Evaluation of Patients with Behçet's Disease Presenting with Pulmonary Symptoms

Pulmoner Semptomlarla Başvuran Behçet Hastalarının Değerlendirilmesi

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ABSTRACT Objective: Behçet's disease (BD) is a multisystem disorder and survival depends on pulmonary involvement, especially pulmonary artery aneurysm. Therefore early diagnosis and treatment of pulmonary involvement are very important. This study was conducted to evaluate clinical features, treatment results and outcome of patients with BD presenting with pulmonary symptoms. **Material and Methods:** Medical records of patients diagnosed as BD over a 17-years period from 1991 to 2008 who presented with pulmonary symptoms in two different chest clinics were reviewed retrospectively. Clinical and radiological findings, treatment and follow-up results were investigated. **Results:** Twenty-two patients (19 males, three females) diagnosed with BD were included. The mean age was 35.4 years. Sixteen of the patients (72.7%) were diagnosed with BD at chest clinics for first time. Main presenting pulmonary symptom was hemoptysis (72.7%) and six of them (27.3%) had massive hemoptysis. Thirteen patients (59%) had pulmonary artery aneurysms, five of them also had thrombosis within the aneurysm. Nineteen patients (86%) were administered immunosupressive therapy. Eighteen (81.8%) of the patients were followed, median follow-up time was four years. Thirteen patients responded to immunosuppressive therapy. Three patients (16.7%) died, two of them with massive hemoptysis. **Conclusion:** BD should be kept in mind in differential diagnosis of hemoptysis in young patients, especially in countries with high incidence of BD. Early diagnosis and aggressive treatment for pulmonary involvement can prevent a fatal outcome.

Key Words: Behçet syndrome; pulmonary artery; hemoptysis

ÖZET Amaç: Behçet hastalığı (BH) multisistemik bir hastalık olup sağkalım pulmoner tutuluma, özellikle de pulmoner arter anevrizmasına bağlıdır. Bu nedenle pulmoner tutulumun erken tanı ve tedavisi çok önemlidir. Bu çalışma pulmoner semptomlarla gelen BD hastalarının klinik bulgularını, tedavi sonuçlarını değerlendirmek amacıyla yürütülmüştür. **Gereç ve Yöntemler:**1991'den 2008'e kadar ki 17 yıllık dönemde iki farklı göğüs hastalıkları kliniğinde pulmoner semptomlarla gelerek BD tanısı konan hastaların tıbbi kayıtları retrospektif olarak incelendi. Klinik ve radyolojik bulgular, tedavi ve izlem sonuçları araştırıldı. **Bulgular:** BD tanısı konan 22 hasta (19'u erkek, üçü kadın) çalışmaya alındı. Ortalama yaş 35.4 idi. On altı hastada (%72.7) BD tanısı ilk kez göğüs hastalıkları kliniğinde konmuştu. Ana pulmoner semptom hemoptizi (%72.7) idi, altısı (%27.3) ise masif hemoptizi ile gelmişti. On üç hastada (%59) pulmoner arter anevrizması bulunuyordu ve beşinde ise aynı zamanda anevrizma ile birlikte tromboz vardı. Ondokuz hastada (%86) immünsüpresif tedavi başlandı. Onsekiz hasta (%81.8) ortalama 4 yıl süreyle izlenebildi. On üç hasta immünsüpresif tedaviye yanıt verdi. İkisi masif hemoptizi nedeniyle üç hasta (%16.7) kaybedildi. **Sonuç:** BD hemoptizi ile gelen genç hastalarda özellikle de BD'nin yüksek insidansla görüldüğü ülkelerde ayırıcı tanıda akılda tutulmalıdır. Pulmoner tutulumda erken tanı ve agresif tedavi fatal seyri önleyebilir.

