# Cryptogenic organizing pneumonia after radiotherapy for breast cancer

## Polmonite organizzativa criptogenetica dopo radioterapia per cancro della mammella

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**ABSTRACT**

**We report a case of fever, dyspnea, respiratory failure and migratory, recurrent and bilateral lung opacities 4 months after radiotherapy and hormone therapy following surgery for breast cancer. Computerized tomography (CT) scans showed infiltrates outside the radiation fields. Bronchoalveolar lavage revealed lymphocytic alveolitis, whereas laboratory analysis demonstrated a mild systemic inflammation. Systemic steroids resulted in clinical and radiological improvement, but a disease relapse was evident at withdrawal of therapy, with definitive clinical and radiological normalization after a second cycle of therapy. This is a case of cryptogenic organizing pneumonia (COP) (previously known as bronchiolitis obliterans organizing pneumonia) primed by radiotherapy, as in previously reported cases. It is extremely important to be aware of the possibility of this complication, in order to optimize radiation and hormone treatment of breast cancer.**

**Keywords:** **Breast cancer, lung function, radiation-primed COP, radiotherapy.**

**RIASSUNTO**

**Descriviamo un caso di febbre, dispnea, insufficienza respiratoria e opacità polmonari migranti, ricorrenti bilateralmente, insorte 4 mesi dopo radioterapia in una paziente sottoposta a radioterapia post-chirurgica e in corso di ormonoterapia per cancro della mammella.**

**La TAC del torace dimostrava la presenza di infiltrati polmonari al di fuori del campo di irradiazione. Il lavaggio bronco-alveolare documentava la presenza di alveolite linfocitaria, mentre gli esami di laboratorio evidenziavano una modesta infiammazione sistemica. La somministrazione di corticosteroidi ad alte dosi *per os* determinava un miglioramento clinico e radiologico, ma la sospensione della terapia steroidea coincideva con una ripresa della malattia. Dopo un secondo ciclo di terapia si aveva la definitiva normalizzazione del quadro clinico e radiologico. Questo è un caso di polmonite organizzativa criptogenetica (precedentemente indicata con il termine di polmonite organizzativa con bronchiolite obliterante) indotta dalla radioterapia, così come riportato precedentemente in altri casi. È molto importante tenere presente la possibilità di questa complicanza per ottimizzare il trattamento radioterapico e ormonale del cancro della mammella.**

**Parole chiave:** **Cancro della mammella, COP indotta da radioterapia, funzione respiratoria, radioterapia.**

### INTRODUCTION

Radiotherapy represents a cornerstone of the treatment of breast cancer. In the past, the less advanced technology was the cause of severe damage to surrounding tissues in the breast, lung and chest wall. Today the planning of irradiation fields guarantees the near total absence of collateral effects, in particular pneumonia and fibrosis induced by radiotherapy [1].

Radiation-induced pneumonia occurs classically 4 to 12 weeks after the radiotherapy and is characterized by fever, dry cough, dyspnea and alveolar opacities confined to the treatment port [2]. However, bilateral lymphocytic alveolitis develops in both lungs after strictly unilateral breast irradiation and it presents with the histological, radiological and clinical pattern of bronchiolitis obliterans organizing pneumonia (BOOP), now currently defined as cryptogenic organizing pneumonia (COP) [3].

COP is a distinct clinico-pathological entity in the wide family of pulmonary fibrosis, and is characterized by patchy and often migratory peripheral air

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space infiltrates on chest radiography [4,5]. COP has been associated with radiotherapy for breast cancer in some case reports, and it has been defined as "radiation-primed COP" [6].
Corticosteroid treatment in COP results in rapid clinical improvement of clinical symptoms and clearing of the opacities on chest imaging without sequelae. Although the efficiency of steroids in COP has long been established, the precise dose, the duration of treatment, the use of boluses and the withdrawal have not been defined in radiation-primed COP [7,8].
We report a case of COP after radiotherapy for breast cancer, presenting with fever, dyspnea, respiratory failure and bilateral pneumonia. The disease was successfully treated with systemic steroids but relapsed after the steroid withdrawal, and was definitively resolved after a second steroid course.
This case emphasizes the importance of taking into account the possible occurrence of radiation-primed COP, and clarifies why only few women become affected with this disease after radiotherapy, what the optimal dose and duration of treatment should be, and if (and, if so, which) respiratory function tests can predict this complication.

