Grand Rounds in Rheumatology

Organizing pneumonia associated with pulmonary artery aneurysms in Behçet’s disease

A. Gül, D. Yılmazbayhan¹, N. Büyükbabani¹, J. T. Lie²†, M. Tunaci³, A. Tunaci³, M. Inanç, L. Öcal, O. Aral and M. Konicė

Division of Rheumatology, Department of Internal Medicine, ¹Department of Pathology and ³Department of Radiology, Istanbul School of Medicine, Istanbul, Turkey and ²Division of Anatomic Pathology, Davis School of Medicine, University of California, Sacramento, CA, USA

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Behçet’s disease (BD) is a relapsing chronic inflammatory disorder of unknown aetiology. Although BD has originally been described as a triad of recurrent oral aphthous ulceration, genital ulceration and uveitis, it is now recognized as a multisystem disease with vasculitis as the main pathological finding [1].

Involvement of the lungs is a rare feature of BD [2–6]. Pulmonary artery aneurysm (PAA) is the best-defined type of pulmonary disease in BD with an important morbidity and mortality [5]. After the widespread use of computed tomographic (CT) and magnetic resonance imaging (MRI) methods, more BD patients with pulmonary parenchymal changes have been noted. However, the pulmonary parenchymal involvement in BD still needs to be explored fully [6].

Herein, we describe a patient with BD who developed multiple PAA and died of massive haemoptysis, and discuss the pathological correlation of his peripheral pulmonary opacities.

Case report

A 26-yr-old male patient was referred to our hospital because of haemoptysis, dyspnoea and cough. The patient was well until 5 yr earlier, when he began to experience recurrent oral and genital aphthous ulceration and erythema nodosum. A skin pathergy test was found to be positive when he was seen in another hospital 4 yr later, and colchicine 0.5 mg t.d.s. was started with the diagnosis of BD [7].

Two months later, he suffered from bilateral pleuritic chest pain with fever, cough and vomiting, and was given antibiotics with a diagnosis of pneumonia. The patient was admitted to the department of chest diseases when he developed haemoptysis 2 weeks later. X-ray (CXR) showed bilateral hilar opacities. A CT scan of the thorax revealed multiple aneurysms in both right and left pulmonary arteries, as well as peripheral nodular opacities (Fig. 1). Multiple aneurysms in the lobar, lobular and even segmental pulmonary arteries were further documented by a digital subtraction angiography. He started to receive 1 mg/kg prednisolone daily and 1 g i.v. pulse cyclophosphamide monthly. A partial remission was achieved both clinically and radiologically with the regression of size of the aneurysms in 3 months, but he continued to suffer from haemoptysis intermittently while he was tapering the dosage of prednisolone. He developed deep vein thrombosis in both his legs following a long journey, and his symptoms improved with bed rest and an increase in the dosage of prednisolone from 5 to 25 mg daily, which was later tapered again to 10 mg.

One month before his last admission, the haemoptysis began to worsen when he experienced another attack of fever, productive cough and right-sided pleuritic chest pain. His symptoms were partially relieved with antibiotics and increased doses of prednisolone (30 mg daily), and he was referred to our clinic.

On examination, the patient appeared chronically ill and pale. His blood pressure was 105/65 mmHg and the pulse rate was 100/min. Inspiratory crackles were heard at both lung bases without a pleural friction rub. Scars of genital ulcers in the scrotum were noted. There was pretibial oedema in his left leg with signs of chronic venous stasis. The erythrocyte sedimentation rate (ESR) was 113 mm/h, white blood count (WBC) was 13.05 × 10⁹/l, haemoglobin was 9.3 g/dl and haematocrit was 29.4%. A CXR and high-resolution CT (HRCT) scan of the thorax did not show any significant changes in the sizes of the PAAs since the last control, but a more marked mural thrombosis and perianeurysmal ground-glass opacities. Nodular or mass-like opacities with ill-defined margins and in broad contact with pleural surface and major fissure were seen in right lower lobe scans (Fig. 2). Parenchymal patchy non-
segmental airspace consolidations with ground-glass opacities were also noted in both lower lobes (Fig. 3). He received 1 g methylprednisolone i.v. pulse for 3 days along with the eighth dose of 1 g monthly cyclophosphamide. He continued to take prednisolone 30 mg/day p.o. and colchicine 0.5 mg t.d.s. His condition was considered unsuitable for elective surgery or balloon embolization for the treatment of aneurysms.

After the second week in hospital, the patient felt better and suffered less from haemoptysis. His ESR was decreased to 47 mm/h, and haemoglobin and haematocrit levels were increased to 10.4 g/dl and 37.9%, respectively.

