D-DIMER LEVELS IN PATIENTS WITH SARCOIDOSIS

SARKOİDOZ HASTALARINDA D-DİMER DÜZEYİ

Gülru POLAT **Duygu ÜNALMIŞ** **Ufuk YILMAZ**

Dr. Suat Seren Göğüs Hastalıkları ve Cerrahisi Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları, İzmir

Key words: Sarcoidosis, d-dimer
Anahtar sözcükler: Sarkoidoz, d-dimer

Received: 23 / 10 / 2011 Accepted: 07 / 02 / 2012

SUMMARY

Coagulation and fibrinolytic systems have both been implicated in the pathogenesis of sarcoidosis. D-dimer (DD) is a fibrin degradation product and can be used as a marker of fibrinolytic system activity.

The purpose of the present study was to determine the relationship between serum D-dimer (DD) levels and clinical findings, pulmonary function test results, and stage of the disease in patients with sarcoidosis.

Thirty-seven patients with newly diagnosed sarcoidosis were included in this prospective study. The relationship of DD levels with age, gender, smoking habits, complaints at the time of admission, treatment status and prognosis, findings on physical examination, laboratory testing, chest radiography, thoracic computed tomography, pulmonary function tests, and single-breath carbon monoxide diffusion capacity was evaluated.

Of the 37 patients, 73% were females and the mean age was 46.14±11.02 years. DD positivity was noted in 12 patients (32.4%). It was observed that the DD levels increased with age, stage of the disease, and sedimentation rate.

The patients with sarcoidosis who were under treatment due to chronic progressive cough and dyspnea were generally DD-positive. Further studies are warranted to confirm the possible use of DD as a marker in the decision making process for recommending initiation of treatment, and in the evaluation of the response to treatment in patients with sarcoidosis.

ÖZET

Bu çalışmada yeni tanı konulan sarkoidoz hastalarında, serum D-Dimer (DD) düzeyinin hastanın klinik bulguları, solunum fonksiyon testleri ve hastalığın evresi ile ilişkisini araştırmayı amaçladık.

Otuzyedi yeni tanı konmuş sarkoidozlu hastayı kapsayan prospektif bir çalışmadır. DD düzeyi ile olguların cinsiyet, yaş ve sigara içme alışkanlıkları, başvuru yakınmaları, fizik muayene ve laboratuvar bulguları, akciğer grafileri, toraks bilgisayarlı tomografileri (BT), solunum fonksiyon testleri ve karbonmonoksit difüzyon kapasitesi (DLCO) ve tedavi arasındaki ilişki değerlendirildi.

Olguların %73'ü kadın olup, ortalama yaş 46.14±11.02 idi. 37 olgunun 12'sinde (%32.4) DD düzeyi yüksek bulundu. Çalışmada, olguların yaşı, hastalığın evresi ve sedimantasyon hızı arttıkça DD düzeyinin arttığı izlendi.

DD kronik progresif öksürük ve dispne nedeniyle tedavi alan olgularda genel olarak pozitif bulundu. DD'in sarkoidozda tedavi başlama kararını vermede, tedaviye cevabı değerlendirmede yardımcı olabilecek bir markır olarak kullanılabileceğini araştırmak üzere ileri çalışmaların yapılmasına gereksinim vardır.

INTRODUCTION

Sarcoidosis is a granulomatous disease of unknown etiology that can affect virtually any organ though the lungs and lymphatic system are most commonly involved. Although sarcoidosis was first described over 100 years ago, many aspects of sarcoidosis have yet to be elucidated. The information on its epidemiology, genetic factors and treatment has gained momentum in the last 20 years with the advances in molecular biology and bronchoalveolar lavage (BAL). However, information on sarcoidosis remains limited and an ideal therapeutic approach has not been established (1-4).

