

¹⁸F-FDG PET/CT imaging in systemic lupus erythematosus related autoimmune haemolytic anaemia and lymphadenopathy

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Abstract

Objective: We present a case of systemic lupus erythematosus (SLE) related autoimmune haemolytic anaemia (AIHA) and lymphadenopathy. AIHA as a serious complication of SLE, requiring urgent appropriate management. The timely differential diagnosis between SLE with lymphadenopathy and lymphoma, primary and SLE-related AIHA often looms as practical challenge under clinical scenario. Fluorine-18 fluorodeoxyglucose position emission tomography/computed tomography (¹⁸F-FDG PET/CT) performed for fever of a known origin and for possible malignancy, showed increased ¹⁸F-FDG uptake in lymph nodes, as well as increased spleen uptake, which was probably due to lymphoma. **Conclusion:** A symmetrically increased ¹⁸F-FDG uptake in small lymph nodes with multiple serous cavity effusion helped the differential diagnosis between SLE related AIHA and lymphoma. In addition, PET/CT can visualize not only the degree of disease activity or the "burden of inflammation" but also the distribution of the disease in the entire body.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune inflammatory disease characterized by the presence of a plethora of autoantibodies and immune complex formation targeted to various organs of the body. The excessive production of autoantibodies as well as the formation and deposition of immune complexes leads to an immunologically mediated multisystemic inflammation with vascular and perivascular damage and mononuclear cells infiltration, often together with complement and immunoglobulin (IgG) deposition [1]. Haematological abnormalities are common in SLE. Autoimmune haemolytic anaemia (AIHA) is found in about 50% of patients with SLE. Impaired erythropoietin response and presence of antibodies against erythropoietin may contribute to the pathogenesis of this type of anaemia. By targeting the increased glucose uptake of infiltrating granulocytes and tissue macrophages, positron emission tomography with fluorine-18 fluorodeoxyglucose (¹⁸F-FDG PET/CT) has been shown to delineate inflammation with high sensitivity. We describe here a case of SLE with AIHA, increased ¹⁸F-FDG uptake in lymph nodes, and increased spleen uptake.

Case Discussion

A 14 years old girl presented with abdominal pain, intermittent fever (maximum 39.5°C) and pallor since 20 days. She had severe anaemia: red blood cells 1.35×10^6 /mL (normal for females: $4-5.4 \times 10^6$ /mL), hemoglobin (Hb) 78g/L (normal:110-150g/L), reticulocytes percentage 9.24% (normal:0.5%-1.5%), leucocytes count 9.4×10^9 /L (normal: $4.0-10 \times 10^9$ /L), platelets count 170×10^9 /L (normal: $100-300 \times 10^9$ /L), total bilirubin 42.2µmol/L (normal:2-20µmol/L), direct bilirubin 20.2µmol/L (normal:1.7-6.84µmol/L), IgE 613IU/mL (normal:0-100IU/mL), IgG 22.9g/L (normal:7-16g/L) and C reactive protein (CRP) 24mg/L (normal:<8mg/L). On further evaluation, the case displayed features of autoimmune haemolytic anaemia: positive antinuclear antibody (ANA) 1:160IU/mL,

(reference value 1:30IU/mL), positive perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) and positive anti Smith antibody/anti-ribonucleoprotein (SM/RNP) (normal:negative). During her hospital stay, her red blood cell and blood hemoglobin dropped further (red blood cell: 0.84×10^6 /mL, Hb:38g/L) without any overt blood loss. Serum lactate dehydrogenase (LDH) elevated to 1437U/L (normal: 106-211U/L).

Fluorine-18-FDG PET/CT scan performed for fever of unknown origin and for possible malignancy (Figure 1) showed slightly increased ^{18}F -FDG uptake in bilateral cervical and maxillary (Figure 2), mediastinum, bilateral groin, iliac, retroperitoneal lymph nodes, as well as splenomegaly with increased splenic uptake (Figure 3). Fluorine-18-FDG PET/CT also showed bilateral pleural, abdominal and pelvic effusion (Figure 4). The diagnosis of SLE related AIHA was suspected with methylprednisolone 40mg/d orally for 7 days. Her abdominal pain and fever subsided and her hemoglobin levels increased to 73g/L. Then the patient was referred to another special hospital to receive further treatment.



Figure 1. Maximum intensity projection images demonstrated slightly hypermetabolic small lymph nodes in bilateral cervical, maxillary, mediastinum, iliac, bilateral groin and retroperitoneal nodal chains.

