Procalcitonin: Is It a Useful Biomarker for Diagnosis and Differential Diagnosis of Sarcoidosis?

Prokalsitonin Sarkoidoz Tanısında ve Tüberküloz ile Ayırıcı Tanısında Kullanılabilir mi?

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ABSTRACT

Objective: We aimed to investigate whether procalcitonin (PCT) is a useful biomarker for diagnosis of sarcoidosis and differentiate it from tuberculosis (TB).

Methods: Thirty-five histopathologically-verified sarcoidosis patients with no previous treatment and 23 tuberculosis patients, who were diagnosed bacteriologically or histopathologically, were included in the study. Demographic data, clinical history, laboratory findings-serum procalcitonin (PCT) level, C-reactive protein (CRP), white blood cell (WBC) and erythrocyte sedimentation rate (ESR) and clinical findings were recorded.

Results: Fifty-eight patients were included in the study. Twenty-three (39.7%) were male; 35 (60.3%) were female. Mean age was 42.6±14.1 and 47.9±15.9 years in sarcoidosis and TB groups respectively. Thirty-five (60.3%) had diagnoses of sarcoidosis and 23 (39.7%) TB. Of patients with TB; 15 were diagnosed via smear and culture while 8 were diagnosed via lymph node biopsies. Of patients with sarcoidosis; 20 were diagnosed with mediastinoscopy and 15 with transbronchial biopsies (TBB). There was no statistically significant difference for serum PCT level between sarcoidosis and tuberculosis (p=0.226). Additionally, PCT had no significant relationship with stages of sarcoidosis (p=0.873).

Conclusion: We estabilished that PCT is not a reliable biomarker neither diagnose of sarcoidosis nor differentiate it from TB.

Keywords: Procalcitonin, sarcoidosis, tuberculosis

ÖZET

Amaç: Prokalsitoninin (PCT) sarkoidoz tanısında ve sarkoidoz ile tüberkülozun ayırıcı tanısında kullanılıp kullanılmayacağını belirlemeyi amaçladık.

Yöntemler: Çalışmaya histopatolojik olarak tanı konulmuş, tedavi almamış 35 sarkoidoz hastası ile, bakteriyolojik veya histopatolojik olarak tanı konulmuş 23 yeni tüberküloz olgusu alındı. Demografik veriler, anemnez, laboratuvar verileri - prokalsitonin (PTC), C-Reaktif protein (CRP), beyaz küre (WBC), sedimentasyon (ESR) ve klinik bulgular kaydedildi.

Bulgular: Çalışmaya 58 hasta alındı. Hastaların 23'ü (%39,7) erkek, 35'i (%60,3) kadın idi. Yaş ortalaması sarkoidoz grubunda 42,6±14,1, tüberküloz grubunda 47,9±15,9 idi. Hastalarımızın otuz beşi (%60,3) sarkoidoz ve 23'ü (%39,7) tüberküloz tanılı idi. Tüberküloz tanısı 15 hastada balgam yayma ve kültürü ile 8 hastada lenf nodu biyopsisi ile kondu. Sarkoidoz hastalarının 20'sinde tanı mediyastinoskopi,15'inde transbronşiyal biyopsi (TBB) ile kondu. PCT düzeyi için sarkoidoz ve tüberküloz arasındaki istatistiksel olarak anlamlı bir fark yoktu (p=0,226). Ayrıca sarkoidozun evreleri ile prokalsitonin arasında istatistiksel olarak anlamlı ilişki yoktu (p=0,873).

Sonuç: Prokalsitoninin sarkoidoz tanısı ve tüberküloz ile ayırıcı tanısında biyobelirteç olarak bir öneminin olmadığını saptadık.

Anahtar Kelimeler: Prokalsitonin, sarkoidoz, tüberküloz

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INTRODUCTION

Sarcoidosis is a systemic granulomatous disease of unknown etiology. Understanding the molecular basis of the disease reveals new researches on new biomarkers and their potential value that indicate disease activity and lung involvement. Unfortunately, current biomarkers fail to assess disease activity and lung involvement which could help identify patients at risk for irreversible damage. On the other hand, unless excluded from all other granulomatous diseases, a distinct diagnosis cannot be made. Tuberculosis is the most challenging diagnostic dilemma for a physician suspecting sarcoidosis. Due to the clinical and histological similarities with tuberculosis (TB), the etiological role of mycobacteria has repeatedly been investigated. The similarities of these two diseases make researchers interested in finding new diagnostic tests (1,2).

Procalcitonin (PCT) is considered an acute phase protein that consists of 116 amino acids with a molecular weight of 13 kDa. PCT is a propeptide of calcitonin, which is normally produced by the c-cells of the thyroid gland. According to a very recent in vivo and in vitro study, the major source of PCT seems to be the liver (3-5). Randomized controlled trials have shown that using different serum levels of PCT indicates algorithms to guide decisions about bacteriemic infections, arthritis, bronchitis, COPD exacerbation, endocarditis, neutropenia, pneumonia, severe sepsis/shock, upper respiratory tract infections and ventilator-associated pneumonia (6-15). Additionally, many studies examined the diagnostic value of PTC on TB (16-19). Serum PCT assessments in patients diagnosed with pulmonary TB or community-acquired pneumonia (CAP) were evaluated for differential diagnosis and were found to have poor effects (17,18).

