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CASE REPORT

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Systemic Lupus Erythematosus Associated Pitfalls on ^{18}F-FDG PET/CT: Reactive Follicular Hyperplasia, Kikuchi-Fujimoto Disease, Inflammation and Lymphoid Hyperplasia of the Spleen Mimicking Lymphoma

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Abstract Systemic lupus erythematosus (SLE) is associated with a variety of inflammatory processes that can affect the lymph nodes, brain, kidneys, and spleen. We present two patients with SLE in whom SLE-associated conditions complicated interpretation of ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) imaging of the lymph nodes and the spleen. The imaging findings mimicked lymphoma, but histopathological evaluation showed benign processes including reactive follicular hyperplasia in the lymph nodes, Kikuchi-Fujimoto disease in perisplenic lymph nodes, and inflammatory changes and lymphoid hyperplasia in the spleen.

Keywords Systemic lupus erythematosus · SLE · Lymphoma · Kikuchi-Fujimoto disease · Spleen · PET/CT

Introduction

Systemic lupus erythematosus (SLE) is an immune complex disease of unknown etiology, which causes excessive production of autoantibodies to components of the cell nucleus. The formation and deposition of immune complexes leads to inflammatory responses that are significant contributors to the pathogenic mechanisms resulting in tissue damage, specifically in the lymph nodes, brain, kidneys and spleen [1]. Lymph nodes are commonly enlarged in patients with active SLE. On histological evaluation, the involved lymph nodes show varying degrees of coagulative necrosis with hematoxyphil bodies or reactive follicular hyperplasia associated with increased vascularity [2–4]. Kikuchi-Fujimoto disease (KFD) is a histiocytic necrotizing lymphadenitis that is found mainly in young women and may be a self-limiting form of SLE, based on similarities in microscopic features. About 35 cases of KFD associated with SLE have been reported in the literature so far [5, 6].

^{18}F-Fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) imaging has been described only in a few SLE patients in the literature. Increased ^{18}F-FDG uptake in lymph nodes affected by SLE has been described and is a known potential mimic of lymphoma [7]. Although ^{18}F-FDG uptake in lymph nodes affected by KFD has been described in a few patients [8, 9], abnormal ^{18}F-FDG uptake in an SLE patient with KFD has not been previously described. Abnormal ^{18}F-FDG uptake in the spleen of SLE patients has also not been described in the literature. We present ^{18}F-FDG PET/CT imaging findings in two SLE patients.

Case reports

Patient 1

A 26-year-old woman presented with a 3-month history of intense fatigue, diffuse myalgia, headaches, palpable cervical lymph nodes and pancytopenia. A bone marrow biopsy did

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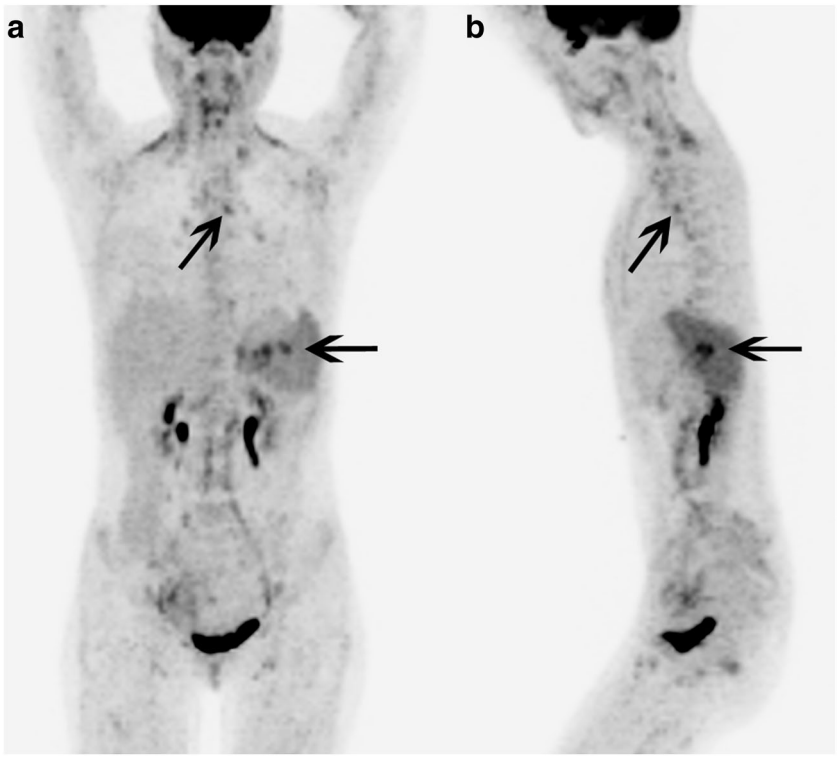

