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FDG PET/CT in bone sarcoidosis

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Abstract. *Background:* Bone sarcoidosis is rare manifestation of disease usually accompanied with pulmonary involvement. Until today, exact prevalence of bone sarcoidosis is not known, since reported prevalence varies widely depending on the studied population and the used diagnostic techniques. *Objective:* To determine the prevalence of bone involvement and distribution pattern in active chronic sarcoidosis by using FDG PET/CT. *Methods:* Between January 2010 and December 2011, 98 patients with chronic sarcoidosis and presence of prolonged symptoms or other findings suggestive of active disease were referred to FDG PET/CT examination. Active disease was found in 82 patients, and they all were screened for presence of bone sarcoidosis on FDG PET/CT. All patients also underwent MDCT and assessment of serum ACE level. *Results:* Bone sarcoidosis was present in 18/82 patients with active sarcoidosis. FDG uptake in bones was focal in 8 (44.4%), diffuse in 6 (33.3%) and both diffuse and focal in 4 (22.2%) patients. CT indicated bone abnormalities only in 5% patients. Osseous involvement was present in: pelvis (61.1%), vertebrae (44.4%), ribs (27.8%) and bone marrow (16.7%). Some patients had two or more locations of disease. Follow-up FDG PET/CT showed normal findings in two patients, same localization of active disease in four patients and progression of disease in one. *Conclusion:* In patients with active chronic sarcoidosis 22% of patients had osseous abnormalities on FDG PET/CT that mostly were not detected on CT. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 66-74)*

Key words: FDG PET/CT, chronic sarcoidosis, osseous sarcoidosis

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown origin (1). It is possible that there is no a specific agent that causes disease, but that the disease is the result of an inadequate immune response to different agents. A pathological hallmark of disease is non-caseating granuloma consisting of a collection of centrally organized macrophages and epitheloid cells encircled by limpocytes (2, 3).

Sarcoidosis presents with various symptoms depending on the degree of involvement of different organs and systems (4). Extrathoracic manifestations are present in 25-50% of cases, usually associated with thoracic involvement. Osseous sarcoidosis is present in 3-5%, but reported prevalence varies widely depending on the studied population and the used diagnostic techniques (5, 6).

Until today, the exact prevalence of bone involvement in sarcoidosis is unknown due to different results and because many lesions are asymptomatic (5-7). It

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is important to be assessed due to the fact that osseous lesions may infiltrate bone and cause bone resorption and bone lose in 13% of patients (8, 9).

Osseous involvement usually happens in phalanges in the hands and feet with multiple joint involvements. Bone involvement is more common in blacks and females and is associated with chronic and severe course of disease (6, 7). Approximately 80-90% patients with osseous sarcoidosis have concurrent pulmonary involvement and progressive disease.

Gold standard for diagnosis of sarcoidosis is pathohistology (10, 11). However, the assessment of activity and extent of disease remains a clinical challenge. The serum level of angiotensin converting enzyme (ACE) produced by sarcoid granulomas is commonly used for evaluation of active disease and therapy planning, despite to his low sensitivity and specificity (12). Chest radiography and MDCT are useful in diagnosis and staging pulmonary sarcoidosis but cannot reveal active inflammation (13).

Nowadays F-18 flour-deoxy-glucose positron emission tomography with computed tomography (FDG PET/CT) is usually used in assessment of infectious and inflammatory diseases including sarcoidosis. It allows detection and localization changes with increased glucose metabolism in activated inflammatory cells (14, 15).

Assessment of active disease in patients with chronic sarcoidosis is necessary in order to provide the best treatment of these patients. This is particularly important in bone sarcoidosis since prolonged use of corticosteroid therapy can lead to bone resorption, bone lose and disability.

The role of FDG PET/CT in bone sarcoidosis has been reported in several case reports and one retrospective study (5, 16-18). To the best of our knowledge, until now no prospective study has been done in this field. Therefore, the aim of this study was to determine prevalence of bone sarcoidosis and distribution pattern bone involvement in patients with active chronic sarcoidosis.

