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Serum Adenosine Deaminase Activity and Neopterin Levels during Therapy in Patients with Pulmonary Tuberculosis and Community-Acquired Pneumonia

Pulmoner Tüberkülozlu ve Toplum Kökenli Pnömonide Tedavi Sırasında Serum Adenozin Deaminaz Aktivitesi ve Neopterin Düzeyleri

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Abstract / Özet

Objective: Adenosine deaminase (ADA) and neopterin are increased in disorders that stimulate cells involved in the immune system. We investigated the effect of therapy on serum ADA activity and neopterin levels in patients with pulmonary tuberculosis (TB) and with community-acquired pneumonia (CAP).

Methods: Seventeen pulmonary TB, 24 CAP, and a control group of 20 healthy volunteers were included in this study. ADA and neopterin assay was performed colorimetrically and by ELISA, respectively, before and 2 months after therapy (rifampicin+isoniazid+ethambutol and pyrazinamide) of patients with TB and before and 15 days after therapy (ampicillin-sulbactam) of CAP.

Results: Serum ADA activity and neopterin levels were significantly higher in patients with TB than those in pneumonia and controls. Serum neopterin levels were significantly higher in patients with CAP than controls. No significant differences were found in ADA levels between pneumonia and control subjects. The ADA and neopterin levels decreased in active tuberculosis at the second month of treatment. No significant differences were found in neopterin levels between CAP and TB after treatment. But, serum neopterin and ADA levels were still significantly higher in patients with tuberculosis than controls despite treatment.

Conclusion: Although ADA activity may be useful for diagnosis and monitoring therapy in both specific and nonspecific pulmonary infections, neopterin values may be used in pneumonia patients along with the traditional biomarkers, such as white blood cell (WBC), erythrocyte rate (ESR), C-reactive protein (CRP).

Key Words: Pulmonary tuberculosis, community-acquired pneumonia, adenosine deaminase, neopterin

Amaç: İmmün sistemi stimüle eden hastalıklarda adenozin deaminaz (ADA) ve neopterin seviyeleri yükselir. Bu çalışmada, toplum kökenli pnömoni (TKP) ve pulmoner tüberkülozlu hastalarda tedavinin neopterin ve ADA seviyelerini nasıl etkilediği araştırılmıştır.

Yöntemler: Çalışmaya 24 TKP'li, 17 pulmoner tüberkülozlu ve 20 sağlıklı gönüllü kontrol grubu dahil edilmiştir. ADA spektofotometrik, neopterin ise ELİSA yöntemleriyle, pulmoner tüberkülozlu hastalarda tedavi öncesi ve tedaviden (rifampisin, izoniazid, etambutol ve pirazinamid) 2 ay sonra, TKP'li hastalarda tedavi öncesi ve tedaviden (ampisilin, sülbaktam) 15 gün sonra ölçülmüştür.

Bulgular: Serum ADA aktivitesi ve neopterin seviyeleri pulmoner tüberkülozlu hastalarda pnömonili hastalardan ve sağlıklı kontrollerden anlamlı olarak yüksek bulunmuştur. Serum neopterin seviyeleri TKP'li hastalarda sağlıklı kontrollerden anlamlı olarak yüksektir ancak pnömonili hastalar ve sağlıklı kontroller arasında ADA seviyeleri açısından anlamlı bir farklılık bulunamamıştır. Aktif tüberküloz grubunda ADA ve neopterin seviyeleri tedavinin ikinci ayından sonra düşmüştür. Tedavi sonrası pulmoner tüberkülozlu ve TKP'li hastalarda neopterin seviyeleri arasında herhangi bir anlamlı farklılık bulunamamıştır ancak serum neopterin ve ADA seviyeleri tedaviye rağmen tüberkülozlu grupta kontrol grubundan anlamlı olarak daha yüksektir.

Sonuç: Hem spesifik hem de non spesifik akciğer infeksiyonları tanısını koymada ve tedaviyi izlemede ADA seviyeleri kullanılabilirken, neopterin seviyeleri pnömonide beyaz kan hücresi (WBC), eritrosit sedimentasyon hızı (ESH) ve C-reaktif protein (CRP) gibi diğer geleneksel yöntemler ile birlikte değerlendirilmelidir.

