

CASE REPORT

Migratory organizing pneumonitis "primed" by radiation therapy

J-Y. Bayle*, P. Nesme*, F. Béjui-Thivolet**, R. Loire+, J.C. Guérin*, J.F. Cordier++

Migratory organizing pneumonitis "primed" by radiation therapy. J-Y. Bayle, P. Nesme, F. Béjui-Thivolet, R. Loire, J.C. Guérin, J.F. Cordier. ©ERS Journals Ltd 1995.

ABSTRACT: We report on two women presenting with cough and fever, 4 and 7 months, respectively, after starting breast radiation therapy following surgery for breast carcinoma. Chest roentgenogram and computed tomographic (CT) scan demonstrated alveolar opacities, initially limited to the pulmonary area next to the irradiated breast, but later migrating within both lungs. Intra-alveolar granulation tissue was found in transbronchial lung biopsies. Corticosteroid treatment resulted in dramatic clinical improvement, together with complete clearing of the pulmonary opacities on chest imaging. However, clinical and imaging relapses occurred when corticosteroids were withdrawn too rapidly; with further improvement when they were reintroduced.

The reported cases clearly differ from radiation pneumonitis. They were fairly typical of cryptogenic organizing pneumonitis, also called idiopathic bronchiolitis obliterans organizing pneumonia, with the exception of the radiation therapy, partially affecting the lung, which had been performed within the previous months. Since focal radiation therapy involving the lung may induce diffuse bilateral lymphocytic alveolitis, we hypothesize that this may "prime" the lung to further injury, leading to cryptogenic organizing pneumonitis.

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*Service de Pneumologie and **Laboratoire d'Anatomopathologie, Hôpital de la Croix Rousse, Lyon, France. +Laboratoire d'Anatomopathologie and ++Service de Pneumologie, Hôpital Cardiovasculaire et Pneumologique, Université Claude Bernard, Lyon, France.

Correspondence: J-Y. Bayle
Service de Pneumologie
Hôpital de la Croix Rousse
93, Grande Rue de la Croix Rousse
69317 Lyon cedex 04
France

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The management of breast carcinoma and various chest neoplasms is, partly or mainly, based on radiation therapy, which gives rise to thoracic complications involving lungs, pleura, and heart [1-3]. Radiation-induced lung injury may result in radiation pneumonitis and radiation fibrosis [4]. Usually, the onset of radiation pneumonitis occurs 2-6 months following the completion of the radiation therapy, but sometimes even earlier, after 2 weeks [1, 2]. The radiation pneumonitis-associated clinical syndrome is characterized by low-grade fever, dry cough, and dyspnoea on exertion. Imaging studies show patchy alveolar opacities, with an air bronchogram confined to the treatment port [5]. Histopathological findings are characterized by: 1) capillary congestion with thrombi; 2) alveolar filling with protein-rich fluid, alveolar cell debris, macrophages, neutrophils and lymphocytes; and 3) alveolar wall-thickening infiltrated by neutrophils and lymphocytes [2]. So far, the pathogenesis of radiation pneumonitis is not well understood. As pulmonary damage is usually limited to the radiation field, a direct lung tissue toxicity is undoubtedly involved. However, bilateral pneumonitis has occasionally been reported after unilateral irradiation [6, 7], and has been attributed to alveolitis induced by radiation therapy [8].

Cryptogenic organizing pneumonitis (COP), also called idiopathic bronchiolitis obliterans organizing pneumonia

(BOOP), is a clinicopathological syndrome associated with characteristic clinical and imaging features and pathological evidence of intraluminal granulation tissue within distal airspaces. Patients show a subacute course, with cough and dyspnoea, a biological inflammatory syndrome, and chest imaging typically revealing multiple alveolar opacities which are often migratory, either spontaneously or on relapse after initial resolution with corticosteroids [9].

We present two cases of migratory and relapsing organizing pneumonitis, occurring a few months after radiation therapy for breast cancer, suggesting that radiation to the lung plays a role in the development of organizing pneumonitis.