## CASE REPORT

A 62-year-old woman was admitted to our outpatient clinic with a 2-week history of fever, dyspnea and dry cough. Her chest radiography revealed pneumonia in the left lower lobe, already treated with antibiotics without benefit. She had undergone left mastectomy 1 year earlier, and subsequent adjuvant radiation treatment after the surgery for 50 days. In addition, immediately after the surgical procedure she had been given therapy with anastrozole (Arimidex©), that was still in course at the onset of symptoms. Computerized tomography (CT) scan showed a pulmonary infiltration with ground glass opacities in the left lower lobe outside the irradiation fields, diagnosed as pneumonia (Figure 1). Biochemical analysis revealed no abnormalities, except for elevated levels of C-reactive protein (CRP) (18 mg/dl), and the arterial blood gas analysis showed a mild hypoxemia ($PaO_2$ 68 mm Hg, $PaCO_2$ 31 mm Hg, pH 7.43, $FiO_2$ 21%).
The initial treatment was based on antibiotics for the clinical diagnosis of pneumonia, but clinical symptoms of dry cough and dyspnea persisted. Given the ineffectiveness of prolonged antibiotic therapy, a fiberoptic bronchoscopy was performed with bronchoalveolar lavage (BAL) and transbronchial biopsy (TBBx). The BAL fluid revealed a mild lymphocytic alveolitis (total cell count: 840/µL; lymphocytes: 15%; macrophages 84%; neutrophils 1%; CD4+/CD8+ T-lymphocyte ratio: 1.1). TBBx was not diagnostic, and no malignant cells or pathogenic bacteria were discovered in the BAL fluid. Pulmonary function tests showed a mild restrictive defect with reduction of CO-transfer: forced vital capacity (FVC) 82% of predicted value (pred.), forced expiratory volume in 1 sec ($FEV_1$) 78% pred., lung diffusion capacity for carbon monoxide ($DL_{CO}$) 67% pred., KCO 82% pred.
Based on clinical, radiographic and laboratory data, radiation-primed COP was diagnosed and a treatment with systemic steroids was started at the dose of 1 mg/kg of body weight with tapering to half dose every 4 weeks (total duration of treatment 22 weeks). The CT scan, pulmonary function tests, blood gas analysis and CRP at 12 weeks after the start of steroids were all normalized.
Four weeks after steroid withdrawal, the patient began to complain again of dry cough and dyspnea. A new CT scan revealed newly formed opacities in the upper right and in the middle lobes (Figure 2). The patient underwent an identical treatment with systemic steroids, that resulted in an immediate improvement of symptoms, that persisted after 6 and 12 months. A complete normalization of CT images, pulmonary function tests (FVC 94% pred., $FEV_1$ 90% pred., $DL_{CO}$ 84% pred., KCO 92% pred.), CRP value (0.5 mg/dl) and blood gas analysis ($PaO_2$ 72 mm Hg, $PaCO_2$ 39 mm Hg, pH 7.40, $FiO_2$ 21%) was present at 12 months of follow up.

