Behçet's Syndrome Complicated with Pulmonary Artery Thrombosis: Response to Tocilizumab Treatment

Morbus Behçet kompliziert durch eine Pulmonalarterienthrombose: Ansprechen auf die Behandlung Tocilizumab

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ABSTRACT

Pulmonary artery involvement is a rare but deadly complication of Behçet's syndrome (BS). This article presents a male patient with BS complicated with Budd-Chiari syndrome and pulmonary artery thrombosis. The patient had recurrent pulmonary artery thrombosis resistant to several immunosuppressive drugs including high-dose glucocorticoids and the anti-TNF agent infliximab. Following multiple relapses, he was effectively treated with tocilizumab, which also achieved complete recanalization of the thrombosed arteries.

ZUSAMMENFASSUNG

Die Beteiligung der Lungenarterie ist eine seltene, aber tödliche Komplikation des Morbus Behçets (MB). Hier berichten wir über einen männlichen MB-Patienten mit zwei vaskulären Komplikationen, nämlich dem Budd-Chiari-Syndrom und der Pulmonalarterienthrombose. Der Patient litt unter einer rezidivierenden Lungenarterienthrombose, die gegen mehrere immunsuppressive Medikamente, einschließlich hochdosierter Glukokortikoide und dem Anti-TNF-Mittel Infliximab, refraktär war. Infolge mehrerer Rezidive wurde er effektiv mit Tocilizumab behandelt, wodurch auch eine vollständige Rekanalisation der thrombosierten Arterien erreicht wurde.

Introduction

Behçet's Syndrome (BS) is a recurrent systemic inflammatory disorder of unknown origin characterized by milder involvements like mucocutaneous and joint involvement – other involvements which might cause morbidity and mortality are ocular, neurological, gastrointestinal and vascular involvement [1]. The typical involvement sites of vascular BS are both venous and arterial systems of all sizes, with pulmonary artery disease being the most frequent form of ar-

terial involvement [2, 3]. Pulmonary artery involvement (PAI) in BS occurs in the form of aneurysms and/or thrombosis [4]. High dose corticosteroids and cyclophosphamide are the mainstay treatment of PAI in BS, and in refractory cases anti-TNF agents might be considered [5]. In this case report, we present a male patient with BS whose course was complicated with recurrent pulmonary thrombosis which was resistant to several immunosuppressive agents and successfully treated with tocilizumab.

Case Presentation

A 33-year-old male patient presented to our hospital with fever, shortness of breath and hemoptysis. In his physical examination, he had evidence of tachypnea but was otherwise normal. His past medical history revealed that he had been diagnosed with Budd-Chiari syndrome in the previous year and been on anticoagulation therapy.

Laboratory testing showed an increased erythrocyte sedimentation rate (ESR) of 36 mm/h (normal range 0–20 mm/h) and C-reactive protein (CRP) of 43.5 mg/L (normal range 0–3 mg/L). His international normalized ratio (INR) was 2.5. D-dimer was 2671 µ/L (normal range 0–243 µ/L). Computed tomography pulmonary angiography (CTPA) was subsequently performed to collaborate with the laboratory findings further since the diagnosis of pulmonary thromboembolism was considered. On CTPA, disseminated multiple thrombi were detected in the left upper lobe and lingula pulmonary artery (PA) branches as well as in bilateral lower lobe pulmonary arteries. Furthermore, thrombus formation was noted in superior vena cava lumen extending into the right atrium and then the right ventricle. Lower extremity venous Doppler ultrasonography revealed thrombus formation in left main femoral vein, which was seen partially recanalized. The thrombophilia panel which would turn out to be negative was assessed to exclude hereditary thrombophilia. Antiphospholipid antibodies were absent as well.