Anahtar Kelimeler: Pulmoner tüberküloz, toplum-kökenli pnömoni, adenozin deaminaz, neopterin

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Introduction

Community-acquired pneumonia (CAP) is typically defined as an infection of the alveolar or gas-exchanging portions of the lungs occurring outside the hospital, with clinical symptoms accompanied by the presence of an infiltrate in the chest radiograph (1). A rapid diagnosis and prompt and appropriate antibiotic selection are essential for recovery and to reduce the morbidity and mortality from CAP. Tuberculosis (TB) is the leading cause of death from infectious disease worldwide. Therapy is directed towards the eradication of viable organisms and the prevention of disease spread. The differential diagnosis of TB from common bacterial CAP is difficult.

Adenosine deaminase (ADA) is an enzyme involved in purine metabolism, and its activity increases in various conditions, such as pneumonia, tuberculosis, sarcoidosis, and malignancies (2-5). In pulmonary tuberculosis, increased levels of ADA have been reported in many studies (2, 4, 6). ADA is divided into two isoenzymes, ADA-1 and ADA-2, which may show different activities and different correlations with lymphocyte subpopulations and disease process (4). Many studies reported that serum ADA levels were higher in patients with pulmonary tuberculosis than healthy controls (3, 6) and correlated with disease severity and bacterial isolation (8). ADA levels were related with the extent of destructive and infiltrative changes and endotoxinemia (9). Kelbel et al. (10) also found that serum ADA levels positively correlated with the disease extent in immunocompetent patients.

Neopterin is produced and released by human macrophages in response to stimulation with interferon-gamma and changes, in neopterin concentrations indicate cellular immune activa-

tion. Tuberculosis infection is associated with increased neopterin levels in body fluids. Neopterin may also be a useful parameter for evaluating the disease activity and response to therapy (11, 12).

The objective of this study was to verify the effect of therapy on serum ADA activity and neopterin levels in patients with pulmonary TB and with CAP.

Methods

The study was approved by the Ethical Committee of İstanbul Training and Research Hospital. A total of 61 participants were enrolled after informed written consent had been obtained.

Study Population

Group TB (TB): Seventeen consecutive patients (mean age: 43.41±11.48 years) with active TB were enrolled for the study at the outpatient tuberculosis clinic of the Istanbul Education and Research Hospital. The diagnosis of pulmonary TB was based on clinical presentation as well as radiology findings and then confirmed by sputum microscopy and culture for *M. tuberculosis*. Group CAP (CAP): Twenty-four patients (mean age: 48.38±10.70 years) with CAP was diagnosed when the patients had clinical signs of pneumonia and a new infiltrate on chest X-ray, and these resolved completely with antibiotic treatment and cultures of sputum or lavage fluid were negative for M. tuberculosis during follow-up. Serum biochemical parameters were performed before and 2 months after therapy (rifampicin+isoniazide+ethambutol and pyrazinamide) of patients with tuberculosis and before and 15 days after therapy (ampicillin-sulbactam) of pneumonia. All our patients were immunocompetent. Group control (C): Twenty volunteers (mean age: 47.70±6.39 years) were enrolled as the control group. Healthy individuals residing in the same area as the other study patients were selected for comparison. These controls had no history or signs of active pulmonary tuberculosis and had no abnormalities on chest x-ray examination. Patients who had other diagnoses, such as pulmonary embolism, acute exacerbation of interstitial lung disease, or lung cancer, were excluded in this study. None of the patients in study was HIV-positive. In this study, ADA and neopterin levels had been compared in pre- and posttreatment tuberculosis and pneumonia patients. We repeated the tests after treatment at the end of second week in CAP patients. For TB patients, the tests were done after 2 months of treatment when their sputum became (-) for AFB.

Specimen Collection and Processing

Blood samples were drawn from the forearm between 8.30 and 10.00 AM after a 12-hour overnight fasting period. For each study, patient specimens were collected in tubes without an anticoagulant. After immediate centrifugation (3000 g, 10 min, 4°C), serum was stored at -80°C until the final analysis. All parameters from all samples were analyzed in a single batch after completion of patient enrollment. All parameters were measured twice at the beginning and at the end of each run.

Biochemical analysis

Assay of serum ADA activity

Serum ADA activity was measured in duplicate aliquots, using a commercial colorimetric assay kit with a cutoff value for a positive test of 30 U/L, in accordance with the manufacturer's instructions (Diazyme General Atomics, CA, USA). The coefficients of the intra- and inter-assay variations were 3.2% (n=20) and 5.3% (n=20), respectively.

