

Bronchiolitis obliterans organizing pneumonia induced by drugs or radiotherapy

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INTRODUCTION

Bronchiolitis obliterans organizing pneumonia (BOOP) is generally idiopathic; however, this lesion may be caused by more than 35 medications and from breast radiotherapy. These drugs include the cancer chemotherapeutic agents, antibiotics, cardiovascular drugs and immunosuppressive agents noted in Table 24.1.^{1,2} Unproductive cough is a common early symptom and shortness of breath occurs later. Fever is also often seen early. Eosinophilia is unusual. The radiograph shows bilateral patchy infiltrates, and the chest CT shows ground-glass opacities, often peripheral and pleural-based (Fig. 24.1).

As this is an inflammatory process, the prognosis is excellent, with almost all patients responding to withdrawal of the medication with or without a brief course of corticosteroid therapy.

DEFINITION AND OVERALL ASSESSMENT OF BOOP

DEFINITION

BOOP is defined as organized granulation tissue in the distal airways extending into the alveolar ducts and alveoli.³ Sometimes organizing pneumonia is seen without the organized process in the bronchioles, although a thorough search of a sufficiently large size of tissue usually shows the typical BOOP lesion. The term 'cryptogenic organizing pneumonia' (COP)⁴ is sometimes used for the idiopathic BOOP, while BOOP is used for known causes such as the drug-induced lesions, or systemic associated conditions such as connective tissue disorders or after organ transplantation. The term 'BOOP' is preferred because this is a distinct simultaneously involved lesion of distal airways and alveoli with internationally well-established causes, clinical course and outcome.

INCIDENCE AND EPIDEMIOLOGY

Drug-induced BOOP may occur as frequently as 15 per cent among individuals taking high-dose amiodarone, but it is generally rare, occurring in less than 0.1 per cent of patients receiving a medication. The process occurs in men and women equally and at all ages. Thus far, there have been no specific risk factors such as genetic pleomorphisms established for the development of the drug-related BOOP lesion.

CLINICAL PRESENTATION

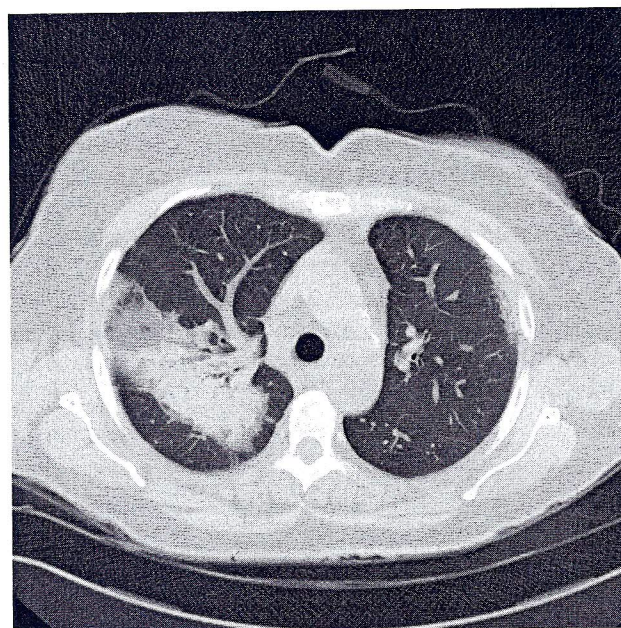
The clinical presentation is usually subacute with a non-specific cough and gradual onset of shortness of breath. There usually is no sputum production although a small amount of clear sputum may occur. Haemoptysis occurs in rare situations if alveolar haemorrhaging is part of the BOOP process.

Physical examination indicates bilateral end-inspiratory fine crackles, and there is no wheezing, rhonchi or finger clubbing. Pulmonary function tests show a decreased vital capacity and total lung capacity with no airflow obstruction. Virtually all patients have a decreased diffusing capacity.

The chest X-ray shows bilateral patchy infiltrates. Computed tomography is helpful in the diagnosis of drug-induced BOOP because the scans show ground-glass opacities located in all regions, often peripherally and pleural-based. During the early stage of drug-related BOOP, the ground-glass opacities may be subtle and sometimes unilateral. Focal nodular BOOP may occur. Honeycombing and traction bronchiectasis do not occur in drug-induced BOOP, but these findings may occur with agents such as amiodarone that are capable of producing concurrent pulmonary fibrosis. Pleural-based 'triangle' infiltrates are a common and specific chest CT finding for BOOP with the base of the triangle located along the pleura and the tip of the triangle towards the central mediastinum.

Table 24.1 Drug-related bronchiolitis obliterans organizing pneumonia (BOOP)

Name of drug	Strength of association ^a
<i>Antimicrobials</i>	
Minocycline	+++
Nitrofurantoin	+++
Cephalosporin	+++
Amphotericin B	+++
Daptomycin	++
Abacavir	+
<i>Anticancer agents</i>	
Bulsulfan	++
Methotrexate	++
Bleomycin	+++
Doxorubicin	++
Thalidomide	+
Cytosine-arabioside (ARA-C)	++
Interferon- α , cytarabine	++
ocfosfate	++
Chlorambucil	++
Rituximab	++
Oxaliplatin	+
<i>Cardiovascular agents</i>	
Amiodarone	+++
Acebutolol	++
<i>Anti-inflammatory agents</i>	
Gold	++
Sulfasalazine	+++
Mesalamine (mesalazine)	++
Bucillamine	++
Infliximab	+
<i>Immunosuppressive agents</i>	
Azathioprine	+++
6-mercaptopurine	+
Tacrolimus	+
Sirolimus	+++
Everolimus	+
<i>Anticonvulsants</i>	
Carbamazepine	+++
Phenytoin	++
<i>Miscellaneous agents</i>	
Interferons	
- α	+++
- β	++
- γ	+
Ticlopidine	++
L-tryptophan	+++
Cocaine (illicit use)	+++
Heroin	+
Fluvastatin	+
Risedronate	+++

^aStrength of association: + minimal; ++ moderate; +++ strong.**Fig. 24.1** Mid-lung computed tomography scan showing BOOP as a posterior ground-glass opacity and consolidation with an air bronchogram that is triangular, with the apex at the mediastinum and the base at the posterior pleura.

