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Bronchiolitis Obliterans Organizing Pneumonia Presenting as Hemoptysis in a Patient of Hodgkin's Lymphoma Undergoing Chemotherapy

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Bronchiolitis obliterans organizing pneumonia (BOOP) is an uncommon pulmonary disorder characterized by plugs of granulation tissue polyps in the lumina of bronchioles and alveolar ducts with inflammatory cell infiltration. Several etiologies of BOOP have been identified, although it is most commonly idiopathic. Hemoptysis is an unusual clinical presentation of BOOP. Here we report a patient with Hodgkin's lymphoma who developed BOOP after chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine. Initially, he was treated successfully with corticosteroids, but still redeveloped BOOP after bleomycin-free chemotherapy.

Key words: bronchiolitis obliterans organizing pneumonia, chemotherapy, hemoptysis, Hodgkin's lymphoma

INTRODUCTION

Hemoptysis is a potentially life-threatening condition for patients with cancer, and delayed diagnosis of the etiology may jeopardize clinical outcomes. Numerous etiologies of hemoptysis have been identified, of which the most common are bronchitis and neoplasms. Patients with Hodgkin's lymphoma (HL) may suffer from hemoptysis, which could be caused by the lymphoma itself. However, etiologies other than HL may be present. A correct diagnosis cannot be made without a thorough investigation. We report here a case of bronchiolitis obliterans organizing pneumonia (BOOP) presenting with moderate hemoptysis during chemotherapy in a young male patient with HL.

CASE REPORT

A 17-year-old boy with a mediastinal tumor was diagnosed with HL, mixed cellularity type, stage III B, in May 2003. Chemotherapy was initiated with an ABVD regimen (doxorubicin 25 mg/m^2 days 1 and 15, bleomycin 10 mg/m^2 days 1 and 15, vinblastine 6 mg/m^2 days 1 and 15, and dacarbazine 375 mg/m^2 days 1 and 15) from June 5, 2003, and the regimen was repeated every four weeks. Six courses of chemotherapy produced partial remission in November 2003. Unfortunately, he began to suffer from fever, chills, dyspnea on exertion, and productive coughing with blood-tinged sputum for one week. He coughed up bright fresh blood (around 100 mL) within four hours before hospitalization on November 26, 2003. On admission, his vital signs were stable and pertinent physical findings included bilateral basilar end-inspiratory crackles on chest auscultation. Laboratory studies showed hemoglobin of 13.5 g/dL, a platelet count of 335,000/μL, and a WBC count of 5,200/μL with a differential count of 65% neutrophils, 22% lymphocytes, 11% monocytes and 2% eosinophils. Serum biochemical profiles were all within normal ranges. The prothrombin time and activated partial thromboplastin time were normal. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were 78 mm/h and 18.6 mg/dL, respectively. Arterial blood gas analysis on ambient air showed a pH of 7.45, a $PaCO_2$ of 36.5 mm Hg, a PO_2 of 94.4 mm Hg, a sodium bicarbonate level of 24.9 mmol/L, and a hemoglobin oxygen saturation of 98%. Gram and acid-fast staining of the sputum were negative. Polymerase chain reaction of the sputum for *Mycobacterium tuberculosis and Pneumocystis carinii* were negative. A chest radiograph showed patchy alveolar consolidation. A chest computed tomography (CT) scan revealed multifocal subpleural areas of airspace consolidation (Fig. 1). A pulmonary function test demonstrated moderately restrictive ventilatory impairment with severely reduced diffusing capacity.

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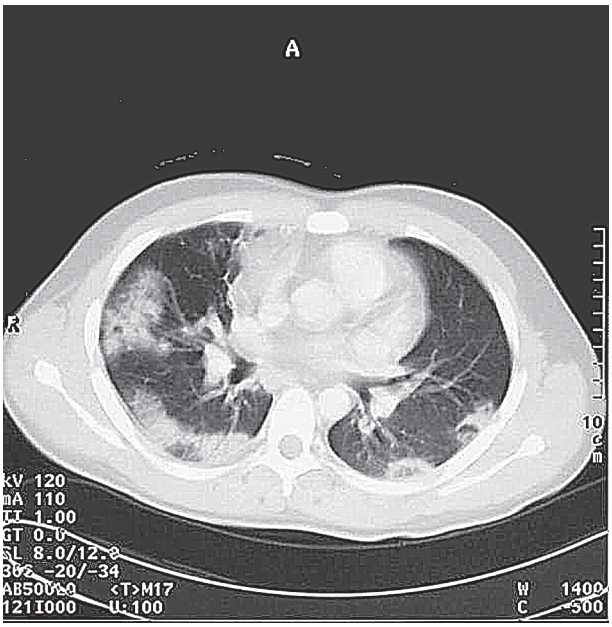