Assay of serum neopterin levels

Serum neopterin levels were measured in duplicate aliquots, using a human enzyme-linked immunosorbent assay (ELISA) in accordance with the manufacturer's instructions (IBL Immuno-Biological- Laboratories, Hamburg). The coefficients of the intra- and inter-assay variations were 4.7% (n=10) and 5.6% (n=10), respectively.

Other biochemical parameters were assessed by the laboratory of the hospital (Abbott Laboratories, Germany). hs-CRP measurements were performed by a nephelometric method (BN II nephelometer; Dade Behring Holding GmbH, Liederbach, Germany). Erythrocyte sedimentation rate (ESR) measurements were performed by the Westergren method.

Statistical analysis

Statistical analyses were performed using SPSS 15.0 for Windows. Data are presented as the mean±SEM. The Kruskal-Wallis analysis of variance test was used to examine significant intergroup differences, and if significant, the Mann-Whitney U-test was used for between-group comparisons. Differences were considered statistically significant when $p<0.05$.

Results

All our CAP patients were immunocompetent and had criteria for hospitalization. But, none of them needed intensive care. Average age was 48±10. We controlled their laboratory parameters at the end of the second week. They were all prescribed ampicillin+sulbactam for 10 days. Because none of them had clinical suspicion of atypical pneumonia, we did not evaluate the subjects with respect to atypic pathogens. All patients improved after treatment for 10 days.

Some clinical and laboratory variables in controls and in patients with pulmonary TB and CAP on admission are given in Table 1. As shown in Table 2, at the end of the second week, WBC counts and ESR and CRP levels were still high despite clinical improvement of pneumonia. Neopterin levels showed a prominent decrease after treatment, whereas ADA levels did not in the CAP group. With regard to the Tbc group, after 2 months of therapy, although white blood cell (WBC) counts were not meaningful, erythrocyte rate (ESR) and C-reactive protein (CRP) levels revealed a slight decrease. Both ADA and neopterin levels were also significantly decreased after tuberculosis treatment.

Biochemical parameters in controls and patients with pulmonary TB and CAP after treatment are shown in Table 3. In patients with pneumonia, when we compared with control subjects, WBC, ESR, and CRP levels were still significantly higher after treatment. But, ADA and neopterin levels were not. With respect to tuberculosis, CRP and ESR, ADA, and neopterin levels declined slightly after treatment compared to pretreatment values.

Discussion

The major blood abnormality is leukocytosis with a leftward shift in pneumonia. Procalcitonin and CRP levels may be useful to distinguish between bacterial and non-bacterial etiology (1, 13). There is not much research in this field concerning ADA and neopterin evalu-

ation. The diagnosis of TB is confirmed by isolation of the organism from secretions or tissues. Blood biomarkers may help to discriminate it from nonspecific infections (1, 13). Fruhashi et al. (14) showed the association between severity of tuberculosis and CRP levels, and it was also related with helper T-cell proportions; but, ESR was associated with cytotoxic T-cell subtypes. Decrease in ESR is found after initiation of therapy. Conversion of sputum smear is accepted as an important indicator for recovery in therapy. ADA-2 activity may be a marker of the effectiveness of therapy (4).

In accordance with the well-established knowledge, we observed that for diagnosis of CAP, WBC, CRP, and ESR measurements are valuable, as these markers are significantly different than control subjects. Neopterin may add little information, but ADA measurement is not useful. With regard to diagnosis of TB, ESR, ADA, and neopterin may be of value. For differential diagnosis of CAP from TB, all parameters may be used except ESR. WBC and CRP levels favors in CAP and the others in TB.

We observed that ADA levels were significantly elevated in tuberculosis compared to controls and pneumonia on admission. They remained high after treatment, and pre- and posttreatment levels showed significant difference from both controls and pneumonia.