TREATMENT AND MANAGEMENT

The BOOP lesion is inflammation, so discontinuation of the drug often results in resolution. In some situations, such as with amiodarone which has a continual effect for several days to weeks, a course of corticosteroid therapy may be needed. Patients have improved symptoms in a few days and the radiograph begins to improve over a period of weeks. In some situations, such as with amiodarone, symptoms begin to improve during a 2- to 4-week period and the radiographs improve in 3 months and may continue to improve for as long as 18 months.

OUTCOME AND COMPLICATIONS

The outcome of drug-induced BOOP is favourable as this is an inflammatory lesion without residual scarring. However, the BOOP lesion may occur secondarily in association with other primary drug-related lung manifestations such as usual interstitial pneumonia (UIP) or constrictive bronchiolitis with obliteration. In this situation, the BOOP lesion may resolve or respond to corticosteroid therapy, yet the fibrosing UIP process or fibrotic bronchiolar lesion does not respond and persists as the primary cause of pulmonary dysfunction. There have been rare reports of a fatal outcome from drug-related BOOP.

ANTIMICROBIAL DRUGS AND BOOP

Minocycline

There have been two reports of women taking minocycline for acne who developed BOOP. The first was a 20-year-old

woman who had taken minocycline for 3 months and developed progressive shortness of breath, a chest radiograph showing alveolar opacities in the upper lobes, and a lung biopsy showing BOOP.⁵ The chest radiograph showed partial improvement 3 weeks after drug cessation. An 8-week course of corticosteroid was given for total symptomatic and radiographic resolution.

The second report was of a 39-year-old woman who was treated with minocycline for 5 months and developed a cough and radiographic infiltrates.⁶ Bronchoalveolar lavage (BAL) showed increased lymphocytes, and a transbronchial biopsy showed BOOP. The minocycline was stopped, resulting in rapid remission without treatment.

Nitrofurantoin

There have been two reports of three women taking nitrofurantoin who developed BOOP. A 34-year-old woman developed cough and progressive shortness of breath beginning 2 years after she had started taking nitrofurantoin.⁷ She had no crackles and the high-resolution chest CT scan showed bilateral patchy ground-glass opacities. The illness responded to corticosteroid therapy.

The second case was a 50-year-old woman who developed cough, shortness of breath, fatigue, anorexia, fever and night sweats. She had bilateral crackles. She had severe pulmonary impairment with a vital capacity of 0.84 litres (22 per cent of predicted); however, she responded to prednisone treatment with resolution of symptoms. The initial high-resolution chest CT scanned showed patchy infiltrates that responded to treatment although there were some residual abnormalities.

The third individual was an 82-year-old woman who had taken nitrofurantoin for 2 years and developed cough with gradual increase in breathlessness.⁸ High-resolution chest CT showed areas of patchy ground-glass opacification. Prednisone treatment at 30 mg was given for 6 weeks and decreased during an additional 4-month period. Within 1 month of beginning treatment there was a decrease in cough and breathlessness. The patient returned to her baseline in 8 months and was well 3 years later.

Nitrofurantoin BOOP was reported in a 71-year-old woman who had taken nitrofurantoin for 6 months prior to developing unproductive cough, fever and shortness of breath.⁹ This represented the seventh reported case. She had bilateral inspiratory crackles, and the chest CT showed peripheral infiltrates and effusions. A video-assisted thoracoscopy (VATS) biopsy showed proliferating fibromyxomatous connective tissue with organization within the air-spaces consistent with BOOP. There was complete resolution of symptoms and lung volumes with prednisone therapy which was discontinued after 16 months; however, the diffusing capacity remained abnormal at 53 per cent predicted.

Cephalosporin

A 61-year-old patient was receiving cephadrine for a urinary tract infection and developed a red, pruritic rash on her trunk during the fourth day of therapy.¹⁰ Several days later she

developed shortness of breath, an unproductive cough and malaise. One year previously she had been given cephalexin for an infected cat scratch and developed a rash without respiratory symptoms. This time there were bilateral crackles, and a chest radiograph showed patchy segmental infiltrates in the right mid-lung and left lower lung. A lung biopsy showed intra-alveolar myxomatous connective tissue consistent with BOOP. The radiograph cleared after discontinuation of the medication. Six months later she was re-challenged with cephadrine 500 mg four times daily. On the third hospital day she developed a lingular infiltrate and progressive cough. The drug was discontinued. Corticosteroid therapy resulted in a prompt disappearance of symptoms and return of normal lung function.

Amphotericin B

A 1990 report described a 52-year-old woman who developed a fever and a right lower lung infiltrate after receiving amphotericin B.¹¹ The drug was continued and the patient developed shortness of breath and hypoxaemia. The chest radiograph showed bilateral diffuse infiltrates. Transbronchial biopsy showed respiratory bronchioles and alveolar ducts filled with polypoid plugs consistent with BOOP. The medication was stopped. The radiograph cleared. Four months later, amphotericin B was given empirically but was stopped because of shortness of breath.

Daptomycin

There have been two case reports of daptomycin-related BOOP. The first individual was an 84-year-old man who was treated for 4 weeks with intravenous daptomycin for an infected knee prosthesis.¹² The chest CT showed bilateral peripheral ground-glass opacities, one of which was triangular. BOOP was the primary histological pattern in this patient, and the transthoracic needle biopsy showed organizing pneumonia with eosinophils. His symptoms and CT scan improved after cessation of daptomycin.

The second individual was a 54-year-old man who developed shortness of breath 14 days after intravenous daptomycin treatment for a methicillin-resistant *Staphylococcus aureus* (MRSA) infection.¹³ The chest CT scan showed bilateral patchy infiltrates and lung biopsy showed organizing pneumonia with eosinophils. After 4 weeks of corticosteroid therapy, the chest radiographic abnormalities resolved.

Abacavir for HIV infection

Abacavir is an HIV nucleoside analogue reverse transcriptase inhibitor and may cause hypersensitivity reactions in 3–5 per cent of patients within 6 weeks of treatment.¹⁴ A case report described a 52-year-old woman infected with HIV who had been started on abacavir 2 weeks previously and developed progressive shortness of breath with cough. The chest radiograph showed bilateral diffuse infiltrates and the biopsy showed patchy areas of organizing pneumonia with alveolar fibrin

deposition. The abacavir was discontinued and she showed a remarkable improvement with dramatic resolution of the diffuse bilateral infiltrates.