Coagulation and fibrinolytic systems have both been implicated in the pathogenesis of sarcoidosis (5). While some studies (6) have claimed elevated procoagulant activity in the BAL fluids of patients with sarcoidosis, others (7) have reported decreased protein C activity in BAL fluids of patients with sarcoidosis. Cell-related procoagulant activity in alveolar macrophages of patients with sarcoidosis has been shown to be associated with the radiographic stage of the disease (5). It has been thought that the intra-alveolar activation of the coagulation cascade leads to fibrin deposition in the pulmonary interstitium and alveoli. Fibrin and fibrin-degradation products enhance inflammation by causing chemotaxis and endothelial cell damage. Histologic studies on certain pulmonary diseases have revealed that sites of subsequent fibrosis correspond to sites of fibrin deposition (8).

D-dimer (DD) is a fibrin degradation product and can be used as a marker of fibrinolytic system activity. Furthermore, DD levels in the circulation can be easily measured. DD levels have been established to be associated with disease activity of Crohn's disease and systemic lupus erythematosus (9,10). The significance of fibrinolysis in sarcoidosis, as well as the relationship between disease activity and elevated DD levels in sarcoidosis-like conditions, suggests that serum DD measurements may reflect the disease activity of sarcoidosis.

In the present study, we determined the serum DD levels in patients with newly diagnosed sarcoidosis and established the relationship between DD levels and clinical findings, pulmonary function test results, and stage of the disease.

MATERIAL AND METHODS

A total of 37 patients who were admitted to the outpatient clinic between 2007 and 2009 and diagnosed with sarcoidosis were enrolled in the study. Patients who were diagnosed with sarcoidosis without histologic confirmation and patients who received inhaled or oral corticosteroid treatment within the last 12 months were excluded. The patients were evaluated in terms of gender, age, smoking habits, complaints at the time of admission, findings on physical examination, laboratory testing, purified protein derivative (PPD) skin testing, pulmonary function tests (PFT), thoracic computed tomography (CT), high resolution computed tomography (HRCT), bacteriologic testing, and histopathologic assessment, and single-breath carbon monoxide diffusion capacity (DLCO). Treatment status and prognosis of the patients were evaluated as well. All patients underwent electrocardiography, abdominal ultrasonography, and eye examination.

The diagnosis of sarcoidosis was based on the establishment of histopathologically non-caseous granulomas. The patients were classified into five stages with respect to their chest radiographic results, as follows (1): stage 0, normal posteroanterior chest radiograph findings; stage 1, bilateral hilar

adenopathy (may be accompanied by paratracheal adenopathy); stage 2, bilateral hilar adenopathy with parenchymal infiltration; stage 3, parenchymal infiltration without hilar lymphadenopathy; and stage 4, pulmonary fibrosis. All patients underwent fiberoptic bronchoscopy. BAL fluid samples were examined for acid-resistant bacilli (ARB) and were cultured. The patients in whom diagnosis could not be ascertained with transbronchial biopsy underwent mediastinoscopy, and peripheral and scalene lymph node biopsies to establish the histopathologic diagnosis.

Clinical and Laboratory Assessment

The patients were informed about the study and informed consent was obtained prior to initiation of the study. The patients, who previously had been instructed about the PFT, underwent the tests on a ZAN 100 spirometer while sitting in the upright position with nose occluded by a clip according to ATS guideline. The PFT were carried out by performing at least three technically acceptable maneuvers. Three separate flow volume curves were obtained and the highest values for forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) were used. The FEV1, FVC, FEV1/FVC, and DLCO were recorded as percentages of normal values for the age, gender, and height. Moreover, DLCO measurements were corrected for hemoglobin concentrations. The results of the PFTs were evaluated as follows: a FEV1/FVC value <70% was consistent with obstructive respiratory dysfunction; a FVC value <80% of the normal value with normal or high FEV1/FVC values was considered to be restrictive respiratory dysfunction; and depressed FEV1/FVC and FVC values were designated as a mixed type respiratory dysfunction. A DLCO value <80% of the normal value was considered to be decreased diffusing capacity.