Review of systems uncovered that he had a history of recurrent oral ulcers and papulopustular skin lesions. Upon this, the pathergy test was performed, which came out negative. Considering thrombotic events in both arteries and veins, he was diagnosed with BS according to international criteria for Behçet's disease [6]. Cyclophosphamide 1 gram monthly was initiated with 1 mg/kg per day prednisolone and colchicine 0.5 mg t.i.d. After 12 cycles of cyclophosphamide, 150 mg/day azathioprine was added to the regimen. Steroids had to to be given the patient due to recurrent peripheral arthritis. However, two years after his BS diagnosis, he was complicated with avascular necrosis. In addition, colchicine and azathioprine had to be ceased due to lymphopenia. Owing to avascular necrosis and lymphopenia inflicted by the medications, maintenance treatment with infliximab at a dosage of 5 mg/kg was considered. During the infliximab treatment was interrupted for 6 months due to septic arthritis. After recovery from septic arthritis, infliximab was reinitiated and the patient had been followed-up on infliximab without steroids for 3 years. However, in the sixth year of infliximab treatment, he presented to our emergency service with ongoing shortness of breath having started 10 days ago. His physical examination on admission revealed no significant findings other than tachypnea. In arterial blood gas analysis, the partial pressure of oxygen was 57.1 mmHg and the oxygen saturation was 85.9 % while he was breathing ambient air. Laboratory test results showed increased ESR with high CRP and D-dimer levels. CTPA revealed acute thromboses in the lobar and segmental PA branches of the right and left upper lobe (▶ **Fig. 1a**). In the light of the evidence of BS flare, 500 mg methylprednisolone was given for 3 days, and then the patient was put on 1 mg/kg prednisolone maintenance therapy backed with 5 mg/kg per day cyclosporine regimen. During his hospitalization period, he became symptom-free and his acute phase reactants were normalized. Ten days later, he was discharged from the hospital on infliximab with cyclosporine and 48 mg methylprednisolone being added.

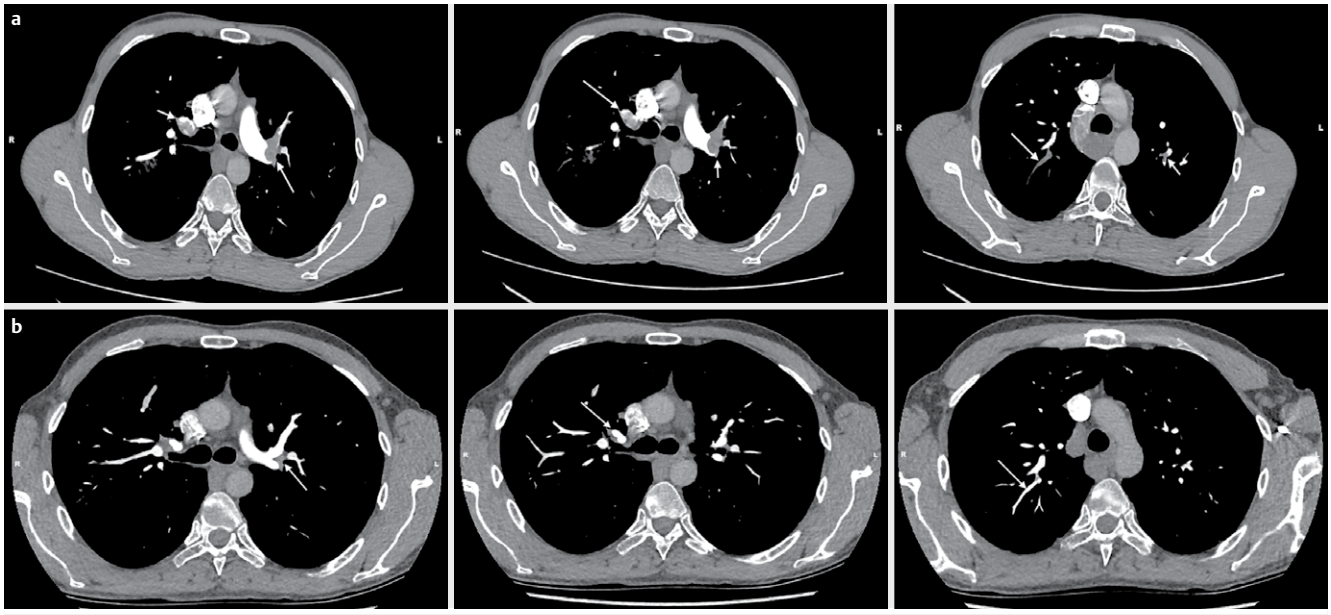
Twenty days after his discharge, he presented to the emergency department with hemoptysis. His acute phase reactant levels were high. Upon intractable disease course, while he was on 5 mg/kg infliximab every 6 weeks, 5 mg/kg cyclosporine per day, and 24 mg/day methylprednisolone, salvage treatment with 500 mg methylprednisolone pulses for three days (later continued as 48 mg methylprednisolone per day) and one cycle of 1 gram cyclophosphamide were administered.