Fig. 1 Chest CT with contrast enhancement disclosed multifocal subpleural areas of air space consolidation and a confluent heterogeneous soft-tissue mass in the the prevascular space of anterior mediastinum, demonstrating residual Hodgkin's lymphoma (lung window).

Video-assisted thoracoscopic lung biopsy was undertaken as the patient's clinical symptoms and chest radiographs had deteriorated despite the use of empirical antibiotics. Surgery revealed vessel engorgement and consolidation of lung parenchyma without tumor masses or thromboemboli. Microscopic examination revealed myxomatous fibroblast plugs in respiratory bronchioles, alveolar ducts, and surrounding alveolar tissue in addition to type II pneumocyte hyperplasia, and foamy macrophage infiltration, which features were compatible with the diagnosis of BOOP (Fig. 2). Methylprednisolone, 40 mg, was administered intravenously every six hours for three days and then tapered off over one week, leading to rapid clinical improvement. Oral prednisolone (1mg/kg/day) was continued for six weeks after discharge, resulting in gradual resolution of the symptoms and improvements shown in follow-up chest radiographs. He was treated with another two courses of chemotherapy using an AVD regimen (doxorubicin 25 mg/m^2 on days 1 and 15, vinblastine 6 mg/m^2 on days 1 and 15, and dacarbazine 375 mg/m^2 on days 1 and 15), because of residual mediastinal uptake of gallium 67 seen by whole body scintigraphy. After this chemotherapy, the original symptoms recurred and chest image studies revealed the characteristic findings of BOOP. He then received oral prednisolone (1mg/kg/day) for two

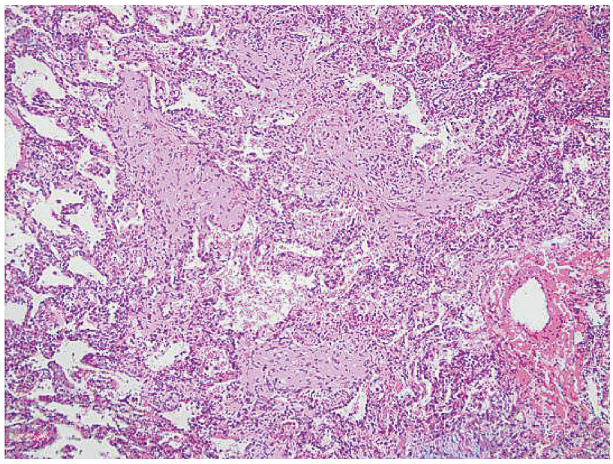

Fig. 2 Histopathology showing patchy distribution of organizing pneumonia and intraluminal myxomatous fibrous plugs that occupy the terminal bronchioles, alveolar ducts, and alveoli (Hematoxylin and eosin stain, original magnification 100x).

months and was maintained on 10 mg per day without exhibiting any subsequent pulmonary infiltrations.

DISCUSSION

When a patient with HL undergoing chemotherapy develops hemoptysis and fever with a chest radiograph showing diffuse patchy alveolar consolidation, an infective etiology is always the diagnosis of choice[1]. BOOP secondary to HL after chemotherapy is rarely considered unless the physician already has evidence of it. BOOP is usually a subacute illness, presenting with nonproductive cough and exertional dyspnea for a few weeks[2]. The constitutional symptoms may include fever, malaise, and weight loss. The most common physical findings are tachypnea and lung crackles, which may mimic community-acquired pneumonia (CAP). Hemoptysis is rare. This patient suffered from fever, chills, and dyspnea on exertion for one week before hemoptysis occurred. He was initially misinterpreted to have CAP.