ANTICANCER AGENTS AND BOOP

Busulfan

For many years busulfan has been a commonly used drug for treatment of lymphoma and leukaemias. There have been reports of busulfan-related BOOP lesions.⁴

Methotrexate

There have been several types of lung lesion associated with methotrexate, including interstitial pneumonia, granulomatous lung lesions, diffuse alveolar damage and BOOP. In a study of 168 patients with rheumatoid arthritis, Carson *et al.* reported that three had a lung biopsy; one showed a bronchiolar lesion.¹⁵ This 74-year-old woman with 7 years of rheumatoid arthritis developed shortness of breath, cough and fever after 1 year of methotrexate therapy. The chest radiograph showed bilateral interstitial infiltrates. The open lung biopsy showed ill-formed interstitial granulomas and bronchiolitis. The patient responded to discontinuation of methotrexate and a brief course of corticosteroid therapy.

In another report, a 67-year-old man with severe rheumatoid arthritis for 8 years had taken 10 mg of methotrexate weekly for 8 months when he developed fatigue, weight loss and an unproductive cough.¹⁶ The chest X-ray showed normal lungs; however, 1 month later, he developed acute-onset right-sided chest pain after an episode of cough. Now, the chest radiograph showed a right upper-lobe triangular consolidation in the axillary area with air bronchograms and an 8th posterior rib fracture. Transbronchial biopsy showed interalveolar septa infiltrated by mononuclear cells along with plugs of granulation tissue within bronchioles consistent with BOOP. The rib biopsy showed a rheumatoid nodule. Eight months later the patient had improved symptoms and the lung consolidation had partially resolved while continuing the methotrexate.

Bleomycin

Focal nodular BOOP has been reported in individuals receiving bleomycin.¹⁷ This report described three patients who were 6, 19 and 19 years of age who received less than 200 mg of bleomycin for treatment of osteogenic sarcoma. The radiographs showed nodular ground-glass lesions, one of them pleural-based without major respiratory symptoms. The lung biopsies showed BOOP, and none progressed to diffuse BOOP.

Doxorubicin

Acute cyanotic respiratory failure and near fatal outcome of drug-related BOOP has been reported. A 56-year-old woman was treated with four cycles of doxorubicin for metastatic

breast carcinoma, and prior to her fifth 21-day cycle of treatment she developed rapid-onset progressive shortness of breath and cyanosis.¹⁸ Bilateral coarse inspiratory crackles were heard. The chest X-ray showed diffuse reticular opacities, and a high-resolution chest CT scan showed bilateral ground-glass opacities in a background of improved pulmonary metastases. Transbronchial biopsies showed intra-alveolar granulation tissue consistent with BOOP. Treatment with oxygen and dexamethasone resulted in rapid improvement.

Cytosine arabinoside (ARA-C)

There have been two reports of four individuals who developed BOOP from cytosine arabinoside. The first report described three children 6, 9 and 12 years of age with acute leukaemias who developed BOOP between 10 and 20 days after intravenous ARA-C for treatment.¹⁹ The chest CT scans showed patchy infiltrates, two of them with the pleural-based triangular shape consistent with BOOP. The lung biopsies showed intraluminal buds of loose connective tissue consistent with BOOP. All three patients recovered completely.

In another report, a 59-year-old man with chronic myelogenous leukaemia was treated with subcutaneous interferon- α and ARA-C and developed a persistent cough 4 weeks later; the chest radiograph was normal.²⁰ Four weeks later he developed spiking fever, fatigue, 20-pound weight loss and shortness of breath. The chest radiograph now showed bilateral infiltrates, and the chest CT scan showed bilateral peripheral ground-glass opacities. The lung biopsy showed polypoid connective tissue plugs in air-spaces consistent with BOOP. The patient was started on 60 mg of prednisone daily and the hydroxyurea was restarted. He showed dramatic clinical improvement and was discharged home within 2 days. One month later his performance status was normal and the radiographic infiltrates had resolved.

Fludarabine, cytosine arabinoside and mitoxantrone (FLAN)

FLAN-related BOOP has been reported in a 31-year-old man treated for acute myeloid leukaemia.²¹ Seven days after cessation of treatment he developed progressive shortness of breath, and high-resolution CT showed ground-glass opacities. Transbronchial biopsy showed patchy interstitial cell inflammation and alveolar loose fibrotic buds. Treatment with intravenous corticosteroid therapy resulted in resolution of symptoms and physiological abnormalities.

Interferon- α and cytarabine ocfosfate

There has been a report of fulminant rapidly progressive BOOP from combined chemotherapy that resulted in death. A 65-year-old man was treated for chronic myelogenous leukaemia with hydroxyurea, oral cytarabine ocfosfate (YNK01) and subcutaneous injections of interferon- α .²² Within 48 hours the patient developed fulminant respiratory failure. The chest radiograph showed bilateral patchy infiltrates, and CT scans showed ground-glass opacity and patchy consolidation with possible cavitation. The patient did not respond to 1 g per

day of methylprednisolone and died 5 days after initiation of the chemotherapy regimen. The post-mortem lung tissue showed intraluminal buds of granulation tissue in the distal air-spaces and foci of organizing pneumonia consistent with BOOP. Interferon- α has been associated with BOOP,²⁰ and as cytarabine ocfosfate is a derivative of cytosine-arabino-side (ARA-C), the cytarabine was the probable causative agent.^{19,20}

Chlorambucil

Haemoptysis and a unilateral focal lesion can occur in patients with drug-related BOOP. A 70-year-old man with chronic lymphocytic leukaemia had been treated with oral chlorambucil and methylprednisolone for 7 weeks and developed cough, chest pain and haemoptysis.²³ The chest CT scan showed a peripheral ground-glass opacity in the right mid-lung, and an open lung biopsy showed typical findings of BOOP with tufts of intraluminal organization and polypoid granulation tissue within alveolar ducts and alveoli. The patient had a complete clinical and radiographic recovery after surgery.