Fig. 1 Patient 1. ^{18}F-FDG PET/CT maximum intensity projection (**a**) anterior and (**b**) left lateral images show diffuse mildly ^{18}F-FDG avid lymphadenopathy with several foci of ^{18}F-FDG uptake in the AP window (*diagonal arrows*), and the right lower paratracheal and subcarinal regions, as well as several foci of intense ^{18}F-FDG uptake in the region of the splenic hilum (*left-pointing arrows*). Histological evaluation of these areas confirmed Kikuchi-Fujimoto disease. There is also diffusely increased ^{18}F-FDG uptake in the entire spleen

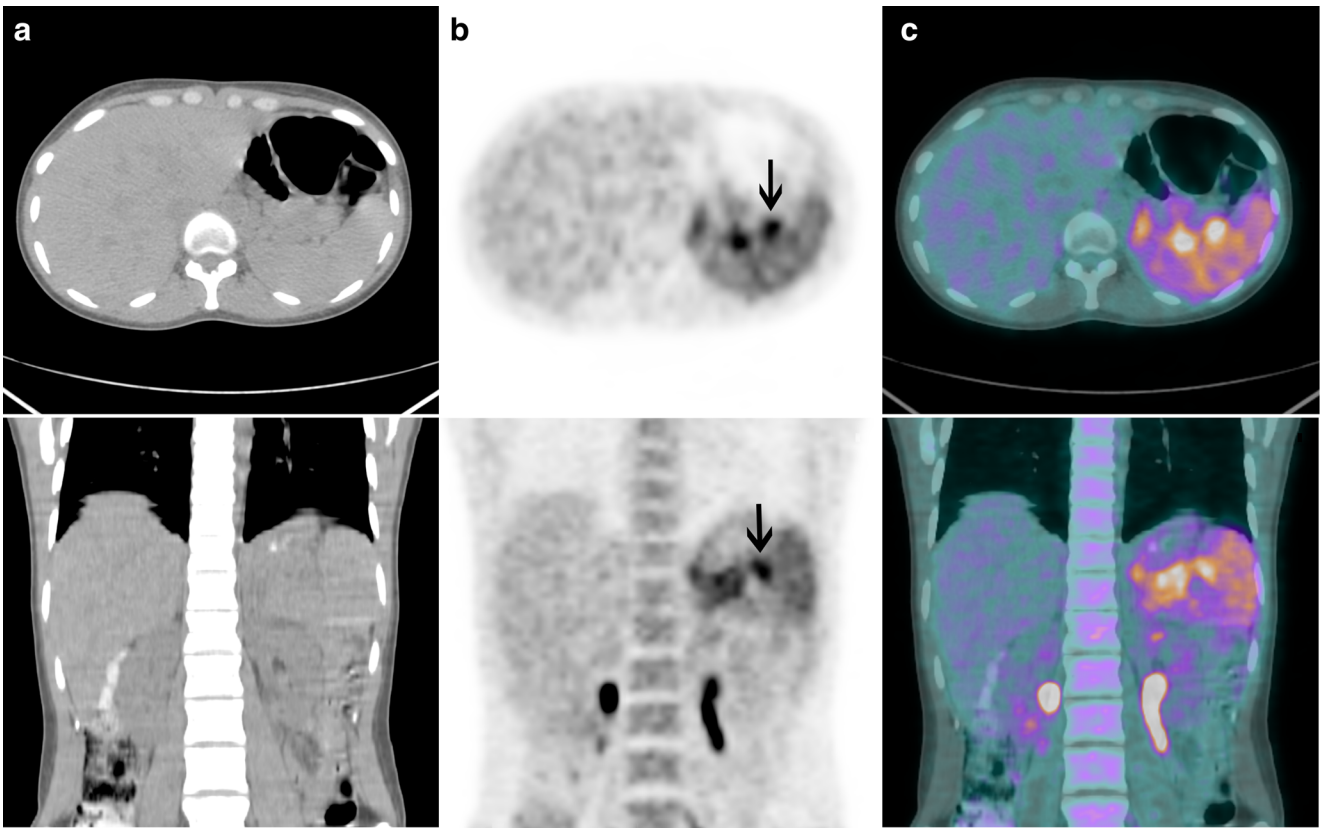

Fig. 2 Patient 1. Transaxial and coronal (**a**) CT, (**b**) PET and (**c**) PET/CT fusion images show intensely ^{18}F-FDG-avid lymph nodes in the splenic hilum (*arrows*) and diffusely increased ^{18}F-FDG uptake in the spleen

not show any abnormalities. She was referred for an ^{18}F-FDG PET/CT scan for the evaluation of possible lymphoma. Maximum intensity projection (MIP) images showed diffuse mildly ^{18}F-FDG-avid lymphadenopathy throughout the body. The most metabolically active foci were a 1-cm node (5) in the aortopulmonary window with a maximum standardized uptake value (SUV_{max}) of 4.3, a 0.8-cm right paratracheal node (4R) with SUV_{max} 3.6 and a 1-cm subcarinal lymph node (7) with SUV_{max} 3.1. There were multiple foci of more intense ^{18}F-FDG uptake in the splenic hilum (SUV_{max} 6.2) which