Case report

Patient No. 1

The patient, a 65 year old nonsmoking woman, underwent breast-conserving surgery (tumourectomy), on April 23 1992, for an *in situ* adenocarcinoma of the right breast. Receptors for oestradiol and progesterone were positive, and axillary lymph nodes normal. External radiation

therapy, using photon X, was given from May 18, 1992, for 5 weeks (2.5 Gy per fraction). The total irradiation dose received by the right breast was 50 Gy. The dosimetry curves, assisted by computed tomograms (CT), showed

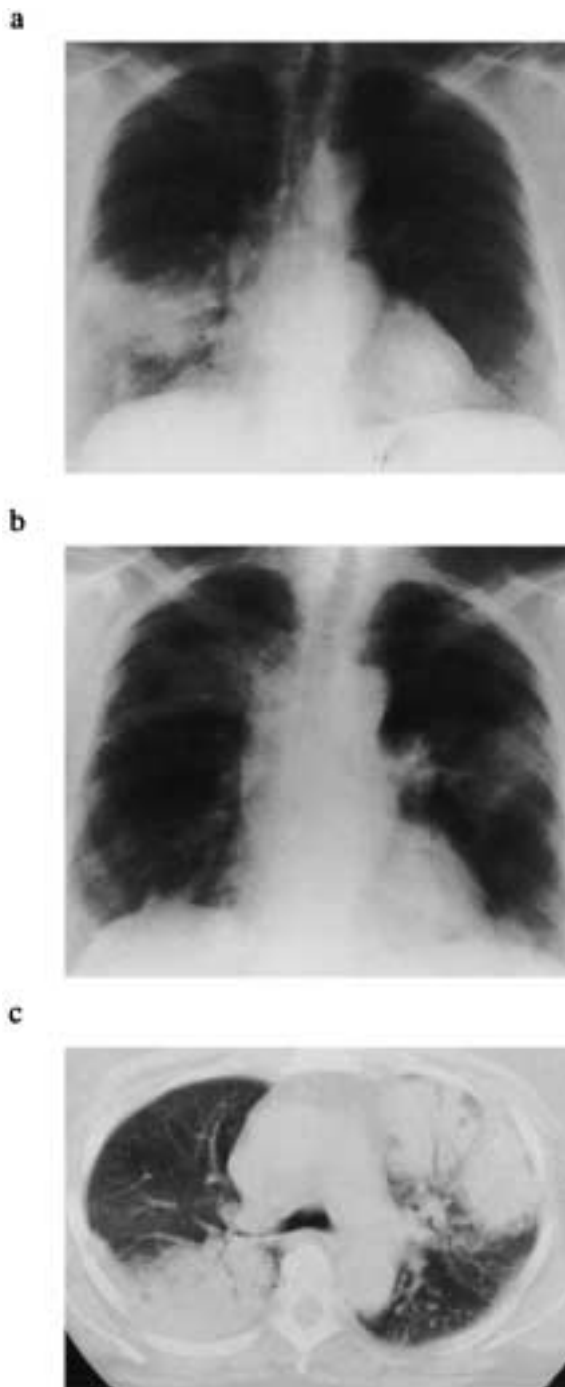


Fig. 1. — Radiological findings in patient No. 1: a) Three months after completion of radiation therapy, in September 1992, the first pneumonitis episode was associated with a segmental alveolar opacity in the right middle lobe on anteroposterior chest radiogram. The first relapse occurred a few days after steroid withdrawal, with a migration of pulmonary infiltrates to the right upper and left lingular lobes as displayed: b) on chest roentgenogram; and c) on lung computed tomographic (CT) scan in December, 1992; typical bronchograms are visible.

that 40% of the total radiation dose was given to a small subpleural slice of the right lung. A 20 mg daily dose of ciproteron acetate was introduced on September 3, 1992, and continued until the present time.