Materials and methods

Study Population

This prospective study included 104 consecutive patients with chronic sarcoidosis referred for FDG PET/CT examination to the National PET Center at the Clinical Center of Serbia between January 2010 and December 2011. Inclusion criteria for this study were: chronic sarcoidosis confirmed by biopsy; presence of prolonged symptoms or new clinical, biochemical, or imaging findings suggestive of active disease. Exclusion criteria were: presence of cancer or other diseases that resemble sarcoidosis on MDCT and PET/CT (Wegener syndrome, tuberculosis, aspergillosis); existence of inflammatory osseous disease; and glucose level greater than 11 mmol/L (19). Of 104 referred patients, 5 were excluded because of the detected cancer (two Hodgkin lymphoma, one lung cancer, one cervical cancer and one rectal carcinoma), and one had tuberculosis in medical history. Thus, the final sample consisted of 98 patients (mean age 47.2±12.0 years, 38 men and 60 women). Then, FDG PET/CT positive patients were screened for the presence of bone involvement. The study protocol was approved by the Ethics Committee of the Faculty of Medicine of the University of Belgrade, and written inform consent was obtained.

Procedures

Before FDG PET/CT examination all subjects underwent standard radiography and high-resolution CT of the chest and serum measurement of ACE level (reference range, 8–52 U/L).

Based on the baseline FDG PET/CT findings 18/98 patients had active bone/bone marrow sarcoidosis. After first FDG PET/CT in 12/18 patients with bone sarcoidosis, physicians changed therapy, and they were invited to participate in the follow-up FDG PET/CT study (one excluded due to living abroad). Medication prescribed by the referring physicians (after first FDG PET/CT) remained the same during the follow-up. Seven patients returned for the follow-up FDG PET/CT 9.6±1.9 months after the baseline. The follow-up ACE data were extracted from medical records.

Data Acquisition, Reconstruction, and Image Analysis

FDG PET/CT examination was performed on a 64-slice hybrid PET/CT scanner (Biograph; Siemens Medical Solutions USA Inc.). Patients fasted for 8 h before receiving an intravenous injection of 5.5 MBq of 18F-FDG per kilogram. PET/CT acquisitions started 60 min after tracer injection. A

three dimensional PET scan (6–7 fields of view, 3 min/field) and low-dose nonenhanced CT scan were acquired from the skull to the mid thigh. If deemed necessary, a total-body study was also performed. MDCT was acquired with 120 kV and with automatic, real-time dose modulation amperage (CareDose4D [Siemens], with the baseline being 45 mA); a slice thickness of 5 mm; pitch of 1.5; and a rotation time of 0.5 s. Low-dose CT, attenuation corrected PET, and combined PET/CT images were displayed for analysis on a syngo Multimodality Workplace (Siemens AG). FDG PET/CT findings were considered positive if FDG uptake was increased above the level in blood vessels in the mediastinum or lung parenchyma, or in extrathoracic sites, including lymph nodes, visceral organs (parotid gland, liver, spleen), nasopharynx, skin, muscle, or bone (20). Quantitative analysis of FDG uptake in the lesion was based on maximum standardized uptake value per focus (SUVmax). This value was calculated as the activity concentration measured at the end of the scan and corrected for individual body weight and dose injected, as follows: tissue activity (counts/pixel/s) multiplied by calibration factor divided by injected FDG dose (MBq/kilogram of body weight) (19). The follow-up FDG PET/CT was done identically as before in terms of the dose given, wait time, data acquisition, reconstruction, and image analysis. FDG PET/CT data were interpreted separately by 3 investigators: 2 nuclear medicine physicians and a radiologist. Consensus was reached in cases of discrepancy.