were concerning for lymphoma. There was also diffusely increased uptake in the spleen with SUV_{max} 4.6, which was also concerning for malignant involvement (Figs. 1 and 2). The patient had a mediastinoscopy, and histological evaluation of a right lower paratracheal node (4R) and a subcarinal node (7) showed anthracosis, follicular hyperplasia and sinus histiocytosis compatible with SLE, and no evidence of malignancy.

The patient underwent splenectomy 2 weeks following the PET/CT scan. Sectioning of four splenic hilar lymph nodes revealed a partly distorted architecture. There were large areas of coagulative necrosis with abundant karyorrhexic debris and basophilic substance having the appearance of hematoxyphil bodies surrounded by a variety of cells including histiocytes, plasmacytoid monocytes, immunoblasts and some small and large lymphocytes. A few residual hyperplastic lymphoid follicles were seen. The findings were consistent with KFD (Fig. 3). Sectioning of the spleen showed splenic tissue whose architecture was partly altered by a variable expansion of white pulp with small to medium sized cells with mildly irregular nuclei and mixed with scattered large cells. The splenic sinuses were dilated and contained macrophages, some of whose cytoplasm was filled with leukocytes having pyknotic and karyorrhexic nuclei. Mildly hyperplastic germinal centers were identified. Multiple blood vessels