Table 1. Some clinical and laboratory variables in controls and in patients with pulmonary tuberculosis (TB) and community-acquired pneumonia (CAP) on admission

	Control (n=20)	CAP (n=24)	TB (n=17)
Age (years)	47.70±6.39	48.3±10.7	43.41±11.48
WBC (10×10^9/L)	7.40±0.85	14.94±7.51^{a***}	8.84±3.15^{b***}
CRP (mg/L)	1.74±0.47	28.55±20.65^{a***}	5.63±3.37^{b***}
ESR (mm/hr)	13.25±3.99	75.08±33.45^{a***}	79.71±25.75^{a***}
ADA (U/L)	17.25±4.71	18.79±5.21	46.71±10.26^{a,b***}
Neopterin (ng/mL)	1.10±0.32	1.80±0.58^{a*}	3.72±1.46^{a,b***}

Values (means±SEM) and statistical significance of the analyzed parameters in the study groups. WBC: white blood cell; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ADA: adenosine deaminase; TB: tuberculosis; CAP: community-acquired pneumonia
[a]:vs. control group; [b]: vs. CAP
*p<0.05, **p<0.01, ***p<0.001

Our finding is in accordance with some other studies. ADA may serve a parameter for evaluating the specific infection in the lung and the adequacy of treatment in adults and children (2, 5, 8). Ishii et al. (4) showed that both ADA-1 and ADA-2 activity decreased after treatment. Rokayan (15) suggested that the ADA2/ADA ratio (>0.75) was a better indicator in terms of diagnosis of tuberculosis and of response to therapy. ADA may be used to evaluate the severity of tuberculosis and immune performance (16); especially, ADA-2 activity is an efficient diagnostic marker for tuberculosis pleurisy (17, 18). Although various studies showed a correlation between serum ADA activity and pulmonary TB (2, 6, 10), Conde et al. (3) suggested that measurement of ADA is not a useful biomarker in the diagnosis of pulmonary TB.

Higher levels of serum ADA concentrations are found in atypical pneumonia patients and subjects with liver disease, diabetes mellitus, and prior antibiotic consumption (19, 20). We did not investigate the relationship of these biomarkers and the severity of disease. But, our patients did not have diabetes mellitus or liver or renal disease that could have affected the ADA levels. They were all suggested to have typical pneumonia. They were prescribed ampicillin-sulbactam according to the Guidelines of the Turkish Thoracic Society (21).

In our study, we observed that neopterin levels were higher on admission in TB than controls and subjects with CAP. Neopterin levels were still higher after treatment in the same manner. Neopterin levels provide an insight for both the immune response of the patient and also allow monitoring of the disease (22). Neopterin levels vary depending on age, etiology, and severity of pneumonia (23). Conditions, such as hepatitis C, sepsis, HIV positivity, and autoimmune diseases, may increase neopterin levels (24). Measurement of urinary neopterin may serve as an additional marker for distinguishing between viral and bacterial infections (25), as well as reflecting pulmonary TB activity and correlating the radiological extent (26). Guler et al. (27) showed that neopterin levels also correlated with the extent of pulmonary TB and decreased at the second month of therapy. Serum neopterin levels are significantly higher in active TB. Measurement of this biomarker may be useful for measuring disease activity and for following up the treatment of TB (11, 26, 28). We observed that ADA and neopterin levels were more valuable for pulmonary TB patients; but, neopterin measurements may be of value in patients with CAP. For following up

Table 2. Biochemical parameters in patients with pulmonary tuberculosis (TB) and community-acquired pneumonia (CAP) before and after treatment

	TB Before treatment (n=17)	TB After treatment (n=17)	CAP Before treatment (n=24)	CAP After treatment (n=24)
WBC (10×10^9/L)	8.84±3.15	8.64±1.81	14.94±7.51	10.45±4.08^{b*}
CRP (mg/L)	5.63±3.37	3.99±2.52^{a}	28.55±20.65	17.20±11.26^{b**}
ESR (mm/hr)	79.71±25.75	43.18±12.65^{a}	75.08±33.45	41.25±18.51^{b**}
ADA (U/L)	46.71±10.26	32.82±10.52^{a}	18.79±5.21	16.46±4.12
Neopterin (ng/mL)	3.72±1.46	1.49±0.69^{a*}	1.80±0.58	1.25±0.33^{b**}

WBC: white blood cell; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ADA: adenosine deaminase; TB: tuberculosis; CAP: community-acquired pneumonia
[a]:vs. pre-treatment of TB; [b]:vs. pre-treatment of CAP
*p<0.05, **p<0.001, ***p<0.001

Table 3. Biochemical parameters in controls and patients with pulmonary tuberculosis (TB) and community-acquired pneumonia (CAP) after treatment

