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Original Article / Orijinal Araştırma

Place of neopterin level in the differential diagnosis of tuberculosis pleurisy

Tüberküloz plörezinin ayırıcı tanısında neopterin düzeyinin yeri

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Absract

Aim. Tuberculous pleurisy is one of the most common form of pulmonary tuberculosis, and may be confused with many other diseases. This study was designed to assess the diagnostic value of pleural fluid neopterin levels in patients with tuberculous pleurisy. **Methods.** A total of 57 patients [tuberculosis pleurisy (n=30), malignant pleural effusion (n=17), pleural effusion due to congestive heart failure (n=10)] were included in the study. The measurement of neopterin levels was conducted by the enzymeimmunassay method and Trinity-Biotech XL fully automatic ELISA kit device and neopterin IBL kit. **Results.** The neopterin levels in patients with tuberculous pleurisy were significantly higher than that of both malignancy and congestive heart failure ($p<0.001$). The neopterin levels of patients with congestive heart failure and malignancy were found as similar ($p=0.920$). There was no significant difference in the neopterin levels with regard to age and sex ($p>0.05$). **Conclusions.** Tuberculous pleurisy increases neopterin levels of pleural fluid when compared with malignancy and congestive heart failure. In this respect, neopterin level in the pleural fluid may be a useful diagnostic marker of tuberculous pleurisy.

Keywords: Neopterin; pleural effusion; tuberculous pleurisy

Özet

Amaç. Tüberküloz plörezi akciğer tüberkülozunun en sık formlarından biri olup birçok hastalıkla karışabilir. Bu çalışma tüberküloz plörezili hastaların plevral sıvılarındaki neopterin seviyelerinin tanısal değerini belirlemek için yapılmıştır. **Yöntem.** Toplam 57 hasta [tüberküloz plörezi (n=30), malign plevral efüzyon (n=17) ve konjestif kalp yetmezliği

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(n=10)] çalışmaya alındı. Neopterin düzeylerinin ölçümü enzimimmünoassay yöntemi ve Trinity-Biotech XL tam otomatik ELISA kit aleti ve neopterin IBL kiti ile gerçekleştirildi. **Bulgular.** Tüberküloza bağlı oluşan plevral sıvıdaki neopterin düzeyi malignite ve konjestif kalp yetmezliğine bağlı olanlarınkine göre anlamlı derecede yüksek bulundu (p<0,001). Konjestif kalp yetmezliği ve maligniteye bağlı plevral sıvıların neopterin düzeyleri benzer bulundu (p=0,920). Yaş ve cinsiyete göre neopterin düzeylerinde anlamlı değişiklik bulunmadı (p>0,05). **Sonuçlar.** Tüberküloz plörezide malignite ve konjestif kalp yetmezliğine göre plevral sıvıdaki neopterin düzeyi daha fazla artmaktadır. Bu nedenle, plevral sıvıda neopterin ölçümü tüberküloz plörezi tanısında kullanılabilecek yararlı bir yöntem olabilir.

Anahtar sözcükler: Neopterin; plevral efüzyon; tüberküloz plörezi

Introduction

Tuberculosis can mimic many diseases and clinical symptoms in many forms. Tuberculous pleurisy, one of these forms, may be confused with many other diseases. It is sometimes inadequate to make diagnosis by bacteriological, pathological and biochemical methods of pleural fluid and also by culture and biopsy. Although tuberculosis is one of the most common causes of pleural effusion, diagnosis of tuberculous pleuritis still remains a challenge. Thus, different biomarkers have been extensively studied in pleural effusion to improve the diagnostic accuracy [1] Therefore, alternative diagnostic methods are needed. Neopterin, a pyrazino-pyrimidine compound, is synthesized by monocytes and macrophages in response to interferon-(IFN-) γ produced by activated T cells. Neopterin levels are elevated by T-cell or macrophages activation [2]. In our study, we aimed to investigate the neopterin level of pleural fluid in the diagnosis of tuberculosis pleurisy.