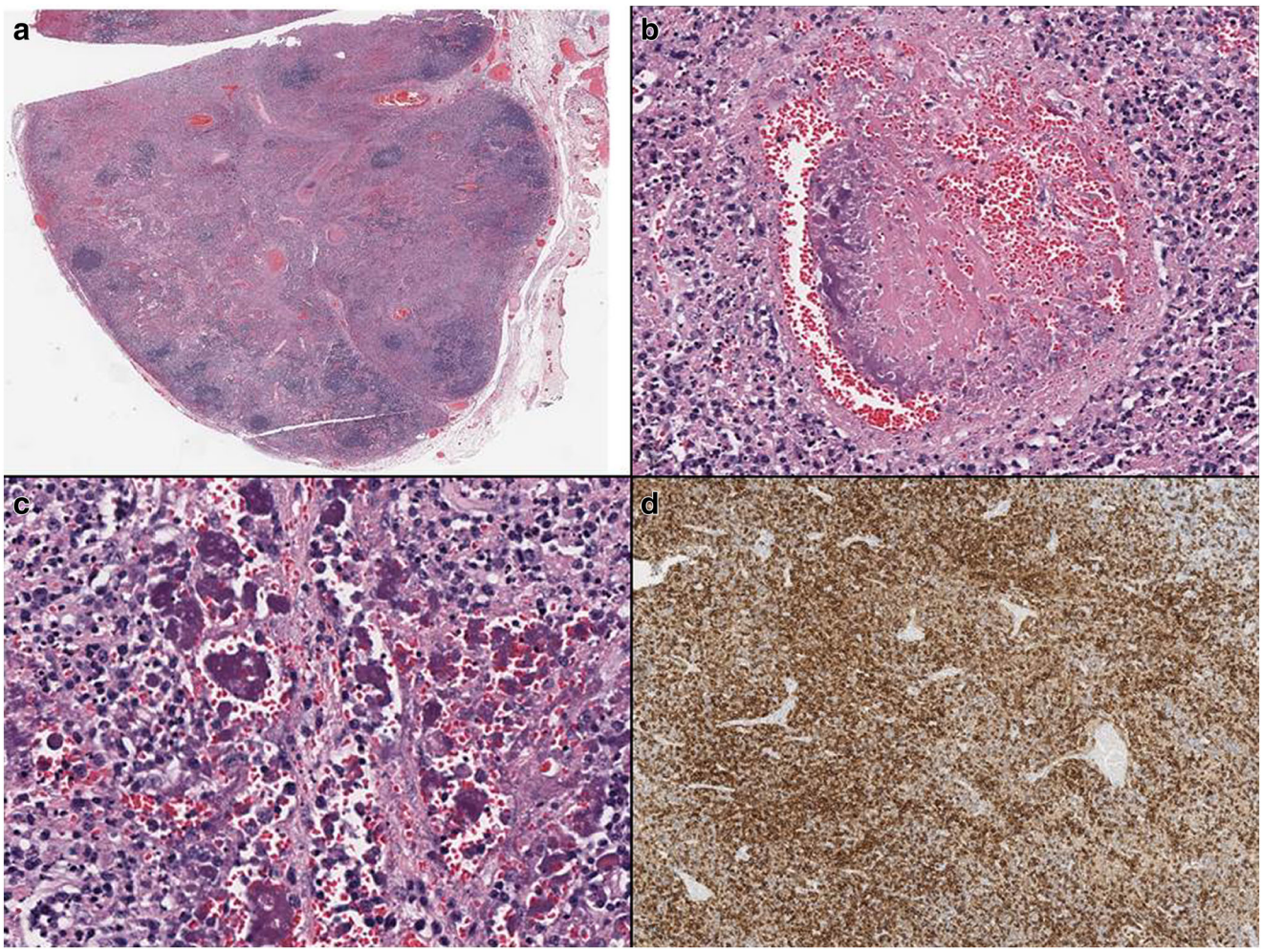

Fig. 3 Patient 1. **a** Immunohistochemical evaluation of a splenic hilar lymph node showing overall preserved architecture and multiple well-circumscribed areas of necrosis. **b** Necrosis of a small blood vessel with hematoxyphil bodies in the blood vessel wall. **c** Multiple hematoxyphil bodies in the sinuses and abundant karyorrhexis. **d** CD8 positivity in a majority of the lymphocytes. The findings were consistent with Kikuchi-Fujimoto disease

showed infiltration by lymphocytes and plasma cells producing vasculitis-like changes with mildly irregular cells in the subendothelium.

The splenic findings were identified as atypical lymphoid hyperplasia with vascular (predominantly subendothelial) infiltration by lymphoid cells, most consistent with an immune disorder and with SLE. There was no evidence of lymphoma in the histology. The patient's serum laboratory values obtained at the time of the PET/CT scan also corresponded to a diagnosis of SLE: parvovirus B19 IgG-positive (IgM-negative), antihistone antibody-positive, antinuclear antibody (ANA) screen positive at 1:160 dilution, anti-DNA antibody >1,000 kIU/L (normal <30 kIU/L). The serum was negative for anti-SSA, anti-SSB, anti-Smith, anti-RNP, anti-Jo-1, anti-SCL-70, anti-smooth muscle, anti-mitochondrial cell, anti-parietal cell, anti-cardiolipin, HIV, hepatitis B and C, and cytomegalovirus (CMV).

Patient 2

A 24-year-old woman with a 4-year history of SLE originally diagnosed after presenting with malar rash, severe polyarthritis, palpable lower extremity purpura and positive antinuclear and anti-DNA antibodies, now presented with recurrent high fever (up to 39°C), myalgia, and enlarged lymph nodes (cervical, axillary, and inguinal). She was referred for an ^{18}F-FDG PET/CT scan to rule out lymphoma. MIP images showed diffuse and extensive intensely ^{18}F-FDG-avid lymphadenopathy throughout the body with the most intense ^{18}F-FDG uptake in a 3.1-cm left axillary lymph node with SUV_{max} 6.8, which was concerning for lymphoma. There was also diffusely increased uptake in the spleen with SUV_{max} 4.1, which was concerning for malignant involvement (Figs. 4 and 5).