Serum amyloid A (SAA), soluble interleukin-2 receptor (sIL2R), lysozyme**,** angiotensin-converting enzyme (ACE) and glycoprotein KL-6 were reported to be useful and accessible biomarkers for diagnosis and follow up of sarcoidosis (19,20). However, according to our knowledge, there is no previous study investigating the relationship between PCT and sarcoidosis.

The present study aimed to determine whether PCT has a diagnostic importance for sarcoidosis and can discriminate it from tuberculosis.

METHODS

Patients

A prospective observational study was designed. Fifty-eight patients (35 sarcoidosis and 23 tuberculosis) were included in the study. Diagnoses of sarcoidosis patients were verified histopathologically. None of the patients had been previously treated for sarcoidosis. Chest x-ray, HRCT and bronchoscopy were routinely performed in all the patients. Patients who could not be diagnosed with these procedures underwent mediastinoscopy. All TB patients were verified with smear, culture or histopathology. Only patients who had a TB diagnosis histopathologically were included in the study. Study population was sampled from cases with only lung and mediastinal involvement. Patients with TB and sarcoid involvement of the liver and kidney were excluded. Demographic data, clinical history, biological markers and clinical findings were recorded for all patients.

Patients; under 18 years old, with a history of smoking, decompensated heart failure, diabetes mellitus, chronic renal disease, chronic pulmonary disease, a current pregnancy, malignancy, liver or pancreatic disease, rheumatic disease necessitating pharmacological treatment, inflammatory bowel disease, delivery or any infections at the time of the study or within two weeks before the study, were also excluded from the study.

Measurement

All subjects underwent venous blood sampling drawn from an antecubital vein after a semi-supine rest of at least 15 minutes. Serum PCT was determined by an immunoluminometric assay (Sphere Light B.R.A.H.M.S PCT; Wako Diagnostics, Tokyo, Japan). Hypersensitive C-reactive protein (Hs-CRP) was measured with a fully-automated particle enhanced immunonephelometry (N High Sensitivity CRP, Dade Behring®). White blood cell and differential cell counts were determined by flow cytometry (XT-2000i; SYSMEX Corporation, Kobe, Japan).

The erythrocyte sedimentation rate was detected in anticaogulated blood by the conventional Westergren method. The upper limits of normal PCT, Hs-CRP, white blood cell and erythrocyte sedimentation rate were 0.5 ng/mL, 5 mg/dL, 10.3 $10^3/\mu L$ and 0-10 mm/first hour, respectively.

Statistical Analysis

Data were expressed as mean±SD and percentage. Statistical analysis was performed using the SPSS for Windows (Version 18.0; SPSS Inc., Chicago, IL, USA). Mean values were compared between related groups. Mann-Whitney U Test was used to compare differences between PCT, Hs-CRP, erythrocyte sedimentation rate, white blood cell and independent groups when the dependent variable was not normally distributed. Spearman's rank correlation coefficients were obtained for the relation between PCT and stages of sarcoidosis. Statistical significance was accepted as $p<0.05$.

All patients were informed about the study and provided consent to participate. The study was planned according to the ethics guidelines of the Helsinki Declaration, and the study protocol was approved by the local ethics committee (B.30.2.ATA.0.01.00/14).

RESULTS

Fifty-eight patients were included in the study. Twenty-three (39.7%) patients were male; 35 (60.3%) were female. Thirty-five (60.3%) had diagnoses of sarcoidosis and 23 (39.7%) tuberculosis. Mean age of sarcoidosis patients was 42.6±14.1 years and 47.9±15.9 years in the tuberculosis group. Of patients with TB; 15 were diagnosed via smear and culture while 8 were diagnosed via lymph node biopsies. Of patients with sarcoidosis; 20 were diagnosed with mediastinoscopy and 15 with transbronchial biopsies (TBB) on bronchoscopy (stage 1: 16 -45.7%, stage 2: 18-51.5% and stage 3: 1-2.8% and stage 4: 0).

Table 1 shows the relationship of laboratory parameters between sarcoidosis and tuberculosis. Levels of PCT and Hs-CRP related with groups were given in **Figure 1** and **2**. PCT level for each stage were 0.054±0.016 ng/mL, 0.58±0.22 ng/mL and 0.26 ng/mL in stage 1, 2 and 3, respectively. There was no statistically significant difference for PCT level between sarcoidosis and tuberculosis (p=0.226). Additionally, PCT had no significant relationship with stages of sarcoidosis (p=0.873, r=-0.028).

