Sarcoidosis mimicking lymphoma on FDG-PET imaging

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Sarcoidosis is an inflammatory, systemic disease characterized by noncaseating granulomas. We describe a case of a 52-year-old female who presented with fevers, chills, night sweats, and weight loss of four months' duration. Lymphoma was suspected, and results of advanced imaging procedures were also consistent with lymphoma. However, mediastinal lymph-node biopsy, bone-marrow aspiration, and biopsy revealed noncaseating granulomas. She was diagnosed with sarcoidosis and had a positive therapeutic response to drug therapy. This case study illustrates that sarcoidosis can be a pitfall in 18-F-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging, which may lead to false-positive diagnosis of malignancy. PET-positive lesions do not always indicate malignancy, and histological confirmation of the lesions with biopsy should always be performed.

Introduction

Sarcoidosis is an uncommon inflammatory disease characterized by the presence of noncaseating granulomas in affected organs (1). It is a multisystem disease with a highly variable clinical course, primarily manifesting with pulmonary involvement. However, any organ may be involved, including the eyes, skin, liver, kidneys, central nervous system, and spleen. Bone-marrow involvement is rare, and isolated extrapulmonary sarcoidosis occurs in fewer than 5% of cases (2). We report a case of a patient who presented clinically as if she had lymphoma (including positive PET findings), but subsequently was diagnosed with sarcoidosis. She responded well to treatment with prednisone and hydroxychloroquine.

Case report

A 52-year-old Caucasian female presented with a 4-month history of fevers, night sweats, weight loss, abdominal pain, and diarrhea. The patient reported an unintentional 50-pound weight loss in the past 4 months. She denied muscle weakness, skin rash, shortness of breath, or vision problems. Her medical history was significant for diabetes and uterine fibroids. Social history revealed no recent travel and no history of smoking or alcohol use. Family history was significant for colon cancer in her mother but no known autoimmune conditions. Review of systems was otherwise negative. Physical exam revealed an afebrile female with normal vital signs and a BMI of 43.4 kg/m2, no palpable lymphadenopathy, and clear lung fields bilaterally. No petechiae, cyanosis, clubbing, neurologic focialy, skin rash, or joint effusions were noted.

Laboratory workup revealed white blood cell count of 3.9 x 10³ and a differential of 70.8% neutrophils, 16.7% lymphocytes, 7.5% monocytes, 4.3% eosinophils, and 0.7% basophils with normal hemoglobin, liver function tests, and calcium level. A workup for lymphoma was started. A CT of the thorax revealed multiple enlarged mediastinal and hilar lymph nodes, the largest located at the subcarinal space and measuring 1.7 x 2.2 cm. This was followed up with a PET scan that showed high FDG uptake in lymph nodes in the neck (SUVmax 7.7), mediastinum (SUVmax 44.7), and pulmonary hila (SUVmax 30.9 on right and 24.0 on left), suggestive of lymphoma (Figs. 1 and 2).
A subcarinal lymph-node biopsy showed noncaseating granulomas with no evidence of necrosis. There were multinucleated giant cells within granulomas, and peripherally the granulomas were surrounded by lymphocytes. The biopsy was negative for fungal and mycobacterial organisms, with negative AFB and PAS stains. Thus, pathology was not diagnostic of lymphoma. However, there was still a clinical suspicion for lymphoma given the lack of any significant pulmonary findings or extrapulmonary findings that would be consistent with sarcoidosis. Angiotensin-converting enzyme concentrations were within the normal range. A CT-guided bone-marrow aspiration and biopsy was done again, showing noncaseating granulomas with cytogenetics indicating no evidence of B-cell or T-cell lymphoma. A peripheral smear revealed normal red- and white-cell maturation with adequate platelets.

With no pathology diagnostic of lymphoma, we started treatment for possible atypical sarcoidosis. The patient was started on hydroxychloroquine 200 mg by mouth twice a day and a prednisone taper starting at 20 mg by mouth twice a day. One month after starting treatment for sarcoidosis, the patient reported almost complete resolution of her symptoms, including resolution of fevers, chills, night sweats, and weight loss and had tapered her prednisone to 10 mg daily. A repeat PET scan showed a decrease in the activity levels of hypermetabolic lymph nodes throughout the mediastinum and bilateral pulmonary hilar regions, suggesting a positive therapeutic response.

