

# Bronchiolitis obliterans organizing pneumonia after radiation therapy for lung cancer: a case report

Lorenzo Falcinelli<sup>1</sup>, Rita Bellavita<sup>1</sup>, Alberto Rebonato<sup>2</sup>, Rita Chiari<sup>3</sup>, Jacopo Vannucci<sup>4</sup>, Francesco Puma<sup>4</sup>, Cynthia Aristei<sup>5</sup>

<sup>1</sup>Radiation Oncology Division, Perugia General Hospital, Perugia - Italy

<sup>2</sup>Radiology Section, Department of Surgical and Biomedical Sciences, University of Perugia and Perugia General Hospital, Perugia - Italy

<sup>3</sup>Medical Oncology Section, Perugia General Hospital, Perugia - Italy

<sup>4</sup>Thoracic Surgery Unit, Department of Surgical and Biomedical Sciences, University of Perugia and Perugia General Hospital, Perugia - Italy

<sup>5</sup>Radiation Oncology Section, Department of Surgical and Biomedical Sciences, University of Perugia and Perugia General Hospital, Perugia - Italy

## ABSTRACT

Bronchiolitis obliterans organizing pneumonia (BOOP), also known as cryptogenic organizing pneumonia, has mainly been described in patients with breast cancer who received radiotherapy after breast-conserving surgery. In this rare case, a 70-year-old man with left apical squamous lung cancer developed BOOP after radiotherapy and only one cycle of concomitant chemotherapy.

This case report draws attention to the development of this syndrome in the unusual setting of lung cancer, advising prompt steroid treatment when diagnostic images reveal the characteristic signs of the disease.

**Keywords:** Bronchiolitis obliterans organizing pneumonia, Cryptogenic organizing pneumonia, Interstitial lung disease, Lung cancer, Radiation therapy, Side effects

## Introduction

Bronchiolitis obliterans organizing pneumonia (BOOP), or cryptogenic organizing pneumonia, has been almost exclusively reported after radiotherapy (RT) in a very small minority of women who received breast-conserving surgery (1, 2). It is characterized by respiratory symptoms such as flu-like illness with or without cough and bronchial crackles (3, 4) and peculiar radiographic lesions such as patchy and ground-glass opacity extending to nonirradiated parenchyma (1, 5, 6). Polypoid fibrino-inflammatory granulation tissue is also observed and eosinophil, neutrophil, and lymphocyte counts are increased in bronchoalveolar lavage fluid.

Although BOOP is unusual in patients with lung cancer who receive RT (7), it has been observed after chemotherapy or treatment with targeted therapies (8). Here we describe a rare case of BOOP in a patient with lung cancer with onset after RT and only one cycle of concurrent chemotherapy.

## Case report

A 70-year-old man with a long history of smoking (15-20 cigarettes daily for 50 years) developed left arm pain that did not respond to analgesics. His performance status was good (90% according to Karnofsky) and he had no relevant comorbidities. After 4 months, a chest X-ray showed an opaque area in the upper left field and a computed tomography (CT) scan detected a 4-cm lesion at the left lung apex, infiltrating the clavicle. Disease extent was confirmed by positron emission tomography/CT (PET-CT). Since there was no radiographic or metabolic evidence of pathologic lymphadenopathy, the disease stage was cT4N0M0.

Spirometry showed that FEV<sub>1</sub> was 78% and hemogas analysis indicated a high pH, normal pCO<sub>2</sub>, and high bicarbonates (pH = 7.45, pCO<sub>2</sub> = 37.5 mm Hg, HCO<sub>3</sub><sup>-</sup> = 26.4 mmol/L), suggesting metabolic alkalosis due to respiratory distress.

Biopsy findings in a sample obtained during bronchoscopy indicated squamous carcinoma (cytokeratine 7+, TTF1-, napsin-, P63+).

