SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2015; 32; 318-324

Angiotensin-converting enzyme as a predictor of extrathoracic involvement of sarcoidosis

Zehra Yasar[1], Mehmet Akif Özgül[2], Erdoğan Cetinkaya[2], Aysel Kargı[3], Şule Gül[2], Fahrettin Talay[1], Elif Tanrıverdi[2], H.Erhan Dincer[4]

[1] Abant Izzet Baysal University School of Medicine, Department of Chest Diseases.Bolu, Turkey; [2] Yedikule Chest Diseases and Surgery Teaching and Research Hospital, Pulmonary Division. Istanbul, Turkey; [3] Izzet Baysal State Hospital,Pulmonary Division.Bolu,Turkey; [4] University of Minnesota, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine. MN, USA

Abstract. *Background:* Sarcoidosis is a multisystem disease, with extrathoracic involvement occurring in 25–50% of patients. Multi-organ involvement is often associated with a more chronic and severe course. The value of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) in diagnosing extrathoracic involvement in sarcoidosis has been demonstrated; however, because of the radiation dose and high cost, indications for its use must be well defined. Angiotensin-converting enzyme (ACE) is produced by active granuloma cells; thus, serum ACE (sACE) levels may reflect the total granuloma load. *Objectives:* In this retrospective study, we evaluated the diagnostic value of sACE in the detection of extrathoracic involvement in sarcoidosis. *Methods:* 43 patients with biopsy-proven sarcoidosis underwent FDG-PET/CT during the initial work-up. Positive findings were classified as thoracic and/or extrathoracic. The diagnostic value of sACE was estimated using sensitivity, specificity, and area under the receiver operating characteristic curves (AUCs). *Results:* Of the 43 patients studied, 17 (39.7%) had extrathoracic involvement. In this group, sACE values were higher than in patients without extrathoracic involvement (331 vs. 150, p=0.002) and correlated positively with extrathoracic involvement (R:0.532 p=0.02). Receiver operator characteristic curve analysis revealed an AUC of 0.816 [95% confidence interval: 0.669–0.963, p=0.002], 70.6% sensitivity and 80% specificity at the sACE cut-off value. *Conclusions:* In sarcoidosis, extrathoracic involvement may be life threatening or indicative of poor outcome. sACE levels are easily determined and may predict extrathoracic involvement. In patients with sarcoidosis, sACE levels can be used to better define those who would benefit from FDG-PET/CT examination to detect extrathoracic involvement. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 318-324)*

Key words: sarcoidosis, ACE, extrathoracic involvement

Introduction

Sarcoidosis is a multisystem disorder of unknown etiology. Its primary pathological characteristic is the formation of non-caseating epithelioid cell granulomas. Sarcoidosis occurs worldwide and commonly affects young and middle age white adults, with a higher incidence in women and non-smokers. Pulmonary involvement, characterized by hilar lymphadenopathy on chest X-ray, is detected in up to 90% of patients, of whom approximately half is asymptomatic (1). Extrapulmonary manifestations are common, with the affected organ varying depending on the sex, age at presentation, and ethnicity of the patient (2, 3). Multi-organ involvement is usual-

Received: 27 December 2014
Accepted after revision: 17 March 2015
Correspondence: Zehra Asuk Yasar, MD
Abant Izzet Baysal University School of Medicine,
Department of Chest Diseases. Gölköy-Bolu, Turkey
Tel. +905055888330
E-mail: zehraasuk@hotmail.com

ly indicative of a chronic and more severe disease course. Moreover, extrapulmonary involvement of the central nervous system, heart, or renal system can be life threatening and might be difficult to diagnose (1). Detection of disease in all affected organs is important in terms of management, follow-up, and prognosis.

On ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) granulomatous tissues show high tracer uptake, indicative of active glucose metabolism (1). Previous studies in sarcoid patients have proposed the fact that FDG-PET/CT may have a role to evaluate inflammation, to confirm the diagnosis, to detect disease activation, and to monitor the response to treatment (4-10). FDG-PET/CT not only allows whole-body mapping of active inflammatory sites in sarcoidosis but can also identify occult disease sites. In the study by Teirstein et al., FDG-PET revealed occult sites that were not detected by physical examination, standard thoracic radiography, or CT in 15% of patients (11). Thoracic and systemic sarcoidosis have been investigated in retrospective studies with small series but the utility of whole-body FDG-PET/CT in the diagnosis and follow-up of these patients has yet to be confirmed in large trials.FDG-PET/CT is a valuable technique for the diagnosis of extrathoracic involvement but, because of the radiation dose and high cost, the indications for its use must be well defined. Angiotensin-converting enzyme (ACE) is a product of active granuloma cells, and serum ACE (sACE) levels reflect the total granuloma load (2-12). sACE was previously shown to be a useful tool in the diagnosis of sarcoidosis, in assessing disease activity, in monitoring the effect of therapy, and in patient follow-up (13-15). A marker that predicts extrathoracic involvement would be useful in the clinical management of sarcoidosis patients with persistent, disabling symptoms. Thus, in this study we evaluated the diagnostic value of sACE in predicting extrathoracic involvement in sarcoidosis.

Materials and methods

Study Population

We retrospectively reviewed the charts of sarcoidosis patients who were referred to our clinic for further investigation. We included the patients who had a definitive histologic diagnosis, demonstrating noncaseating epitheloid cell granulomas and no evidence of cancer or other diseases that may resemble sarcoidosis on PET / CT; glucose level no greater than 11 mmol /L (16). A total of 43 patients enrolled based on the criteria. The study subjects was divided into two groups according to disease topography: one group specified as thoracic sarcoidosis showing either pulmonary and /or mediastinal involvement, the other group specified as thoracic sarcoidosis plus extrathoracic involvement. The Medical Research Ethics Committee of the Abant Izzet Baysal University Medical Centre approved the study protocol.

Procedure

The patients underwent chest X-ray, CT chest and pulmonary function tests before PET / CT. Serum measurement of ACE level (reference range) and blood counts were assessed in peripheral blood at the time of diagnosis.

The procedure used for measurement of SACE levels is a rapid, convenint spectrophotometric method[7], utilizing the synthetic tripeptide substrate N-~3-(2fuiyl)acrylol]-L-phenylalanylglyclglycine (FAPGG) from Sigma-Aldrich, Poole, UK and analyzed on Roche MIRA Analyser; Roche Diagnostic Systems, Welwyn Garden City, UK.

The following reaction is catalyzed by ACE: FAPGG > FAP+glycylglycine

FAPGG is hydrolyzed to fuiyleacryloylphenylealanine (FAP) and glycyiglycine. Hydrolysis of FAPGG results in a decrease in absorbance at 340 urn. The ACE activitiy in the sample is determined by comparing the sample reaction rate to that obtained with ACE calibrator.

The normal range of SACE activity is defined as mean value “2SD1. The mean value by the described method was 30 I.U/L (SD=l l) and the reference range was 8-52 I.U/L.

Imaging

PET/CT had been performed in all patients at two different PET/CT centers using a multi-detector CT integrated high-resolution PET/CT scanner (Siemens Biograph LSO HI-REZ PET/CT scanner, Chicago, IL). The patients were fasted for at least 6

hours and adequately hydrated before the procedure. 370 to 555 MBq of 18 F-fluorodeoxyglucose (FDG) was administered intravenously, if serum glucose values were below 150 mg/dl. Following injection, patients were left to rest in comfortable room for 60 to 90 minutes. After waiting period whole-body PET imaging was performed from the head to feet in all patients (16). A low dose CT scan was performed without intravenous contrast and was used for the purpose of attenuation correction of the PET images. PET images were acquired at 7-8 bed position(3 min/bed).