Anahtar Kelimeler: Behçet sendromu; pulmoner arter; hemoptizi

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Behçet's disease (BD) is a multisystemic disorder of unknown origin and is characterized by systemic vasculitis affecting arteries and veins of all sizes. It was first described by Turkish dermatologist Hulusi Behçet in 1937 and consists of a triad of recurrent ulcers of the oral and genital mucosa with relapsing uveitis.[1] The disease shows itself with vascular, cutaneous, pulmonary, neurologic, rheumatologic, gastrointestinal and genitourinary manifestations.[2-4]

Pulmonary involvement in BD is seen in 1-10% of patients.[5-7] The most common pulmonary manifestations are pulmonary artery aneurysm (PAA), pulmonary artery thrombosis (PAT) and pulmonary infarction.[5-10] These patients may present with hemoptysis, dyspnea, coughing or signs of superior vena cava syndrome to the chest clinics. This study was conducted to evaluate clinical features, treatment results and outcome of patients with BD who presented with pulmonary symptoms.

MATERIALS AND METHODS

Medical records of patients diagnosed with BD over a 17-year period from 1991 to 2008 and presented with pulmonary symptoms to two different chest clinics were retrospectively reviewed. All patients fulfilled the International Study Group Criteria for the diagnosis of BD.[11] Symptoms and age at presentation, sex, coexisting pulmonary conditions, radiological findings and diagnostic methods, treatment results were abstracted from the medical records of the cases. All patients had a chest radiograph, spiral thorax CT and/or thorax MR angiography. The vital status of patients was determined by reviewing medical records or via telephone calls with the patient or with his or her relatives. Follow-up data were obtained from visits of cases. Survival analysis was done with Kaplan-Meier method.

RESULTS

Twenty-two patients diagnosed with BD were included in the study. Nineteen (86.4%) patients were males and three patients (13.6%) were females. Mean age was 35.4 years (range 17-68). Six patients (27.3%) were previously diagnosed with BD. The remaining 16 patients (72.7%) were newly diagnosed with BD in our chest clinics.

PULMONARY SYMPTOMS AND SIGNS ON ADMISSION

Symptoms and signs on admission and in the past history of the patients are shown in Table 1. Hemoptysis was present in 16 patients (13 PAA, two PAT and one pulmonary abscess). Six of them had massive hemoptysis (over 600 ml/day). All patients with PAA presented with hemoptysis. Fifty-four percent of the cases with PAA (seven out of 13) had deep venous thrombosis.

TABLE 1: The symptoms and signs of Behçet's diseases present on admission and/or in the past.

	Behcet's Disease	(+) on admission	(+) in history	Total n (%)
Oral ulceration	Pre-diagnosed	-	6	22 (100)
	Newly diagnosed	4	12	
Genital ulceration	Pre-diagnosed		6	20 (90)
	Newly diagnosed	2	12	
Uveitis	Pre-diagnosed	-	5	5 (23)
	Newly diagnosed	-	-	
Skin involvement	Pre-diagnosed	-	6	6 (30)
	Newly diagnosed	-	-	
Neurologic involvement	Pre-diagnosed	-	1	2 (10)
	Newly diagnosed	1	-	
Trombophlebitis	Pre-diagnosed	-	5	11 (50)
	Newly diagnosed	6	-	
Positive pathergy test	Pre-diagnosed	-	6	17 (77)
	Newly diagnosed	11	-	

Second most common symptom was dyspnea (54.5%). Other presenting symptoms were cough (22.7%), symptoms of superior vena cava occlusion (SVCO) (13.6%), and chest pain (4.5%).

RADIOLOGIC FINDINGS

Thirteen (59.1%) of 22 patients had pulmonary artery aneurysm; four bilateral PAA, four left PAA and five right PAA (Figure 1a,b). Five patients with PAA also had thrombosis within the aneurysm (Figure 2). Three patients had superior vena cava occlusion with thrombus (one of these patients had also PAT). Three patients had only PAT. One BD patient presented with lung abscess, but no other pulmonary involvement. Another patient with known BD presented with pneumonia and tracheobronchial amyloidosis was diagnosed after bronchoscopy. Three patients had cardiac thrombus in addition to pulmonary involvement. Eleven patients (nine with PAA and two with PAT) also had deep venous thrombosis confirmed by Doppler ultrasonography.