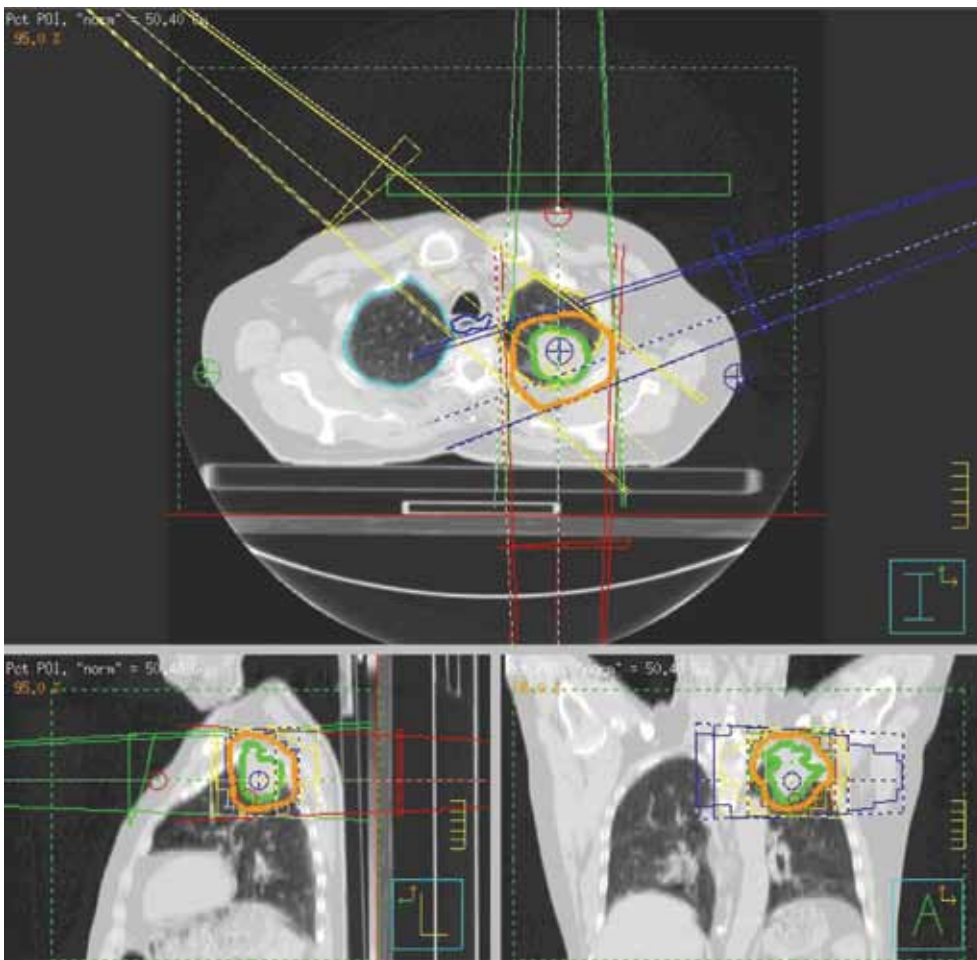
As the disease was nonoperable, neoadjuvant treatment was started with RT and concurrent chemotherapy (cisplatin 80 mg/mq and etoposide 80 mg/mq every 28 days). Only 1 cycle of chemotherapy was administered because of acute grade 3 fatigue and grade 2 thrombocytopenia according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.0; 2010) (9). Radiotherapy was administered according to a 3-dimensional conformal technique. Regions of interest were contoured on CT scan images, acquired without contrast medium. Gross tumor volume measured 54.77 cm<sup>3</sup>,

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## Corresponding author:

Lorenzo Falcinelli  
Radiation Oncology Division  
Perugia General Hospital  
Perugia, Italy  
falcinellil@libero.it