Biopsy and histological evaluation of the 3.1-cm left axillary node showed a reactive lymphocyte population identified as reactive follicular hyperplasia, with no evidence of lymphoma (Fig. 6). Biopsy and histological evaluation of the spleen showed lymphoid hyperplasia and inflammatory changes consistent with SLE, with no evidence of lymphoma. Serum laboratory tests done at the time of the PET/CT scan showed positivity for anti-DNA antibody 623 kIU/L (normal <30 kIU/L), ANA speckled at 1:160 dilution, anti-cardiolipin IgM 35 MPL U/mL (normal range 5–15 MPL U/mL; IgG was 9 U/mL and within the normal range), anti-SSA 165 U/mL (normal range 0–20 U/mL), anti-SSB 117 U/mL, anti-Smith 190 U/mL, anti-RNP 228 U/mL, erythrocyte sedimentation rate 56 mm/h (normal range 0–10 mm/h), and C-reactive protein 4.5 mg/L (normal range 0–5.0 mg/L).

Discussion

SLE is a multisystem disorder that is associated with localized or generalized lymphadenopathy at some stage in the

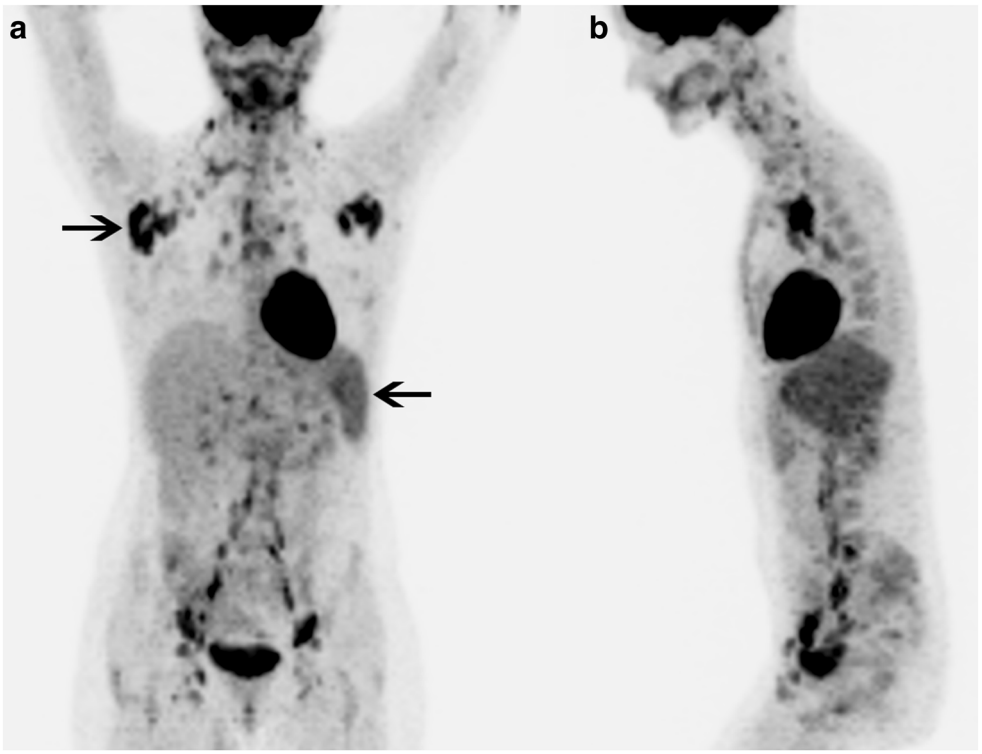

Fig. 4 Patient 2. ^{18}F-FDG PET/CT MIP (**a**) anterior and (**b**) left lateral images show diffuse intensely ^{18}F-FDG-avid lymphadenopathy throughout the body, with the most intense ^{18}F-FDG avidity in the axillae (*right-pointing arrow*). There is also diffusely increased ^{18}F-FDG uptake in the entire spleen (*left-pointing arrow*)