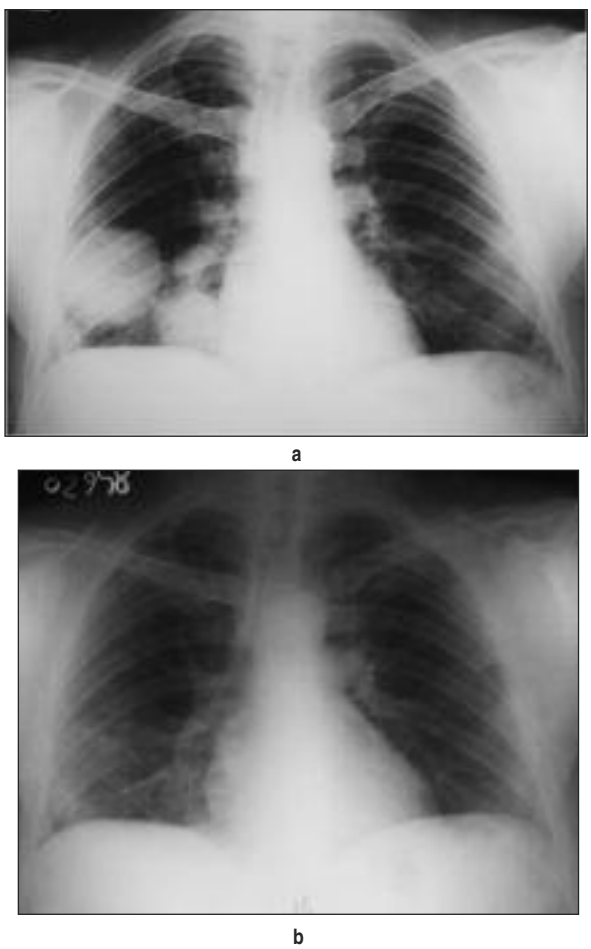

FIGURE 1: Behçet's diseases patient with two pulmonary aneurysm on chest X-ray **(a)**. X-ray of same patient after one year immunosuppressive treatment **(b)**.

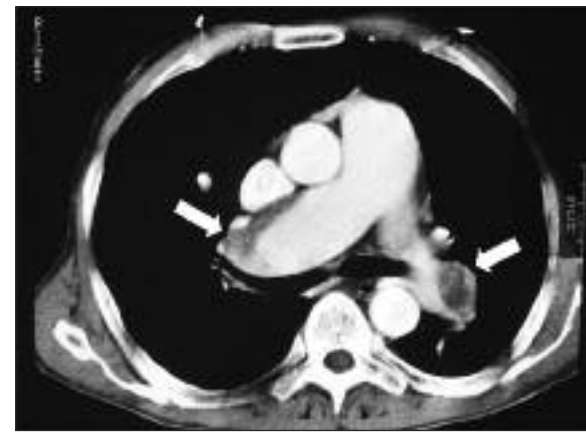

FIGURE 2: CT image of Behçet's diseases patient with thrombus within pulmonary aneurism.

TREATMENT AND OUTCOME

All patients, except three (one with pneumonia and tracheobronchial amyloidosis, one with lung abscess and one with PAA) received immunosuppressive therapy (cyclophosphamide or azathioprine + corticosteroids) (Table 2). One patient with PAA refused treatment. Other two patients received antibiotics in addition to their maintenance therapy for BD. Two patients (case 7 and case 19) had anticoagulant therapy in addition to their immunosuppressive therapy (Table 2).

Eighteen (81.8%) patients were followed-up, four patients did not show up after the diagnosis and did not respond to our phone calls. The median follow-up period after the diagnosis of BD was five years (range 1-18 years). Thirteen (81.3%) of the patients under immunosuppressive treatment showed significant regression in their symptoms and radiologic findings. Two patients (26 and 33 years old) with PAA died in hospital due to massive hemoptysis under immunosuppressive treatment. During the follow-up period, one patient (27 year old) died because of neurologic involvement after three years. The estimated mean survival time was 14 ± 2 (SE) years (95% CI 11; 8). The estimated five year-survival was 83.3%. No association between survival and PAA presence was found with univariate analysis (p= 0.254).

TABLE 2: Treatment regimen and outcome of the patients.