Table 1. The relationship of laboratory parameters between sarcoidosis and tuberculosis

	Sarcoidosis	Tuberculosis	P value
Procalcitonin	0.055±0.020 ng/mL	0.058±0.025	0.556
Hs-CRP	5.73±5.38 mg/L	6.92±11.11	0.333
WBC	7940±2350 /µL	6400±1600	0.034
Sedimentation	15.11±10.7 mm/hr	27.90±22.2	0.038

Hs-CRP: Hypersensitive C-reactive protein, WBC: White blood cell

DISCUSSION

This study was designed with the aim to find whether PCT is a useful biomarker to diagnose sarcoidosis and differentiate it from TB. Levels of this biomarker are selectively elevated in patients with bacterial infections. We found that serum levels of PCT do not increase in patients with sarcoidosis. Therefore, we advance an opinion that PCT is not a reliable marker for diagnosis and follow up of sarcoidosis, which is thought to be due to an inflammatory response to mycobacterial infections.

Reliability of increased levels of PCT for diagnosis and follow up in systemic bacterial infections and early onset sepsis has been proven. However, there is no significant evidence for nonbacterial inflammatory diseases. No helpful results have been achieved for diagnosis and monitoring of another bacterial infection, TB (3-5,16-21). Both TB and sarcoidosis are granulomatous diseases of the lung. Distinguishing sarcoidosis from pulmonary TB can sometimes be a challenging issue to physicians. High prevalence of tuberculosis results in these patients receiving repeated courses of tuberculosis therapy while lung damage continues to progress. The present study aimed to determine whether increased serum PCT levels have a diagnostic accuracy for detecting sarcoidosis that cannot be discriminated from tuberculosis clinically**.**

Due to clinical and pathological similarities with other granulomatous diseases of lungs, an infectious etiology of sarcoido- sis has long been investigated. New diagnostic techniques, like PCR and ELISPOT, showed no benefit in determining microbiological roles of etiology of sarcoidosis. Specific roles of microbial agents in the development of sarcoidosis have remained indeterminate. Most of the suspicious agents are *Mycobacterium tuberculosis*, *Propionibacterium,* viruses *(Epstein Barr Virus*, *Herpes Simplex virus, and Human herpesvirus 8)* and fungi (9,22-25).

To date, no single biological marker that reflects lung involvement and activity of the disease adequately has been found. Most of the current viewed markers, erythema nodosum, clinical symptoms, chest X-ray and pulmonary function tests contribute very little regarding the disease. Additionally, none of biological markers predicts the outcome at all (20,26). The present study evaluated the diagnostic and prognostic accuracy of PCT with sarcoidosis on the basis of its possible infectious etiology. The mean value of PTC levels was found within the normal reference range. No significant relationship was determined between PCT and stages of sarcoidosis. Moreover, among TB patients, levels of PTC did not differ statistically significantly from those of sarcoidosis patients.

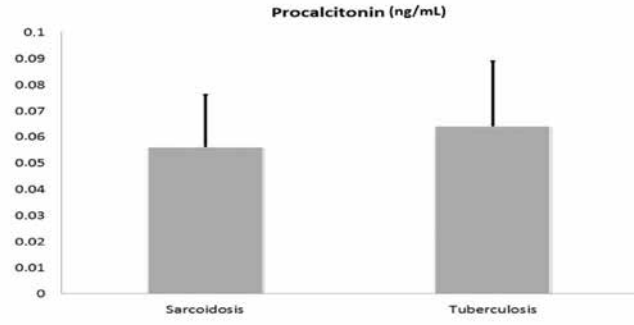

Figure 1. The association of procalcitonin level between sarcoidosis and tuberculosis

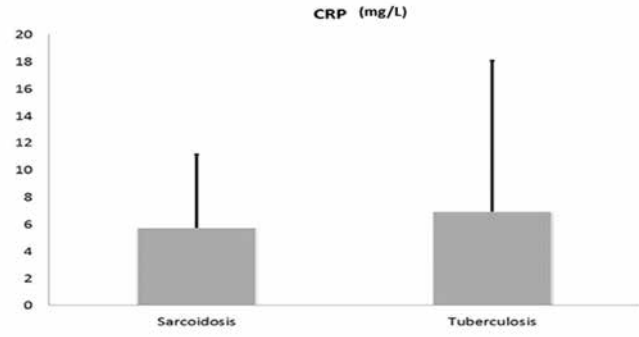

Figure 2. The association of Hs-CRP level between sarcoidosis and tuberculosis

CONCLUSION

Diagnosis and follow up of sarcoidosis requires a cluster of complex procedures. No single diagnostic test for this disease has yet been identified. A wide range of new biological markers have been expected to reflect the disease activity and predict prognosis but their usefulness is still controversial. This study was designed to elucidate whether PCT can be used to diagnose sarcoidosis and differentiate it from TB. According to our findings, we suggest this biomarker should no be used for this purpose. Further studies are required to define more reliable biochemical markers to name or predict the prognosis of a patient with sarcoidosis.

Conflict of Interest
No conflict of interest was declared by the authors.

Peer-review: Externally peer-reviewed.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Atatürk University Faculty of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study

Author Contributions
Concept - Ö.A., M.A.; Design - M.M.; Supervision - M.A.; Data Collection and/or Processing - A.Y., F.K.; Literature Review - F.K.; Writing - Ö.A., M.G.; Critical Review - M.A., E.Y.U.

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Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

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