The role of PET/CT SCAN in addressing autoinflammatory diseases; A case report of a young man presenting with fever, splenomegaly and exanthem

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Abstract

Objective: Adult-onset Still's disease (AOSD) is an uncommon autoinflammatory syndrome characterized by quotidian fever, arthritis, evanescent exanthem and splenomegaly. Lymphadenopathy is present in about a half of patients; it is usually symmetrical with the cervical area being most commonly involved. When constitutional symptoms are present, an extensive work-up should be performed in order to exclude hematological malignancies, such as lymphoma. **Subject and Methods:** A 38-year-old male is presented due to fatigue and high-grade fever that first appeared a month ago. He did also refer night sweats, arthralgias and an evanescent erythema on the trunk and anterior thigh area. Serology testing for bacteria and viruses as well as autoimmune rheumatic diseases was requested. Whole body computed tomography (CT) scan was ordered and displayed a marginal lymph node in the right hilum and smaller ones in the axillary region. Positron emission tomography/CT (PET/CT) with fluorine-18-fluoro-deoxy-glucose (^{18}F-FDG) showed hypermetabolic lymph nodes, with the right upper internal jugular lymph node being the most dominant, as well as diffusely increased ^{18}F-FDG uptake by bone marrow and spleen, posing in the differential diagnosis a neoplastic disease of the hematopoietic tissues. **Results:** Further laboratory testing showed high ferritin levels. It was decided to procced with biopsy of the aforementioned hypermetabolic internal jugular lymph node and bone marrow. Histopathological examination did show hyperreactivity and no malignant cells neither in the lymph node nor in the bone marrow. **Conclusion:** Adult-onset Still's disease is a rare disorder and it is a diagnosis of exclusion. High-grade fever along with arthralgias, splenomegaly, high serum ferritin levels and the presence of exanthem should pose high in the differential the AOSD. In this case, PET/ CT guided the anatomical location for lymph node biopsy in order to differentiate AOSD from lymphoma. The dissociated increased ^{18}F-FDG uptake from the cervical and axillary lymph nodes is characteristic of AOSD.

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Introduction

Adult-onset Still's disease (AOSD) is a rare inflammatory clinical entity that along with systemic juvenile idiopathic arthritis (sJIA), is encompassed under the term Still's disease [1]. The nomenclature is dichotomized depending on the age. Adult-onset Still's disease affects young adults, above sixteen years of age and the disease has a bimodal age distribution; one peak between the ages of 16 and 25 and the second between the ages of 36 and 46 [1]. The clinical clues of AOSD are the following; quotidian fever, pharyngitis, arthritis, evanescent exanthem, splenomegaly, lymphadenopathy and high levels of serum ferritin. Due to the fact that the disease is a diagnosis of exclusion, the differential diagnosis should include viral diseases, malignancy, drug reactions and other autoimmune rheumatic diseases [2]. In our case, positron emission tomography/computed tomography (PET/CT) displayed essential characteristics of the disease's lymphadenopathy and guided clinicians to proceed with precise diagnostic tests that excluded hematological malignancy, posing a final diagnosis.

Case Report

A 38-years-old male patient is admitted to the internal medicine department due to persistent high-grade fever and pharyngeal pain that did not respond to oral antibiotics. The patient reported body temperature up to 39°C, generalized fatigue, soreness and joint pain on the right knee and left shoulder, as well as a transient rash on the trunk and anterior area of the right knee. He admitted for further investigation. During physical exa-

mination, the patient was hemodynamically stable, however febrile (38.7°C) with the metacarpophalangeal joints being edematous and painful symmetrically. Liver and spleen were also palpable. Small lymph nodes were palpated at the upper right cervical area, that were nimble and not painful. Initial laboratory findings were the following; white blood cells (WBC) 11.37x10^3/μL [4-10.5x10^3/μL], with neutrophils' predominance, hematocrit 38% [41%-51%], platelets 212x10^3/μL [150-400x10^3/μL], fibrinogen 499mg/dL, aspartate aminotransferase (AST) 76IU/L [5-37IU/L], alanine aminotransferase (ALT) 144 IU/ L 5-40IU/L and C-reactive protein (CRP) 5.8mg/dL [0-0.5mg/dL]. Upon his admission blood and urine cultures were obtained. Antinuclear antibodies, rheumatoid factor and serum globulins were also measured. The results came up negative, hence did not point either to bacteremia nor to an autoimmune rheumatic disease. Whole body CT was ordered. Small axillary lymph nodes, a hilar lymph node on the right and splenomegaly were noted. Positron emission tomography/CT was requested to examine the scenario of hematological malignancy and the results did exhibit increased fluorine-18-fluoro-deoxy-glucose (^{18}F-FDG) uptake in lymph nodes upper and below the diaphragm, especially in the right upper internal jugular area, with a maximum standardized uptake value (SUVmax) equal to 9.3 (Figure 1). Furthermore, diffusely ^{18}F-FDG uptake was noted in the spleen, with SUVmax value equal to 5.1 (while the liver SUVmax was 2.7) as well as in the bone marrow, which showed SUVmax value equal to 6.4 (Figure 2). Additionally, there was no ^{18}F-FDG uptake in the joints. The results of the PET/CT posed in the differential diagnosis a neoplastic disease of the hematopoietic tissue and indicated the need for lymph node biopsy, while suggesting the anatomical area that would be more accessible; right internal jugular area. Bone marrow biopsy was also performed. Histopathological findings from the bone marrow study were consistent with hypercellular marrow that accompanies infectious or systemic inflammatory diseases (Figure 3), while the results from the cervical lymph node excision did exhibit reactive lymphadenitis (Figure 4). Summarizing that all the diagnostic tests had non-conclusive results along with the clinical syndrome; presence of high-grade fever, pharyngitis, exanthem, migratory arthritis, splenomegaly and high serum ferritin, the diagnosis of AOSD was made.