Statistical Analysis

Independent samples T test was used to evaluate differences in numeric variables (age, SUV max, ACE) between patients with and without bone involvement on FDG PET/CT. For testing difference between dichotomous variables (gender, therapy, symptoms) in these two populations X^2 was used (Fischer exact test was used were appropriate). We used the paired t-test to compare SUVmax between the baseline and follow-up in 7 subjects who underwent two FDG PET/CT evaluations. Changes in the ACE levels were also compared with the paired t-test. The results were presented as mean ± standard deviation (SD) and p-value of less than 0.05 was considered significant.

Results

Patient Characteristics

Out of 98 patients referred to FDG PET/CT examination, 82 (83.7%) had positive findings. Bone sarcoidosis was present in 18 (22%) patients with positive finding (9 men and 9 women; mean age 51±12 years). They usually had active disease in lungs (72.2%), while isolated extrathoracic localizations were less frequent (27.8%). Bone pain was present in 10 patients with bone sarcoidosis, while the others had nonspecific symptoms (fatigue, cough, fever, and headache). Fourteen patients with bone and/bone marrow involvement had high ACE level (70.82±19.70 U/L).

Baseline FDG PET/CT findings

Clinical and FDG PET/CT findings of patients with active chronic sarcoidosis are shown in Table 1. FDG uptake in osseous lesions was focal in 8 patients (44.4%). Diffuse accumulation was present in 6 (33.3) patients and 4 (22.2%) patients had both diffuse and focal uptake (Figures 1, 2). Osseous involvement was usually seen in: pelvis (61.1%), vertebrae (44.4%), ribs (27.8%), and bone marrow (16.7%). Less frequent localizations were femur, scapula and zygomatic bone. Some patients had two or more of these locations (Table 2). SUV max in bone lesions was 5.1±2.2.

CT has indicated bone abnormalities in 4 patients (2 patients had osteolytic lesions and 2 had cystic changes in the lumbar spine).

Table 1. Characteristics of the study population with positive FDG PET/CT findings

	Bone negative (n=64)	Bone positive (n=18)	p
Mean age (yr)	45.86±12.01	50.56±12.43	0.849
Gender (female)	40 (62.50%)	8 (44.44%)	0.170
ACE (mean± SD,U/L)	51.13±19.82	65.31±22.47	0.997
ACE range (U/L)	5-142	33-124	
SUV max (mean± SD)	8.08±4.16	7.62±3.69	0.421
SUV max range	1.00-23.96	2.50-17	
Therapy (yes)	34 (53.13%)	5 (27.78%)	0.749
Symptoms (yes)	41 (64.1%)	14 (77.8%)	0.280