In the fourth week, he experienced another attack of fever, productive cough and right-sided pleuritic chest pain. Inspiratory crackles were heard over the middle and lower lobes of the right lung. Repeated CXR showed a new consolidation area adjacent to the opacity of the right PAA. Although the throat and sputum cultures yielded no pathogenic bacteria, treatment with

![Fig. 1. CT scans of the thorax showing partially thrombosed aneurysms in both right and left pulmonary arteries (A), as well as a peripheral nodular opacity (B).](image1)

![Fig. 2. Thoracic HRCT scans of the lower lobe showing nodular or mass-like opacities with ill-defined margins and in broad contact with the pleural surface (A) or major fissure (A, B).](image2)

![Fig. 3. Thoracic HRCT scan showing parenchymal patchy non-segmental airspace consolidations with ground-glass opacities in both lower lobes.](image3)
ampicillin–sulbactam 1 g q.d.s. was started. On the next day, he suffered from massive haemoptysis and underwent a right pneumonectomy for this uncontrolled haemoptysis. He died on the following day from another attack of massive haemoptysis from the left-sided PAA. His family did not give consent for autopsy.

The gross pathological examination of the right lung obtained at the operation revealed an aneurysm wall extending from the superior segment of the lower lobe to the middle and superior lobes, bleeding into the adjacent lung parenchyma, and emphysematous changes in other areas. There was no overt inflammatory cellular infiltration in the wall of the PAA, although some perivascular infiltrates around the vasa vasorum were noted. A marked intimal thickening with degenerative changes in the elastic lamina was the most striking feature in most of the medium-sized or large arteries. Thrombotic occlusion and recanalization were observed in some vessels, as well as fresh thrombi. In the periphery of the aneurysm, there were widespread areas showing pneumatic infiltration featuring chronic and acute inflammation with abscess formation and bronchiolitis obliterans organizing pneumonia (BOOP) pattern (Fig. 4). Thickening and inflammatory cellular infiltration were noted in the interalveolar septa. Prominent vasculitis with mixed cellular infiltration of intima and media could only be seen within the areas of BOOP.

Discussion

Pulmonary involvement in BD

Behcet's disease is a systemic vasculitis affecting virtually all types and sizes of vessels [8]. Pulmonary manifestations of patients with BD are mainly related to vasculitis involving pulmonary arteries, veins and septal capillaries [2, 5, 9, 10]. Pulmonary vascular involvement can lead to aneurysm formation (PAA), thrombotic occlusion, pulmonary infarction and pulmonary haemorrhage [2, 4, 10]. PAA is one of the characteristic arterial lesions of BD and it is mostly seen in males. Venous thrombosis of lower extremities frequently accompanies PAA [2, 4, 5], but thrombosis of superior vena cava and intracardiac mural thrombi can also be seen in these patients [2, 4, 5, 11, 12].

The leading manifestation of PAA is haemoptysis, which is mainly caused by erosion of the bronchial tree by the aneurysm. PAA has a very poor prognosis and it is one of the leading causes of death in BD. Although there are reports of successful treatment results and regression of aneurysm with immunosuppressive drugs [5, 12–14], the mean survival after the onset of haemoptysis was around 10 months in a series of BD patients with PAA, suggesting a high short-term mortality despite treatment [5]. Lobectomy, pneumonectomy or embolization of the aneurysm may be considered along with the medical therapy for selected cases only, because of a high perioperative mortality, especially in patients with multiple and/or bilateral aneurysms [15–17].

Pleural effusions and peripheral pulmonary infiltrates have also been described in BD. Pleural effusion with or without chest pain may result from thrombosis of superior vena cava, pulmonary infarction or pleural vasculitis [3, 6]. However, less is known about the pathological correlation of the pulmonary parenchymal opacities found in patients with BD. Subpleural nodular or triangular opacities in CT scans are generally accepted as foci of pulmonary haemorrhages and/or infarcts [6, 18]. Eosinophilic pneumonia was diagnosed in a male patient with BD and peripheral pulmonary infiltrates by transbronchial biopsy [6].

BOOP and pulmonary vasculitis in BD

Organizing pneumonia, or BOOP, a non-specific pathological response to lung injury, is characterized by airspace organizing granulation tissue in alveolar spaces, alveolar ducts and small airways [19]. BOOP may accompany various conditions like collagen vascular diseases, haematological disorders, drug toxicities, infections and organ transplantations (secondary BOOP) [19, 20]. However, there are also cryptogenic cases of BOOP with no underlying disorder.

BOOP can commonly be found as a focal incidental finding in the biopsy or autopsy materials of tumours, infarcts or granulomatous disorders. However, findings of widespread BOOP may be the initial manifestation of a collagen vascular disease [21], and it may be the main histological finding in some patients with Wegener's granulomatosis [22].

Petty et al. [23] reported a female patient with BD and a long history of recurrent attacks of unilateral pneumonia. An open lung biopsy specimen revealed prominent alveolar septal infiltration and polypoid mass of granulation tissue obliterating the alveolar duct, which was consistent with BOOP, and no vasculitis was observed. Attacks of fever and non-productive cough in that patient responded very well to corticosteroid treatment. Lie [11] described acute interstitial pneumonitis and bronchiolitis obliterans among the autopsy findings of a BD case with pulmonary and cardiac involvement who died of rupture of a PAA.