PET /CT images were visually and quantitively assessed by an experienced nuclear physicians. PET /CT findings were scored as positive or negative for inflammation. The findings were considered as positive in cases with increased 18F-FDG uptake above the level in blood vessels in the mediastinum or lung parenchyma, or in extrathoracic sites, including lymph nodes, skin, or visceral organs (liver, spleen,pancreas) (4). Quantitative analysis of 18F-FDG uptake in the lesion was based on maximum standardized uptake value per focus.

Statistical analysis

Statistical analyses were performed using SPSS, version 15.0 for Windows. Differences were tested for statistical significance using the Student's t-test for independent samples in case of continuous variables or chi-square test in case of categorical variables. A p value of <0.05 (two sided) was considered to indicate statistical significance. Receiver operating characteristic (ROC) curves were constructed to evaluate the value of serum ACE to predict the presence of extrathoracic involvement in PET positive patients. Areas under the curve (AUC) values with 95% confidence intervals (CI) were used to quantify and visualize the strength of the association.

Results

Fourty three patients were enrolled during the study period. Out of 43 patients, 24 (8 male, 16 female) were diagnosed as thoracic sarcoidosis while 17 (6 male, 11 female) were found to have thoracic sarcoidosis with extrathoracic involvement. Thoracic sarcoidosis with extrathoracic involvement was present in 39,7 % of patients and thoracic sarcoidosis in 60,3% of patients. The median age in all patients was 44,8 ± 14,8 years. Patients were mostly non-smokers 96,8%. There was no difference in the and proportion of gender among patients with limited form and those with extrathoracic involvement (males 33,3 %vs.35,3%). When assessing radiologic stage 1 was more frequently seen in patients with pulmonary form than in extrathoracic group, stage 2 was more frequent in extrathoracic group. Between the patients with accompanied extrapulmonary sarcoidosis and pulmonary group there were no significant difference in age, gender smoking and stage. These characteristics are summarized in Table 1.

Patient id

In patients with extrapulmonary involvement, the most commonly affected area was abdomen with abdominal lymphadenopathy (64,7%), liver (35,2%), spleen (23,5%) and pancreas (23,5%). Heart, brain, skin and adrenal glands were involved rarely (Table 2). Regarding number of disaesed organs, the majority of patients with extrathoracic sarcoidosis had one additional organ involvement (36,5%), followed by two extrathoracic organ affected (29,4%).

No difference in functionl parameters between the patients with both groups (Table 1). sACE values in sarcoidosis patients with extrathoracic involvement were higher than patients without extrathoracic involvement (331 vs. 150, p<0,001). sACE showed a positive correlation with extrathoracic involvement (R:0.532 p=0.02) (Figure 1). Receiver operator characteristic (ROC) curve analysis revealed a 0.816 [%95 confidence interval (CI) 0.669-0.963, p=0.002] area under the curve, 70,6% sensitivity and 80% specificity at the cut-off of sACE (Figure 2) 197,5.

Discussion

Sarcoidosis is a multisystem disease characterized by abnormal cellular immune activity. Up to 33% of patients have chronic disease, leading to significant organ impairment (1). Extrathoracic involvement occurs in 25–50% of patients, typically in combination with thoracic disease (1-12, 16, 17). In patients with sarcoidosis, the detection of inflammatory and granulamatous reactions in the lungs and elsewhere in the body is an important component of disease management. In this study, the percentage of patients with extrathoracic involvement in addition to pulmonary

Table 1. Demographic and clinical characteristics of the sarcoidosis patients categorized by absence or presence of extrathoracic involvement