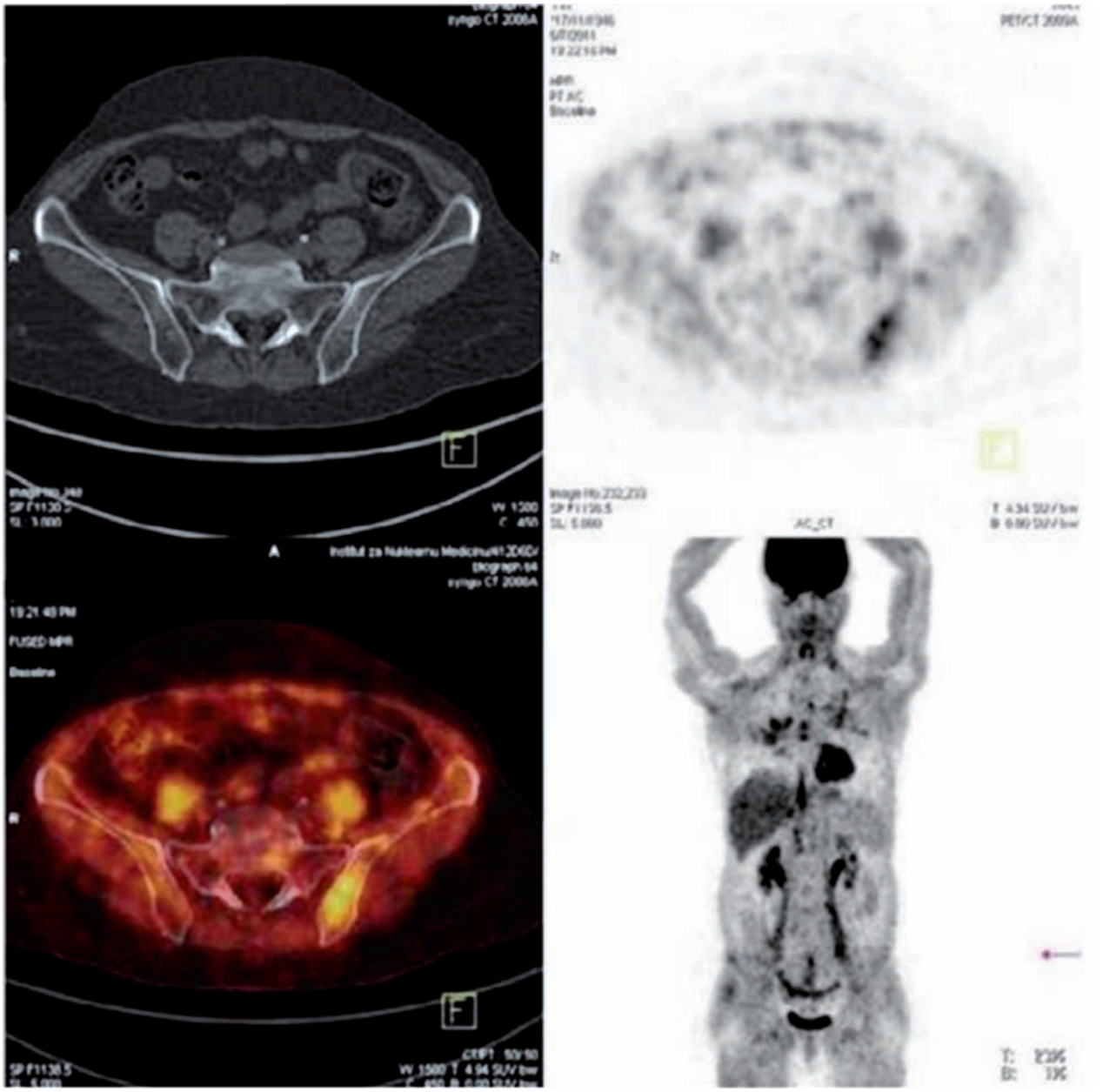

Fig. 1. A 68-year-old female with chronic sarcoidosis and diffuse FDG uptake in the left iliac bone on the FDG PET/CT. Transversal PET/CT image: diffuse intense uptake in the left iliac bone; transversal CT image: no signs of bone involvement. On the maximum intensity projection picture (MIP): increased FDG uptake in the lungs, medastinal and retroperitoneal lymph nodes and pelvis

Changing of therapy and follow-up FDG PET/CT findings

After first FDG PET/CT examination referring physicians changed therapy 12 (66%) patients with bone sarcoidosis based on clinical, biochemical and imaging indicators of disease activity.

Clinicians usually replaced corticosteroid therapy and/or introduced other drugs such as: metotrexat and azathioprine. In one patient methotrexate was introduced besides prednisone therapy and in one patient azathioprine was introduced (Table 3).

Seven to thirteen months after first FDG PET/CT, 7 patients returned to follow up FDG PET/CT

