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# Clinical importance of serum neopterin level in patients with pulmonary tuberculosis

Salih Cesur [a,*], Turan Aslan [b], Nevin Taci Hoca [c], Filiz Çimen [c], Gülnur Tarhan [d], Aydın Çifçi [e], İsmail Ceyhan [f], Tuğrul Şipit [c]

[a] Ankara Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey
[b] Bezmialem Foundation University School of Medicine, Infectious Diseases and Clinical Microbiology Department, Istanbul, Turkey
[c] Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Chest Diseases Department, Ankara, Turkey
[d] Adıyaman University, Faculty of Medicine, Department of Medical Microbiology, Adıyaman, Turkey
[e] Kırıkkale University, Faculty of Medicine, Department of Internal Medicine, Kırıkkale, Turkey
[f] Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Microbiology Laboratory, Ankara, Turkey

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ABSTRACT

*Objective:* Neopterin is a sensitive marker for cell-mediated immune response. Because of this, the neopterin levels of body fluids show cell-mediated immune response in different infectious diseases which involve T cells and macrophages.

The aim of this study was to determine the clinical importance of neopterin levels in patients with tuberculosis and compare with those levels of healthy subjects.

*Methods:* Seventy patients with tuberculosis (46 newly diagnosed cases, 15 relapse cases, and 9 multidrug-resistant tuberculosis cases) and 18 healthy adult individuals were included in the study. Neopterin concentrations were measured by the ELISA method according to the protocol of the manufacturer. Chi-square test was used in statistical analysis; $p \leqslant 0.05$ was considered statistically significant.

*Results:* Serum mean neopterin levels were 23.74 ± 21.8 nmol/L (median: 18.3) in newly diagnosed patients with pulmonary tuberculosis; 28.69 ± 21.2 nmol/L (median: 21.2) in relapse patients and 31.28 ± 14 nmol/L (median: 25.4) in multidrug-resistant tuberculosis cases, respectively. Serum mean neopterin levels were 4.03 ± 5.12 nmol/L (median: 5.1) in healthy subjects. The serum neopterin levels were found to be significantly higher in patients with tuberculosis than the control group.

There was a statistically significant correlation between neopterin positivity (neopterin level ⩾10 nmol/L was accepted to be positive) and clinical symptoms of hemoptysis and weight loss. Besides statistically significant correlations between neopterin positivity and hemoglobin level, sedimentation rate, mean leukocyte count and radiological involvement (localized or diffuse) were determined.

*Conclusion:* Serum neopterin levels can be used as a helper laboratory finding for the diagnosis of patients with tuberculosis. For this aim, further controlled studies are needed.



* Corresponding author. Address: S.B. Ankara Eğitim ve Araştırma Hastanesi, Enfeksiyon hastalıkları ve Klinik Mikrobiyoloji Kliniği, Ulucanlar Cad. Cebeci-Ankara, Turkey. Tel.: +90 312 5655690.
E-mail address: scesur89@yahoo.com (S. Cesur).

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## Introduction

Neopterin is a pyrazino-pyrimidine compound belonging to the pteridine class, which is only produced by living cells [1]. Neopterin is produced from guanosine triphosphate by stimulated macrophages under the effect of lymphocyte-originated gamma interferon. Neopterin is an important marker which plays a key role in the interaction of monocyte/macrophage activation [2]. Neopterin was demonstrated to be a sensitive marker of cell-mediated immune reactions; therefore, the identification of neopterin levels in various body fluids has diagnostic significance in numerous diseases including the diseases of T-lymphocytes and macrophages [1,3].

*Mycobacterium tuberculosis* (MTB) is an intercellular pathogen with the ability to live for a long time in macrophages. Tuberculosis (TB) bacilli that are phagocyted by macrophages cannot be killed by polymorphonuclear leukocytes. Neopterin is released by the stimulation of intracellular viruses and bacteria, such as TB, and provides information about the status of cell-mediated immunity [1,4]. The aim of this study is to determine the clinical importance of serum neopterin levels and compare them with those levels of a control group.

