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Positron emission tomography/computed tomography (PET/CT) as a predictor ofsarcoidosis activity: A case series

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Abstract

Introduction: Sarcoidosis is a multisystemic granulomatous disease that can present different clinical and radiological manifestations, while nospecific exams exist to monitor its activity and spontaneous or drug-induced remission. Objective: This study aimed to evaluate the degree of consistency between patients' symptoms and Positron emission tomography/computed tomography (PET/CT) results in patients with sarcoidosis. Methods: Patients with sarcoidosis underwent two PET/CT scans, which were performed at the nuclear medicine sector of the National Cancer Institute (INCA) at two different times during a four-year period, to assess disease activity. The SUVmax value was noted and its consistency with the clinical status of the disease was checked. The analysis was performed using the maximum standardized uptake value (SUVmax). Results and Discussion: Twenty-seven patients were recruited, totaling 54 exams. The median SUVmax was 8.1 (range 3.5–16.1). Most examinations that showed hypermetabolism included both lung and extrapulmonary sarcoidosis sites in the same patient. The most affected sites with uptake by PET/CT were the lungs, followed by the intra-abdominal, pelvic, and peripheral lymph nodes. Other organs with glycolytic hypermetabolism included the spleen, subcutaneous tissue, bones, and heart. In 44% of the patients, the PET/CT scans and clinical status were not consistent. This result occurred mainly in: patients with cutaneous manifestations that exhibited no metabolic correspondence on PET/CT; patients with pulmonary fibrosis and dyspnea not attributable to disease activity; extrapulmonary sites such as the spleen, abdominal and peripheral lymph nodes, and bone without symptoms; and patients with pulmonary uptake on PET/CT despite being asymptomatic. Conclusions: The applicability of PET/CT should be discussed ineach case to ensure that the information will assist the patient's diagnosis and management.

Keywords: PET/CT; pulmonary sarcoidosis; nuclear medicine.

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Introduction

Sarcoidosis is a multisystemic granulomatous disease that, in the majority of patients, affects the lungs but can occur in most organs. A major challenge to monitoring these patients is identifying disease activity. Biomarkers—such as angiotensin-converting enzyme, chitotriosidase, and interleukin-2 receptor—have already been studied.[1]

Positron emission tomography/computed tomography (PET/CT) has gained relevance in the treatment of sarcoidosis since the 1990s, when Lewis and colleagues[2] reported two cases of tracer uptake at various sites. Studies have shown its usefulness for various purposes, such asidentifying possible biopsy sites, detecting extrapulmonary and pulmonary active disease, identifying inflammatory activity in fibrosing disease and assessing myocardial involvement. In addition, PET/CT scans are useful in the detection of metabolic treatment response.[3-9]

Some authors have proposed associating the metabolic activity found in PET/CT with patients' clinical symptoms. Teirstein and colleagues[9] reported on 137 patients with sarcoidosis who underwent PET/CT and observed tracer uptake mainly in the mediastinal and extrathoracic lymph nodes and lungs, with SUVmax ranging from 2.0 to 15.8.[9] In their sample, 15% of tests with PET/CT tracer uptake did not correspond to the diagnoses suggested by clinical examinations or other imaging tests. A comparable situation was observed by Guleriaand colleagues[6]who reported a complete clinical response and evidence of uptake on PET/CT in 22% of patients, showing moderate consistency between clinical findings and metabolic expression.

Despite many decades of studying tools that help identify sarcoidosis activity, we remain unsure about the applicability of complementary exams, such as PET/CT, in the management ofsarcoidosis. Since it is a heterogeneous disease, with diverse clinical and radiological presentations, the group of patients who stand to benefit from PET/CT must be better understood.

This study aimed to describe cases of patients who underwent PET/CT and the applicability of this tool in the management of sarcoidosis.

Methodology

This is a prospective and observational study consisting of a case series of sarcoidosis patients, selected by convenience sampling, diagnosed with sarcoidosis treated and monitored at the interstitial diseases outpatient clinic of the Piquet Carneiro University Polyclinic (UERJ), during four years (2016 to 2020). Patients with infectious insults detected at the time of assessment were excluded, as were those who did not remain in follow-up care at the facility due to abandonment or death (Figure 1). All participants consented to participate in the study, which was approved by the Research Ethics Committee (CAAE: 46767915.8.00005259). Patients were diagnosed at the time of inclusion in the study or up to 48 months beforehand. Sarcoidosis diagnosis was determined according to the American Thoracic Society (ATS), European Respiratory Society (ERS), and World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) guidelines on sarcoidosis.[10] Individuals underwent two PET/CT scans. The median interval between the two exams was 19 months (15-33). During this period, the patient continued to be monitored by medical appointments, underwent complementary tests and received treatment with immunosuppressive drugs as sarcoidosis activity was identified. All patients were examined by a pulmonologist for clinical assessment of the signs and symptoms of pulmonary and extrapulmonary sarcoidosis.