	Control (n=20)	CAP After treatment (n=24)	TB After treatment (n=17)
WBC (10×10^9/L)	7.40±0.85	10.45±4.08[a**]	8.64±1.81
CRP (mg/L)	1.74±0.47	17.20±11.26[a***]	3.99±2.52[b***]
ESR (mm/hr)	13.25±3.99	41.25±18.51[a***]	43.18±12.65[a***]
ADA (U/dL)	17.25±4.71	16.46±4.12	32.82±10.52[a,b***]
Neopterin (ng/mL)	1.10±0.32	1.25±0.33	1.49±0.69[a*]

WBC: white blood cell; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ADA: adenosine deaminase; TB: tuberculosis; CAP: community-acquired pneumonia
[a]: vs. control group; [b]: vs. CAP
*p<0.05, **p<0

therapy, laboratory tests do not provide accurate guidance for TB. All markers except WBC showed a slight decrease after 2 months. For CAP, CRP and ESR seem adequate for monitoring. Neopterin measurement may also be useful.

There are many limitations of our study. First, the groups were small. Second, we did not investigate the severity and the extent of CAP and pulmonary TB. Third, we did not study the subgroups of ADA. Fourth, the CAP group was not divided as typical or atypical. We did not have blood culture tests, and lastly, we did not evaluate lymphocyte ratios of the patients.

Conclusion

Serum ADA activity and neopterin levels significantly increase in pulmonary TB; combined antituberculosis treatment decreases the levels of serum ADA and neopterin values. Measurements of serum ADA and neopterin levels may be useful in following up the immune response to tuberculosis and drug treatment. Although we observed neopterin measurement to be valuable for pneumonia, we did not find an association for ADA levels. In particular, serum neopterin levels may also be helpful in discriminating pulmonary TB from CAP. Further studies with a greater number of patients are needed to confirm this hypothesis.

Ethics Committee Approval: Ethics committee approval was received for this study from the local ethics commitee (2009/26).

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

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References

1. Lippi G, Meschi T, Cervellin G. Inflammatory biomarkers for the diagnosis, monitoring and follow-up of community-acquired pneumonia.: clinical evidence and perspectives. Eur J Intern Med. 2011; 22: 460-5. [CrossRef]
2. Alataş F, Uslu S, Moral H, Alataş O, Metintaş M, Erginel S, et al. Serum adenosine deaminase activity in pulmonary tuberculosis. Tuberk Toraks 2003; 51: 277-81.
3. Conde MB, Marinho SR, Pereira Mde F, Lapa e Silva JR, Saad MH, Sales CL, et al. The usefulness of serum adenosine deaminase 2 (ADA2) activity in adults for the diagnosis of pulmonary tuberculosis. Respir Med 2002; 96: 607-10. [CrossRef]
4. Ishii S, Nagasawa H, Tai H, Noda Y, Akiyama K, Takeda H, et al. Relationship between the activity of serum adenosine deaminase including its isozymes and lymphocyte subpopulation in patients with pulmonary tuberculosis. Kekkaku. 1997; 72: 153-9.
5. Kartaloglu Z, Okutan O, Bozkanat E, Ugan MH, Ilvan A. The course of serum adenosine deaminase levels in patients with pulmonary tuberculosis. Med Sci Monit 2006; 12: 476-80.
6. Kuyucu N, Karakurt C, Bilaloğlu E, Karacan C, Teziç T. Adenosine deaminase in childhood pulmonary tuberculosis: diagnostic value in serum. J Trop Pediatr 1999; 45: 245-7. [CrossRef]
7. Titarenko OT, D'iakova ME, Perova TL, Riasnianskaia TB. The activity of adenosine deaminase and its isoenzymes in patients with different forms of pulmonary tuberculosis. Probl Tuberk 2002; 3: 43-5.
8. Titarenko OT, Esmedliaeva DS, Perova TL, Alekseeva NP, D'iakova ME, Popov MIu. Comparative significance of the biochemical markers of cell-mediated immunity in the diagnosis of tuberculous pleurisy. Klin Lab Diagn. 2010; 1: 46-9.
9. Balasaniants GS, Titarenko OT, D'iakova MN. Diagnostic and prognostic significance of adenosine deaminase in acutely progressive pulmonary tuberculosis. Probl Tuberk 2001; 8: 46-9.
10. Kelbel C, Stumpf B, Schmidt W, Wetzel E, Lorenz J. Role of serum adenosine deaminase as an immune parameter of tuberculosis. Pneumologie 1995; 49: 684-8.
11. Horak E, Gassner I, Sölder B, Wachter H, Fuchs D. Neopterin levels and pulmonary tuberculosis in infants. Lun 1998; 176: 337-44. [CrossRef]
12. Tozkoparan E, Deniz O, Cakir E, Yaman H, Ciftci F, Gumus S, et al. The diagnostic values of serum, pleural fluid and urine neopterin measurements in tuberculous pleurisy. Int J Tuberc Lung Dis 2005; 9: 1040-5.