Typical laboratory tests for patients with BOOP show a high ESR as well as a high CRP level. A third of patients have leukocytosis. The chest radiograph may show patchy peripheral migratory alveolar infiltrates, or diffuse reticular or nodular opacities. Pleural effusion may appear in 30% of patients with secondary BOOP, and high-resolution CT chest scans show patchy consolidation, ground glass opacity, and nodularity with a subpleural predilection. Bronchial wall thickening and dilatation denote severe

Table 1 Hemoptysis as cardinal manifestation in bronchiolitis obliterans organizing pneumonia

Patient No.	Age/Sex	Clinicopathological diagnosis	Prodromal period	Symptoms and signs	Radiographic findings	Diagnostic procedure	Response to corticosteroids	Reference
1	68/M	Idiopathic BOOP	Two months	Fever, chills, moderate hemoptysis	Diffuse alveolar infiltrates	Lobectomy	NR (surgical resection)	5
2	55/F	RA associated BOOP	Ten days	Chest pain, mild hemoptysis	Solitary alveolar opacification	Transbronchial biopsy	Resolution after 1 month	5
3	47/F	Idiopathic BOOP	Two months	Cough, mild hemoptysis	Multiple cavitary nodules	Open lung biopsy	No relapse after 1 year	6
4	17/M	Chemotherapy-induced BOOP	Two weeks	Fever, chills, dyspnea on exertion, moderate hemoptysis	Multifocal subpleural airspace consolidation	Video-assisted thoracic surgery	Resolution after 6 weeks; relapse after another 2 courses of bleomycin-free chemotherapy	Our patient

Abbreviation: BOOP=bronchiolitis obliterans organizing pneumonia, RA=rheumatoid arthritis, NR=not received.

disease. The gold standard for diagnosis of BOOP is an open lung biopsy (OLB) or a video-assisted thoracoscopic lung biopsy for histopathology[4]. It may be difficult to attain definite diagnosis through clinical and radiographic interpretation without tissue documentation. OLB has been advocated as beneficial in patients with hematological malignancy with undiagnosed pulmonary infiltrates[4]. In our patient, the laboratory and image results were characteristic of BOOP.

Generally, the onset of symptoms of BOOP is usually subacute with a prodromal flu-like illness. In our review of the literature, submassive hemoptysis has rarely been described as the cardinal presentation of BOOP (Table 1). Mroz et al. demonstrated two cases of BOOP presenting with mild to moderate hemoptysis[5]. Froudarakis et al. reported another case of idiopathic BOOP characterized by mild hemoptysis[6]. All patients showed satisfactory responses and good prognosis after treatment. Hence, the clinician should be aware of this rare entity and proceed to proper intervention immediately.

Once BOOP is documented in a patient, the physician should look for a precipitating factor[7]. In the present patient, the etiology of the BOOP was deemed chemotherapy because he did not respond to antibiotic therapy, and his chest radiographs showed progressive deterioration. His symptoms and laboratory findings resolved gradually only after corticosteroids had been instituted. Initially, bleomycin was thought to be the precipitating factor of this patient's BOOP. However, the BOOP recurred after another two courses of bleomycin-free regimen. Therefore, chemotherapeutic agents other than bleomycin may have been causative.

The optimal treatment of patients with BOOP is corticosteroids. According to the literature, patients should be treated with corticosteroids for one year[2]. However, in this case we encountered a dilemma because the patient only obtained partial response after six courses of ABVD regimen. If we had discontinued the chemotherapy and treated his BOOP with corticosteroids for one year, his HL might have recurred. We therefore restarted chemotherapy immediately after the first complete resolution of the BOOP, without concomitant administration of corticosteroids. Unfortunately, the BOOP recurred rapidly although we did not use bleomycin. We are not sure whether such a recurrence of BOOP is normal after the early discontinuation of corticosteroids, or if it was caused by chemotherapeutic agents other than bleomycin. If the latter is true, further chemotherapy including planned high-dose chemotherapy with stem cell support for the patient's HL needs to be approached cautiously. His BOOP has now been controlled using minimal daily doses of corticosteroids for one year. Fortunately, his HL remains in remission.

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