Thalidomide

Thalidomide is an angiogenesis inhibitor and decreases tumour necrosis factor. A 58-year-old man with multiple myeloma developed low-grade fever, cough and shortness of breath after two complete cycles of thalidomide at 200 mg per day.²⁴ He had bilateral crackles and the high-resolution chest CT scan showed diffuse ground-glass opacities peripherally. The thalidomide was discontinued. The bronchoalveolar lavage showed 31 per cent neutrophils, 40 per cent lymphocytes, 8 per cent monocytes and 20 per cent eosinophils. Transbronchial biopsy showed fibroblastic plugs in the alveolar spaces with surrounding interstitial inflammation consistent with BOOP. The chest CT scan 6 weeks later showed significant improvement and he had no recurrence of pulmonary symptoms after a 3-month course of corticosteroid therapy.

Rituximab

Rituximab is a chimeric monoclonal antibody that may induce apoptosis of B-cells and is used in treatment of lymphoma. There have been two reports of rituximab-related BOOP, one in combination with other chemotherapy and one as the sole treating agent.

In the first report, a 52-year-old man was treated with rituximab and CHOP (cyclophosphamide, vincristine, doxorubicin and prednisolone) for an abdominal lymphoma mass.²⁵ Ongoing medications included carbamazepine, pravastatin and warfarin. The R-CHOP regimen was given at 3-week intervals, and after three courses there was a more than 50 per cent decrease in tumour size with no abnormal lung parenchyma. Pegylated filgrastim, a neutrophil colony-stimulating factor, was given subcutaneously on day 2 of courses three and four. Two weeks after the fourth course, the patient developed acute-onset shortness of breath, pleuritic chest pain, hypoxaemia and fever. The chest X-ray showed

bilateral patchy ground-glass opacities. Transbronchial biopsy showed fibroblastic tissue arising within alveoli and pigmented foamy macrophages consistent with BOOP. The radiographic appearance improved with prednisolone at 60 mg daily for 2 weeks. Additional courses of CHOP without rituximab or filgrastim were given for a complete lymphoma remission and no development of respiratory symptoms. The filgrastim may have been related to the BOOP although rituximab is the most likely cause.

In the second report,²⁶ a 61-year-old man developed gastric and duodenum lymphoma treated with four weekly intravenous doses of rituximab at 375 mg/m². Two months later the patient was asymptomatic, but the chest CT showed two new parenchymal opacities in the left lung, one in the left upper lobe and one in the left lower lobe. The patient was treated with an antibiotic and repeat CT scan 1 month later showed a stable left lower lobe nodule, but the left upper lobe nodule had increased to 3 cm and with spiculated margins. A wedge resection of this nodule showed BOOP. One month later the patient developed a cough and shortness of breath. Pulmonary function tests showed a decrease in function compared to preoperative values, and the chest CT scan showed increased size of the left lung nodules and a new right lower lobe nodule. Treatment with prednisone 40 mg daily was begun, and within 4 days the patient reported a dramatic improvement. By 1 month the cough and shortness of breath had resolved. The pulmonary function tests normalized.

Oxaliplatin

A 30-year-old woman with rectal cancer and a single liver metastasis received pelvic radiotherapy and 5-fluorouracil (5-FU).²⁷ After liver tumour resection, adjuvant therapy with 5-FU, leucovorin and oxaliplatin was given. After 10 weeks and the sixth cycle she developed cough and progressive shortness of breath. The chest CT scan showed ground-glass patchy infiltrates and the biopsy showed peribronchial thickening and alveolar plugs of fibrous tissue. The patient had resolution of shortness of breath and cough after 4 days of corticosteroid treatment and resolution of the chest CT scan 4 weeks later.

CARDIOVASCULAR AGENTS

Amiodarone

Amiodarone-related BOOP is the most commonly reported drug-related BOOP reaction. In a 2004 review of amiodarone pulmonary toxicity, Camus and Rosenow reported the occurrence is from 1 per cent to as high as 15 per cent.²⁸ There are several types of pulmonary lesions associated with amiodarone toxicity. BOOP is common as it was found in 6 out of 197 patients (3 per cent) in a study in Spain.²⁹

Amiodarone and the metabolite desethylamiodarone are cationic amphiphilics that accumulate in tissues including the lungs. These compounds localize in cell lysosomes and block turnover of endogenous phospholipids, which explains the presence of foamy lipid-laden macrophages in lavage or lung tissue.

Clearance of these substances from tissues is very slow as autopsy studies have shown significant amounts of both compounds persisting in the lung 1 year after cessation of treatment.

The pathological findings show BOOP with foamy macrophages. High-resolution chest CT scan shows the typical BOOP pattern of ground-glass opacities, air bronchograms and subpleural opacities. These radiographic findings may wander from one lung region to other lung regions over time. The clinical and radiographic findings resolve from 3 months to as long as 18 months after cessation of amiodarone.³⁰ A small percentage of patients with amiodarone lung toxicity have subpleural honeycombing and traction bronchiectasis reflecting usual interstitial pneumonia (UIP) and fibrosis, which is a distinctly different lesion from BOOP.^{28,30}

The occurrence of amiodarone-related BOOP is higher among patients receiving high doses; however, BOOP also occurs among patients taking 200 mg daily. Ott *et al.* reviewed eight patients receiving 200 mg daily.³¹ The duration of therapy prior to symptoms was as short as 3 months, but most were 2 years and one patient had 5 years of treatment. Shortness of breath and cough were the most common symptoms. The light microscopy finding of vacuolization in pneumocyte cytoplasm and the electron microscopy findings of whorled, lamellar, membranous inclusions in alveolar pneumocytes are characteristic of amiodarone-related BOOP. These findings were illustrated in the lung biopsy of an 82-year-old man who had taken amiodarone, 400 mg daily, reduced to 200 mg daily during a 15-month course.³² The amiodarone was discontinued, prednisone was begun, his condition improved and within a few weeks he no longer needed supplemental oxygen. The prednisone was decreased, and he was well 15 months after discharge.