## Materials and methods

This study was performed in cooperation with the Ankara Training and Research Hospital and Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Chest Diseases Department.

Diagnosis of pulmonary tuberculosis (PTB) was made with clinical symptoms, acid fast bacillus (AFB) smear positivity in sputum microscopy, culture positivity for MTB, and radiologic findings.

Symptom control among the healthy individuals was eliminated with physical examination and PA chest radiography.

The patients were comprised of three groups, including newly diagnosed, relapse and multidrug-resistant (MDR) patients with TB.

Newly diagnosed patients with TB: These are the patients that have not taken TB treatment before or the patients that have taken TB treatment less than one month.

Relapse case of TB: The patient was accepted as a relapse if the patient who had been diagnosed with TB and who had completed the treatment successfully was diagnosed with TB again; in other words, the presence of AFB smear positivity in sputum microscopy.

Multidrug-resistant tuberculosis (MDR-TB) cases: Resistance of a patient to both isoniazid and rifampicine, which are used in the treatment of TB.

Blood samples were taken from all TB patients before the diagnosis and before beginning the treatment.

After separation, the serum samples were stored at −40 °C in a deep freezer. Neopterin levels were determined by ELISA method in accordance with the instructions of the producing company (IBL Medical, Turkey). Data were recorded using SPSS software. Chi-square test was used for statistical evaluation. Patients were evaluated in three groups, including newly diagnosed (Group 1), relapse (Group 2) and MDR patients (Group 3), respectively. The associations of the groups with gender, symptoms (production of sputum, dyspnea, hemoptysis, chest pain, fever, and weight loss), duration of symptoms and degree of radiological involvement (diffuse cavitary, localized cavitary) were statistically evaluated.

Cases with neopterin levels $\geqslant$10 nmol/L and <10 nmol/L were determined as positive or negative, respectively. Duration of symptoms between patients with positive and negative Neopterin symptoms (coughing, sputum, dyspnea, hemoptysis, and chest pain), duration of symptoms and laboratory findings (hemoglobin levels, leukocyte count and sedimentation rate) were also compared statistically; $p$ levels $\leqslant$0.05 were accepted to be significant.

Informed consent forms were received from the patients, and approval of the Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital Ethic Committee was obtained for the study.

## Results

A total of 70 inpatients from Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Chest Diseases Department, including 46 newly diagnosed patients with TB (Group 1), 15 relapse patients (Group 2), 9 patients with MDR-TB patients (Group 3) and a total of 18 healthy subjects as the control group were enrolled in the study.

Time to onset of the symptoms was 62 ± 39 days in Group 1, 17 ± 61 days in Group 2, and 58 ± 13 days in Group 3. There was a statistically significant difference between the Groups 1 and 2 ($p < 0.01$) regarding the time to onset of the symptoms, but not between the Groups 1 and 3 ($p > 0.01$).

Neopterin levels were significantly higher in the patient groups versus the control group ($p < 0.05$). Results are presented in Table 1.

Neopterin levels were positive (neopterin level $\geqslant$10 nmol/L) in 45 of 70 (64.3%) patients with TB and 4 of 18 (22%) in the control group. Neopterin positive patients (34 males, 11 females) and neopterin negative patients (16 males and 9 females) did not differ significantly in terms of gender ($p > 0.05$). Comparison of neopterin levels between the patient groups did not reveal any difference ($p > 0.05$).

The associations of neopterin levels with clinical symptoms (for example, time to onset of the symptoms, sputum formation and dyspnea, etc.) and laboratory findings (for example, existence of cavitation, involvement degree of the lungs, microscopic gradient [from 1+ to 4+ positive], sedimentation rates, etc.) were statistically compared between the groups. Results are shown in Table 2.

## Discussion

Detection of neopterin concentrations in body fluids provides information about cell-mediated immune response. Neopterin is a biologically stabilized molecule, thus the messages generated during the immune responses can be detected easily. It is widely used in the follow-up of HIV infection. Neopterin is produced by macrophages as a response to interferon gamma stimulation, and neopterin concentrations show cellular immune activation [2–5].