Materials And Methods

The study was conducted on 100 patients with pleural effusion who admitted to the Heybeliada Chest Diseases and Chest Surgery Education- Research Hospital, and Siyami Ersek Thoracic- Cardiovascular Surgery Education- Research Hospital between May 2004 - January 2005. All of the patients were informed about the process and written informed consent was taken from all patients. The patients with additional dieseases, especially impaired renal functions were excluded from the study, because neopterin is excreted from kidneys. None of the patients had an additional disease after follow-up of specific treatment. The pleural fluid was diagnosed radiologically and fluid materials were taken by thoracentesis and sent to pathology, bacteriology and biochemistry laboratories in order to distinguish the etiology of fluid. All cases were divided into three groups according to their etiology; Group 1: 30 patients with tuberculosis pleurisy, diagnosed by cope biopsy and / or bacteriological tests, Group 2: 17 cases with malignant pleural effusion diagnosed by cytologically, Group 3: 10 cases who had heart failure with pleural effusions diagnosed by cardiological examination, electrocardiography, and echocardiography. The samples were wrapped in aluminum foil to prevent from the light and transported in the ice bucket. All samples were stored in the freezer (with -22°C) until the moment of work. Materials were brought to room temperature before the study and confirmed by processing twice. The study was conducted by the Enzyme Immun Assay (EIA) method and Trinity-Biotech XL

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fully automatic ELISA kit device and neopterin IBL kit. The results were evaluated by Mann-Whitney U statistical test.

Results

Forty three cases were excluded from the study because of additional diseases and 30 cases (16 male, 14 female, mean age 25.9 ± 10.2 years) with tuberculosis pleurisy , 17 cases (11 male, 6 female, mean age 54.7 ± 16.5 years) with malignant pleural effusion and 10 cases (4 male, 6 female, mean age 67.4 ± 11.3 years) with pleural effusion due to congestive heart failure were evaluated. The neopterin levels were measured as 43.3 ±14.3 nmol/L, (20.3-87.0), 24.1 ± 11.7 nmol/L, (5,4- 42.2) and 24.4 ± 12.7 nmol/L (7.1 - 47.2) in pleural effusions of patients with tuberculosis, malignancy, and congestive heart failure, respectively (Fig. 1). The neopterin levels in pleural fluid were found significantly higher in the patients with tuberculosis pleurisy when compared to those in the patients with malignancy and congestive heart failure ($p < 0.001$), where there was no significant difference in the neopterin leves between the patients with congestive heart failure and malignancy ($p = 0.920$). There was no significant difference in the neopterin levels with regard to age and sex ($p>0.05$).

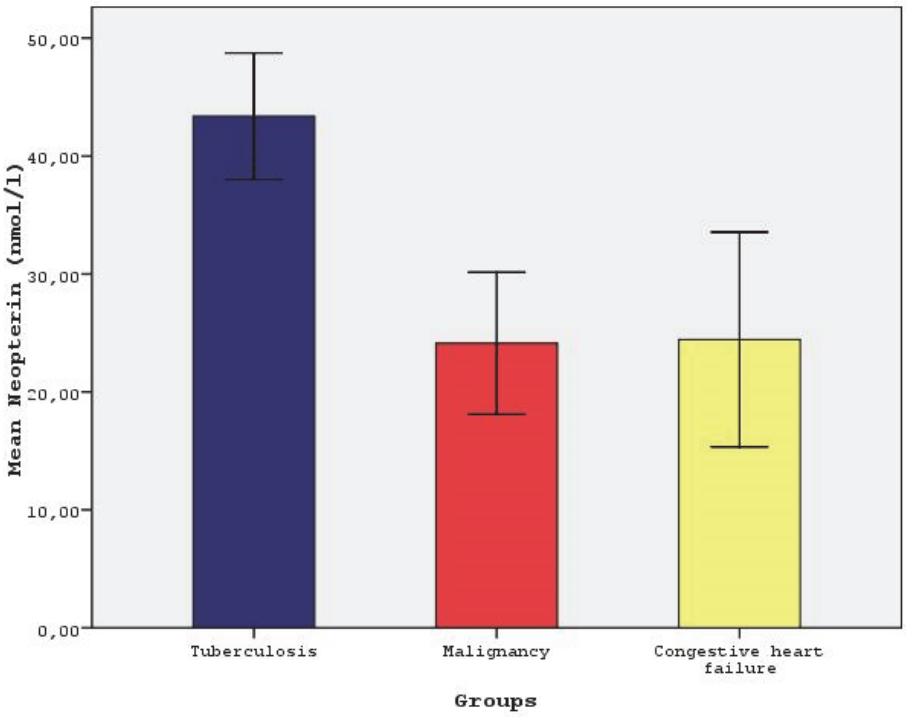

Figure 1. Mean values of neopterin in the pleural fluid samples of patients with tuberculosis, malignancy, and congestive heart failure. In patients with tuberculosis, neopterin level was significantly higher ($p < 0.001$).