Adenopathy may occur in drug-related BOOP. A 67-year-old man had a pre-cardiac transplant evaluation that showed bilateral small parenchymal opacities in the lower lungs and a nodule in the right lower lobe.³³ A follow-up CT scan 3 months later showed persistence of the small opacities as well as bilateral ground-glass opacities, and an enlarged pre-carinal lymph node. The patient had shortness of breath, fatigue, cough and occasional chest pain that were attributed to his cardiac condition. A CT-guided fine-needle aspiration of the right lower lung nodule showed abundant foamy macrophages admixed with benign bronchial epithelial cells. A subsequent thorascopic biopsy showed typical BOOP as well as abundant foamy macrophages. The amiodarone was discontinued, and 2 months later a chest CT showed no new abnormalities and improvement in the lymphadenopathy. Four months later the patient had a successful heart transplantation. One year later a follow-up CT study showed significant improvement in the bilateral pulmonary opacities and lymphadenopathy.

Acebutolol

Acebutolol is a beta-blocker used for treatment of hypertension. There has been one report of acebutolol-related BOOP. A 59-year-old man had been taking acebutolol 200 mg daily for 1 month and developed a fever, cough and increasing shortness of breath.³⁴ The chest radiograph showed alveolar opacities. Bronchoalveolar lavage showed 15 per cent neutrophils.

A transbronchial biopsy showed organizing pneumonia and obstruction of small air passages by buds of connective tissue consistent with BOOP. After discontinuation of acebutolol, the fever remitted rapidly. Over several months the patient was symptom free and had a normal chest radiograph. The finding of lavage neutrophils is unusual because patients with BOOP usually have a high percentage of lymphocytes, not neutrophils. Whether the presence of neutrophils is suggestive of drug-related BOOP is not known.

ANTI-INFLAMMATORY AGENTS

Gold

Costabel *et al.* cited seven reports of possible gold-related BOOP.³⁵ One of these reports included a 49-year-old woman with rheumatoid arthritis who was treated with 2 months of weekly intramuscular gold injections and developed shortness of breath, cough, and a chest radiograph that showed nodular opacities and an air bronchogram.³⁶ The patient had also received naproxen 500 mg twice daily. The lung biopsy showed bronchiolitis obliterans with small bronchioles occluded by inflammatory cells, and their walls thickened by granulation tissue. The photomicrographs suggested BOOP although the authors note there was destruction of the alveolar structures, a finding usually not seen in BOOP. The patient had a prolonged post-biopsy course requiring assisted ventilation for 4 weeks. The patient gradually responded to corticosteroid and cyclophosphamide therapy. The chest radiograph was normal 18 months later.

Sulfasalazine

Sulfasalazine is commonly used for individuals with inflammatory bowel disease, and there have been several reports of sulfasalazine-related BOOP. In a review of inflammatory bowel disease by Camus *et al.* a 26-year-old woman with Crohn's disease developed BOOP after sulfasalazine treatment.³⁷ A previous report was of a 66-year-old man with ulcerative colitis who had taken sulfasalazine for 4 months and developed a cough with a chest X-ray showing patchy upper lung infiltrates.³⁸ The patient continued with progressive shortness of breath, cough and fever despite discontinuing the sulfasalazine. There was no eosinophilia. A biopsy showed BOOP. The patient was treated with prednisone 60 mg daily and began improving in 1 week. A follow-up chest radiograph showed residual apical fibrotic strands. This BOOP reaction may have been related to the inflammatory bowel disease since the process progressed after the sulfasalazine was stopped.

A report in 1988 described an individual with ulcerative colitis who developed shortness of breath, cough productive of white sputum, mild fever, bilateral crackles, and a chest radiograph showing patchy infiltrates.³⁹ There was associated eosinophilia. After cessation of the sulfasalazine, symptoms subsided and the chest radiograph returned to normal. This report was consistent with sulfasalazine-related BOOP although there was no biopsy confirmation of BOOP, and the patient had taken the drug for 6 years.

A 68-year-old woman with seronegative rheumatoid arthritis developed progressive shortness of breath and pruritus 4 months after initiation of sulfasalazine.⁴⁰ She had bilateral crackles and pulmonary function tests showed a vital capacity of 75 per cent of predicted, an FEV₁/FVC ratio of 75 per cent, and a decreased diffusing capacity to 49 per cent of predicted. The chest radiograph showed diffuse, bilateral reticular-nodular infiltrates in the middle and lower lobes, and the chest CT scan showed alveolar consolidation, pretracheal, carinal and prevascular bilateral axillary lymphadenopathy. Thoracoscopic lung biopsy showed plugs of granulation tissue within the lumina of small airways and alveolar accumulations of foamy macrophages and inflammation consistent with BOOP. The sulfasalazine was stopped and the patient was given prednisolone daily for 3 months, in decreasing doses. Respiratory symptoms improved and the previously elevated eosinophil count returned to normal within a few days. After 45 days, radiological improvement was seen on the chest CT scans.

Mesalamine

Mesalamine (mesalazine) is a preparation of 5-aminosalicylate (5-ASA), available in oral and rectal forms, which does not contain sulfonamide. It is used for the treatment of inflammatory bowel disease. BOOP has been reported in patients taking the oral as well as the rectal preparation. In the 1993 Camus review of inflammatory bowel disease, three patients with BOOP had received mesalamine treatment.³⁷ In a prior report, a 20-year-old woman with ulcerative colitis was initially treated with sulfasalazine that was changed to mesalazine, 800 mg three times daily, and 1 year later developed fever, anorexia, unproductive cough, central pleuritic chest pain and shortness of breath.⁴¹ The chest radiograph showed a large peripheral infiltrate in the right mid-lung and right lower lung. Lung biopsy showed knots of granulation tissue in respiratory bronchioles, alveolar ducts and alveoli consistent with BOOP. Mesalamine was discontinued. There was rapid symptomatic and radiological improvement after 1 week of prednisolone 40 mg daily.

A 2001 report described an 18-year-old woman who developed ulcerative colitis and was treated with intravenous corticosteroids, oral sulfasalazine and parenteral nutrition.⁴² She improved and 1 month later her medications were changed to oral mesalamine. Oral 6-mercaptopurine (6-MP) was added because of persistent bowel symptoms. Within 3 years she was in complete remission and all medications were stopped. She had an exacerbation of ulcerative colitis treated with oral mesalamine, oral 6-MP and mesalamine enemas. Two months later she developed fever, cough, pleuritic chest pain and shortness of breath. There were no increased eosinophils. The chest radiograph showed patchy peripheral densities with areas of consolidation in the left lung. All medications were stopped. Video-assisted thoracoscopy showed typical BOOP with a polyp of young connective tissue inside the bronchiolar lumen and organizing pneumonia. Treatment was begun with intravenous methylprednisolone 40 mg every 6 hours. The patient quickly improved during the ensuing 4 days. Within 3 weeks the patient had returned to almost all physical activity with almost complete clearing of the radiographic infiltrates. The symptoms of colitis were minimal and

6-MP was restarted without recurrence of the pulmonary disease.