Characteristic	Thoracic	Extrathoracic	p value
Number of patients	24 (58.5%)	17 (41.5%)	
Age (y)			
Mean ± SD	45.9 ± 8.9	44.8 ± 14.8	0.778
Range	25-64	18-64	
Sex(n)			
Male	8 (33.3%)	6 (35.3%)	0.896
Female	16 (66.7%)	11 (64.7%)	
Smoking			
Yes	3 (12.5%)	2 (11.8%)	0.943
No	21 (87.5%)	15 (88.2%)	
Stage			
1	19 (75%)	7 (41.2%)	
2	3 (12.5%)	7 (41.2%)	0.042
3	2 (8.3%)	3 (17.6%)	
Pulmonary function tests			
FVC (L)	2.9 ± 0.8	2.8 ± 0.8	0.647
FVC%	83.5 ± 17	87.5 ± 19.6	0.549
FEV1 (L)	2.4 ± 0.6	2.5 ± 0.7	0.794
FEV1%	82.5 ± 16.8	86.8 ± 15.0	0.451
DLCO ()	17.3 ± 5.6	16.4 ± 6.2	0.667
DLCO%	61.6 ± 19.9	63.9 ± 15.4	0.709
Ca ()	9.7 ± 1.2	9.4 ± 0.4	0.454
ACE (U/L)			
Mean level ± SD	122.1± 92.5	331.6 ± 183.5	0.000
Range	35-342	65-654	

Table 2. Most common sites of extrathoracic sarcoidosis on 18F-FDG PET/CT Scans

Site*	Number of patients
Cervical lymph nodes	6
Abdominal lymph nodes (mesenteric.coeliac.gastric)	11
Inguinal lymph nodes	2
Liver	6
Spleen	4
Pancreas	4
Brain	1
Heart	1
Skin	1
Adrenal	1

* Some patients had more than 2 different extrathoracic sites

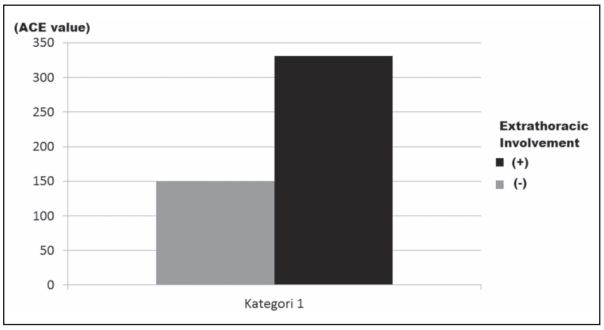

Fig. 1. ACE serum levels for patients with negative and positive extrathoracic involvement in patient with sarcoidosis

disease (39.7%) was similar to that reported in previous studies**.**

In sarcoidosis, there are several extrathoracic locations that are life threatening or indicative of chronic disease or poor prognosis. In these patients, diagnosis and treatment at an early stage have been shown to improve outcome (18-22). Identification of extrapulmonary activity may help in clinical decision-making, especially with respect to treatment initiation or as a potential explanation for persistent symptoms. PET/CT is the preferred imaging modality for identifying active sites of sarcoidosis, based on FDG accumulation within the macrophage- and lymphocyte-rich granulomas. It has largely replaced ^{67}Ga scintigraphy in the diagnosis of sarcoidosis, including disease localization in

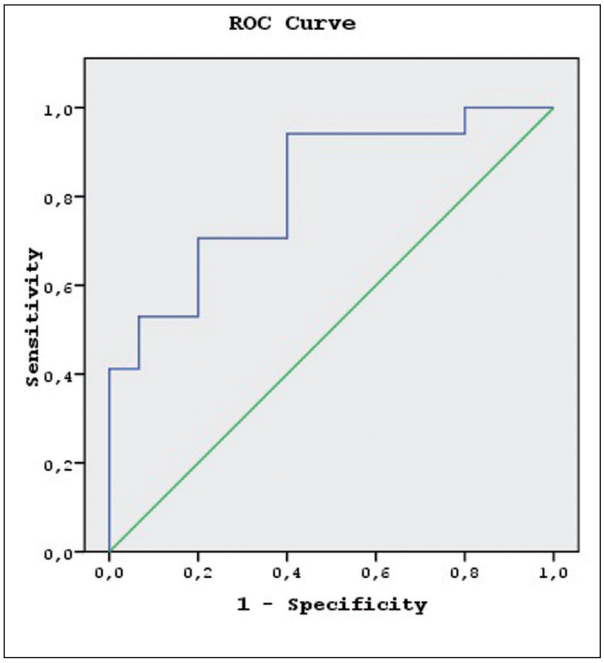

Fig. 2. Receiver operating characteristic (ROC) curve of the ACE serum levels to discriminate extrathoracic involvement –negative and extrathoracic involvement –positive patients with sarcoidosis