Fig. 4. Granulation tissue filling terminal bronchioles and alveolar spaces (BOOP pattern) and a mixed cellular infiltrate. H&E staining, ×125 magnification.
Our case has the prominent clinical, radiological and pathological findings of BOOP associated with pulmonary vasculitis since the diagnosis of PAA. Peripheral opacities were noted in his first (Fig. 1) and following CT scans along with PAAs, and these consolidations were evaluated as the necrotic and haemorrhagic pulmonary infarcts or intra-alveolar haemorrhages then [6, 18]. However, findings of ill-defined pulmonary nodules and triangular masses in broad contact with pleural surface and major fissure as well as peripheral patchy non-segmental airspace consolidations with air bronchogram and ground-glass opacities in both lungs at the follow-up CT and HRCT scans were consistent with the diagnosis of BOOP [24, 25].

The pathogenesis of BOOP is unknown. It has been suggested that organizing pneumonia or BOOP is a common repair mechanism in response to epithelial injury. Mucosal ulcers in the bronchial tree have previously been documented in BD [10]. Distal airways might also be affected in BD and the marked vasculitis within the areas of organizing pneumonia in this case suggests that both pulmonary vasculitis and BOOP may have a common pathogenesis.

Diagnosis and differential diagnosis of BOOP in BD

BOOP may cause cough, dyspnoea, chest pain, haemoptysis, fever and an acute-phase response, but it is difficult to differentiate the exact causes of these manifestations in a patient when the underlying disorder is BD and PAA, as in our case [20, 26]. Flu-like symptoms can be seen in a third of patients with BOOP, but no causative microbial agent has been isolated or pathologically documented up to now [20]. However, exclusion of a superimposed pulmonary infection is very important in the management of a patient with suspected secondary BOOP, especially if the patient is on an immunosuppressive treatment [20].

Although deep vein thrombosis of lower extremities frequently accompanies PAA, pulmonary thromboembolism is seen very rarely in BD because of the strictly adherent thrombus in inflamed veins [5]. Endothelial changes accompanying vasculitis may trigger in situ development of thrombi in arteries and veins which lead to pulmonary infarctions. Bilateral and diffuse defects in radionuclide pulmonary perfusion scintigraphy in BD patients with pulmonary vasculitis are consistent with this hypothesis [2–5]. Administration of heparin or oral anticoagulants with the misinterpretation of peripheral pulmonary opacities as findings of thromboembolism may cause fatal bleedings from aneurysms, and it should be avoided in BD patients with PAA [2, 5].

The most common findings in CT scans of patients with BOOP are bilateral consolidations predominantly in subpleural and/or peribronchovascular regions [24]. Ground-glass attenuation and nodules are more commonly seen in immunocompromised patients with BOOP [24]. Large nodules or masses found in BOOP cases may have the features of irregular or spiculated lesion margins, a broad pleural tag, air bronchogram within the lesions and close proximity of lesions to the pleural surface or a fissure [25]. Transient interlobular septal thickening can also be seen near the nodules or masses [25].

Histopathological investigation is necessary to confirm the diagnosis of BOOP, and an open lung biopsy by video-assisted thoracoscopy is the recommended method for tissue sampling [20]. Transbronchial biopsy may also be sufficient for the diagnosis of BOOP in some patients, but this procedure may carry a very high risk in BD patients with PAA. Pathological examination can help to exclude chronic eosinophilic pneumonia, pulmonary infarction and haemorrhage, interstitial pneumonia, infections and tumours in BD patients with peripheral pulmonary opacities.

**Treatment and prognosis of patients with BOOP**

Patients with BOOP usually respond to high-dose corticosteroid treatment tapered slowly in 6 or more months [20]. Achieving a complete resolution may take longer in patients with a secondary BOOP. A favourable response of cough and pleuritic chest pain, as well as laboratory findings, to increased doses of prednisolone in our case supports the view that corticosteroids are effective for the treatment of BOOP. However, prolonged corticosteroid treatment with a slower tapering is advised because symptoms may recur when the prednisolone dose is reduced to maintenance levels, as occurred in this case.

Patients with secondary BOOP have a worse prognosis than cryptogenic or primary cases [19, 20]. A regression in the size of aneurysms was observed with treatment with prednisolone and cyclophosphamide, but a massive and fatal haemoptysis could not be prevented in our patient. Apart from the size and number of bilateral PAAs, accompanying BOOP may also have contributed to the fatal course of this patient with pulmonary vasculitis.

**Concluding remarks**

In conclusion, this is the first case of BD with prominent radiological and pathological features of BOOP associated with pulmonary vasculitis. BOOP should be considered in the differential diagnosis of BD patients with pleuritic chest pain and peripheral pulmonary opacities. BD patients with pulmonary vasculitis and BOOP may have a worse prognosis.

**References**