Bucillamine

Bucillamine is an anti-inflammatory agent developed in Japan with a structure similar to D-penicillamine. A 74-year-old woman with rheumatoid arthritis for 10 years had been taking bucillamine at 100 mg per day for 3 months and developed unproductive cough and shortness of breath.⁴³ Fine crackles were detected at both lung bases. The chest X-ray showed patchy infiltrates bilaterally predominantly in the lower lungs. The chest CT scan showed ground-glass opacities adjoining bronchovascular bundles and air bronchograms with no honeycombing. The features were suggestive of BOOP. Because of severe hypoxaemia, a transbronchial biopsy and lavage were not performed. However, a drug lymphocyte stimulation test with bucillamine was positive. The bucillamine was discontinued and prednisolone 30 mg daily was given. She gradually improved, and by 2 months she had no cough or shortness of breath and the patchy infiltrates seen on the chest CT scan had nearly resolved.

Infliximab

Infliximab is an antitumour necrosis factor (anti-TNF) agent given by infusion for the treatment of rheumatoid arthritis. A 70-year-old man had been receiving methotrexate at 22.5 mg per week for 3 years and infliximab was added at 3 mg/kg. Nine days after the third infusion he was seen in the emergency room because of fever, fatigue and increasing shortness of breath.⁴⁴ He was febrile to 104.3°F (40.2°C) with oxygen saturation of 94 per cent. Lungs were clear to auscultation. The chest X-ray showed bilateral interstitial infiltrates in the upper two-thirds of the lungs. There were no eosinophils. High-resolution chest CT scan showed bilateral ground-glass opacities in the upper two-thirds of the lung without nodules, lymphadenopathy or fibrosis. Lavage revealed lymphocytic predominance. The methotrexate was discontinued and prednisone at 50 mg per day was begun and increased to 100 mg daily because of lack of improvement. The patient slowly improved and was discharged from the hospital 1 month later with home oxygen therapy. Methotrexate at 22.5 mg per week was reinstituted without respiratory symptoms. Six months later the chest X-ray showed improvement yet the chest CT continued to show the ground-glass opacities. The authors reported eight other patients who had received infliximab, some without methotrexate, who developed interstitial lung disease.

IMMUNOSUPPRESSIVE DRUGS

Azathioprine

Azathioprine is a purine analogue used as a corticosteroid-sparing agent for the treatment of inflammatory bowel disease and other diseases. A 71-year-old man with Crohn's disease for 12 years developed an exacerbation treated with mesalamine

for 3 months without respiratory symptoms.⁴⁵ The mesalamine was discontinued, and azathioprine was added at 100 mg daily. Within 2 weeks the patient developed fever, with progressively worsening unproductive cough and shortness of breath; he required supplemental oxygen. A chest CT scan showed ground-glass opacities predominantly in the upper lungs bilaterally. An open lung biopsy showed histological features of BOOP. He was treated with intravenous corticosteroid therapy and the azathioprine was continued. The severe illness persisted with a white blood cell count of 27 000/mm³ and a fever of 104°F (40°C). The patient was transferred to a new institution, and the azathioprine was immediately stopped. Within 3 days the WBC count had returned to normal with resolution of the fever. The corticosteroid therapy was gradually decreased over 6 months, with eventual complete recovery of pulmonary function.

Tacrolimus

Tacrolimus was one of the early macrolide preparations used as an immunosuppressive agent in organ transplant recipients. A 23-year-old woman who received a bone marrow transplantation for acute lymphocytic leukaemia developed BOOP after receiving FK506 (tacrolimus) for 7 weeks and died from respiratory failure 15 days later.⁴⁶ Autopsy showed BOOP without findings of graft-versus-host disease.

Sirolimus

Sirolimus is a macrolide that is used as an immunosuppressive agent in organ transplant recipients and causes inhibition of T-cell response to interleukin-2. In 2005, Lindenfeld *et al.* described seven patients who developed sirolimus-related BOOP.⁴⁷ The BOOP lesion developed 1–7 months after initiation of sirolimus, and fever, cough and shortness of breath were common presenting symptoms. The chest CT scans were consistent with BOOP, and the available lung biopsies showed BOOP. Two of the seven patients had complete resolution after withdrawal of the medication, four after corticosteroid therapy; one developed respiratory failure and died.

One year later, Champion *et al.* reported sirolimus-associated pneumonitis in 24 renal transplant recipients.⁴⁸ These patients had received sirolimus for a median of 5.5 months, and they developed fever, fatigue, cough and shortness of breath. Crackles occurred in ten patients (42 per cent). All patients had pulmonary infiltrates radiographically, and in four patients CT scans showed patchy bilateral asymmetrical peripheral consolidation and ground-glass opacities. The pulmonary infiltrates resolved after discontinuation of the medication.

Everolimus

Everolimus is a derivative of sirolimus. There has been a report of a 56-year-old woman with a renal transplant from polycystic kidney disease who developed focal nodular BOOP while receiving everolimus.⁴⁹ Whether there is a cause and effect relationship between the agent and BOOP is not known

as BOOP may occur in patients with polycystic kidney disease and has been reported in renal transplant recipients.

ANTICONVULSANT DRUGS

Carbamazepine

Carbamazepine is an established anticonvulsant medication used for treatment of epilepsy. A 72-year-old man was treated with carbamazepine for focal seizures and admitted to the hospital with fever, unproductive cough and progressive shortness of breath after 7 weeks of treatment.⁵⁰ He had bilateral crackles. The chest radiograph showed right upper lung consolidation. There was no eosinophilia. He was treated with antibiotics for community acquired pneumonia with worsening of symptoms. Transbronchial biopsy showed organizing tissue filling small bronchioles and alveolar spaces consistent with BOOP. Treatment with oral prednisolone at 60 mg daily was begun and the carbamazepine discontinued. He had a dramatic improvement and after 2 weeks was asymptomatic and the chest radiograph was normal.