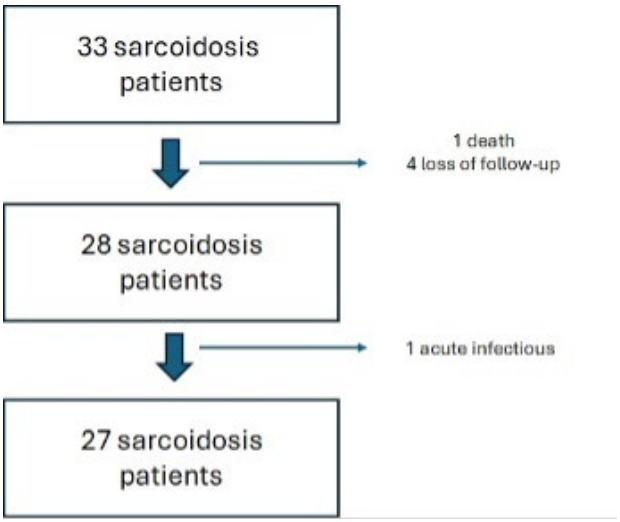

Figure 1. Recruitment and follow-up of sarcoidosis patients

Non-contrast tomography images and then three-dimensional volumetric PET images were obtained by PET/CT, in the nuclear medicine sector of the National Cancer Institute (INCA), both from the vertex of the skull to the middle of the thighs using Philips Gemini TF w/ToF 64 equipment (Cleveland, OH, USA). Images were reviewed in the transaxial, coronal and sagittal planes. The patients' metabolism was assessed via whole-body PET/CT scans that used 18 F-fluorodeoxyglucose (FDG) with tomography and PET images acquired 60 minutes after tracer infusion andsemi-quantitative analysis using the maximum standardized uptake value (SUV-max).[11] Reports were prepared after evaluation by two radiologists from the medicine service.

During follow-up, we collected data on clinical features, clinical manifestations and patients' evolution according to treatment. Respiratory clinical manifestations included chest pain, dyspnea, coughing and wheezing. The constitutional symptoms were fever, weight loss, fatigue, arthralgia, and night sweats. Palpitations and angina were listed as cardiac symptoms. Facial palsy and balance disturbance were considered as neurological symptoms.

All data were entered in spreadsheets (MS Office/Excel 2010, Microsoft Co., CA, USA) by the first author of the present study. GraphPad Prism version 10.0 (GraphPad Software Inc., La Jolla, CA, USA) was used for the statistical analysis. The chi-square test (with Fisher's correction when necessary) and the Mann-Whitney test were used to compare the differences between categorical variables and the differences between continuous unpaired variables, respectively. The paired t-test and Wilcoxon's test were used to compare continuous paired variables. A significance level of 5% was used. Concordance was measured by use of the Kappa coefficient.

Results

Twenty-seven patients with sarcoidosis were evaluated (Table 1). The reported respiratory symptoms were dyspnea and coughing. The cutaneous lesions compatible with sarcoidosis included plaques, papules, subcutaneous nodules, erythema nodosum, and scars (tattoos) (Figure 2 A, 3C).

Table 1. Data of sarcoidosis patients

Data	Allpatients (n. 27)
Age	51.35 (SD 10.29)
Sex (female: male)	22:5
Smoker	
Former	7
Never	20
PET CT +	15
Findings of thoracic CT:	
Ground glass opacities	5
Reticular opacities	8
Small nodules	20
Mediastinal and hilar lymph node	17
Thickened peribronchovascular bundles	5
Consolidation	3
Fibrosis	6
Signs and symptoms	
Dyspnea	9
Cough	3
Skin lesions	12
Fever	1