	Pulmonary manifestation	Treatment	Treatment duration	Outcome
1	Multiple right PAA	cyc+cs	2 years	R/C regression, alive
2	Right PAA	cyc+cs+c	1 year	R/C regression, alive
3	Left PAA	cyc+cs	3 months	Died with massive hemoptysis
4	Right PAA	cyc+cs	1 month	Died with massive hemoptysis
5	SVCO	cyc+cs	n/a	n/a
6	SVCO	cyc+cs	1 year	R/C regression, alive
7	Bilateral PAT	cyc+cs+ac	n/a	n/a
8	Left PAA	cyc+cs	1 year	Died due to neurologic involvement
9	Bilateral PAA	cyc+cs	n/a	n/a
10	Right PAA	cyc+cs	1 year	R/C regression, alive
11	Left PAA with T	aza+cs	6 months	R/C regression, alive
12	Lung abscess	ab	6 weeks	R/C regression, alive
13	Tracheobronchial amyloidosis and pneumonia	c, ab	10 years	R/C regression, alive
14	Right PAA with T	cyc+cs	1 year	R/C regression, alive
15	SVCO	aza+cs	6 months	R/C regression, alive
16	Bilateral PAA with T	cyc+cs	3 years	R/C regression, alive
17	Bilateral PAA	-	n/a	n/a
18	Left PAA with T	cyc+cs	1 year	R/C regression, alive
19	SVCO and PAT	cyc+cs+ac	1 year	R/C regression, alive
20	Bilateral PAA with T	cyc+cs+aza	6 months	R/C regression, alive
21	Bilateral PAT	cyc+cs	6 months	R/C regression, alive
22	Bilateral PAT	cyc+cs	8 months	R/C regression, alive

SVCO: Superior vena cava occlusion, PAA: pulmonary artery aneurysm, PAT: pulmonary artery thrombosis, T: thrombus, cyc: cyclophosphamide, cs: corticosteroid, aza: azathioprine, c: colchicine, ab: antibiotic, ac: anticoagulant, n/a: not available, R/C: radiologic and clinical.

DISCUSSION

Pulmonary involvement in BD is rare (1-10%) but might follow a fatal course.[7,12] Pulmonary artery aneurysm, pulmonary artery thrombosis and pulmonary infarction are the main features of pulmonary involvement.[5-9,12] Among them, pulmonary arterial aneurysm is the most common one and it particularly affects the survival. Hamuryudan et al. reported that 12 of 24 patients with PAA (50%) died within an average period of 10 months after the onset of hemoptysis.[5] In our case series, all of the 13 patients with PAA admitted with hemoptysis. Of these 13 patients, six had massive hemoptysis and two of them died in the hospital despite immunosuppressive treatment. The advent of advanced radiologic diagnostic technologies after 1990s might be related with earlier diagnosis of pulmonary manifestations and thereby with a lower death rate among our patients.

PAA is mostly identified with hilar expansion and round opacity under radiological inspection. Most of the time, it is possible to observe thrombus within the pulmonary artery aneurysm.[8,9] Of our cases, 38.5% (five out 13 cases) had thrombosis within the aneurysm. Another characteristic of PAA is the high incidence of lower extremity deep venous thrombosis.[5,13] In our study, 53% of the cases with PAA (nine out of 17) had deep venous thrombosis.

Most authors believe that pulmonary arterial involvement in BD occurs during later stages of the disease.[5,8,9,14-16] Among 2179 patients with BD followed in a rheumatology clinic, 24 patients (1.1%) developed PAA within 7.5 years as a mean, after the diagnosis of BD.[5] None of these patients had hemoptysis as the initial symptom of BD. Uzun et al. evaluated 15 patients with BD and they reported that seven of the 15 patients with BD had the first

diagnosis at their chest clinic.[6] In our case series, 16 of the patients (72.7%) were diagnosed with BD on admission to our chest clinic while six was previously diagnosed. Our patients with PAA who admitted with hemoptysis had pre-existing conditions such as oral and genital aphtous lesions. Our high diagnosis rate might be explained by the fact that these patients ignored their aphtous lesions and did not consult health professionals. Most of the patients who were diagnosed in chest clinics were young and all admitted due to serious pulmonary symptoms for the first time such as dyspnea and hemoptysis.