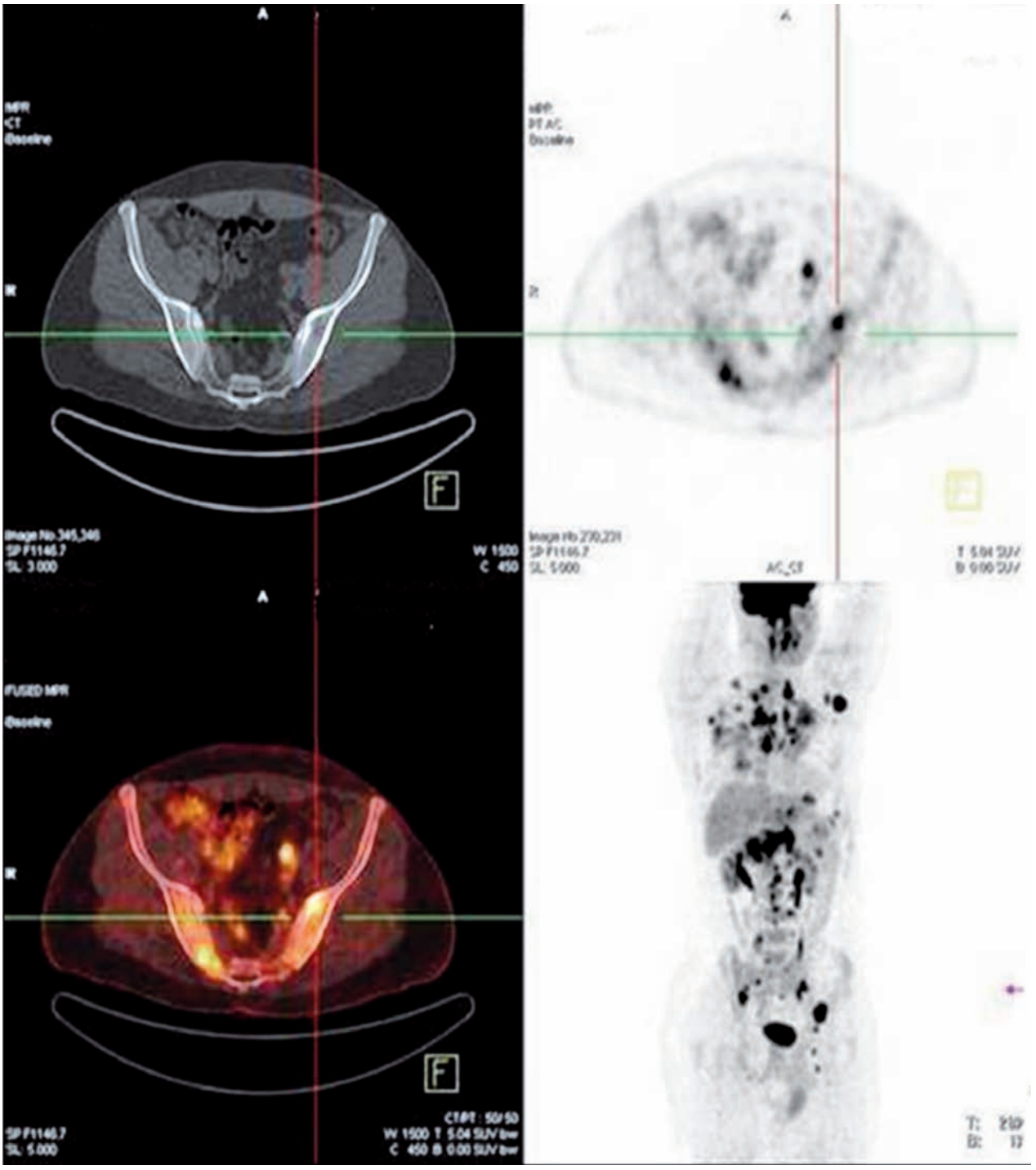

Fig. 2. A 65-year-old male with chronic sarcoidosis and focal FDG uptake in the iliac bone on the FDG PET/CT. Transversal PET/CT image: focal intense uptake in the iliac bone; transversal CT image: no signs of bone involvement. On the maximum intensity projection picture (MIP): increased FDG uptake in the lungs, medastinal lymph nodes, left axillary lymph nodes, retroperitoneal and inguinal lymph nodes, lien, vertebras and pelvis.