After a 12-hour fast, the following were assessed: complete blood count; urea; creatinine; uric acid; fasting blood glucose; sodium; potassium; calcium; DD level; erythrocyte sedimentation rate (ESR); prothrombin time; and hepatic function. Urine calcium was measured in a 24-hour urine sample. Although the 24-hour urine calcium reference values vary depending on the diet, the normal range was accepted as 50-300 mg/day. All samples were delivered to the laboratories in the first 15 minutes after collection. Routine biochemical analyses were carried out using an Olympus AU 2700 automated analyzer (Tokyo, Japan). Blood samples were transferred into coagulation tubes containing 2 mL of sodium citrate for DD measurements. The samples were evaluated in the first 2 hours using a DD plus kit with an enzyme-linked fluorescent assay (ELFA) method on a Mini Vidas. DD values <500 ng/mL were considered normal.

The indications for initiating treatment were chronic progressive cough in 6 patients, dyspnea in 4 patients, eye involvement in 1 patient, liver involvement in 1 patient, and impaired vision due to lymphadenopathy in 1 patient.

Statistical analyses were conducted using SPSS for Windows (Version 16.0, SPSS Inc., Chicago, IL, USA). Normally distributed continuous variables were compared using a Student's t-test, and non-normally distributed variables were compared using a Mann-Whitney U test. Categorical variables were compared using a chi-square test. A Fisher's exact test was used if expected frequencies are too low. A two-tailed p value was used, and a p value <0.05 was considered statistically significant.

RESULTS

Thirty-seven patients (27 females (73%); and 10 males (27%)) with sarcoidosis were enrolled in the present study. The mean age was 46.14±11.02 years. Of the patients, 22 (59.5%) had never smoked, while 15 (40.5%) were active smokers.

Of the 37 patients, a diagnosis of sarcoidosis was established in 18 patients (48.64%) via mediastinoscopy, 9 patients (24.3%) by transbronchial parenchymal biopsy (TBB), 8 patients (21.6%) by lymph node biopsy, and 2 patients (8.1%) by thoracotomy wedge resection. The patients were classified as follows: 45.9% (n=17), stage 1; 51.4 (n=19), stage 2; and 2.7% (n=1), stage 3. No patients in the study group were classified as stage 0 or 4. Extrapulmonary involvement existed in 8 patients (21.6%). Of those, 1 had eye, 1 had liver, and 6 had skin involvement.

Elevated levels of calcium existed in 2.7% (n=1) of the patients; the mean calcium level was established 9.18±0.43 mg/dL. An elevated ESR (normal, >20 mm/h in females and >15 mm/h in males) was noted in 29.7% of the patients (n=11). The mean ESR was 18.4±16.4 mm/h.

PFT revealed respiratory dysfunction in 32.4% of 12 patients, while 91.6% of those had restriction and 8.4% had a mixed pattern. No patient had obstruction. Of the stage 1 patients, 29.41% had respiratory dysfunction, all of which were of the restrictive type. Respiratory dysfunction existed in 31.57% of the stage 2 patients (26.31% were restrictive and 5.26% were of the mixed type). Only 1 patient with stage 3 sarcoidosis had restriction based on RFT. Of the patients, 64.8% (n=24) had impaired diffusion capacity.

All patients, including 13 patients (35.1%) receiving systemic steroid treatment and 24 patients (64.9%) without medication, were monitored. Of the patients, 12 (32.4%) were DD-positive (Table 1). There were 3 male (25%) and 9 female patients (75%) positive for DD; the difference was not significant (p=1.000). The mean age of DD-positive and –negative patients was 53.50±10.63 and 42.60±9.49 years, respectively. The difference between the groups in terms of age was established to be significant (p=0.003).

Table 1. Demographic characteristics of the patients.

Gender; n (%)	
Female	27 (73.00)
Male	10 (27.00)
Age (mean±SD)	46.14±11.021
Smoking habit; n (%)	
Smoker	15 (40.60)
Non-smoker	22 (59.40)
Diagnostic method; n (%)	
Forceps biopsy	9 (24.30)
Thoracotomy wedge resection	2 (5.40)
Scalene lymph node biopsy	7 (18.90)
Cervical lymph node biopsy	1 (2.70)
Mediastinoscopy	18 (48.64)
Organ involvement; n (%)	
Skin	6 (16.20)
Liver	1 (2.70)
Eye	1 (2.70)
Stage; n (%)	
1	17 (45.90)
2	19 (51.40)
3	1 (2.70)
4	-
Symptoms; n (%)	
Cough	23 (62.20)
Dyspnea	10 (27.00)
Chest pain	5 (13.50)
Arthralgia	5 (13.50)
Treatment status; n (%)	
Receiving treatment	13 (35.10)
No treatment	24 (64.90)
D-dimer status; n (%)	
Positive	12 (32.40)
Negative	25 (67.60)