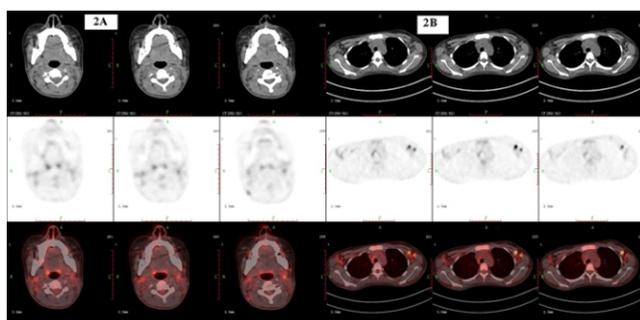


Figure 2. Fluorine-18-FDG PET/CT image demonstrated slightly increased uptake with a maximum standardized uptake values 2.6 and 9.1 in the bilateral cervical (2A) and the maxillary lymph nodes (2B).

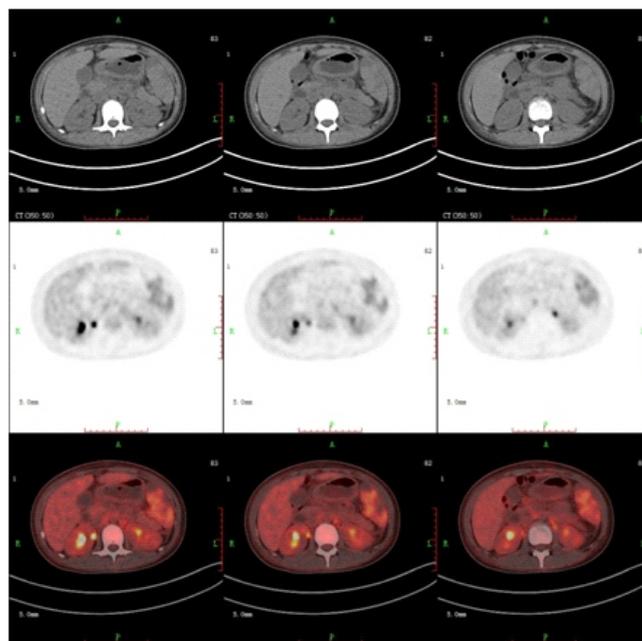


Figure 3. Fluorine-18-FDG PET/CT image showed splenomegaly with multiple low density and slightly increased uptake with a SUVmax of 3.2.

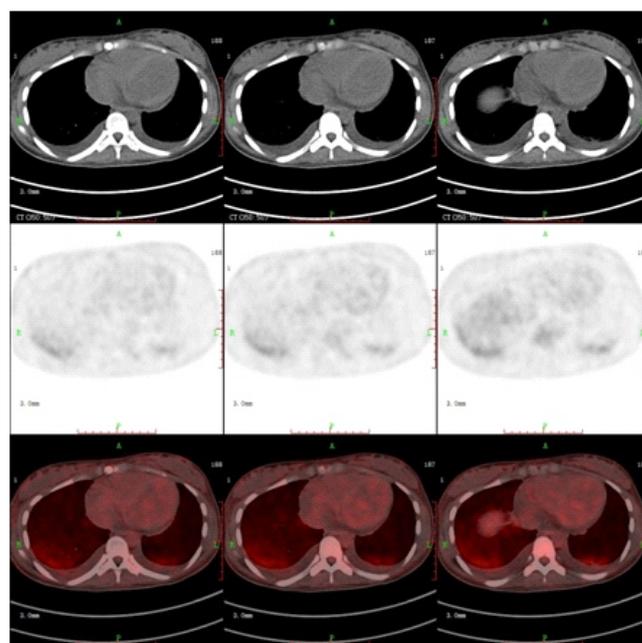


Figure 4. Fluorine-18-FDG PET/CT image demonstrated bilateral pleural effusion.

Subjects and Methods

Patients with SLE present with various clinical and serological manifestations according to age at disease onset [2]. The most common presenting symptoms of juvenile SLE in Egypt were pallor and fever (in 51.2% and 43.9% of the cases, respectively) as in our case [3]. Systemic LE involvement of vital organs, particularly kidneys and brain, accounts for significant morbidity and mortality. Studies from Korea [2], UK [4] and China [5] indicated that severe organ involvement and significant disease activity are primary characteristics in

children with SLE. Our case had no kidney and nervous system involvement of SLE. A rare combination of haematological and gastrointestinal complication was found in a patient with SLE [6] and also in our case.