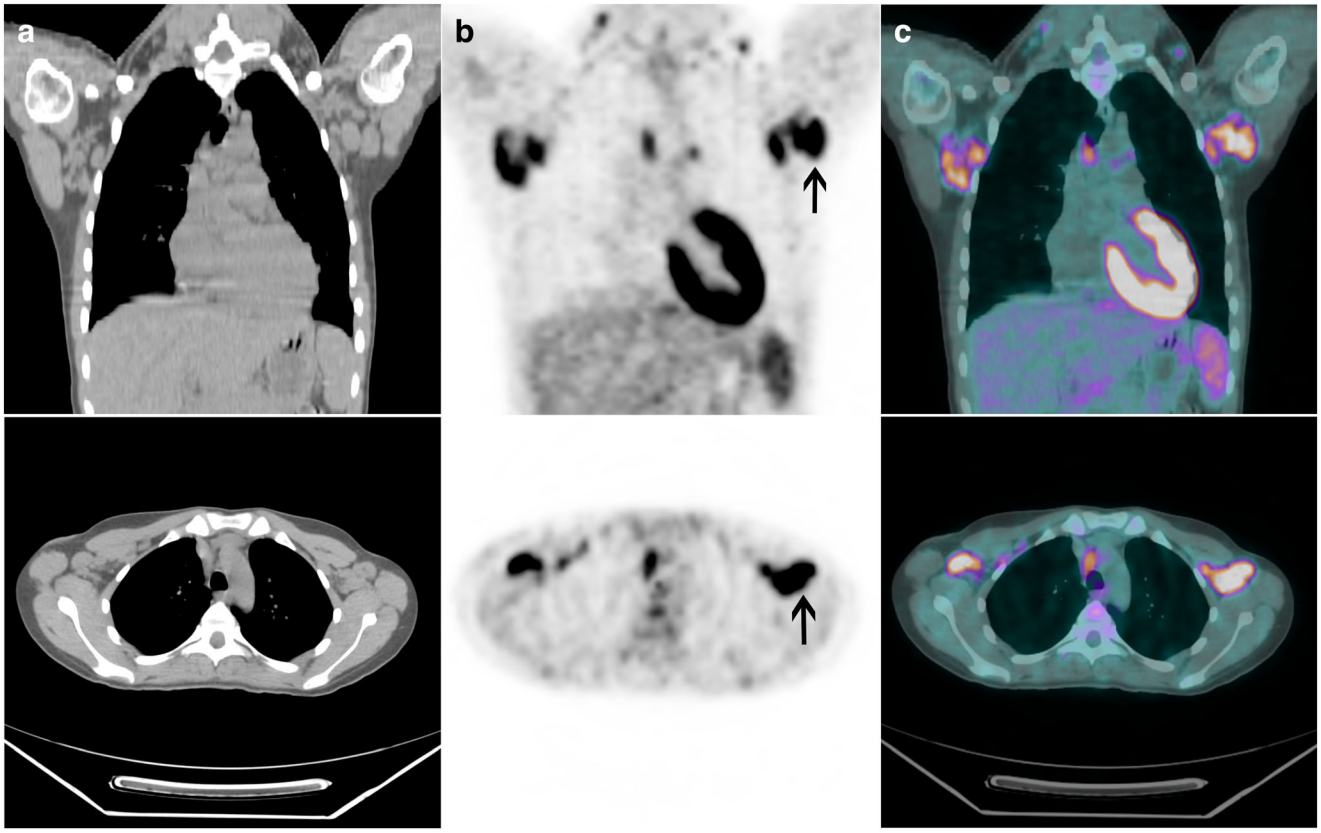

Fig. 5 Patient 2. Coronal and transaxial (**a**) CT, (**b**) PET and (**c**) PET/CT fusion images show intensely ^{18}F-FDG avid axillary lymph nodes (*arrows*). Histological evaluation of these nodes confirmed reactive follicular hyperplasia

evolution of the disease in up to 60% of patients. SLE patients also have an increased risk of developing non-Hodgkin lymphoma [2]. SLE lymph nodes contain varying degrees of coagulative necrosis with hematoxyphil bodies, or reactive follicular hyperplasia. Reactive follicular hyperplasia was considered to be a nonspecific change and received little attention in the literature, although recent studies have shown a rather wide variety of identifiable histological patterns, one of which is similar to Castleman disease [3, 4]. The differences between the histological subtypes of SLE reactive follicular hyperplasia may affect the ^{18}F-FDG avidity of the affected lymph nodes. A few patients with increased ^{18}F-FDG uptake in SLE-associated lymphadenopathy have been described in the literature [7], although the role of ^{18}F-FDG PET/CT imaging in SLE patients has never been investigated. In our case series, patient 1 showed mild ^{18}F-FDG uptake in her SLE-associated lymphadenopathy while patient 2 showed much more intense ^{18}F-FDG uptake in her SLE-associated lymphadenopathy.