**FIGURE 1: COMPUTERIZED TOMOGRAPHY (CT) SCAN AT FIRST OCCURRENCE OF SYMPTOMS**

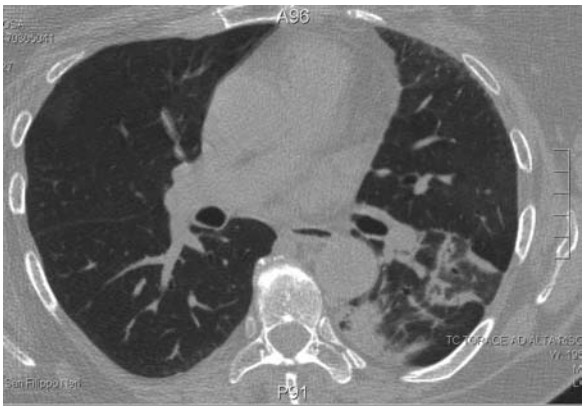
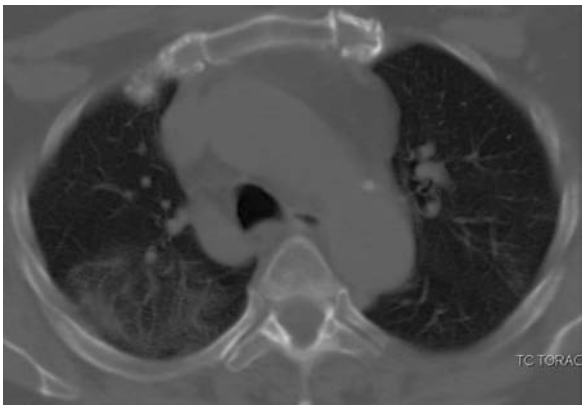


**FIGURE 2: SECOND CT SCAN AT THE RELAPSE OF DISEASE**



## DISCUSSION

Reports of COP related to radiotherapy in breast cancer, in the form of case reports or literature analysis [9,10], date back to 15 years ago. COP is very similar to radiation pneumonia, but it involves lung segments that are far from the radiation field. Patients who undergo radiation therapy to the breast may present alveolar lymphocytosis, even if they do not develop pneumonia. The negative effects of radiotherapy are well documented in the literature (Table 1), but the histological and clinical pattern of radiation-primed COP in the lung seems to depict a distinct entity, with the epidemiological data, diagnostic and therapeutic algorithm not well defined yet. The prevalence of radiation-primed COP ranges between 2.5% and 1.8% [11-13], but, to our knowledge, there are no Italian or more local data available, that could be very useful to clarify the influence of differences in radiation method, dosing, and collimation on the occurrence of this pulmonary complication.

The primary role of pleural factors has been described in one sole report [9] but not confirmed in an analysis of the recent literature [8]. Currently, an immunological mechanism is thought to be at the base of the disease development, as in hypersensitivity pneumonitis: irradiation provokes a tissue damage with sensitization of autoreactive lymphocytes, which react with pulmonary tissues [14]. However, it is also possible that lymphocytes are not the key cells in the pathogenesis of radiation primed COP; mast-cells could play a role, as in idiopathic COP and hypersensitivity pneumonia caused by inhaled antigens [15]. In addition, some studies [16] have shown that radiotherapy induces gene activation and transcription, cytokine release and fibroblasts activation. The cause of the migratory pattern and involvement of lung tissue away from the radiation fields remains unclear.

Therefore, the role of diagnostic methods like bronchoscopy with BAL appears essential and well defined to identify the alveolar pattern of lung involvement. Not equally defined is the role of TBBx, because a specific histological pattern has never been reported. From a clinical point of view, we limited the invasive procedures to TBBx due to the first result of absence of malignant cells or specific bacterial results, and the fast response to treatment.

Considering how many women undergo surgery and radiotherapy for breast cancer, radiation-primed COP is not so common, and probably different individual elements and/or factors related to the dose and length of radiation therapy are implicated in the occurrence and progression of this pulmonary complication.

A general review of the literature by Cordier [8] shows that the modifications of pulmonary function tests are generally mild or moderate, frequently consisting in a restrictive defect, even if an obstructive pattern can be present in patients with smoking habit or affected by chronic obstructive pulmonary disease. However, since the second half of the 1980s no report has clarified the changes of lung volume, blood gas analysis or CO-transfer factor during COP, nor the possible risk patterns of lung damage detectable before the breast surgery and