Legend: PET-CT – Positron Emission Tomography and Computed Tomography

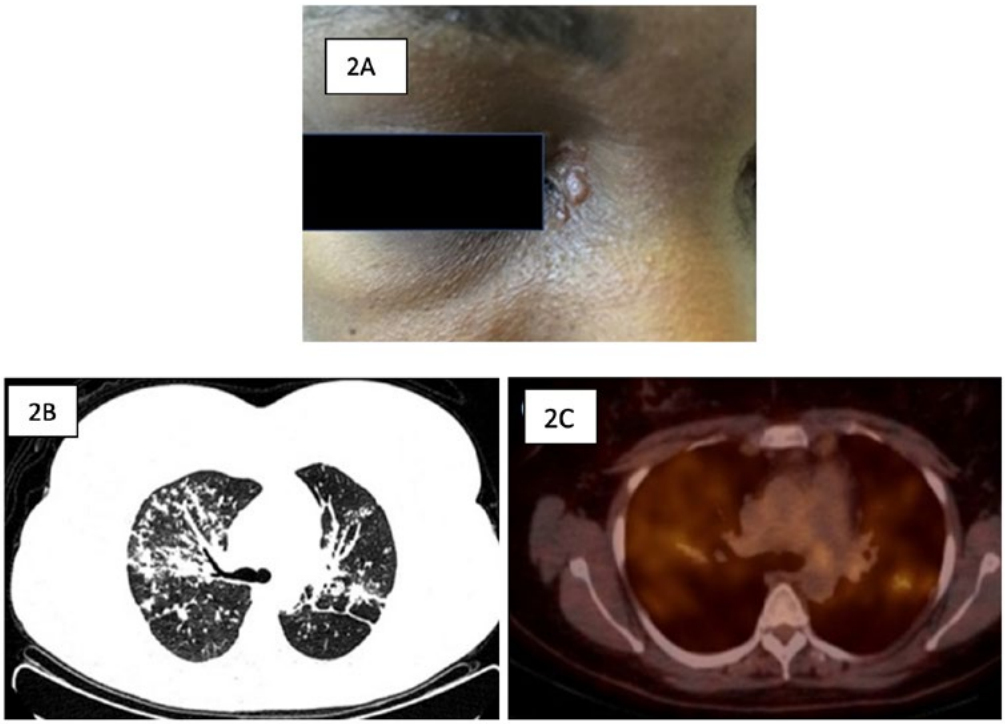

Figure 2. Consistency of CT and PET/CT

Legend: 2A: Woman, 36 years, papule in the corner of the eye; 2B and 2C: bilateral micronodules and nodules in fissures with metabolic activity.

Fifty-four PET/CT scans were performed, 24 of which showed tracer uptake (SUVmax-,8.439;range 3.5–16.1; SD 3.013; 95%CI 7.13 6-9.742). Five scans revealed uptake in extrapulmonary sites only, 8 in pulmonary sites only, and 11 in both extrapulmonary and pulmonary sites. (Figure 3, Table 2)

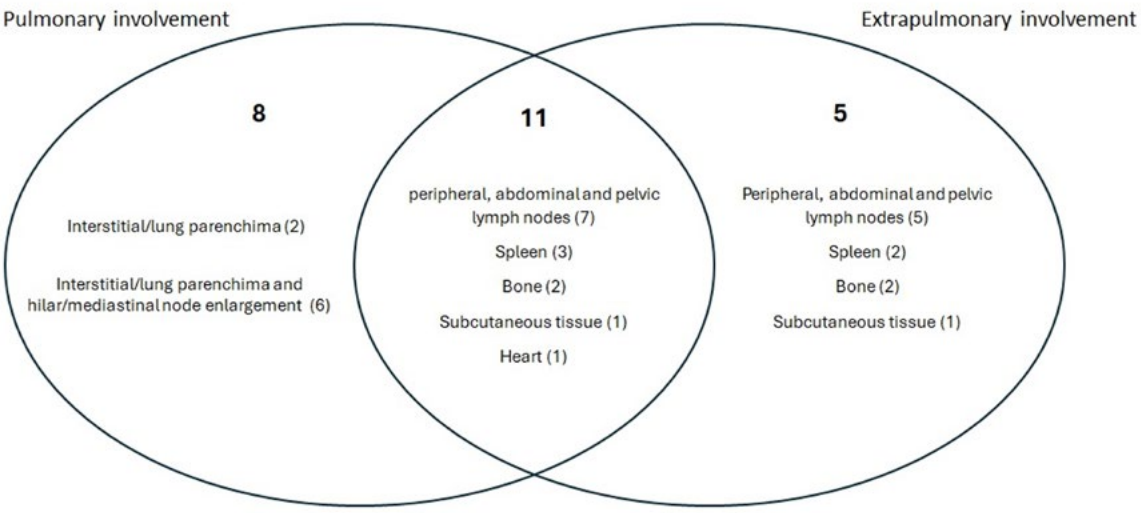

Figure 2. Activitity of sarcoidosis detected by PET/CT

Legend: Observation: 11 patients had pulmonary and extrapulmonary involvement.