Discussion

Autoinflammatory diseases, including AOSD, are uncommon in daily clinical practice [1]. These syndromes differ from other autoimmune rheumatic diseases. Adult-onset Still's disease is

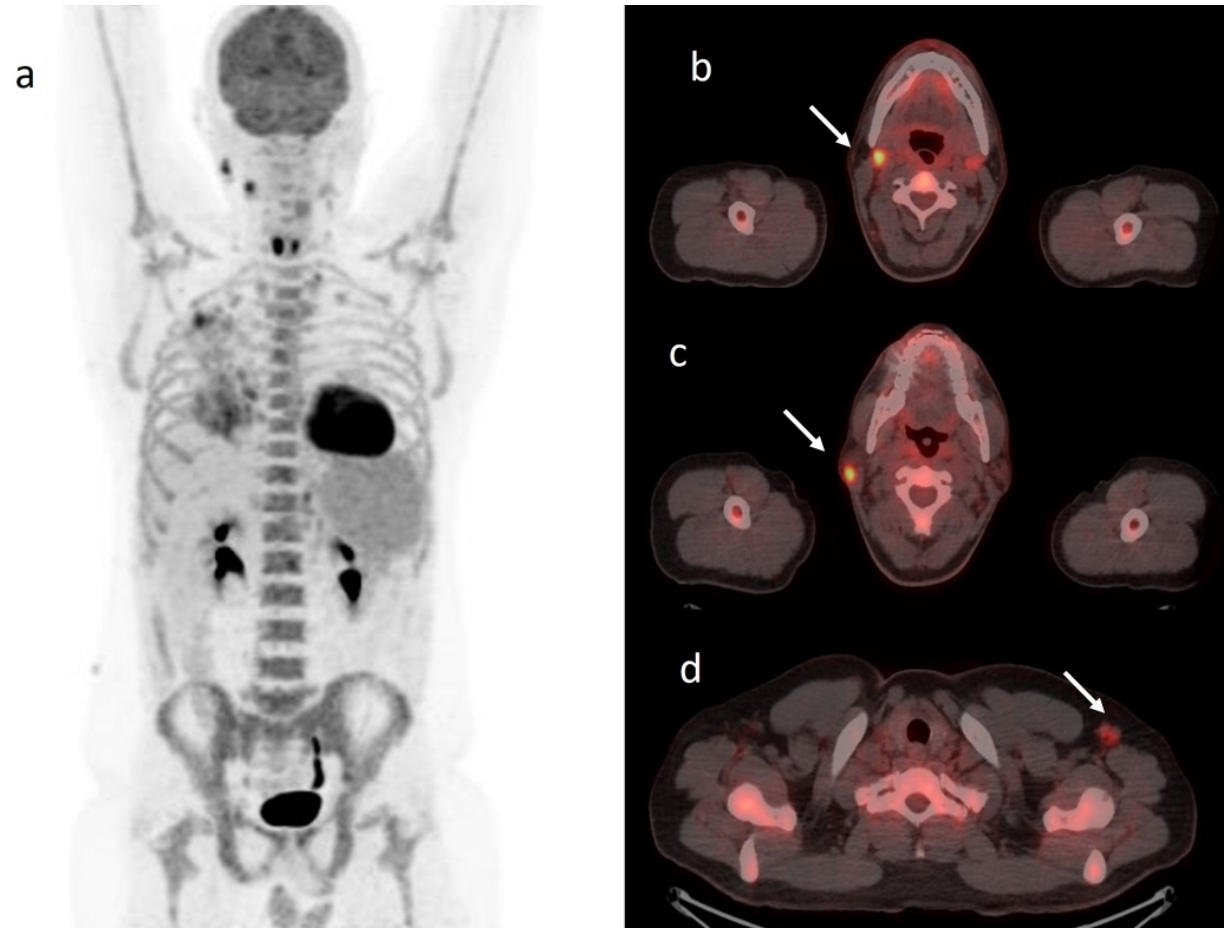

Figure 1. Maximum intensity projection (MIP) image of ^{18}F-FDG PET (a) and fused ^{18}F-FDG PET/CT images showing hypermetabolic cervical (b and c) and axillary (d) lymph nodes (white arrows).