**TABLE I: SYNOPSIS OF THE LITERATURE ON COLLATERAL EFFECTS OF RADIOTHERAPY**

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|---|---|---|---|---|---|
| Lung | Pneumonia | 1-3 months (acute)<br>12-15 months (late) | 30 Gy | Mosvas et al. | Chest 1997;111:1061 |
| | Necrosis | 12 months (1-7 years for cavitations) | > 60 Gy | | |
| | Pneumothorax | 16 months | > 30 Gy | Penniment et al. | Thorax 1994;49:936 |
| Breast | COP | 6 wk to 10 months | no minimal dose defined | Crestani et al. | ERJ 1995;8:318 |
| Lymph nodes | Calcifications | 12 months | no minimal dose defined | Bereton et al. | Radiology 1974;112:705 |
| Esophagus | Stricture | 3-18 months | 60 Gy | Lepke et al. | Radiology 1993;148:375 |
| Vascular tree | Stenosis or occlusion | 10-15 years | Aorta and pulm. artery 24-44 Gy<br>Subclavian 40-60 Gy | Fajardo et al. | Pathol Ann 1988;23:297 |
| Heart | Coronary artery disease | 10-15 years | > 30 Gy age < 20 | Kopelson et al. | Int J Radiat Oncol Biol Phys 1978;4:895 |
| | Pericarditis | 12-48 months | 40 Gy | Applefeld et al. | Ann Intern Med 1981;94:338 |
| | Conduction abnormalities | 10 years | 40 Gy | Cohen et al. | Arch Intern Med 1981;141:676 |
| Chest wall | Sarcoma | > 5 years | no minimal dose defined | Libshitz | Semin Roent 1994;29:15 |
| | Rib fractures | > 12 years | 50 Gy | Pierce et al. | Int J Radiat Oncol Biol Phys 1992;23:915 |
| | Breast carcinoma | 15-19 years | > 20 Gy age < 35 | Bhatia et al. | NEJM 1996;334:745 |

radiotherapy.
Katayama et al. [17] showed a relation between radiation-primed COP and hormone therapy with tamoxifen, anastrozole and toremifen, reporting a significant association (OR 3.12, 95% CI 1.12-8.68, p = 0.03). Our patient received anastrozole, but it was interrupted at the first occurrence of respiratory symptoms. However, it is rather difficult to precisely determine the influence of the withdrawal of this drug on the occurrence of the pulmonary complication, and alternatively on the outcome of the breast cancer.
It seems really important to know which drugs represent a real risk factor for this complication, when they are able to exert a significant role and why this disease occurs in only few patients, with a reported greater incidence in subjects aged more than 50 years [17].
In radiation-primed COP, as in other unknown diseases, therapy with systemic steroids is effective even if relapses are described after withdrawal [6]. The doses of systemic steroids range from 0.5 to 1 mg/kg of body weight a day, but due to the serious unwanted effects of these drugs, like diabetes and osteoporosis, especially in elderly women, the literature is not updated about the lowest effective dose that can be used and the timing of dose tapering.
This case report shows a postmenopausal woman submitted to surgery and radiotherapy and successively to hormone-therapy for breast cancer. The patient presented symptoms of fever, dry cough and dyspnea 4 months after radiotherapy; radiological signs resembled pneumonia; BAL was suggestive of lymphocytic alveolitis; all therapies were ineffective, but systemic steroids induced the complete resolution of lung opacities and symptoms. This case, by and large, is similar to previous case reports.
However, to date, radiation primed COP still remains unclear, with unknown causes, risk factors, role and timing of non invasive diagnostic tests, e.g. pulmonary function tests, and of invasive tests such as bronchoscopy with BAL and TBBx, except for the possibility of excluding a diagnosis of cancer or tuberculosis.
Thus, we think it would be very useful to obtain epidemiological data about all women undergoing surgery and radiotherapy for breast cancer, to reveal possible relationships between radiation, hormone-therapy, and individual factors, in particular concerning the respiratory function before and during the treatment.