Twenty-five PET/CT scans revealed discrepancies with the clinical status (Table 3), since the Kappa indexes disagreed. Three asymptomatic patients showed infiltrates with metabolic activity (Figure 2B - 2C). Four patients showed uptake in extrapulmonary sites, such as the spleen, bone, and abdominal and retroperitoneal lymph nodes, without clinical correlation (Figure 4A - 4B). However, 8 patients with skin lesions suggestive of active sarcoidosis (Figure 4C) and 4 individuals who complained of dyspnea showed no expression on PET/CT. Of these, 3 had characteristic infiltrates of sarcoidosis on tomography, such as micronodules, peribronchovascular bundle thickening, ground-glass nodules, and fibrotic areas.

Table 2. Activitity of sarcoidosis detected by PET/CT

PET/CT+	Number
Pulmonary sites	8
Extrapulmonary sites	6
	2
Abdominal/pelvic lymph node	6
Peripheral lymph node	1
Spleen	1
Subcutaneous tissue	1
Bone	1
Pulmonary and extrapulmonary sites	10
Abdominal/pelvic lymph node	7
Peripheral lymph node	4
Spleen	1
Subcutaneous tissue	1
Heart	1

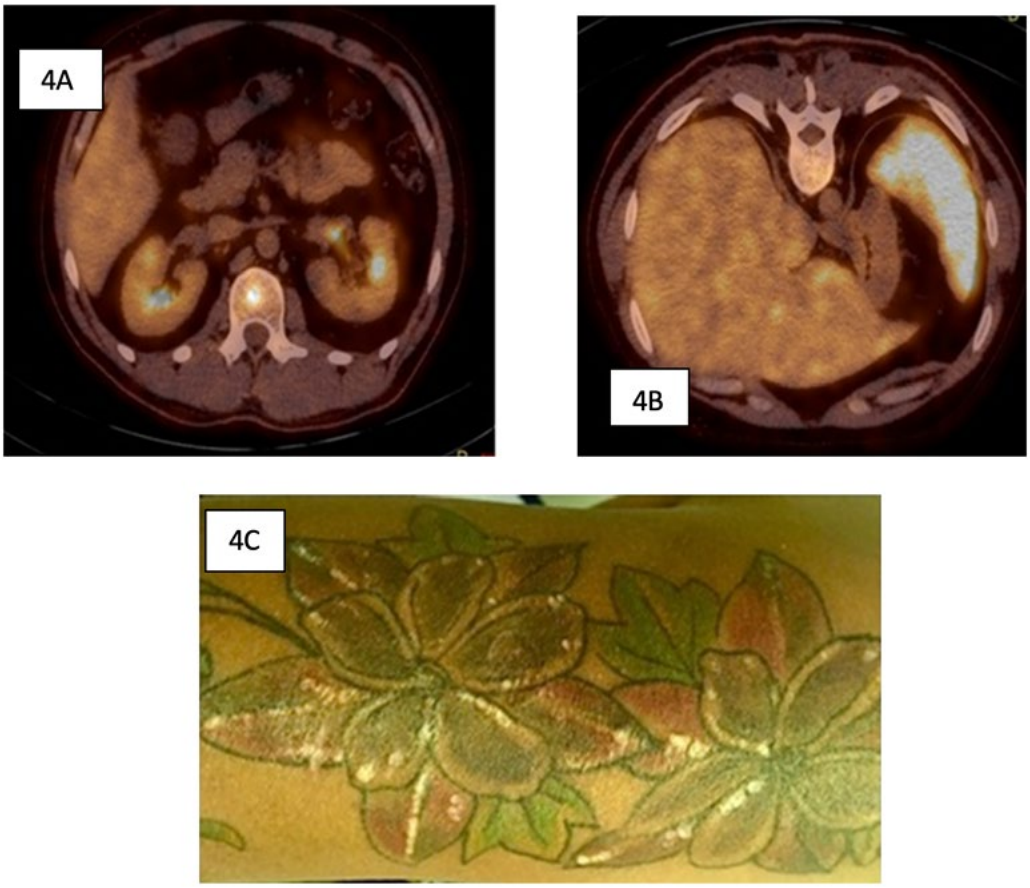

Figure 4. PET/CT and extrapulmonary disease

Legend: 4A-4B: man, 36 years, bone (vertebra) and spleen intense uptake (SUVmax 8,4), without associated symptoms. 4C: woman, 39 years, papular lesions on the arm tattoo.

Table 3. Clinical and radiological dissociation

	PET/CT +	PET/CT -
Symptom +	13 patients	14 patients
Symptoms -	11 patients	16 patients

Legend: PET-CT = Positron Emission Tomography and Computed Tomography. The Kappa agreement was 0.074 (SE 0.135, 95%CI -0.190 to 0.338)

The number of observed correlations was 29 (53.70% of the observations) and the number of correlations expected by chance was 27 (50% of the observations), with Kappa = 0.074 (SE 0.135, 95%CI -0.190to 0.338) (Table 3).

Discussion

The definition of disease activity progression in sarcoidosis is important for the therapeutic management of patients, including choice of drugs, changes in treatment, and assessment of patient response to the proposed therapy.[6]

In this case series, we studied the degree of consistency between sarcoidosis activity evaluated using signs and symptoms on physical examination as well as PET/CT. We found a weak consistency between these two variables but evaluated each case to identify situations in which PET/CT proved useful.

Among the PET/CT scans that disagreed with the clinical assessment, skin lesions were observed on physical examination but not identified on PET/CT. However, these patients were treated with either prednisone or methotrexate. Skin lesions may not show metabolic expression, especially when undergoing treatment.[12,13]