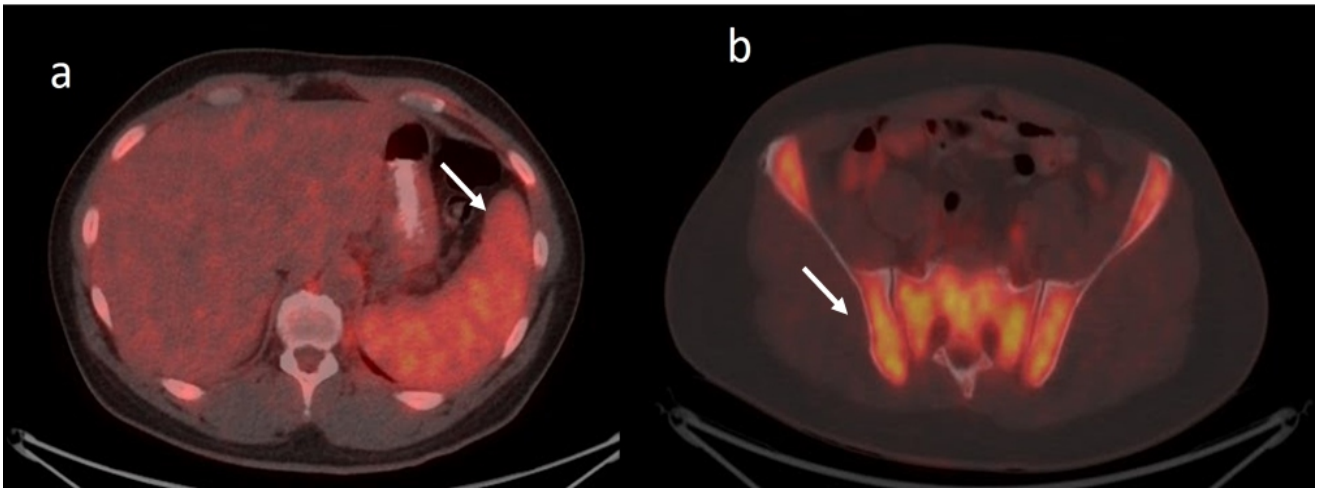

Figure 2. Fused ^{18}F-FDG PET/CT images showing diffusely increased ^{18}F-FDG uptake in spleen (a) and bone marrow (b) (white arrows).

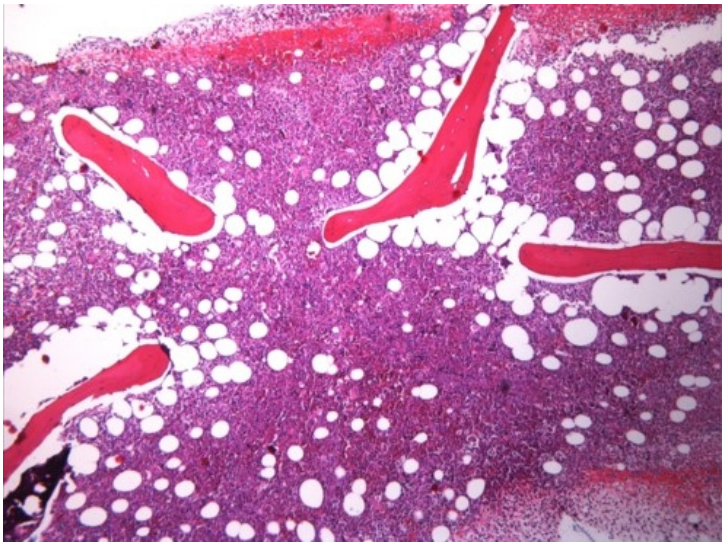

Figure 3. Bone marrow biopsy findings point to a hypercellular bone marrow that could be the expression of an infectious, autoinflammatory or systemic process. Bone marrow infiltration by neoplastic cells, of hematological or solid tumors' origin is not documented.