**Fig. 1** - Treatment plan: isodoses distribution around neoplastic lesion.

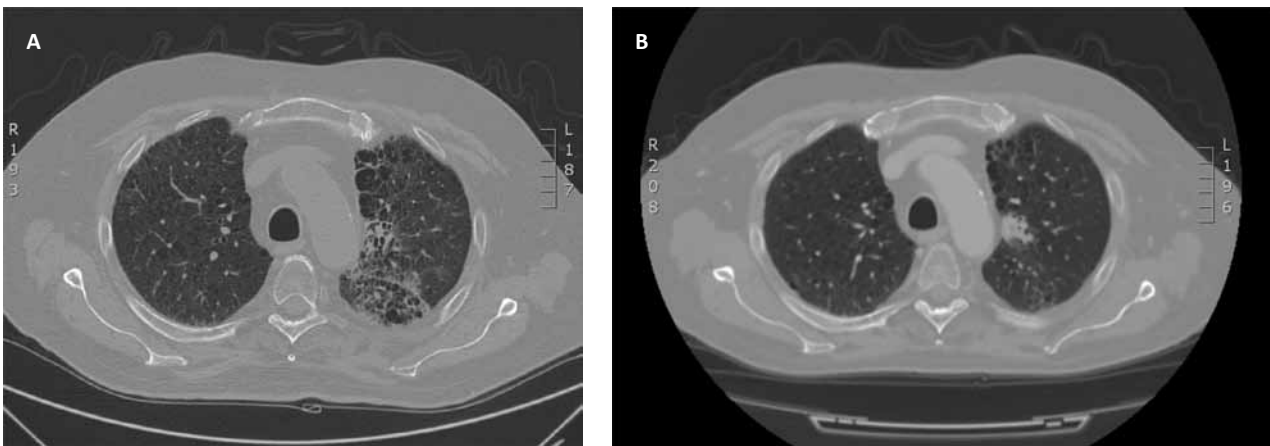
planning tumor volume 170.19 cm<sup>3</sup>, right lung volume 1618.27 cm<sup>3</sup>, and left lung volume 1373.24 cm<sup>3</sup>. Dose constraints were assessed for all organs at risk. Lung constraints were  $V_{30} = 0\%$  and  $V_{20} = 2\%$  for right lung,  $V_{30} = 16\%$  and  $V_{20} = 20\%$  for left lung, and  $V_{30} = 4\%$  and  $V_{20} = 8\%$  for total healthy lung. The total dose of 50.4 Gy (10) was administered in 28 fractions (5 days a week for 5.5 weeks). Figure 1 illustrates isodoses distribution around the neoplastic lesion. The patient continued smoking throughout the treatment period.

During RT, the patient did not report any treatment-related symptoms. Four weeks after RT ended, while waiting for surgery, his clinical condition deteriorated markedly, with fatigue, dry cough, dyspnea at rest, and a confused mental state. Upon hospital admission, arterial blood analysis showed hypoxemia ( $\text{SatO}_2 = 77\%$ ). A chest X-ray detected widespread interstitial reticular infiltrates with bilateral alveolar involvement. A CT scan showed the primary tumor was slightly reduced in size. Bilateral interstitial pneumonia was present with honeycombing lung, widespread ground-glass opacities, and small dense areas in the parenchyma, outside the RT volume (Fig. 2). As clinical and radiologic patterns indicated BOOP, a bronchoalveolar lavage was not performed. Therapy was started with oxygen through a Ventimask ( $\text{FiO}_2 60\%$ ) and methylprednisolone (40 mg 3 times daily). On day



**Fig. 2** - Diagnosis: Chest computed tomography scan with widespread ground-glass opacities and small nodular areas in the parenchyma.

+3 dyspnea and cough were reduced and  $\text{SatO}_2$  had risen to 90%. The patient was more lucid, suggesting his mental confusion had been caused by hypoxemia. On day +7, a chest



**Fig. 3 - (A)** 21 days after steroid treatment: chest computed tomography scan with minimal residual ground-glass opacities. **(B)** Three months after steroid treatment: chest computed tomography scan with no signs of bronchiolitis obliterans organizing pneumonia.

