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Rare disease

PET/CT images of a patient with haemophagocytic lymphohistiocytosis

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Summary

Haemophagocytic lymphohistiocytosis (HLH) is a rare immune disorder that predominantly affects macrophages and T lymphocytes and leads to multiple organ disease and death. The characteristic pathological finding in the bone marrow and the other affected tissues is haemophagocytosis of macrophages (macrophages digesting erythrocyte). Primary (hereditary) and secondary (acquired) forms of the disease are present. A patient with documented HLH disease revealed by positron emission tomography/CT is reported in this paper.

BACKGROUND

Haemophagocytic lymphohistiocytosis (HLH) is a rare immune disorder that predominantly affects macrophages and T lymphocytes and leads to multiple organ disease and death. The characteristic pathological finding in the bone marrow and the other affected tissues is haemophagocytosis of macrophages (macrophages digesting erythrocyte). Primary (hereditary) and secondary (acquired) forms of the disease are present.[1–3] A patient with documented HLH disease by positron emission tomography (PET)/CT has been reported in this paper.

CASE PRESENTATION

A 14-year-old male patient with fever and a sore throat attended our hospital. The patient's history had no exceptional features except for his family history, which includes larynx cancer in his aunt, liver cancer in his father's cousin and colon cancer in his grandfather. Physical examination of the patient revealed the fever as 39.5°C, severe macular rash all over the body and hepatomegaly. However, there was no palpable lymph node. The thorax tomography of the patient showed bilateral pleural effusion, cardiomegaly and hepatomegaly. Pleural fluid aspirate included Gram-negative basils (*Acinetobacter baumannii*/calcoaceticus complex) but no malign cells were observed. His cranial CT and MRI were normal. Laboratory analysis of blood showed leucocytosis with 95% neutrophil (19 320/mm^3), mild anaemia (10.2 g/dl), increased liver function tests and a sedimentation rate of 88 mm/h. The patient's ferritin level was also elevated (30 000 ng/ml). He was referred to our department for bone scintigraphy with the diagnosis of fever of unknown origin (FUO). As his bone scintigraphy was normal, PET/CT imaging was recommended. PET/CT imaging showed generalised hypermetabolic lymphadendopathy especially in the servical and mediastinal regions (figure 1A,B), diffuse increased bone marrow uptake and increased uptake of spleen (figure 1C). In addition, increased uptake at subcortical nuclei was observed (figure 1D). According to these findings the PET/CT images were interpreted as lymphoma or diffuse inflammatory reaction. Bone marrow biopsy revealed haemophagocytosis with an increased myelocyte count. The patient's diagnosis was confirmed according to the diagnostic criteria (continuous fever, development of bysitopenia and decreasing fibrinogen level). Dexametasone, etoposid and syclosporine treatments were started in accordance with the HLH-2004 protocol. Intratecal metotracsate and steroid treatments were also administered.

OUTCOME AND FOLLOW-UP

The patient responded to the treatment.

DISCUSSION

The first presentation of this patient was FUO, which is described as 'having a level of at least 38.3°C fever and lasting more than 3 weeks without any documented origin despite hospitalisation for 1 week'.[4] In addition, the patient had undefined symptoms. Since the aetiology of FUO involves infectious, malign or inflammatory diseases, PET/CT is used as an accurate method for identification of the origin of FUO. Previous studies in both adults and children with FUO have confirmed this idea.[5 6] Jasper *et al*.[6] have considered PET helpful in 45% of patients and scan findings contributed to final diagnosis in 73% in their large series of child patients. In the results of Jasper's study, 20% of patients had multisystem diseases, 15% infection and 8% malign diseases.[6] Most of the children with FUO remain undiagnosed despite regular investigations. Thus, PET should be considered as a helpful tool in detecting the aetiology of FUO. PET is an important method for the identification of the origin of FUO because its use can diagnose a large number of diseases of malignant, inflammatory and infectious origin as vasculitis, granulomatous infectious diseases, bacterial diseases of unexpected localizations, lymphoma or other malign