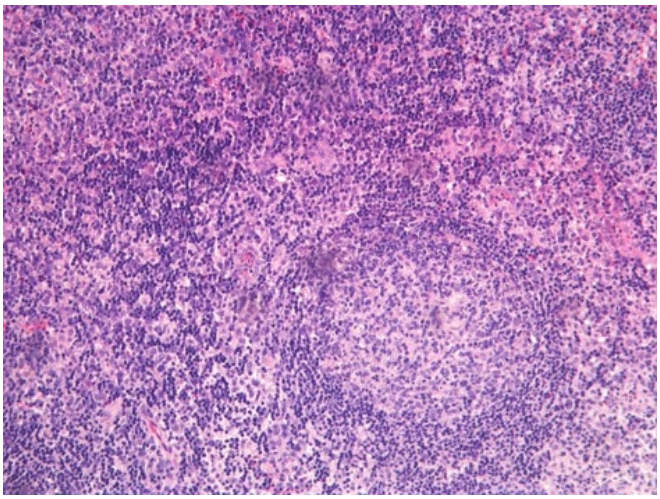

Figure 4. Lymph node biopsy corresponds to reactive lymphadenitis in the context of an underlying disease. Maintenance of normal lymph node architecture with distinct T and B zone and presence of normal lymphoid follicles without immunomorphological deviations. Identification of mild polyclonal plasma cell infiltration and scattered, activated, CD30+ small lymphocytes within the lymph node was subsequently detected with immunohistochemistry (not shown).

characterized by innate immune cell activation that leads to an autoinflammatory cascade, also known as "cytokine storm". Autoantibodies or autoantigen-specific T and B cells that trigger inflammation and tissue damage do play an essential role in immune mediated inflammatory syndromes and not in autoinflammatory conditions such as AOSD [3]. The etiology of the syndrome is unknown and a hypothesis is that environmental factors, e.g. viral causes, trigger an autoinflammatory cascade in a genetically predisposed patient [2]. When the inflammation cataract cannot be controlled, then it may progress to a secondary form of hemophagocytic lymphohistiocytosis (HLH), called macrophage activation syndrome (MAS) [3]. Elevated inflammatory markers, such as erythrocyte sedimentation rate (ESR), CRP and serum ferritin are characteristics [4]. Ferritin synthesis from hepatocytes is enhanced in response to inflammatory cytokines [3]. Early recognition of the syndrome is of utmost importance as it may be evolved in a potentially fatal condition. Although there are "alarm" features; quotidian high-grade fever, evanescent exanthem, arthralgias and or arthritis, pharyngitis, lymphadenopathy, splenomegaly and to a lesser extent serositis and myocarditis, its definite diagnosis is a diagnosis of exclusion [2]. Imaging studies on the region of the neck, do support that cricothyroid perichondritis or aseptic non-exudative pharyngitis could be the etiology of the sore throat [5]. Zhou et al. (2020) studied the use of ^{18}F-FDG PET /CT in identifying AOSD in connective tissue diseases (CTD) and concluded that although CTD may manifest as diffusely increased ^{18}F-FDG uptake in the spleen, bone marrow as well as cervical and axillary lymph nodes, its incidence and uptake value were higher in AOSD. Specifically, if two or more of the following criteria; a. spleen SUVmax/liver SUVmax ≥1.2 and/or bone marrow SUVmax/liver SUVmax ≥1.4, b. symmetrically distributed reactive hyperplastic lymph nodes mainly in the neck and axilla with a lymph node SUVmax/liver SUVmax ≥1.8 and c. no other abnormal uptake by other organs, were met, as in our case, then the sensitivity, specificity, and accuracy of diagnosing AOSD could reach 90.7%, 92.4%, and 91.7%, respectively [6]. Our case is a typical case of AOSD, nonetheless the gold-standard test for its diagnosis does not exist. The necessity to exclude other clinical entities impelled clinicians to order a PET/CT scan. Positron emission tomography/CT scan however, should not be performed in any case of non-remitting fever, since PET/CT findings alone are not sufficient to make a differential diagnosis of AOSD versus other clinical entities [7]. It should be ordered when the clinical signs and symptoms, along with the rest of the diagnostic work-up, do not "complete the puzzle" of a clinical scenario. In this clinical case, PET/CT guided clinicians to proceed with biopsy from the most representative and accessible anatomical area in order to conclude or exclude a specific diagnosis. The ^{18}F-FDG preference for cervical and salivary glands along with the cricothyroid area seems to enhance the imaging profile of AOSD in nuclear medicine. Larger studies are needed, that will study patients with autoinflammatory syndromes, assessing the imaging characteristics in the field of nuclear medicine and comparing them with other syndromes that do cause prolonged fever, such as infections and hematological malignancies. Should ever be possible the gold-standard test, for making the diagnosis for autoinflammatory syndromes, being the PET/CT scan?

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