No significant relationship was established between the presence of symptoms and DD positivity (p=1.000). At the time of admission, 33 patients had symptoms. The most common symptom was cough. DD positivity was not associated with any of the symptoms. Of the 12 DD-positive patients, 11 (91.7%) had symptoms, while of the 25 DD-negative patients, 22 (88%) had symptoms. Of the 33 patients with symptoms, 11 patients (33.3%) were DD-positive, and of the 4 patients without symptoms, 1 patient (25%) was DD-positive; the difference was not significant (p=1.000). No significant difference was noted between the DD-positive and -negative patients with respect to history of smoking (p=1.000, Table 2).

Table 2. Clinical characteristics of the patients with sarcoidosis according to D-dimer positivity.

	DD (+) patients	DD (-) patients	p
Age	53.50±10.63	42.60±9.49	0.003*
Gender			
Male	3 (25%)	7 (28%)	
Female	9 (75%)	18 (72%)	
	1.000		
Cough			
No	5 (44.7%)	9 (36%)	
Yes	7 (58.3%)	16 (64%)	
	1.000		
Dyspnea			
No	8 (66.7%)	19 (76%)	
Yes	4 (33.3%)	6 (24%)	
	0.696		
Chest pain			
No	10 (83.3%)	22 (88%)	
Yes	2 (16.7%)	3 (12%)	
	1.000		
Erythema nodosum			
No	9 (75%)	22 (88%)	
Yes	3 (25%)	3 (12%)	
	0.367		
Complaints			
No	1 (8.3%)	3 (12%)	
Yes	11 (91.7%)	22 (88%)	
	1.000		
Smoking			
Non-smoker	7 (58.3%)	15 (60%)	
Smoker	5 (41.7%)	10 (40%)	
	1.000		

D: D-dimer

While the only stage 3 patient who was DD-negative was not included in the analysis, 36 patients who had stage 1 or 2 sarcoidosis were compared in terms of DD positivity. DD positivity was established in 2 of the 17 patients (11.7%) in the stage 1 sarcoidosis group and 10 of the 19 patients (52.6%) in the stage 2 sarcoidosis group. The difference between the groups was established to be significant (p=0.025), (Table 3).

Spirometric and diffusing capacity measurements of DD-positive and -negative patients were compared. Of the 12 DD-positive patients, 6 (50%) had abnormal PFT results. Of those 6 patients, 5 had restrictive and 1 had a mixed pattern. Similarly, 9 of the 12 DD-positive patients (75%) had decreased diffusing capacity. However, no significant differences were established between the groups in terms of FVC, FEV1, FEV1/FVC, and DLCO values (Table 4). However, the Pearson correlation test revealed that the lower the FVC value (as restriction severity increased), the higher the DD level (r=-3.77). The mean ESR per

Table 3. Disease stage of the patients with sarcoidosis according to D-dimer positivity.

	DD (+) patients	DD (-) patients	p
Stage; n (%)			
1	2 (16.7)	15 (60.0)	
2	10 (83.3)	9 (36.0)	
3	0 (0.0)	1 (40)	
	0.026*		

DD: D-dimer

Table 4. Respiratory function parameters of the patients with sarcoidosis according to D-dimer positivity.

Respiratory function parameters	DD (+) patients (mean±SD)	DD (-) patients (mean±SD)	p
FVC	78.00±15.82	87.32±14.38	0.083
FEV1	81.17±16.17	83.88±16.33	0.638
FEV1/FVC	106.08±18.39	96.80±9.79	0.052
DLCO	66.67±22.94	73.92±20.97	0.346

DD: D-dimer; FVC: Forced vital capacity; FEV1: Forced expiratory volume in one second; DLCO: Single-breath carbon monoxide diffusing capacity.