Pediatric patients presenting with autoimmune multi-lineage cytopenias should undergo investigation for underlying autoimmune lymphoproliferative syndrome, other primary immunodeficiencies and autoimmune disorders [7]. Haematological abnormalities, anaemia in particular, are common in SLE. Autoimmune HA was found in about 50% of patients with SLE which was mainly a result of antibody induced damage of erythrocytes. Recent evidence showed that causes of anaemia in SLE vary and its pathogenesis may be immune or non-immune [8]. Our data showed that haemolytic anaemia and thrombocytopenia were associated with ANA. The timely differential diagnosis between primary and SLE-related AIHA often remains unclear. Systemic lupus erythematosus related AIHA patients are significantly younger than patients with primary AIHA at the time of diagnosis and the serological parameters for haemolysis including LDH, total bilirubin, and conjugated bilirubin in SLE related AIHA are less prominently elevated [9, 10]. Detection of anticardiolipin antibody and higher levels of plasma tumor necrosis factor receptors (sTNFR_{II}) may favor the diagnosis of SLE-related instead of primary AIHA [10]. Immunosuppressive agents are used to achieve prompt control of disease activity and improve survival of patients with SLE [5]. It has been reported that Egyptian children at the time of first diagnosis of SLE appeared to have severe disease and high SLE disease activity, high index scores and high prevalence of lupus nephritis, but responded well to therapy with a favorable short-term prognosis [3]. Our case also responded well to steroid treatment and as we have been informed, the patient had no relapse over one year of follow-up.

Systemic lupus erythematosus patients with lymphadenopathy show significantly more constitutional symptoms such as fatigue, weight loss, and fever; more cutaneous and mucosal signs malar rash, purpura, skin ulcers, mouth ulcers, alopecia, and discoid lesions, higher rates of hepatomegaly and splenomegaly, increased double stranded DNA antibodies (anti-dsDNA) and decreased complement levels [10, 11]. Our case had intermittent fever for 20 days and anaemia as the first clinical findings but without cutaneous and mucosal signs related to SLE.

The 3 major categories that account for most cases of fever of unknown origin are infections, malignancies, and noninfectious inflammatory diseases [12]. If the potential cause of fever is unknown, ¹⁸F-FDG PET has the potential to play a central role as a second-line procedure [12] and in our case ruled out malignancy. Generalized or peripheral lymphadenopathy as the first clinical manifestation of the disease has also been reported [13]. The cervical group is the most common nodal group to be involved; followed by mesenteric, maxillary, and inguinal groups of lymph nodes [14, 15]. Because activated lymphocytes have increased glucose metabolism ¹⁸F-FDG PET has been successfully used to visualize large concentrations of these cells in lymphoid organs where antigen presentation and lymphocyte activation occur. Widespread increased ¹⁸F-FDG uptake in

lymph nodes of patients with active lupus (as well as increased thymic uptake) has been described [16, 17]. In patients with severe haematological manifestations of SLE, active disease in other organs is likely to be present [18], as was shown in our case by pleural and abdominal ¹⁸F-FDG PET scans. Furthermore, in our case, large splenomegaly, with slightly increased uptake of ¹⁸F-FDG PET/CT was also observed which was not reported before, in similar cases although such a finding is expected in cases of haemolytic anaemias. Differentiating benign from malignant uptake of ¹⁸F-FDG may be particularly challenging because PET/CT is not specific in this aspect [19]. Besides SLE, other causes of lymphadenopathy, such as infections and malignant diseases, must be considered in the differential diagnosis. Lymphoma, with a predominance of aggressive histological sub-types (in particular diffuse large B cell lymphoma) is the most prominent concern [14, 20, 21]. Patients with SLE presenting with fever constitute a clinical challenge because of the myriad of potential causes inducing fever. Patient's age, associated physical and serologic findings can be helpful, but lymph nodes biopsy may be necessary [14, 21]. It has been suggested that autoimmune anemias are due, at least partly, to impaired response of the patients' autoimmune lymphatic system which thus becomes unable to protect the viability of endogenous red blood cells [22]. A typical location of unusually large lymph nodes on ¹⁸F-FDG PET/CT should raise suspicion of lymphoma. Our case showed symmetrically increased ¹⁸F-FDG uptake in small lymph nodes, and in pathology multiple cavities in lymph nodes with serum infusion that supported the diagnosis of SLE related AIHA rather than that of lymphoma.

In conclusion, ¹⁸F-PET/CT in SLE can visualize not only the degree of disease activity or the "burden of inflammation" but also the distribution of the disease in the entire body. A very large spleen with low uptake of ¹⁸F-FDG was also detected for the first time in SLE patients with AIHA. A symmetrically increased ¹⁸F-FDG uptake in small lymph nodes and also multiple cavities in lymph nodes with serum effusion detected in pathology, supported the diagnosis of SLE related AIHA rather than that of lymphoma.

The authors declare that they have no conflicts of interest

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The Petruzzelli Theatre, named after the Petruzzelli brothers, who provided the funding for it, Province of Bari, Italy.