Nonetheless, PET/CT can greatly contribute to the definition of metabolic activity in pulmonary fibrosing disease.[14] This prospect was observed in this series of cases, in which two patients had dyspnea that was considered to be a consequence of pulmonary fibrosis, while PET/CT did not identify pulmonary metabolic activity.

The identification of extrapulmonary sites may be important for determining biopsy sites when a definitive diagnosis has not been made. However, this procedure is questionable as a screening tool because the clinic defines the need for treatment in most cases.[5]In our patients, the lesions in the spleen and bone showed no clinical correspondence and did not require therapeutic interventions.

Patients with asymptomatic metabolic pulmonary activity should be evaluated with pulmonary function tests for therapeutic purposes. Keijsers and colleagues[15] demonstrated that patients with metabolic activity in the lung parenchyma exhibit significant improvements in vital capacity (VC), forced expiratory volume in 1[st] second (FEV1), and diffusing capacity of the lungs for carbon monoxide (DLCO) when treated.[15]This group of patients often presents an exuberant image with clinical dissociation and is challenging to define, whether by use of pharmacological treatment or other means. We opted to treat asymptomatic patients with alterations in pulmonary function tests (FVC, FEV1, and DLCO) and pulmonary infiltrates with hypermetabolic activity on PET/CT.

We observed discrepancies between clinical status and PET/CT scans in cases of extrapulmonary disease, pulmonary fibrosis, and asymptomatic respiratory patients. Therefore, PET/CT is useful in the study of heart disease, in which cases even asymptomatic patients should be encouraged to undergo treatmentsinceit is one of the main causes of sarcoidosis mortality.[16] In patients with pulmonary fibrosing disease with symptoms of dyspnea, PET/CT is a helpful tool to guide treatment decision.

Despite PET/CT's high sensitivity and accuracy in assessing the evolution of sarcoidosis, its applicability should be questioned, when considering its high cost and low availability in treatment centers. Nonetheless, its use to detect sarcoidosis activity in individuals with fibrosis and heart diseases seems promising, since it can change the therapeutic plan.

The limitations of this study include the lack of a cardiac protocol for PET/CT, which prevents the implementation of an adequate cardiological study. Therapeutic interventions between the two PET/CT scans were not evaluated for possible metabolic changes.

Conclusion

The disease course of patients with sarcoidosis must be followedup at specialized facilities by a professional trained to identify clinical signs of disease activity and the use of PET/CT in selected cases.

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