of pediatric patients with diffuse Langerhans cell histiocytosis infiltration of the thymus and a few adults—some with myasthenia gravis—have been reported, none imaged with F-18 FDG PET/CT [6].

The thymus has been known to be active on F-18 FDG PET/CT in very young patients, with maximal size and uptake at birth, and involution around puberty [7]. Uptake is also demonstrated following chemotherapy (thymic rebound). However, in both instances, thymus contours are curvilinear and uptake is homogenous. Those findings have been correlated by our own experience.

As for fever of unknown origin, the combination of whole-body MRI and F-18 FDG in a single session may become the modality of choice to evaluate Langerhans cell histiocytosis [8].

While thymic uptake is the norm in young children or following chemotherapy, the presence of heterogeneous uptake, hypoactive lesions and irregular contours of thymus in a young patient imaged with F-18 FDG PET/CT must raise the possibility of Langerhans cell histiocytosis.

Conflicts of interest None

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