A fatal case of Behçet's disease with rare complications

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ABSTRACT

Behçet's disease (BD) may involve in any large or small artery, vein. We present a case of BD with multiple venous thromboses, cardiac and pulmonary involvements, and renal failure. A 22-year-old man admitted with progressive dyspnea and edema on his face and neck. He had the history of recurrent oral and genital ulcers, and pustular skin lesions for 4 years. Doppler ultrasonography revealed right internal jugular vein thrombosis. Transthoracic echocardiography showed a pericardial effusion, decreased left ventricular ejection fraction. While his symptoms were regressing moderately with a pulse cyclophosphamide, prednisolone, and low molecular weight heparin treatment, new thromboses occurred in vena cava inferior, and bilateral renal veins after the third and 7th dosages of pulse cyclophosphamide. Creatinine levels increased progressively, which required hemodialysis. However, he died after the second session of hemodialysis. Patients with BD should be followed up for new developing thrombosis even during an immunosuppressive treatment.

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Behçet's disease (BD) is a multisystemic chronic relapsing inflammatory disease classified among the vasculitides, which may involve both arteries and veins of all sizes from different systems and organs. It affects male and female patients almost equally, although men have often more severe disease. Recurrent mucocutaneous lesions may be the only symptom in mild cases, but articular, ocular, vascular, gastrointestinal, and central nervous system involvement may occur. Despite the course of inflammation is classically intermittent, the disease can stabilize in a significant number of patients and become chronic in a given organ system. Ocular disease is the most frequent cause of morbidity, leading to blindness in 25% of those affected.[1] Mortality ratio was reported in Turkish patients as 9.8%, mainly due to major vessel disease and neurological involvement.[2] Treatment remains largely symptomatic and empiric. The goal of management is to treat early, to avoid recurrences and irreversible damage to the vital organs. Multiple venous thromboses, even under immunosuppressive treatment, pulmonary, cardiac, and renal involvement are quite rare conditions in BD.[3] We present a fatal case of BD with multiple venous thrombosis, pulmonary and cardiac involvement, and renal failure as a complication despite immunosuppressive treatment.

Case Report. A 22-year-old man admitted with remitting oral aphthae, genital ulcers recurring 4 to 5 times annually for 4 years. He had also oral aphthae, scrotal ulcers, and arthralgia at knees one month ago. He was admitted with edema and cyanosis on his

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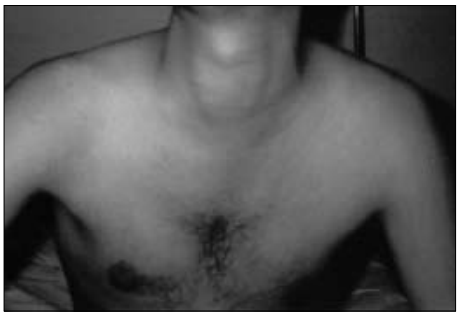

Figure 1- Diminished venous congestion seen on neck several days after the initial treatment.

face and neck, headache, dyspnea, and fatigue for a week. Dyspnea and edema of the face and neck had increased for 2 days. Multiple venous collaterals were evident on his neck and chest (**Figure 1**). There were 3 aphthae bigger than 1 cm at different sites of oral mucosa. He had 2 active ulcers, approximately 1 cm width and 0.2 cm depth, and scars of the old ulcers at scrotum. There was acneiform skin lesions at different sites of the trunk. Ophthalmological examination was normal. Laboratory findings were as follows: erythrocyte sedimentation rate (ESR) 77 mm/h. C-reactive protein (CRP) 163 mg/l (N: <5mg/l). Routine biochemical analyses, complete blood count, urine microscopy, prothrombin time, activated partial thromboplastin time were all normal. Viral hepatitis serology was negative. The serum rheumatoid factor, anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, IgM and IgG anticardiolipin antibodies, and cryoglobulins were all negative. Protein-C, protein-S, and anti-thrombin III levels were in normal range. Homocysteine was 68 mg/dl (N: <12mg/dl). Doppler ultrasonography showed thrombosis of the right jugular vein at the proximal part near to superior vena cava and venous collaterals were evident. Pathergy test was negative. Transthoracic echocardiography revealed a minimal pericardial effusion, decreased left ventricular wall movements and left ventricular ejection fraction (LVEF) as 50%. Computerized tomography of the thorax was normal except bilaterally mild pleural effusions. Pleural fluid was transudate and poor from cells. Cytology revealed no malignant cells. He was given low molecular weight heparin (LMWH) 0.1 ml/kg bid subcutaneously (sc), 1000 mg cyclophosphamide, 1 mg/kg prednisolone intravenously, and warfarin 10 mg daily. The LMWH was stopped when international normalized ratio (INR) reached at 2.5. Edema on face and neck, and dyspnea regressed. The CRP decreased to 35 mg/l and ESR to 2 mm/h. Pulse cyclophosphamide doses were planned to continue as monthly. Methyl prednisolone dosage was reduced to 24 mg daily after 2 months.