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## References

1. Davis SD, Yankelevitz DF, Henschke CI. Radiation effects on the lung: clinical features, pathology and imaging findings. AJR Am J Roentgenol 1992;159:1157-1164.
2. Cherniack RM, Abrams J, Kalica AR. NHLBI Workshop summary. Pulmonary disease associated with breast cancer therapy. Am J Respir Crit Care Med 1994;150:1169-1173.
3. Roberts CM, Foulcher E, Zaunders JJ, Bryant DH, Freund J, Cairns D, Penny R, Morgan GW, Breit SN. Radiation pneumonitis: a possible lymphocyte-mediated hypersensitivity reaction. Ann Intern Med 1993;118;696-700.
4. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000;161:646-664.
5. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 2002;165:277-304.
6. Akita K, Ikawa A, Shimizu S, Tsuboi K, Ishihara K, Sato S, Ueda R. Cryptogenic organizing pneumonia after radiotherapy for breast cancer. Breast Cancer 2005;12:243-247.
7. Lazor R, Vandevenne A, Pelletier A, Leclerc P, Court-Fortune I, Cordier JF. Cryptogenic organizing pneumonia. Characteristics of relapses in a series of 48 patients. The Groupe d'Etudes et de Recherche sur les Maladles "Orphelines" Pulmonaires (GERM"O"P). Am J Respir Crit Care Med 2000;162:571-577.
8. Cordier JF. Cryptogenic organising pneumonia. ERJ 2006;28:422-446.
9. Crestani B, Valeyre D, Roden S, Wallaert B, Dalphin JC, Cordier JF. Bronchiolitis obliterans organizing pneumonia syndrome primed by radiation therapy to the breast. The Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires (GERM"O"P). Am J Respir Crit Care Med 1998;158:1929-1935.
10. Bissoli L, Di Francesco V, Valbusa F, Zivelonghi A, Fantin F, Zamboni M. A case of bronchiolitis obliterans organising pneumoniae (BOOP) after nine months post-operative irradiation for breast cancer. Age Ageing 2008;37:235.
11. Takigawa N, Segawa Y, Saeki T, Kataoka M, Ida M, Kishino D, Fujiwara K, Ohsumi S, Eguchi K, Takashima S. Bronchiolitis obliterans organizing pneumonia syndrome in breast-conserving therapy for early breast cancer: radiation-induced lung toxicity. Int J Radiat Oncol Biol Phys 2000;48:751-755.
12. Ogo E, Komaki R, Fujimoto K, Uchida M, Abe T, Nakamura K, Mitsumori M, Sekiguchi K, Kaneyasu Y, Hayabuchi N. A survey of radiation-induced bronchiolitis obliterans organizing pneumonia syndrome after breast conserving therapy in Japan. Int J Radiat Oncol Biol Phys 2008;71:123-131.
13. Miwa S, Morita S, Suda T, Suzuki K, Hayakawa H, Chida K, Nakamura H. The incidence and clinical characteristics of bronchiolitis obliterans organizing pneumonia syndrome after radiation therapy for breast cancer. Sarcoidosis Vasc Diffuse Lung Dis 2004;21:212-218.
14. Nakayama Y, Makino S, Fukuda Y, Min KY, Shimizu A, Ohsawa N. Activation of lavage lymphocytes in lung injuries caused by radiotherapy for lung cancer. Int J Radiat Oncol Biol Phys 1996;34:459-467.
15. Majori M, Poletti V, Curti A, Corradi M, Falcone F, Pesci A. Bronchoalveolar lavage in bronchiolitis obliterans organiz-

ing pneumonia primed by radiation therapy to the breast. J Allergy Clin Immunol 2000;105:239-244.
16. Brach MA, Hass R, Sherman ML, Gunji H, Weichselbaum R, Kufe D. Ionizing radiation induces expression and binding activity of the nuclear factor kappa B. J Clin Invest 1991;88:691-695.
17. Katayama N, Sato S, Katsui K, Takemoto M, Tsuda T, Yoshida A, Morito T, Nakagawa T, Mizuta A, Waki T, Niiya H, Kanazawa S. Analysis of factors associated with radiation-induced bronchiolitis obliterans organizing pneumonia syndrome after breast-conserving therapy. Int J Radiat Oncol Biol Phys 2009;73:1049-1054.