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Discussion

This study investigated the neopterin level in tuberculosis pleurisy, malignancy and heart failure. Results indicated that tuberculosis caused significant increase in neopterin level in pleural fluid. Many factors play a role in the etiology of pleural effusion. It has been identified that nearly 1/30 of tuberculosis causes pleural effusion and 3% of pleural effusion is caused by tuberculosis [3, 4]. In Turkey, it has been reported that 9% of pleural effusion is caused by tuberculosis, and 5-50 % of tuberculosis results in pleural effusion [5, 6]. From these data, high ratio of pleural effusion due to tuberculosis in our country is remarkable. However, diagnosis is very low by sputum smear and / or culture (50%) in patients with pleural effusion. Routine use of molecular methods in the laboratory for diagnosis of tuberculosis is still controversial. With different meta-analysis, it is shown that the average sensitivity and specificity of polymerase chain reaction (PCR) is 85 % and 95% respectively [7]. There are important studies (ADA, CA-125, α-IFN, TNF-α, IL-2) in the literature related to the differential diagnosis of pleural effusions due to tuberculosis [2, 8, 9]. Determination of the pleural fluid as transudate or exudate is the first step in the differential diagnosis. Light et al. [10] has been reported that if pleural fluid total protein / serum total protein ratio is greater than 0.5, pleural fluid lactate dehydrogenase (LDH) / serum LDH ratio is greater than 0.6 and pleural fluid LDH is greater than ⅔ the normal upper limit for serum, it should be classified as exudate. In our study all effusions were evaluated according to the Light's criteria. All cases of tuberculosis and malignancy groups had the criteria of exudate, and heart failure group had the criteria of transudate.

Some of the publications reported that pleural fluid characteristics may change from transudate to exudate as a result of diuresis. Diuretics can change level of many substances such as protein, albumin, LDH, cholesterol and cholinesterase in the pleural fluid [11, 12]. However, Romero-Canderia et al. [13] showed that the lowest changing markers are protein and albumin gradients. Similar to this study, we did not observe any conversion to exudate in pleural effusions of congestive heart failure patients, although they were using the diuretics. A lot of work associated with neopterin metabolism were based on the measurement of completely oxidized neopterin with high-performance liquid chromatography (HPLC) or radioimmunassay [14-16]. In our study, we used the enzyme-immune-assay method to find pleural fluid neopterin level.

Plasma and cerebrospinal fluid (CSF) concentrations of neopterin are at least 20 times less than the urine, because pterin is secreted actively by the kidneys. Biopterin and neopterin concentrations in blood are high in patients with renal insufficiency. It is elevated and correlates with the severity of chronic kidney disease [17, 18]. For that reason, we have excluded the patients with renal failure in our study.

Although it is lower in malignant pleural effusion than tuberculosis, an increase in serum neopterin level indicates the stimulation of monocyte-macrophage line. Neopterin, regarded as a biochemical marker of cell-mediated immune response, is produced by stimulated macrophages under the influence of gamma interferon of lymphocyte origin. [2, 18]. Although CD4/CD8 ratio is normal or decreased in neoplastic effusions, this situation is the result of increased secretion of interferon-α from natural killer cells □or the result of the production of tumor necrosis factor-α. This is a result of a response to antigenic stimulation of T cells [19]. In fact, normal or decreased levels of neopterin in most

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malignancy are attributed to the defect in immune response. In the malignancy group of our study neopterin level was not increased. Similar results were also found in the malignancy group of Immanuel et al. [20]. When compared to each other, Baganha et al. [19] found that, the level of neopterin in the serum and in the pleural fluid of malignancy group was lower than that of tuberculosis group. These results are similar to our study. In our study, the significant difference in the average age between tuberculosis, malignancy and heart failure seems to be tipping the balance between the groups statistically. But in similar studies with the same age groups, the results were obtained in parallel with us [19, 20]. Gender is not a factor that affects the level of neopterin. In our study, no significant differences were detected between female and male in all three groups. The neopterin levels of pleural effusions of patients with pleural tuberculosis in similar studies are almost identical to our study.

In the study of Immanuel et al. [20] although a slightly lower level of neopterin was found in the tuberculosis group, it was significantly higher than that of the malignancy and control group. Because pleural fluids cannot be received from healthy people, heart failure group was considered as the control group. The increase of the level of neopterin, in patients with heart failure formation, has been already shown in other studies [11, 12]. Neopterin kits can help patients in whom the cellular immunity should be checked frequently and also distinguish immune-mediated tissue damage from metabolic one. Further studies are needed to evaluate the results of neopterin in clinical decision.

In conclusion, neopterin concentration of pleural fluid increases due to tuberculosis pleurisy when compared to pleural effusions related to malignancy and congestive heart failure. A high neopterin level in the pleural fluid may be a good parameter in supporting the diagnosis of tuberculosis.

Conflict of Interest

The authors declare that there is no scientific and/or financial conflicts of interest.

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