When he was admitted for the 4th pulse cyclophosphamide treatment, he suffered from dyspnea, abdominal distension, and edema at both lower extremities. He could walk approximately 10 meters only due to the dyspnea and fatigue. His liver was palpated 6 cm beneath the right costal edge and engorgements of the superficial abdominal veins were present. He had ascites and non-pulpy edema at lower extremities. Doppler ultrasonography, showed thromboses of the inferior vena cava and right jugular vein. Portal, renal, hepatic veins, and low extremity deep veins were normal. Laboratory findings were as follows: ESR; 68 mm/h, CRP; 120 mg/l, white blood cell; 10.420/mm^3, aspartate amino-transferase; 131 U/l (10-40), alanine amino-transferase; 304 U/l (10-35), alkaline phosphatase; 192 U/l (25-125), gamma-glutamyl transpeptidase; 192 U/l (0-50), total bilirubin; 1.5 mg/dl (0.2-1), direct bilirubin; 1.1 mg/dl (0.1-0.5), blood urea nitrogen (BUN); 33 mg/dl (7-18), creatinine; 1.2 mg/dl (0.7-1.3). The INR was low as 1.3 probably due to the uncompliant warfarin usage. Thyroid function tests, serum albumin, globulin, glucose, and electrolytes were all normal. He had 176 mg/day proteinuria, and microscopic examination of urine was normal. Kidneys were in normal size and echogenicity at ultrasonography. Transthoracic echocardiography, showed a decreased LVEF (40%), systolic and diastolic dysfunction, severe global hypokinesis at anteroseptal and posterior wall, moderate hypokinesis at septum and inferior wall, and minimal pericardial effusion. Electrocardiogram revealed no ischemic changes. Trans-esophageal echocardiography also showed, there was no thrombus in atria or ventricles. Approximately 1000 mg/day pulse cyclophosphamide dosage was administered, and the dosage intervals reduced to 3 weeks. Superficial thrombophlebitis and deep venous thrombosis occurred at right lower extremity during the follow up. Doppler ultrasonography showed right femoral vein thrombosis. Oral Azathioprine 150 mg daily was added to the treatment, and since then, 500 mg intravenously pulse prednisolone was administered intermittently for several times. He was given LMWH until the INR reached to 2.5 levels with warfarin. Also, furosemide was begun intravenously for the ascites and edema. Angiography was performed for the coronary artery involvement. However, coronary arteries were normal. Creatinine levels were between 0.9-1.2 mg/daily, and his ascites, edema, and dyspnea regressed a little. After

the 7th pulse cyclophosphamide treatment, he had lumbar pain at both sides. Within 4 weeks, oligo-anuria developed and creatinine levels increased progressively. Doppler ultrasonography showed bilaterally renal vein thrombosis. When BUN was 110 mg/dl, creatinine 9.8 mg/dl, and metabolic acidosis occurred, hemodialysis treatment was begun. However, he died after the second session of dialysis that was attributed to the metabolic imbalance, which occurred during renal failure.