13. Barlett J. Diagnostic approach to community-acquired pneumonia in adults. www.uptodate.com Jul 2012.
14. Furuhashi K, Shirai T, Suda T, Chida K. Inflammatory markers in active pulmonary tuberculosis: association with Th1/Th2 and Tc1/Tc2 balance. Kekkaku 2012; 87: 1-7.
15. Rokayan SA. Serum adenosine deaminase activity and its isoenzyme in patients treated for tuberculosis. J Coll Physicians Surg Pak 2003; 13: 11-4.
16. Knoring BE, Titarenko OT, Sakharova IIa, Loginova GP, D'iakova ME, Perova TL, et al. Cytokine production-adenosine deaminase activity relationship in pulmonary tuberculosis. Probl Tuberk 2000; 3: 38-41.
17. Valdés L, Alvarez D, San José E, Juanatey JR, Pose A, Valle JM, et al. Value of adenosine deaminase in the diagnosis of tuberculous pleural effusions in young patients in a region of high prevalence of tuberculosis. Thorax 1995; 50: 600-3. [CrossRef]
18. Gorguner M, Cerci M, Gorguner I. Determination of adenosine deaminase activity and its isoenzymes for diagnosis of pleural effusions. Respirology 2000; 5: 321-4. [CrossRef]
19. Molinos L, Fernandez R, Dominguez MJ, Riesgo C, Escudero C, Martinez J. Adenosine deaminase activity in the aetiological diagnosis of community-acquired pneumonia. Scand J Infect Dis 1997; 29: 287-90. [CrossRef]
20. Fernández AR, Molinos ML, Gullón BJA, Rubinos Cuadrado G, Jiménez A, Martínez GRJ. Community-acquired pneumonia: serum adenosine-deaminase activity in the aetiological diagnosis. Med Clin (Barc) 2002; 119: 481-4.
21. Toraks Derneği Erişkinlerde Toplum Kökenli Pnömoni Tanı ve Tedavi Rehberi 2002. Solunum Sistemi İnfeksiyonları Çalışma Grubu.
22. Berdowska A, Zwirska K K. Neopterin measurement in clinical diagnosis. J Clin Pharm Ther 2001; 26: 319-29. [CrossRef]
23. Prat C, Domínguez J, Andreo F, Blanco S, Pallarés A, Cuchillo F, et al. Procalcitonin and neopterin correlation with aetiology and severity of pneumonia. J Infect 2006; 52: 169-77. [CrossRef]
24. Cok G, Parildar Z, Basol G, Kabaroglu C, Bayindir U, Habif S, et al. Pleural fluid neopterin levels in tuberculous pleurisy. Clin Biochem 2007; 40: 876-80. [CrossRef]
25. Denz H, Fuchs D, Hausen A, Huber H, Nachbaur D, Reibnegger G, et al. Value of urinary neopterin in the differential diagnosis of bacterial and viral infections. Klin Wochenschr 1990; 68: 218-22. [CrossRef]
26. Yuksekol I, Ozkan M, Akgul O, Tozkoparan E, Al-Rashed M, Balkan A, et al. Urinary neopterin measurement as a non-invasive diagnostic method in pulmonary tuberculosis. Int J Tuberc Lung Dis 2003; 7: 771-6.
27. Güler M, Hüddam D, Unsal E, Ciftçi B, Bukan N, Erdoğan Y, et al. The role of serum neopterin level in the evaluation of activation and response to treatment in the patients with pulmonary tuberculosis. Tuberk Toraks 2006; 54: 330-5.
28. Turgut T, Akbulut H, Deveci F, Kacar C, Muz MH. Serum interleukin-2 and neopterin levels as useful markers for treatment of active pulmonary tuberculosis. Tohoku J Exp Med 2006; 209: 321-8. [CrossRef]