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This is an atypical presentation for sarcoidosis. However, the pathology findings, a positive response to treatment, and improvement on PET scan make a convincing case that our patient has underlying sarcoidosis.

**Discussion**

Sarcoidosis is a systemic, chronic, granulomatous disorder. Although the cause is unknown, the immune system clearly plays a central role in pathogenesis (3). The sarcoid granuloma contains a central follicle of tightly packed epitheloid cells and multinucleated giant cells surrounded by lymphocytes, macrophages, monocytes, and fibroblasts. The initial inflammation is mainly composed of activated CD4 T helper cells whose cytokines recruit other cells to help form the granulomas (4).

Respiratory symptoms are the most common presenting complaints and include dry cough, dyspnea, and non-specific chest pain—none of which our patient had. Fever, weight loss, fatigue, and malaise are the presenting symptoms in 25% of patients (5). At presentation, 95% of patients have clinical evidence of pulmonary sarcoidosis, and more than 40% of sarcoidosis patients have evidence of involvement of the skin, peripheral lymph node, eye, or liver (6).

Radiographic findings alone are inadequate to make a diagnosis of sarcoidosis. Likewise, the presence of noncaseating granulomas on biopsy is not definitive (7). It is essential to rule out other causes of noncaseating granulomas first. Thus, every biopsy should be searched for other causes of noncaseating granulomas including malignancy, mycobacteria, fungi, parasites, other infections, and foreign bodies (8).

PET, a molecular functional imaging technique, has become the most important nuclear medicine imaging modality in the field of lymphoma. It is able to detect occult disease missed by conventional imaging techniques (9). This case clearly illustrates that not every PET-positive lesion represents malignancy, and a tissue biopsy is mandatory to confirm the diagnosis.

Inflammatory cells such as neutrophils, activated macrophages, and lymphocytes have increased 18F-FDG uptake, causing important tracer accumulation in inflammatory and infectious processes (10). Thus, false-positive findings with an SUV higher than 2.5 (which is suggestive of malignancy) have been reported in inflammatory and granulomatous diseases, such as aspergillosis, tuberculosis, Wegener’s granulomatosis, and sarcoidosis (11). In one case series, five patients with mediastinal lymph node enlargement suggestive of lymphoma, lung cancer, or sarcoidosis were studied with 18F-FDG PET/CT. This study illustrated that sarcoidosis can be a pitfall in PET/CT imaging, and may lead to false-positive results of malignancy (12). Another study of 20 cases demonstrated the 18F-FDG PET sensitivity for sarcoid lesions in several areas: thoracic (100%), sinonasal (100%), and pharyngolaryngeal (80%). A high standardized uptake value on PET could be misconstrued as indicative of malignancy, and clinical factors, patterns of FDG uptake, and newer PET radiotracers such as 18-fluoro-methylxosine (18F-MMT) may aid in distinguishing this benign disease from malignant tumor (13).

A study group of 24 sarroid patients with suspected malignancy underwent both 18F-FDG and 18F-FMT PET (14). All patients showed increased uptake of 18F-FDG and no increase in the accumulation of 18F-FMT in their lymphadenopathy. No neoplasm was confirmed in any patient. Since the uptake of 18F-FDG was positive in these sarcoideal lesions, 18F-FDG PET could not differentiate sarcoidosis from malignant disease. This suggests that use of 18F-FMT PET in combination with 18F-FDG PET may be an effective method to distinguish sarcoidosis from malignancy.

Our case shows that PET scans can aid in the diagnosis of sarcoidosis and might also be used to monitor therapeutic response. Further research needs to be performed regarding the usefulness of 18F-FDG PET, as well as the use of newer radiotracers such as 18F-FMT, for the diagnosis and followup of sarcoid patients as well as for differentiating sarcoid from malignant lymphoma (10).

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