Discussion. This is an unusual case of BD presented with myocarditis, pericarditis, pleural effusions, and multiple venous thromboses complicating with acute renal failure, which required dialysis treatment. Despite immunosuppressive and anticoagulant treatment, recurrent venous thromboses occurred. In our case, venous thrombosis was found in right jugular vein, inferior vena cava, right femoral vein, and bilateral renal veins. Vascular involvement is the leading cause of death in BD.[3] The incidence of vascular involvement reported in the literature, ranges from 7-29%. In a report of 1200 BD patients, 12.8% were reported with venous thrombosis. Approximately 1.4% of these patients were with vena cava superior, approximately 0.4% with inferior vena cava thrombosis, and one patient (0.8%) with jugular vein thrombosis. Jugular vein involvement, is an unusual manifestation of BD.[4] Inferior vena cava and bilateral renal vein thromboses are also rare manifestations. Inferior vena cava thrombosis generally precedes Budd-Chiari syndrome.[5] However, in our case hepatic veins were intact. Pathergy test positivity and eye involvement, were reported to be frequent in patients with vascular involvement.[3] However, pathergy test was negative in our case and he had no history of eye involvement. Homocysteine level was high. Though, Factor-V Leiden mutation could not be tested.

Cardiac involvement is also rare in BD. It includes coronary artery disease generally at young subjects, and is often expressed by myocardial infarction and angina. A few cases of pericarditis have been reported. Myocardiopathy can be inflammatory nature or secondary to coronary artery disease.[6] However, in our case coronary angiography was normal. Endocardiac involvement may be found, which is limited to valve disease or spread to ventricular wall. No valvulopathy was demonstrated in our case. Cardiac involvement in BD is reported as a diffuse process, which involves both cardiac structure and vascular elements.[6] Interatrial septum aneurysm, mitral valve prolapsus, mitral regurgitation, aneurysmal dilatations of sinus valsalva and ascending aorta, diastolic and systolic dysfunction, ventricular arrhythmia, sudden cardiac death, and dispersion of ventricular repolarization were reported to be more frequent in BD than normal subjects.[6] Myocarditis, pericarditis, diastolic and systolic dysfunction were demonstrated in our case by echocardiography. Asymptomatic or life-threatening relapsing pleurisy and pericardial effusion were reported in a few number of cases.[7] Pleurisy and mostly pericardial effusion, might be related to the inflammatory process at parenchyma of the lungs, and myoepicardium by the disease itself or to the prevented venous return by the thrombotic veins.

Renal failure is a rare endpoint in BD. Renal amyloidosis, is the most common cause of chronic renal failure. However, renal vein thrombosis must be suspected in patients especially with vascular involvement.[8] The kidney is one of the organs that can alter the prognosis of BD, thus, it must be screened in each patient. It was reported, that another type of renal disease (amyloidosis or glomerulonephritis) and other major vascular involvements were present in cases with renal vein thrombosis.[8] However, we could not perform renal biopsy due to some fatal complications. It was shown that aggressive surgical or interventional therapy was not efficient in altering the course of the pathology itself. Thus, medical treatment is crucial to suppress the exacerbations. However, it is sometimes hard to manage.

Existence of extensive large vein occlusion in BD is associated with limited therapy and poor prognosis especially when multiple sites of involvement are present. Medical management must be directed to the primary disease and to the pro-thrombotic state. Immunosuppressive treatment and anticoagulants are the most rational choices in such a case. Sometimes it is not possible to suppress the disease and complications. Colchicine and thalidomide are effective for mucocutaneous manifestations. Combination of corticosteroids and non-selective immunosuppressive drugs, including azathioprine, methotrexate, cyclosporine A, tacrolimus, chlorambucil, or cyclophosphamide is used when vital organs are involved.[1]

There are some reports of beneficial effects of interferon-alpha and anti-tumor necrosis factor (anti-TNF).[9,10] Anti-TNF treatment particularly, seems to be an effective new therapeutic approach for patients with refractory disease.[9] However, there are conflicting results of which, anti-TNF agent is superior to another.[9] Whether such treatment is superior to the conventional therapeutic approaches, it remains

to be determined by carefully controlled studies. No enough data are present from controlled studies regarding the treatment modalities of patients with BD complicated by concurrent thromboses. This lack of evidence implicates the need for large scale and coordinated registries, including data on the acute and chronic treatment as well as the prevention of future thrombotic events in this clinical setting. Patients with BD, should be followed up for new developing thrombosis even during an immunosuppressive treatment. New treatment modalities should be searched and begun in the early stage when needed.

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