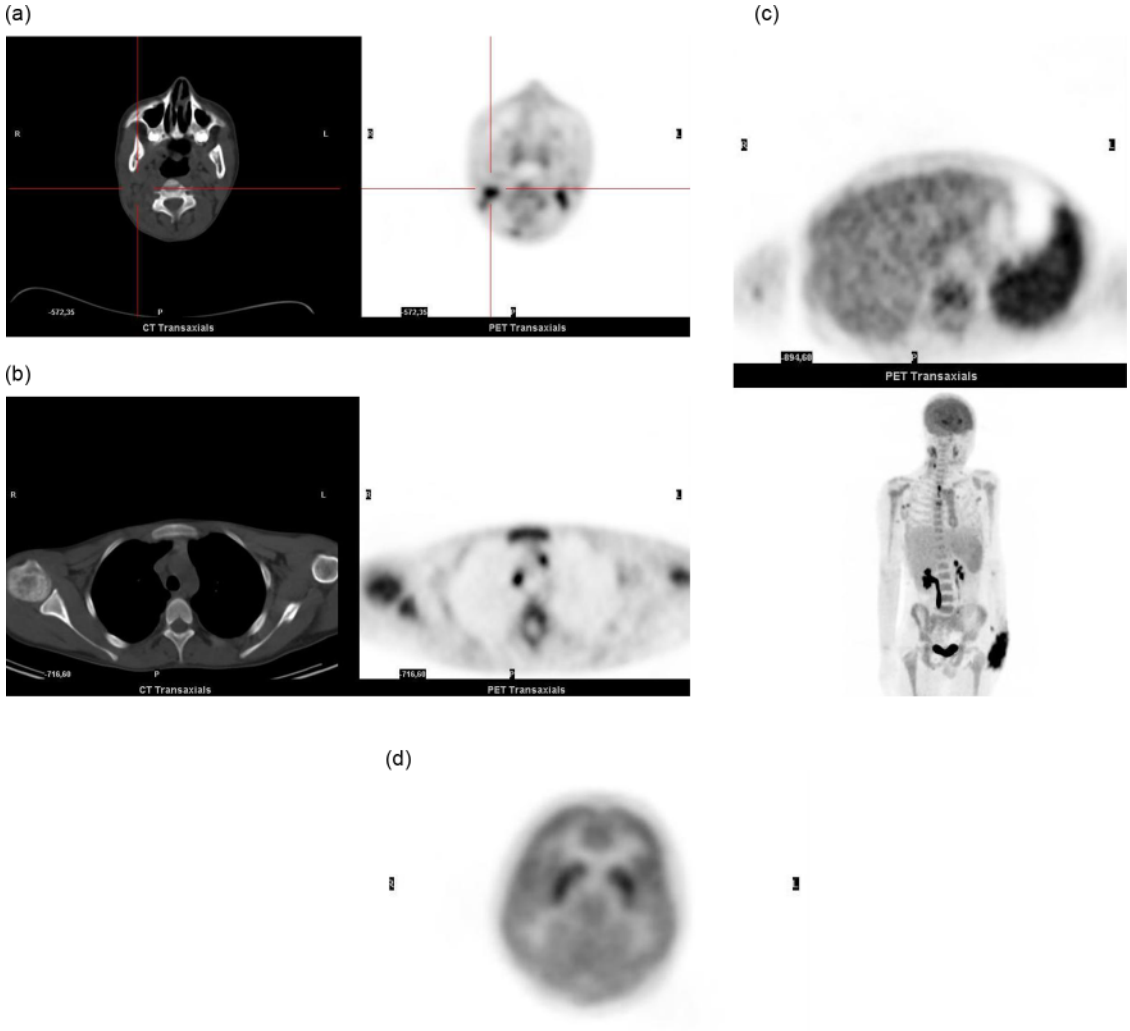

Figure 1 (A) Axial positron emission tomography and CT images of the cervical region. (B) Axial positron emission tomography and CT images of the mediastinal region. (C) Axial positron emission tomography images corresponding to the spleen and liver and multiple intensity projection images. (D) Axial positron emission tomography images from the brain region to show subcortical nuclei.

diseases. Low-dose CT protocols for PET/CT examinations are preferred as additional information obtained from CT is essential for accurate interpretation of the PET data.

Our patient had clinical findings of a malign disease and FUO and thus PET/CT imaging was the appropriate method of his evaluation. Although PET/CT could not provide a clear diagnosis in this patient, we were able to direct the clinicians to an inflammatory disease involving bone marrow, lymph nodes and spleen. Detailed examination of the bone marrow biopsy and clinical evaluation of the parameters according to diagnostic criteria guided us for the diagnosis. HLH was not actually the expected first-order diagnosis in PET/CT.

Previous reports regarding PET/CT images of haemophagocytic syndrome include two case reports with lymphoma-associated haemophagocytic syndrome.[7 8] In one of these reports, the patient showed the same fluoro-deoxy-glucose uptake pattern as our patient and the site of lymphoma (perianal region) was depicted unexpectedly by means of PET/CT.[8] The other report, which includes three cases that showed the same uptake pattern of PET/CT as our case, also supported the idea that PET/CT is a valuable tool in the diagnosis of haemophagocytic syndrome associated with lymphoma.[7]

In addition, another patient with HLH was reported by Ersahin *et al*.[9] with PET/CT images and one more patient was presented in a Letter to the editor, due to false positivity in PET/CT.[10]

There are two presentations of HLH. One of them is the primary form, which is usually associated with genetic disorder or with hereditary inheritance. The secondary form is associated with malignant or rheumatological disorders.[1 11] Since our patient did not have a primary disease, his HLH was probably the primary form. As the patient's family history included multiple malign diseases, the aetiology of HLH might be hereditary.

The presentation of HLH in older children includes more complicated findings such as fever, cytopaenia, hepatitis and neurological disorders.[1] Our patient also had fever, elevation of liver function tests at the beginning and later on bicytopaenia and neurological findings participated in the follow-up. Bilateral increased hypermetabolism of basal ganglions in PET/CT might be attributed to the apathetic state of the patient during the procedure.

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The diagnosis of HLH depends on some clinical parameters such as blood ferritin and CD25 levels. The ferritin level of our patient was also extremely elevated (30 000 ng/ml), which provided us with one of the diagnostic criteria.

Since HLH shows typical appearance in PET/CT, the PET/CT imaging might be a part of the diagnosis of this rare disease and HLH might be on the list of aetiological origins of FUO in PET/CT.

Learning points

- Haemophagocytic lymphohistiocytosis is a rare disease of cellar immunity.
- HLH has a typical appearance in positron emission tomography/CT.
- HLH can be presented with fever of unknown origin.

Patient consent Obtained.

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