One of our patients had tracheobronchial amyloidosis which was confirmed by biopsy. Although amyloidosis was documented in the tonsils of this patient three years ago, evaluation for systemic amyloidosis yielded negative results. In the largest case series which was reported by Melikoglu et al., 14 out of 4000 BD patients followed-up were discovered to have renal amyloidosis.[17] No tracheobronchial amyloidosis has been reported in the literature so far, just an isolated intestinal amyloidosis case has been reported previously in BD.[18]

In BD, perfusion defects on lung scintigraphy or the presence of pulmonary arterial thrombosis can be diagnosed as pulmonary embolism (PE). The main cause of these findings in BD is inflammation of pulmonary artery. Although deep venous thrombosis is common in BD, pulmonary embolism is rare due to adherent thrombi in the inflamed veins of the lower extremities.[19] Therefore, we think that the term pulmonary arterial thrombosis should be used instead of pulmonary emboli in BD. There was thrombus in pulmonary artery in nine patients (40.9%); five within PAA, four without aneurysm. However, only two patients received anticoagulant treatment in addition to immunosuppressive treatment. Anticoagulant treatment is not recommended in BD. If anticoagulant treatment is indicated it is recommended to start in conjunction with immunosuppressive treatment.[12]

There are some superior vena cava (SVC) syndrome case reports in the literature.[20] The evaluation of 3500 patients with BD revealed only 14 patients with SVC syndrome.[21] The most frequently observed cause of SVC syndrome is occlusion by thrombus. Recently SVCO has been reported due to thickening of the wall by inflammation in vena cava.[22,23] In our series, four patients had SVCO due to thrombosis and three of them had findings of SVC syndrome in addition to dyspnea. The other patient with SVCO had bilateral PAT and presented with hemoptysis and dyspnea.

One of the rare but serious complications of BD is intracardiac thrombus. Young male patients with a mass in right heart chambers should be investigated for BD.[24] Cardiac thrombosis was detected in three of our patients, two with PAA and one with PAT.

Pulmonary involvement in BD is usually treated with a combination of cyclophosphamide or azathioprine and prednisolone, although there is no convincing evidence about the efficacy of this combination.[25-27] A recent follow-up study of 13 patients showed complete resolution or regression of pulmonary artery aneurysms with three to 42 months immunosuppressive treatment.[28] In another study conducted by Santana et al., three-year survival rate was 89%, as was the five-year survival rate.[29] They identified nine patients with BD-related pulmonary involvement. They used prednisone plus chlorambucil (or cyclophosphamide or mycophenolate mofetil) in all patients, and all patients with PAA showed partial or complete resolution.

The main cause of mortality is the involvement of large arteries (such as pulmonary artery) which is observed more frequently in young males.[30] All of our patients with PAA were males and the mean age of our BD patients was 32.4 years. Three of our patients died, two with massive hemoptysis and one due to neurologic involvement.

In conclusion, hemoptysis was a common presenting symptom, sometimes massive with fatal outcome. Therefore BD should be considered in the differential diagnosis in young males presenting with hemoptysis or SVC syndrome to chest clinics in countries with high BD prevalence like Turkey. Mortality can be reduced with early diagnosis and immunosuppressive treatment.