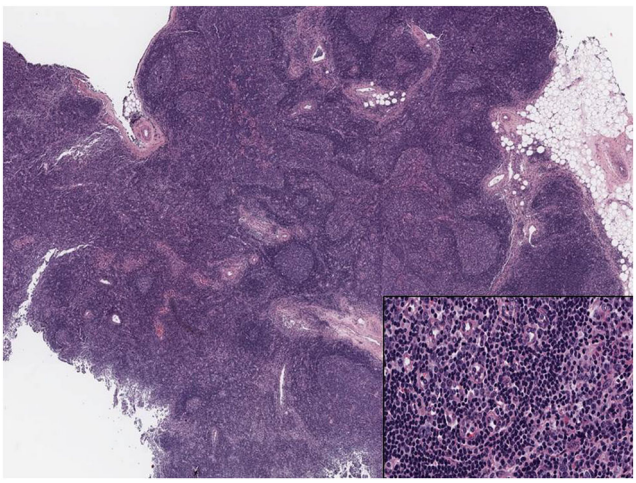

Fig. 6 Patient 2. Immunohistochemical evaluation of a left axillary lymph node showing follicular hyperplasia with enlarged germinal centers, intact mantle zones and follicles of variable size and shape. *Inset*: High-power view of the germinal center with multiple tingible body macrophages and apoptotic bodies. There was no evidence of lymphoma

KFD is a histiocytic necrotizing lymphadenitis first described in Japanese women by Kikuchi [5] and Fujimoto et al. [6] in 1972, but later described worldwide. Patients usually present with enlarged cervical lymph nodes and fever. The course of KFD is almost always benign with excellent outcomes and spontaneous resolution between 1 and 4 months. The etiology of KFD is unknown, but several infectious agents have been proposed as the causative agents of the disease that initiate a hyperimmune response of T cells and histiocytes including Epstein-Barr virus, HTLV-1, HHV-6,

toxoplasma, parvovirus B19, CMV, *Brucella*, *Yersinia enterocolitica*, and parainfluenza virus. An autoimmune origin and association with SLE has also been suggested due to a number of patients in whom SLE was diagnosed before, simultaneously with, or after KFD. Approximately 35 patients with KFD associated with SLE have been reported in the literature [10–15]. Increased ^{18}F-FDG uptake in lymph nodes involved by KFD has been found in a few patients [8, 9], however abnormal ^{18}F-FDG uptake in SLE patients with KFD has not been previously reported.

SLE can cause numerous inflammatory changes as well as lymphoid hyperplasia within the spleen [16]. Abnormal diffusely increased ^{18}F-FDG uptake in the spleen of SLE patients (as seen in both of our patients) has not been previously reported in the literature, and is a potential pitfall in the evaluation of malignancy such as lymphoma, especially since diffusely increased ^{18}F-FDG uptake in the spleen typically represents disease involvement in lymphoma [17]. The etiology of the increased ^{18}F-FDG uptake in the spleen of our patients, whether due to inflammatory changes or lymphoid hyperplasia typical of SLE, remains unknown. The abnormal ^{18}F-FDG uptake seen in the lymph nodes and spleen of both of our SLE patients represents a significant challenge in the evaluation and interpretation of PET/CT scans for the presence of a malignancy such as lymphoma and further investigation of PET/CT findings in SLE patients and their clinical significance is warranted.

Compliance with Ethical Standards

Conflict of interest William Makis, Anthony Ciarallo, Milene Gonzalez-Verdecia and Stephan Probst declare that they have no conflict of interest.

Ethical statement The study was approved by an institutional review board or equivalent and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All subjects in the study gave written informed consent or the institutional review board waived the need to obtain informed consent.

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