Table 2. Characteristics of patients with bone/bone marrow sarcoidosis

	Gender	Age (yr)	Localization of bone sarcoidosis seen on FDG PET/CT	SUVmax in bone	FDG uptake in bones Diffuse/focal/both	CT abnormality (Yes/No)
1.	F	33	Pelvis, bone marrow	4,81	Both	No
2.	F	71	Zygomatic bone	11,59	Focal	No
3.	F	53	Pelvis, vertebrae L2-L5	5,49	Both	No
4.	M	58	Pelvis, vertebrae	5,05	Focal	Yes (cyst)
5.	M	44	Femur, bone marrow	5,04	Focal	No
6.	M	52	Vertebrae Th10-L5	5,32	Diffuse	No
7.	F	39	Pelvis, vertebrae th10-Th12	5,43	Both	Yes (cyst)
8.	F	72	Pelvis	3,8	Focal	No
9.	M	36	Rib, pelvis, vertebra L1	8,98	Focal	No
10.	M	40	Pelvis	3,7	Diffuse	No
11.	M	42	Vertebra Th11	5,28	Diffuse	No
12.	M	49	Rib, vertebrae Th11, L1, L3, L5	4,12	Focal	No
13.	M	45	Rib	2,5	Focal	Yes (osteolityc lesion)
14.	F	60	Pelvis, bone marrow	4,83	Diffuse	No
15.	M	47	Pelvis, scapula, ribs, vertebrae	4,13	Both	No
16.	F	37	Pelvis, vertebrae Th11, L4-L5	3,30	Diffuse	No
17.	F	68	Rib	5,53	Focal	Yes (osteolytic lesion)
18.	F	64	Pelvis	2,4	Diffuse	No

Table 3. Clinical management after first 18F-FDG PET/CT ex amination

Management	Existing therapy			Total
	Corticosteroids	Corticosteroids + methotrexate	None	
No change in therapy	4	2	0	6
Increased corticosteroids	4	0	6	10
Corticosteroids + methotrexate/azathioprine	2	0	0	2
Total	9	2	6	18

in order to assess therapy response. On the follow up FDG PET/CT scan SUV max decreased but it was not statistically significant (8.0±4.4 vs. 6.5±5.4, p=0,256). However, there was difference in the FDG PET/CT findings. One patient had more spread disease and 4 had active disease but with lower SUV max values. In two patients SUV max decreased for 55% from baseline values, which corresponded to complete remission (Table 4).

ACE levels also decreased (53.00±14.25 vs. 61.86±32.63, p=0,439) but results were in discrepancy with PET/CT findings. Patient who had progression of the disease had normal ACE values (45 U/L), while two patients with complete remission had high ACE levels (113 U/L and 55 U/L) (Table 4). Also, symptoms of disease were less intensive or less frequent on the follow-up.

Discussion

This study prospectively examined prevalence of osseous involvement in chronic sarcoidosis by FDG PET/CT examination. Results show that FDG PET/CT detect more bone involvement than CT in patients with chronic sarcoidosis. They also sug-

Table 4. Biochemical, clinical and FDG PET/CT characteristics of patients with bone/bone marrow sarcoidosis on the follow-up

	Gender	Age	First FDG PET/CT examination		Follow-up FDG PET/CT examination			
	(yr)		SUV max in bone	ACE (U/L)	SUVmax in bone	ACE (U/L)	More spread disease (yes/no/same localization)	Symptoms*
1.	F	53	5.5	69	2.5	113	No	No
2.	M	58	5.1	58	5.2	104	Same localization	Less
3.	M	44	5.0	67	3.7	40	No	Less
4.	M	52	5.3	37	2.4	55	No	Equal
5.	M	36	8.9	33	9.3	45	Yes	Less
6.	M	42	5.3	47	3.3	43	No	No
7.	F	64	3.3	60	3.0	33	Same localization	Equal

* Symptoms on the follow-up in comparison with those on the first FDG PET/CT examination

gest that FDG PET/CT can be used in evaluation of therapy response in patients with bone sarcoidosis, which can be helpful in obtaining best possible treatment in these patients.