REFERENCES

1. Behçet H. [About recurrent aphtous ulcerations on mouth, eyes, and genitals caused by a virus]. Dermatol Monatsschr 1937;105(1): 1152-5.
2. Shimizu T, Ehrlich GE, Inaba G, Hayashi K. Behçet's disease. Semin Arthritis Rheum 1979;8(4):223-60.
3. Yazıcı H, Yurdakul S, Hamuryudan V. Behçet's disease. Curr Opin Rheumatol 2001; 13(1):18-22.
4. Sakane T, Takeno M, Suzuki N, Inaba G. Behçet's disease. N Engl J Med 1999;341 (17): 1284-91.
5. Hamuryudan V, Yurdakul S, Moral F, Numan F, Tüzün H, Tüzüner N, et al. Pulmonary arterial aneurysms in Behçet's syndrome: a report of 24 cases. Br J Rheumatol 1994;33 (1):48-51.
6. Uzun O, Erkan L, Akpolat, I Findik S, Atici AG, Akpolat T. Pulmonary involvement in Behçet's disease. Respiration 2008;75(3):310-21.
7. Erkan F, Kıyan E, Tunacı A. Pulmonary complications of Behçet's disease. Clin Chest Med 2002;23(2):493-503.
8. Gunen H, Evereklioglu C, Kosar F, Er H, Kızkin O. Thoracic involvement in Behçet's disease and its correlation with multiple parameters. Lung 2000;178(3):161-70.
9. Numan F, Islak C, Berkmen T, Tüzün H, Cokyüksel O. Behçet's disease: pulmonary arterial involvement in 15 cases. Radiology 1994;192(2):465-8.
10. Karincaoglu Y, Kandi Coskun B, Seyhan M, Aki T. [Demographical and clinical characteristics of Behcet's disease patients in Malatya and Elaziğ]. Türkiye Klinikleri J Dermatol 2005;15(2):65-70.
11. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet 1990;335(8697):1078-80.
12. Uzun O, Akpolat T, Erkan L. Pulmonary vasculitis in Behçet's disease: cumulative analysis. Chest 2005;127(6):2243-53.
13. Sullivan EJ, Hoffman GS. Pulmonary vasculitis. Clin Chest Med 1998;19(4):759-76.
14. Grenier P, Bletry O, Cornud F, Godeau P, Nahum H. Pulmonary involvement in Behçet's disease. Am J Roentgenol 1981;137(3):565-9.
15. Emad Y, Abdel-Razek N, Gheita T, el-Wakd M, el-Gohary T, Samadoni A. Multislice CT pulmonary findings in Behçet's disease (report of 16 cases). Clin Rheumatol 2007;26(6):879-84.
16. Raz I, Okon E, Chajek-Shoul T. Pulmonary manifestations in Behçet's syndrome. Chest 1989;95(3):585-9.
17. Melikoğlu M, Altiparmak MR, Fresko I, Tunç R, Yurdakul S, Hamuryudan V, et al. A reapprasial of amyloidosis in Behçet's syndrome. Rheumatology (Oxford) 2001;40(2):212-5.
18. Hamza M, Wechsler B, Godeau P, Hamza H, Ayed K. Intestinal amyloidosis: an unusual complication of Behçet's disease. Am J Gastroenterol 1988;83(7):793-4.
19. Durieux P, Bletry O, Huchon G, Wechsler B, Chretien J, Godeau P. Multiply pulmonary arterial aneurysms in Behçet's disease and Hughes-Stovin syndrome. Am J Med 1981; 71(4):746-1.
20. Sezer I, Melikoglu MA, Cay HF, Kocabaş H, Bütün B. Superior vena cava syndrome associated with Behçet's disease and 18 months follow up: a case report. Rheumatol Int 2008; 28(8):807-9.
21. Oh SH, Lee JH, Shin JU, Bang D. Dermatological features in Behçet disease associated vena cava obstruction. Br J Dermatol 2008; 159(3):555-60.
22. Vandergheynst F, Francois O, Laureys M, Decaux G. Superior vena cava syndrome without thrombosis revealing Behçet's disease: two cases. Joint Bone Spine 2008;75(3):359-61.
23. de Paiva TF Jr, Ribeiro HB, Campanholo CB, Gonçalves CR, Terigoe DY, de Souza BD. Behçet's disease associated with superior vena cava syndrome without thrombosis. Clin Rheumatol 2007;26(5):804-6.
24. Mogulkoc N, Burgess MI, Bishop PW. Intracardiac thrombus in Behçet's disease: a systematic review. Chest 2000;118(2):479-87.
25. Fresko I, Yurdakul S, Hamuryudan V, Ozyazgan Y, Mat C, Tanverdi MM, et al. The management of Behçet's syndrome. Ann Med Intern 1999;150(7):576-81.
26. Yazici H, Yurdakul S, Hamuryudan V. Behçet's syndrome. Curr Opin Rheumatol 1999; 11(1):53-7.
27. Erkan F. Pulmonary involvement in Behçet disease. Curr Opin Pulm Med 1999;5(5):314-8.
28. Tunaci M, Özkorkmaz B, Tunaci A, Gül A, Engin G, Acunaş B. CT findings of pulmonary artery aneurysms during treatment for Behçet's disease. Am J Roentgenol 1999;172 (3):729-33.
29. Santana AN, Antunes T, Barros JM, Kairalla RA, Carvalho CR, Barbas CS. Pulmonary involvement in Behçet's disease: a positive single-center experience with the use of immunsupressant therapy. J Bras Pneumol 2008;34(6):362-6.
30. Yazici H, Esen F. Mortality in Behçet syndrome. Clin Exp Rheumatol 2008;26(5Suppl 51):138-40.