the heart and elsewhere in the body (23, 24). In patients with sarcoidosis, FDG PET alone, without CT, may play an important role in lesion detection, the identification of accessible biopsy sites, the quantification of disease activity, predicting outcome, and in assessing the response to treatment (1, 5, 11, 17-22, 25, 26). Braun et al. reported that PET/CT allowed the identification of sites of extrathoracic involvement (5). In our study, we found that PET/CT was a useful tool for identifying an accessible biopsy site for further examination and for detecting extrathoracic involvement.

Increased serum levels of ACE and the interleukin-2 receptor (IL-2R) are indicative of inflammation and are associated with PET-positive findings in patients with sarcoidosis (7, 26). In fact, the positive predictive value of serological inflammatory markers for the presence of inflammatory activity on PET has high sensitivity, although the negative predictive value has only moderate sensitivity (26). Active granuloma cells produce ACE and sACE has been shown to correlate with the total granuloma load in the body.Previous studies demonstrated significantly higher sACE levels in patients with positive FDG-PET findings than in those who had negative FDG-PET (27). Similar to recent studies,our sarcoidosis patients with extrathoracic involvement had higher sACE levels than those without extrathoracic involvement. Moreover, sACE levels correlated well with extrathoracic involvement above the cut-off value 19.75.

Symptoms related to sarcoidosis may differ from objective parameters as disease indicators, and serum markers may be increased, even in patients without symptoms or functional impairment. Our patients did not have any organ-specific symptoms indicative of extrathoracic involvement; nonetheless, those with extrathoracic involvement had significantly higher sACE values.

In view of the radiation dose and costs, a PET scan cannot be recommended for all patients with sarcoidosis; rather, the appropriate indications must be defined. Mostard et al. showed that clinical prediction of sarcoidosis activity based on IL-2R levels and high-resolution CT scoring can be used to identify the subgroup of patients with a high probability of PET positivity, which may allow the more effective use of PET examination (28). Keijsers et al. showed that positive ACE and IL-2R correlated well with PET/CT findings and suggested that PET/CT might be omitted when these markers are elevated (26). Increased sACE levels were previously shown to be associated with worsening clinical status and positive findings on ^{67}Ga scintigraphy (29). Our results are consistent with those findings, and further demonstrated that high sACE levels were indicative of extrathoracic involvement. The cut-off value of sACE determined in this study can be used to select patients in whom further examination such as FDG-PET might be warranted. The sACE-based approach may also be useful in the early prediction of extrathoracic involvement and in assessing the response to treatment, especially in patients with life-threatening extrapulmonary sarcoidosis.

This retrospective study has several limitations. First, the study population was from a single center where more severe, refractory patients are referred. Thus, these patients may not have been representative of the general sarcoidosis population. Second, not all patients seen at the center underwent FDG-PET or FDG-PET/CT - only those in whom it was used to establish the differential diagnosis. Since only these latter patients were included in the study, this might have caused selection bias.

In conclusion, our study showed that sACE levels in sarcoidosis patients with extrathoracic involvement were higher than in those without extrathoracic involvement. sACE values above the cut-off level correlated well with the presence of extrathoracic involvement, suggesting that this subgroup might benefit from further examination by FDG-PET or FDG-PET/CT, for example, to confirm extrathoracic involvement and thereby optimize treatment planning. Further studies with larger cohorts are necessary to confirm these results.

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