The role of FDG PET/CT in detection of bone/bone marrow involvement in sarcoidosis is usually described in several case reports and retrospective studies (5, 16-18, 21). To the best of our knowledge, no prospective study has been done in this field. Prevalence of bone sarcoidosis of 22% in our study is in agreement with the rate previously reported (22). Majority of patients had thoracic disease spread into the extrathoracic localizations, while isolated extrathoracic localizations were less frequent. In contrast to reported data that osseous lesions occur in the short tubular bones of the hands and feet (23) in our study active inflammatory sites were usually seen it the pelvis, vertebrae and ribs. Less common localizations were zygomatic bone, femur, scapula. Phalanges were not involved in our patients with sarcoidosis which is in agreement with results reported by Mostard (5). Bone marrow involvement was present in three patients who had active disease in vertebrae.

There were 4 patients with bone lesions seen on the CT (2 had osteolityc lesions and two osteosclerotic). Similar low rate of anatomic abnormalities was reported in other studies (5, 24). MDCT and MR diagnosis of bone involvement in sarcoidosis could be difficult and similar to haemangiona, eosinophilic granuloma and metastasis. This may suggest that molecular abnormalities seen on PET/CT precede morphological changes, which can facilitate the assessment of active disease in bones in patients with chronic sarcoidosis (5, 19, 20, 24-26).

In this study bone infiltration of spine, pelvis and long bones, usually impeded normal physical activity of patients. Since our study population was mostly population in working age, bone sarcoidosis represented a real clinical problem, where clinicians tried with adequate modification of therapy to prevent potential disability in this population and to enhance their quality of life. A general consensus for treatment of osseous sarcoidosis has not been reached. However, it is known that the status of bone health can be complicated by the use of corticosteroids in treating the active disease which may cause increased bone resorption, decreased bone formation and net bone loss in response to corticosteroid use (9). In our study population clinicians changed therapy in two third of patients, after first FDG PET/CT examination. They usually changed corticosteroid therapy and added metotrexat/azathioprine in agreement with other clinical and biochemical patient data.

Follow up FDG PET/CT showed variable response to treatment across the group. The inflammatory activity appeared absent on visual examination in two patients, which corresponded to the 55% decrease in SUVmax from baseline and almost equal to the normal value at the follow-up. Mostard et al. reported three patients who returned to follow up FDG PET/CT examination, in whom SUV max decreased by 76% in bone and by 68% in other areas (5). More significant decrease in SUV max levels is probably due to longer follow up period (18 months), during which the effects of therapy were fully manifested (5).

Our results showed that ACE levels decreased during the follow up, but this was not statistically significant. Patient with progression of the disease on the follow up FDG PET/CT, had normal level of ACE and normal findings on CT, while patients with normal FDG PET/CT findings (complete re-

mission) had high ACE. These results reaffirm low sensitivity of ACE in assessment of disease activity in patients with sarcoidosis and may indicate the usefulness of FDG PET/CT (1).

This study had several limitations. Potential limitation is relatively small follow-up sample size. However, to our best knowledge, this is the largest follow-up sample size with bone sarcoidosis evaluated with FDG PET/CT. Also, an observation period of seven to thirteen months may be potentially short to fully evaluate effects of corticosteroid therapy (27). Future studies should be done in a larger sample, with longer follow up. Another limitation is that not all patients had histological proof of osseous sarcoidosis (similar problem also had Mostard at al.) (5). Before FDG PET/CT examination all patients had patohistologic verification of disease, with biopsy in other easily available regions. Since we excluded patients with malignancy, other granulomatous and inflammatory bone diseases that could have similar appearance on a FDG PET/CT as sarcoidosis, intensive FDG uptake in bones was interpreted as the presence of active disease.

Conclusion

FDG PET/CT can be a useful tool for detection of bone/bone marrow sarcoidosis, especially in patients with normal CT findings. Also, FDG PET/CT can be helpful in the evaluation of therapy response in patients with bone sarcoidosis. This examination was informative to clinicians who modified patients therapy taking into account also other clinical data in order to prevent bone loss due to long-term therapy with corticosteroids. Further prospective multicenter studies are necessary to confirm these finding and refine the clinical role of FDG PET/CT in bone sarcoidosis.

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