Due to recurrent, life-threatening pulmonary thrombosis despite intensive immunosuppression, intravenous 8 mg/kg tocilizumab at 4-week intervals was initiated. Complete cessation of corticosteroids was achieved in the second month of tocilizumab treatment, and the patient has been followed-up with tocilizumab monotherapy for 11 months. However, within the 8th month of tocilizumab treatment, he had multiple painful oral ulcers which necessitated treatment with azathioprine. During the tocilizumab treatment, the patient showed no symptoms related to the respiratory system. In the follow-up CTPA in the 7-month of tocilizumab treatment, complete recanalization was noted in the diseased PA branches (▶ **Fig. 1b**). No adverse events related to tocilizumab were recorded in this time course.

Discussion

Venous vessels are the main target of BS and deep vein thromboses are the most frequent form of vascular BS, generally being the sole vascular event in the disease course [2, 7]. Arterial system is also affected and the most common arterial structures involved are pulmonary arteries. Pulmonary artery aneurysms are reported to be the most frequent presentation of PAI [4, 8]. Nevertheless, in recent years, an increasing trend of pulmonary artery thrombosis has been demonstrated [9]. There is a clear distinction between PAI and other types of arterial involvements, such as peripheral and visceral aneurysms, in BS; the latter occurs in the later stages of the syndrome [2].

PAI is considered as one of the most dreadful type of vascular BS owing to the high mortality rates [4, 10]. The cornerstone treatment of PAI is high dose glucocorticoids and cyclophosphamide; in resistant cases, anti-TNF agents are an option [5]. Anti-TNF agents are used in refractory cases, and prolonged treatment with these agents are recommended; nevertheless, pulmonary artery involvement while using anti-TNF agents for other complications of BS were also reported, indicating that tumor necrosis factor blockage is not a panacea [11]. Previous studies showed higher serum interleukin-6 (IL-6) levels in serum samples, cerebrospinal fluid, and vitreus humor of BS patients, which was positively correlated with disease activitiy



▶ **Fig. 1** CTPA findings before and after tocilizumab treatment. CTPA images show acute thromboses in the lobar and segmental pulmonary artery branches of the right and left upper lobe **a**. Complete recanalization of the thrombosed vessels was noted on the follow-up CTPA after 7 months **b**. CTPA = Computed tomography pulmonary angiography.

[12–14]. Furthermore, in a recently published case series with 7 patients, tocilizumab, a humanized monoclonal antibody against IL-6 receptor, was found to be effective in vascular BS concomitant with steroids; however, the involvement sites of arterial vasculature did not include the pulmonary arteries which have completely different structure from the other arterial sites [15]. However, tocilizumab has no efficacy in mucocutaneous involvement and arthritis, and might even exacerbate these symptoms [16].

Tocilizumab was effective in our patient complicated with pulmonary artery thrombosis and provided the complete recanalization of the thrombosed arteries despite the discontinuation of glucocorticoids, which could not be achieved with infliximab treatment. In a prospective observational study, it has been shown that recanalization is an only and stronger indicator of relapses in lower extremity deep vein thrombosis of BS [17].

Our case is unique in terms of the patient's clinical course and his response to tocilizumab treatment. In the light of all evidence, these results suggest that tocilizumab might be a therapeutic option to achieve recanalization of diseased vessels in refractory cases of vascular BS and even prevent further relapses.

Conflict of Interest

The authors declare that they have no conflict of interest.

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