X-ray showed less reticular interstitial thickening. The primary tumor was unchanged. On day +21, a chest CT scan visualized marked improvement in both lungs, with only minimal residual ground-glass opacities (Fig. 3A). Spirometry indicated  $FEV_1 = 52\%$ ,  $SatO_2 = 92\%$ .

The patient was discharged from the hospital. No surgery was scheduled because of his poor lung function. On day +90, a CT scan showed no signs of interstitial pneumonia (Fig. 3B) but local and systemic progression of the primary tumor. Spirometry results were better ( $FEV_1 = 73\%$ ,  $SatO_2 = 94.5\%$ ). Corticosteroid therapy was continued up to 6 months. The patient died of disease progression 11 months after BOOP diagnosis.

## Discussion

The most common side effect of RT to the lung is radiation pneumonitis with onset in irradiated parenchyma and risk linked to the dose delivered to the ascertained healthy lung volume (11).

We did not expect radiation pneumonitis to develop in our patient since the RT dose was administered to a restricted lung area and the RT plan met all lung dose constraints. Furthermore, chest X-rays and CT findings showed the affected areas extended beyond the area that had been irradiated. Consequently, symptoms, X-rays, and CT findings led us to diagnose BOOP and to start steroid therapy, to which the patient responded rapidly, confirming the diagnosis.

Bronchiolitis obliterans organizing pneumonia is a rare syndrome (1, 12). First described by Epler et al (5) in 1985 in a heterogeneous group of patients, it is a flu-like illness with or without cough and bronchial crackles, lasting for 4-10 weeks (3, 4). As in our patient, chest X-rays and CT scans show, in both lungs, peculiar patchy areas of ground-glass densities and migratory, peripheral air-space infiltrates, extending to nonirradiated parenchyma (1, 5, 6). Polypoid fibrino-inflammatory granulation tissue is also observed, extending from the bronchioles into adjacent alveoli, where pneumonia develops. Eosinophil, neutrophil, and lymphocyte counts are increased in bronchoalveolar lavage fluid. The etiology of BOOP

is unknown. Although most cases are idiopathic, connective tissue disease (13), drugs (8, 14-17), infection (18, 19), toxic inhalation (20), and RT have been proposed as causes. In BOOP, RT (21, 22) is hypothesized to activate pulmonary lymphocytes, leading to immunologic and hypersensitivity reactions in the nonirradiated lung. As our patient actively smoked during radiation treatment, he was at higher risk than a nonsmoker of developing interstitial lung disease, but we are unable to link smoking with BOOP development.

The present case of BOOP after RT in a patient with lung cancer is unusual. The disease was almost exclusively reported in a very small minority of women who received RT after breast-conserving surgery (1, 2) in whom concomitant risk factors might be hormonal therapy and age over 50 years (1).

Although the incidence of BOOP may be low because lung cancer is less frequent than breast cancer, BOOP may be mistakenly diagnosed as the more frequently observed and better known radiation pneumonitis in patients with lung cancer, thus leading to an underestimated incidence. We agree with Crestani et al (3), who hypothesized in 1995 that BOOP development depended on how much pleural tissue was irradiated, which is a wide area in patients with breast cancer because RT uses tangential fields. Although this does not usually happen during irradiation for lung cancer, our patient received extensive pleural irradiation because the lesion was located in the lung apex.

As observed in our patient, BOOP responds well to systemic steroid therapy, which rapidly resolves symptoms and normalizes radiologic patterns. Even though BOOP and its adverse effects cannot be prevented, members of the multidisciplinary team who are involved in care of patients with lung cancer should be aware of the syndrome, recognize the signs on images, and realize prompt steroid treatment is urgently needed. Therapy needs to be protracted even for up to a year (2, 21), to reduce the risk of recurrence.

## Disclosures

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Conflict of interest: None.

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