Review article

Positron Emission Tomography Imaging in Sarcoidosis

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Abstract

Sarcoidosis is a chronic granulomatous disease of unknown origin. There are several modalities for diagnosis, staging and therapeutic management of patients with sarcoidosis. Among these, whole-body F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography is found to useful in patients with complex and multisystem forms of sarcoidosis. Other modalities include Gallium scanning, assesment of angiotensin converting enzyme levels in blood, chest radiography, mediastinoscopy etcetera.

Keywords: Granulomatosis, nuclear imaging, positron emission tomography imaging, sarcoidosis

Introduction

Sarcoidosis is a chronic multisystem granulomatous disease of unknown origin. Non caseous epitheloid cell granulomas are observed in the affected tissue.[1,2]

Distribution

Although all parts of the body may be involved, the lung is most frequently involved. Involvement of the skin, eye and lymph nodes is also common.[1,2] The lungs are involved in 90% of patients, ranging from absence of symptoms to severe interstitial lung disease.[3]

Karalezli *et al*. studied 50 cases with histopathologic diagnosis of sarcoidosis and reported 40% extrapulmonary involvement.[4] Ocular involvement in sarcoidosis is the second most frequent clinical manifestation, exceeded only by pulmonary symptoms. The incidence of ocular inflammation has been reported between 22% and 47% of patients with sarcoidosis.[5,6]

Neurosarcoidosis accounts for approximately 5-16% of systemic sarcoidosis cases.[7] The most common symptoms are attributed to cranial nerve involvement. Involvement of the spinal cord, while recognized, is rare and can lead to abnormal sensation or weakness in one or more limbs, or cauda equina symptoms.[8]

Pathogenesis

This diseaseis characterized by non-caseating granulomas with proliferation of epitheloid cells.[9,10]

Sarcoidosis has been suggested to be a granulomatous disease with high-turnover characteristics. Specimens from neurosarcoidosis have shown a granuloma rich in epithelioid cells and surrounded by other immune cells (e.g. plasma cells and mast cells).[8]

Etiology

Sarcoidosis is a systemic disease of unknown etiology with a wide variety of clinical and radiological manifestations.[9] It seems that individuals with a particular genetic predisposition[11] experience systemic

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granuloma formation owing to at least three major events: Exposure to antigen; acquired cellular immunity directed against the antigen; appearance of immune cells that promote the inflammatory process.

Clinical Presentation

The clinical presentation of sarcoidosis varies widely.[12] Previous studies have reported that 30-50% of patients with sarcoidosis are asymptomatic at the time of diagnosis.[13-15] Symptoms of sarcoidosis are largely non-specific. Low-grade fever (sometimes up to 40 C), weight loss (usually limited to 2-6 kg during the 10-12 weeks before presentation), night sweats and arthralgias can be found in about 20-30% of patients. Sarcoidosis is an important and frequently overlooked cause of fever of unknown origin. Fatigue and skeletal muscle weakness are more common, present in up to 70% of patients when carefully looked for.[16] According to their initial presentation, sarcoidosis patients can be divided two distinct subgroups: The acute form and the chronic form. The acute form can present as classical Löfgren's syndrome, which is characterized by fever, bilateral hilar lymphadenopathy, arthritis in ankle joints and erythema nodosum.[17] The chronic form is characterized by an insidious onset. Lupus pernio, chronic uveitis, higher age at onset, chronic hypercalcemia, nephrocalcinosis, black race, progressive pulmonary sarcoidosis, nasal mucosal involvement, cystic bone lesions, neurosarcoidosis and myocardial involvement are associated with chronic or progressive course.[18]

Chest Radiography

The chest radiograph in sarcoidosis is divided into four stages:[19] Stage I, bihilar adenopathy alone; Stage II, adenopathy with infiltrates; Stage III, infiltrates alone; Stage IV, fibrosis. Patients with no significant changes in chest radiograph are described as Stage 0.

Certain radiographic findings, although not diagnostic, are highly suggestive of sarcoidosis. The finding of enlarged bilateral and symmetric bronchopulmonary and paratracheal lymph nodes has been recognized in sarcoidosis since at least 1940.[20] The parenchyma of the lung may be normal or may demonstrate a variety of abnormalities.[21]

Mediastinoscopy

Mediastinoscopy remains the "gold standard" for the diagnosis of pulmonary sarcoidosis,[21] but mediastinoscopy is invasive and costly with greater morbidity.[22-26]

Gallium Scanning

The gallium scan is useful for detecting inflammation throughout the body, which can show characteristic uptake in patients with sarcoidosis, such as lambda sign (positive uptake in the hilum of the chest) and Panda sign (positive uptake in lacrimal glands).[27] These findings are useful for confirming the diagnosis of sarcoidosis; however, a few months of systemic corticosteroid therapy rapidly downregulates the transferring receptor, leading to a false-negative gallium scan.[28]

Combined Gallium Scan and Angiotensin Converting Enzyme (ACE) Levels

Gallium 67 scanning may be helpful in determining sights of inflammation for potential biopsy. Serum ACE is a helpful diagnostic test, elevated in 56-86% of patients with sarcoidosis. ACE is felt to be released from epithelioid cells derived from macrophages. The combination of an abnormal gallium scan and elevated serum ACE levels yields a specificity of 83-99% in patients with sarcoidosis.[3]

Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET) Scanning

Although F-18 FDG is established and used as an oncological agent,[29] it is also readily taken up in various infectious and inflammatory conditions.[30] 18F-FDG–PET can also be of value for evaluating systemic inflammatory activity[31] and is more sensitive than gallium scanning.[32,33]

FDG PET has been proposed to have considerable potential in the evaluation of inflammatory and infectious processes.[34-39] It is known that there is significant FDG accumulation in sarcoid lesions.[40-42]

The increased activity on FDG is present not only in the malignant tumors but also in granulomatous lesions such as sarcoidosis.[42-46]

Increased F-18 FDG uptake is well-known in active sarcoidosis.[41] Recently, F-18 FDG PET/computed tomography (CT) has been used to aid in the diagnosis and management of sarcoidosis.[39,47]

In a study by Teirstein *et al*.[48] have demonstrated in 88 patients with sarcoidosis that FDG–PET scans are of value in detecting occult diagnostic biopsy sites in patients with sarcoidosis. Teirstein *et al*. have also demonstrated that a positive uptake in FDG–PET could

be found in two-thirds of patients with radiographical Stage II and III sarcoidosis, whereas negative uptake in FDG–PET was common in patients with radiographical Stage 0, I and IV sarcoidosis. These findings support the possibility that FDG–PET may be able to assess the reversible activity in patients with sarcoidosis.[48]

Follow-up F-18 FDG PET/CT showed an important reduction of metabolic abnormalities intensity without reaching complete remission.[49]

It also seems to be a useful tool for testing the efficacy of the administered therapy in this disorder.[48,50-56]

Comparison with other modalities

Molecular imaging with FDG-PET and PET/CT can provide valuable information in sarcoidosis both evaluating pulmonary sarcoidosis and extrapulmonary involvement of the disease and is more sensitive than conventional gallium scintigraphy.[48,50-56]

G crack 1 study showed a patient with a negative Ga 67 scan but showed significant FDG PET abnormalities.[54]

L crack 1 FDG PET is a very sensitive technique (94%) in demonstrating active disease in sarcoidosis, unlike genotype corrected ACE (36%) and sIL-2R (47%). The specificity of PET in sarcoidosis could not be determined although FDG is known to be a non specific marker.[57]

Ohira *et al*.[58] have studied the sensitivity and specificity of FDG–PET and cardiac magnetic resonance imaging (MRI) (high signal intensity on T2-WI or delayed enhancement) for diagnosing cardiac involvement in 21 patients. These authors have demonstrated a sensitivity of 88% and a specificity of only 39% for FDG–PET and 75 and 77% for cardiac MRI, respectively.

Multiple F-18 FDG-avid lymphadenopathies with mild F-18 FLT uptake can be characteristic findings of sarcoidosis. The combination of F-18 FDG and F-18 FLT PET/CT can be helpful in differentiating granulomatous inflammatory diseases such as neurosarcoidosis from malignancy and in localizing the most appropriate biopsy site.[59]

There is a report showing increased F-18 FDG uptake in lymph nodes as well as the spinal cord where there was intense gadolinium enhancement on MRI in a case of neurosarcoidosis.[47]

Drawbacks

However, F-18 FDG uptake in sarcoidosis is nonspecific in both intensity and pattern and is not generally useful in making an initial diagnosis. In addition, intense F-18 FDG uptake in lymph nodes and the parenchyma of other organs can be an important mimic of malignancy, specifically of aggressive lymphoma, diffuse metastatic disease, as well as of other active inflammatory lesions.[60] Therefore, there are limitations in differentiating malignancies from active inflammatory or granulomatous disease based solely on F-18 FDG uptake.[32]

The limitation of FDG–PET is that a false-positive uptake in FDG–PET could be observed in patients with other granulomatous diseases, infections and neoplasms[48]

Treatment

Treatment of sarcoidosis in general and neurosarcoidosis in particular may be extremely difficult.[61]

Corticosteroids are frequently used to treat sarcoidosis, although the optimal dose and duration of treatment has not been studied in randomized prospective trials.[21] Patients with nodular sarcoidosis tend to have a favorable prognosis with significant improvement of the infiltrates.[62-65] Complete resolution of the masses, either spontaneously or with corticosteroid treatment, has been seen.[62,63,66-68]

FDG-PET in a 52-year-old man diagnosed with sarcoidosis, following 6 weeks of oral corticosteroid therapy demonstrted remarkable improvement of the disease status with near total resolution of FDG hypermetabolism at the involved sites.[69]

Sarcoidosis is easily treatable with steroids or cytotoxic agents such as methotrexate.[70,71] Ketoconazole may also be considered in patients who have contraindications to corticosteroids.[72]

Outcomes

In sarcoidosis, spontaneous remission occurs in nearly two-thirds of the patients.[21]

There is progression in 10-30% of patients. Morbidity and mortality are closely related to pulmonary manifestations. Fatalities occur in 1-5% owing to respiratory insufficiency, central nervous system involvement or myocardial involvement[9,10]

Conclusion

Whole-body F-18 FDG PET/CT could be considered as a noninvasive imaging technique useful in both primary staging and therapeutic management of patients, with complex and multisystemic forms of sarcoidosis.[73]

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