Table 5. Treatment status of the patients with sarcoidosis according to D-dimer positivity.

Treatment status	DD (+) patients n (%)	DD (-) patients n (%)	p
Receiving treatment	8 (66.7)	5 (20.0)	
No treatment	4 (33.3)	20 (80.0)	
	0.010*		

DD: D-dimer

hour was observed to be significantly different in DD-positive and -negative patients (p=0.04); however, a comparison with respect to calcium levels revealed no significant relationship (p=0.655).

No significant differences existed between the two groups regarding the presence of extrapulmonary involvement (liver, eye, and skin; p=0.324, p=0.324, and p=0.367, respectively).

It was also observed that DD positivity was more common in the patient group receiving treatment (13 patients (35.1%)) when compared with those without medication (24 patients (64.9%)); the difference was significant (p=0.01; Table 5). DD positivity was observed in the patients in whom treatment had been initiated due to chronic progressive cough and dyspnea.

DISCUSSION

The results of the current study revealed that as the age of the patient, stage of the disease, and ESR increased, DD levels increased as well. It was also observed that the majority of the patients who received treatment were DD positive.

Coagulation and fibrinolytic systems are associated with various acute and chronic inflammatory pulmonary conditions, such as acute respiratory distress syndrome (ARDS), interstitial lung disease, and sarcoidosis. It has been suggested that intra-alveolar activation of the coagulation cascade leads to fibrin deposition in the pulmonary interstitium and alveoli Elevated levels of DD in the circulation indicate that the fibrinolytic system is active in certain patients with sarcoidosis. Several studies have been performed considering the relationship between this phenomenon and disease activity (6-10).

Once the coagulation system is activated in the alveolar region, thrombin converts fibrinogen into fibrin. Under normal conditions, fibrin deposition in the intra-alveolar space is rapidly eliminated by fibrinolytic mechanisms. This local fibrin dissolution occurs because

BAL fluid in normal individuals contains urokinase, which is a plasminogen activator converting plasminogen into plasmin. Urokinase is synthesized in macrophages and alveolar epithelial cells. The plasminogen-plasmin system activity in the alveolar area is regulated by urokinase receptor and plasminogen activator inhibitor-1 (11-13). Activated protein C (APC), which is an effective enzyme of the anticoagulant protein C system, may have an impact on fibrinolytic activity in addition to its effect on anticoagulant function. APC may in part stimulate fibrinolysis. It decreases the amount of plasminogen activator inhibitor, which restricts the plasmin production, by degrading it or by forming a complex with it. Persistent fibrin deposition in the alveolar area may stimulate the growth of fibroblasts and deposition of collagen, and consequently may lead to pulmonary fibrosis (10).

While Hasday et al. (9) reported elevated procoagulant activity in BAL fluids in patients with sarcoidosis; Kobayashi et al. (10) reported decreased protein C activity in BAL fluids of sarcoidosis patients. Other studies investigating coagulation in patients with sarcoidosis have revealed an elevated presence of coagulation activity markers in BAL fluids of those patients, such as APC, thrombin-antithrombin 3 complex, thrombo-plastin, and fibrin degradation products (5,14).

The ratio of procoagulant activity over plasminogen activator was shown to be associated with the degree of alveolitis measured by BAL fluids. Cell-related pro-coagulant activity in alveolar macrophages of patients with sarcoidosis was shown to be also associated with the radiographic stage of the disease (5,15).

The studies mentioned above were based on BAL fluids rather than serum markers of inflammation. Evaluation of BAL fluids alone in patients with sarcoidosis may result in overlooking inflammatory activity in extrapulmonary tissues. Perez et al. (16) established that 8 of 10 patients had detectable DD levels in BAL fluids, while 7 of those patients had detectable DD levels in serum samples as well. Furthermore, DD levels in BAL fluids were associated with lymphocyte levels detected on the cellular analysis of fluids and it was suggested that they could be used as a marker of disease activity. The present study is consistent with previous studies focusing on the coagulation cascade in sarcoidosis and offers additional information.