Phenytoin

A 40-year-old man began taking phenytoin 300 mg daily after a craniotomy, and in 4 weeks developed fever, rash, unproductive cough, shortness of breath and bilateral crackles.⁵¹ The chest radiograph showed bilateral patchy infiltrates, and the open lung biopsy showed myxoid granulation tissue in the bronchioles extending to alveolar ducts and alveoli consistent with BOOP. The patient had also developed new-onset cold agglutinin disease. Corticosteroid therapy was given for 1 year. The chest radiograph, liver function and haematological abnormalities resolved.

Sometimes, BOOP occurs in the context of a drug rash with eosinophilia and systemic symptoms (DRESS), a generalized syndrome that has been associated with anticonvulsant drugs such as carbamazepine and phenytoin.⁵²

MISCELLANEOUS DRUGS

Interferons

The interferons have been used for treatment of hepatitis C, multiple sclerosis, malignant melanoma and idiopathic pulmonary fibrosis. In addition to the two reports that included interferon- α noted earlier,^{20,22} a 1994 report described a 64-year-old man with hepatitis C who was treated with interferon- α for 11 weeks and developed fever, unproductive cough and shortness of breath.⁵³ The liver function tests had returned to normal. The chest radiograph showed bilateral patchy infiltrates. The biopsy showed BOOP. The interferon was stopped. Prednisolone at 40 mg per day was begun. The dyspnoea and radiographic infiltrates disappeared promptly within 1 week.

A 49-year-old man with multiple sclerosis for 8 years was treated with interferon- β .⁵⁴ Three months after beginning the

interferon he developed a progressive unproductive cough and right-sided chest pain. The chest radiograph showed a single right basal infiltrate. Transbronchial biopsy showed BOOP. The symptoms and radiographic findings resolved after 2 months of prednisone treatment. A 77-year-old woman with malignant melanomas was treated with interferon- β and after a total cumulative dose of 5.4×10^7 units she developed shortness of breath.⁵⁵ Chest CT scan showed bilateral lower lung peripheral infiltrates, and a wedge biopsy showed BOOP. Prednisone at 30 mg daily resulted in improved symptoms and resolution of the radiographic abnormalities.

A 2003 report described four patients treated with interferon- γ for idiopathic pulmonary fibrosis who developed acute respiratory failure and new alveolar opacities radiographically.⁵⁶ The chest CT scan showed diffuse ground-glass opacities superimposed on the existing usual interstitial pneumonia pattern. A lung biopsy of one of the patients showed extensive interstitial fibrosis with honeycomb change and foci of BOOP. Whether the BOOP was related to the interferon- γ or was part of the inflammatory exacerbation component of UIP is not known.

Ticlopidine

Ticlopidine is a platelet aggregation inhibitor used as a preventive agent in patients with temporal arteritis, strokes or transient ischaemic attacks. A 76-year-old woman was taking prednisone 45 mg daily, plus ticlopidine 250 mg twice daily, for giant-cell temporal arteritis.⁵⁷ In 1 month she developed a pruritic skin rash, increasing shortness of breath and bilateral crackles. The chest radiograph showed diffuse bilateral peripheral infiltrates. Transbronchial biopsy showed air-spaces filled with organizing connective tissue plugs consistent with BOOP. The ticlopidine therapy was stopped. Prednisone was continued. The dyspnoea and blanching cutaneous lesions improved. Shortness of breath with exertional activities disappeared in 3 months and the interstitial radiographic pattern had resolved at 5 months.

L-tryptophan

L-tryptophan has been used as a dietary supplement usually with no adverse reactions at a small daily dose. A report described a 51-year-old woman who had taken 2668 mg daily for 2.5 months and was admitted to hospital because of fever, weakness, nausea, productive cough and bilateral crackles.⁵⁸ The chest radiograph showed bilateral infiltrates, and the open lung biopsy showed granulation tissue plugs in the bronchioles, alveolar ducts and adjacent alveoli consistent with BOOP. Treatment with intravenous methylprednisolone resulted in prompt resolution of symptoms and clearing of the chest radiographic abnormalities.

Illicit use of cocaine

The use of freebase cocaine was described as the cause of BOOP in a 1987 report.⁵⁹ A 32-year-old man had 10 days of

fever, unproductive cough and shortness of breath. He had bilateral crackles. The chest radiograph showed bilateral nodular opacities. An open lung biopsy showed granulation tissue in the bronchioles and alveoli consistent with BOOP. He received corticosteroid therapy for 6 months with resolution of the chest radiograph findings.

Intravenous use of heroin

A 24-year-old woman with 7 years of active intravenous heroin use developed progressive shortness of breath. A chest CT scan showed dense bilateral ground-glass opacities, and a lung biopsy showed patchy, temporally homogeneous pneumonia with intraluminal fibroblastic proliferation consistent with BOOP.⁶⁰ After cessation of heroin, respiratory symptoms subsided without corticosteroid therapy and follow-up chest CT scan showed marked improvement.

Fluvastatin

The statins may cause a BOOP reaction as shown by a report of a 66-year-old woman who had 3 weeks of progressive shortness of breath.⁶¹ She had taken fluvastatin for 1 year prior to the onset of dyspnoea. She had bilateral crackles and a chest CT scan showing bilateral patchy consolidations. Transbronchial biopsy showed organizing pneumonia and proliferating fibroblasts extending along and branching within alveolar ducts. She had a favourable response with prednisone after cessation of the fluvastatin. She developed new-onset shortness of breath and linear opacities at the lung basis. A biopsy showed UIP. There was sustained improvement with azathioprine and prednisone therapy without a relapse.

Risedronate

The drug lymphocyte stimulation test (DLST) can be useful for the diagnosis of drug-related BOOP. Risedronate is used for the treatment of osteoporosis by inhibiting osteoclast resorption. A 66-year-old woman was given risedronate for osteoporosis and 2 months later developed fever, unproductive cough and a chest radiograph showing bilateral patchy infiltrates. The chest CT scan showed several ground-glass opacities and a large, pleural triangular-based infiltrate in the left mid lung.⁶² A transbronchial lung biopsy showed cellular alveolitis with intraluminal polypoid organization consistent with BOOP. All of the drugs were stopped. The fever resolved after 5 days and the radiographic infiltrates disappeared 2 weeks later. A drug lymphocyte stimulation test on her peripheral lymphocytes gave a positive reaction to risedronate with a stimulation index of 265 per cent and negative reaction to the other four drugs, all of which had been administered to her for at least 4 years.

BOOP AFTER BREAST IRRADIATION

Post-breast-radiation BOOP has emerged as an important iatrogenic development as this lesion may occur in up to 2.3 per cent of women (Fig. 24.2).

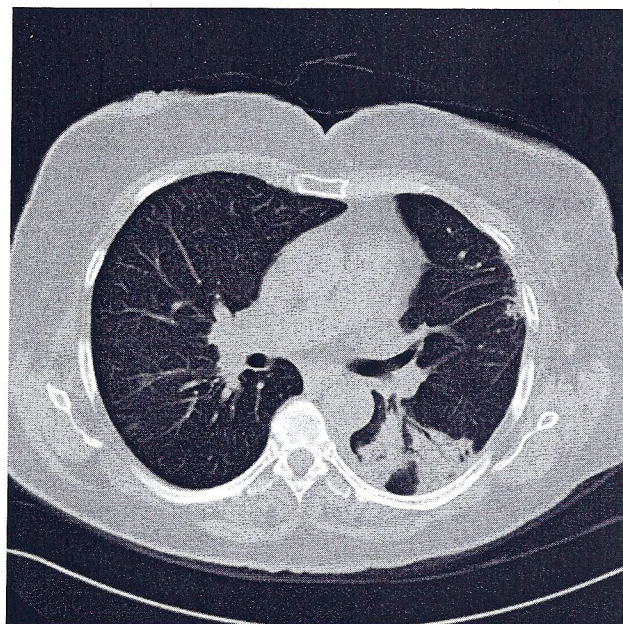


Fig. 24.2 Chest CT scan of a 46-year-old woman who had radiation for a left breast carcinoma. There is subpleural peripheral fibrosis in the left upper lung secondary to the radiation, and BOOP as a right mid-lung ground-glass opacity with air bronchograms. The BOOP resolved rapidly with prednisone therapy.

In a 1997 report, Van Laar *et al.* reported two women who developed BOOP after receiving adjuvant radiotherapy for breast carcinoma.⁶³ Both patients were treated with prednisone 60 mg daily, leading to rapid and dramatic clinical improvement of symptoms and infiltrative abnormalities with no subsequent relapse. A later report showed that symptoms may occur 1–12 months after completion of radiation therapy, and the chest X-ray shows peripheral patchy or alveolar infiltrates often outside of the radiation field.⁶⁴ In a 2000 report of 11 patients, Majori *et al.* reported spontaneous migration of infiltrates from the irradiated lung to the contralateral non-irradiated lung.⁶⁵ There can be a dramatic improvement with corticosteroid therapy, but relapses do occur.^{64,66} Some investigators have suggested that radiation therapy may ‘prime’ the development of BOOP.^{64,65} Bronchoalveolar lavage studies of these patients indicated an increase in lymphocytes, mast cells, CD3 cells and CD8 cells, and a decrease in CD4 cells and the CD4/CD8 ratio.⁶⁵

In a 2008 Japanese study, Ogo *et al.* reported a 1.8–2.19 per cent incidence of BOOP among 2056 women receiving radiation therapy for breast carcinoma.⁶⁷ Most developed BOOP within 6 months of therapy. Cough, fever and sputum were the most common symptoms. They showed that the ground-glass opacities were unilateral in 70 per cent and often occurred outside of the radiation field. They found the BOOP resolved in 20 per cent of patients who received no medication. In another 2008 study of 702 women, 16 individuals (2.3 per cent) developed post-radiation BOOP.⁶⁸ Risk factors included age ≥ 50 and women who had received concurrent endocrine therapy, while tamoxifen was not found to be a risk factor. The mean latency of BOOP was 4.4 months after the end of radiation therapy (range 2.3–7.9). The lesion was radiographically unilateral in the majority, occurring in 10 patients. All 16 patients

improved, 5 without corticosteroid therapy; and among the others, corticosteroid therapy was used for between 1–3 weeks and 3.7 years, with a median of 1.1 years. Cataracts developed in two women on long-term therapy.

One case report showed a 71-year-old woman who completed right-sided breast radiation and developed a fever, sweats and unproductive cough 9 months later.⁶⁹ A chest CT scan showed a dense infiltrate with air bronchograms in the right mid-lung. Bronchoscopy lung biopsy showed BOOP. There was a dramatic resolution of symptoms within a week, and 3 weeks later the chest CT scan showed complete resolution.

A case report has described the recurrence of BOOP after low-dose breast cancer radiation in a woman with BOOP 1 year earlier.⁷⁰ Another 51-year-old woman developed idiopathic BOOP that was successfully treated with prednisone. Five months later she was found to have left-sided breast cancer, and intensity-modulated radiotherapy (IMRT) was begun to the left breast while she was taking prednisone 5 mg every other day and concluded after 25 treatments. Two months after completion of radiation therapy she developed cough. The chest CT scan showed a peripheral triangular ground-glass opacity with an air bronchogram in the left mid-lung. Prednisone was begun. No new respiratory symptoms developed and the CT scan showed improvement.

In conclusion, BOOP may occur as frequently as 2.3 per cent among women after breast radiotherapy and may resolve through monitoring without therapy or through treatment with corticosteroid therapy.

KEY POINTS

- BOOP is an inflammatory lung process and there are more than 35 medications associated with its development. Radiation therapy can also trigger BOOP.
- Fever, unproductive cough and progressive shortness of breath are common symptoms.
- Bilateral crackles occur in most individuals. Eosinophilia rarely occurs. The chest radiograph shows bilateral patchy infiltrates, and chest high-resolution CT (HRCT) shows ground-glass opacities and air bronchograms.
- There is a suggestion that drugs such as amiodarone or statins may cause the newly described entity name afop.⁷¹
- Although in very rare situations the outcome may be fatal, the prognosis is usually excellent, with complete resolution of the BOOP with cessation of the medication or a brief course of corticosteroid therapy.

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Drug-induced and Iatrogenic Respiratory Disease

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