In the present study, the relationship between DD positivity and parenchymal involvement was determined and the relationship was shown to be significant (p=0.034). This particular result suggests that DD positivity is more common in patients with parenchymal involvement. We observed DD positivity in patients with chronic progressive cough, patients under treatment due to dyspnea, and patients observed to have pulmonary infiltration on chest radiography. DD positivity was established in 8 of 13 patients receiving treatment. Of those 8 patients, treatment had been initiated due to chronic progressive cough or dyspnea. The results of the present study were consistent with Shorr et al. (6), who noted DD positivity in 39.9% of 28 patients with sarcoidosis and reported that DD positivity was associated with disease stage, DLCO level, serum ACE level, and the presence of dyspnea. Shorr et al. (6) also reported that serum DD-positive patients were 3.8 times more likely to have interstitial involvement. Further, Shorr et al. (6) proposed the use of the DD level as a criterion of disease activity. That particular study had certain advantages as it was carried out on

a larger study sample and conducted with patients who had not undergone any previous treatment; the assessment of routinely used data is another advantage of their study. Previous studies had not emphasized a relationship between DD levels and chest radiographic findings, pulmonary function test findings, and respiratory symptoms (6). Similar to the study of Shorr et al., our study sample was also larger than the previous studies.

Gupta et al. (15) established that 30% of the newly diagnosed patients with sarcoidosis were DD-positive. Symptoms, as well as physiologic and radiologic abnormalities, were more frequently observed in DD-positive patients. Gupta et al. (15) concluded that DD was a weak marker for the evaluation of the therapeutic response.

Although it was established that the DD level was associated with pulmonary infiltrates on chest radiography in the present study, it was not observed to be associated with PFT findings and DLCO. However, the Pearson correlation test revealed that as the FVC value increased (as restriction decreased), the DD levels increased as well (r=-3.77). Other studies reported DD levels to be significantly associated with DLCO (6).

Sarcoidosis peaks in the 20-29-year age group, and is most commonly observed in individuals <40 years of age. A second peak is observed in women >50 years of age living in Scandinavian countries and Japan. The mean age of patients with sarcoidosis in the present study was 46.14±11.02 years. Although this figure is not consistent with those reported in the world literature, it is consistent with the results of previous studies conducted in Turkey, in which the mean age of sarcoidosis patients was reported to be between 30 and 50 years of age (17-20). Furthermore, the present study established a positive correlation between the age of sarcoidosis patients and the DD levels (r=0.494).

Sarcoidosis which is commonly observed throughout the world, affects men and women of all races and ages. Although some studies have reported that the frequency of sarcoidosis in women is two times greater than in men, generally the reported prevalence in women is not so high (19-21). In the present study, 73% of the 37 patients (n=27) with sarcoidosis were women, whereas 27% (n=10) were men. We established no significant relationship between gender and DD level, consistent with the results of the other studies focusing on the coagulation cascade in sarcoidosis.

Of the 37 patients with sarcoidosis in the present study, 6 (16.2%) had skin involvement, 1 (2.7%) had liver involvement, and 1 (2.7%) had eye involvement. Extrapulmonary involvement rates were observed to be low. We did not observe a significant relationship between extrapulmonary involvement and DD positivity in the present study, consistent with the results of the study conducted by Shorr et al. (6).

In conclusion, patients with sarcoidosis who were under treatment due to chronic progressive cough and dyspnea were generally DD-positive. This result indicates that the coagulation cascade is active in patients with sarcoidosis receiving treatment. DD levels were also associated with parenchymal involvement, age, and ESR.

It remains unclear whether DD is elevated due to a general stimulation in various inflammatory cascades or it results from a more specific pathophysiologic process.

REFERENCES

1. Costabel U. Sarcoidosis: clinical update. Eur Respir J 2001; 18: 56-68.
2. Moller DR. Systemic Sarcoidosis. In: Fishman AP, Elias JA, Fishman JA, Fishman's Pulmonary Diseases and Disorders. 1998; 1055-1084.
3. Fanburg BL, Villa O. Sarcoidosis. In: Murray JF, Nadel JA (eds) Textbook of Respiratory medicine. 3rd WB. Saunders Company London 2000; 1717-1733.
4. Hunninghake GW, Costabel U, Ando M, et al. AT/ERS//WASOG statement on sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 1999; 16: 149-73.
5. Chapman HA, Allen CL, Stone OL. Abnormalities in pathways of alveolar fibrin turnover among patients with interstitial lung disease. Am Rev Respir Dis 1986; 133: 437-43.
6. Hasday JD, Bachwich PR, Lynch JP 3rd, Sitrin RG. Procoagulant and Plasminogen activator activities of broncho-alveolar fluid in patients with pulmonary sarcoidosis. Exp Lung Res 1988; 14: 261-78.
7. Kobayashi H, Gabazza EC, Taguchi O, Wade H, Takeya H, Nishioka J, et al. Protein C anticoagulant system in patients with interstitial lung disease. Am J Respir Crit Care Med 1998; 157: 1850-4.
8. Shorr AF, Hnatiuk OW. Circulating D dimer in patients with sarcoidosis. Chest 2000; 117: 1012-6.
9. Inoh M, Tokuda M, Kiuchi H, Kurata N, Takahara J. Evaluating systemic lupus erythematosus disease activity using molecular markers of hemostasis. Arthritis Rheum 1996; 39: 287-91.
10. Souto JC, Martínez E, Roca M, et al. Prothrombotic state and signs of endothelial lesion in plasma of patients with inflammatory bowel disease. Dig Dis Sci 1995; 40: 1883-9.
11. Chapman HA Jr, Bertozzi P, Reilly JJ Jr. Role of Enzymes mediating thrombosis and thrombolysis in lung disease. Chest 1988; 93: 1256-63.
12. Vassalli JD, Baccino D, Belin D. A cellular binding site for the Mr 55,000 form of the human plasminogen activator, urokinase. J Cell Biol 1985; 100: 86-92.
13. Chapman HA Jr, Vavrin Z, Hibbs JB Jr. Macrophage fibrinolytic activity: identification of two pathways of plasmin formation by intact cells and of a plasminogen activator inhibitor. Cell 1982; 28: 653-62.
14. Hillyard CJ, Blake AS, Wilson K, Rylatt DB, Miles S, Bunch R, Elms MJ, Barnes A, Bundesen PG. A latex agglutination assay for D-dimer: Evaluation and application for the diagnosis of thrombotic disease. Clin Chem 1987; 33: 1837-40.
15. Gupta D, Gupta S, Balamugesh T, Aggarwal AN, Das R. Circulating D dimers as a marker of disease activity in pulmonary sarcoidosis. Indian J Chest Dis Allied Sci 2005; 47: 175-9.
16. Perez RL, Duncan A, Hunter RL, Staton GW Jr. Elevated D dimer in the lungs and blood of patients with sarcoidosis. Chest 1993; 103: 1100-6.
17. Tuncer LY, Sevim T, Mihmanli A, et al. 48 Sarkoidoz Olgusunun Degerlendirilmesi. 21. Ulusal Turk Tuberkuloz ve Gogus Hastalıkları Kongresi Özet Kitabi 1996; SB20.
18. Yalnız E, Komurcuoglu A, Polat G, et al. Sarkoidozda Klinik, Radyolojik, Laboratuvarla Ilgili Parametreler ve Tani Yontemleri. Toraks Dergisi 2003; 4(1): 48-52.
19. American Thoracic Society. Statement on Sarcoidosis. Am J Respir Care Med 1999; 736-55.
20. Musellim B, Kumbasar O, Ongen G, et al. Epidemiological features of Turkish patients with sarcoidosis. Respiratory Medicine 2009; 103(6): 907-12.
21. Tabak L, Kilicarslan Z. 147 Sarkoidoz Hastasının Klinik Özellikleri. Solunum 2001; 3: 80-8.

Corresponding Author:

Dr. Gülru POLAT
Dr Suat Seren Göğüs Hastalıkları ve
Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi,
Göğüs Hastalıkları, İZMİR
e-posta: gulruerbay@yahoo.com