On September 5, 1992, 10 weeks after completion of the radiation therapy, the patient developed fever, dry cough, and progressive dyspnoea on exertion. On September 21, 1992, a chest roentgenogram showed the presence of an airspace consolidation in the right middle lobe (fig. 1a).

A combination of amoxycillin, clavulanic acid and ofloxacin was given for 10 days, and resulted in no clinical improvement. The patient was admitted on October 9, 1992, with unchanged complaints, and with alveolar opacities extending to the right upper lobe. Lung function tests showed that vital capacity (VC), forced expiratory volume in one second (FEV_1), total lung capacity (TLC) and carbon monoxide transfer coefficient (Kco) were normal: VC 106% predicted (pred); FEV_1 98% pred; FEV_1/VC 79%; TLC 96% pred; Kco 107% pred. Arterial blood gases at rest showed hypoxaemia (arterial oxygen tension (Pao_2) 9.2 kPa (69 mmHg)) and hypocapnia (arterial carbon dioxide tension ($Paco_2$) 3.5 kPa (26 mmHg)). Laboratory test abnormalities were characterized by an elevated erythrocyte sedimentation rate (ESR) of 80 mm·h⁻¹; increased serum C reactive protein (180 mg·l⁻¹), fibrinogen (9 g·l⁻¹), alpha₁-globulin (5.6 g·l⁻¹) and alpha₂-globulin (8.7 g·l⁻¹), and by slightly decreased gammaglobulins (6.2 g·l⁻¹) at serum electrophoresis. White blood cell count and serum carcinoembryonic antigen (CEA) level were normal. Differential cell count of the bronchoalveolar lavage (BAL) performed in the right middle lobe, showed a "mixed" pattern, with 36% lymphocytes, 19% neutrophils, 10% eosinophils and 34% macrophages. Investigations for micro-organisms in blood, urine, and BAL fluid were negative, as were serological tests for *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Chlamydia*, *Rickettsia* and viruses. A diagnosis of radiation pneumonitis was made, and treatment with prednisone, 80 mg·day⁻¹, was instituted on October 15, 1992, for 10 days. Resolution of clinical symptoms was obtained after 3 days, and arterial blood gases improved (Pao_2 10 kPa (75 mmHg); $Paco_2$ 4.7 kPa (35 mmHg)). The patient was discharged with tapering oral steroid doses.

One month later, on November 24, 1992, whilst she was still taking 10 mg·day⁻¹ prednisone, a chest roentgenogram showed that the right middle lobe opacity had cleared but a contralateral alveolar opacity was present. Fever, cough and dyspnoea relapsed on December 7, 1992, 10 days after steroid withdrawal, leading to a new hospital admission on December 9, 1992. Crackles were heard in the upper parts of both lungs; airspace consolidations were present on chest roentgenograms and lung CT scan, localized in the right upper lobe, left lower lobe and the lingula (fig. 1b and c). Spirometric tests were still normal, but severe hypoxaemia and hypocapnia were present at rest (Pao_2 7.9 kPa (59 mmHg); $Paco_2$ 4.5 kPa (34 mmHg)). ESR was 70 mm·h⁻¹. BAL of the lingula disclosed an increased cell count (5.6×10^5 cells·ml), with 41% lymphocytes, 10% neutrophils and 22%

eosinophils; whereas, in the right middle lobe there were 7% lymphocytes, 32% neutrophils and 3% eosinophils. Eosinophil blood cell count was 650 cell-mm^{-3} (9%). A transbronchial lung biopsy (TBLB) was performed in the lingula. Histological findings were characterized by intra-alveolar organizing granulation tissue with collagen deposition, fibroblasts, numerous leucocytes, and a normal alveolar wall. These lesions were consistent with a diagnosis of COP. Neither infection, neoplastic disease, thrombosis, inhalation toxicity, connective tissue disease or drug-induced lung disease was identified. Prednisone was reintroduced with a rapid effect on clinical signs, arterial blood gases, and chest roentgenogram opacities.

After 12 months of progressively reduced treatment, symptoms recurred on November 8, 1993, two weeks after steroid withdrawal, with presence of alveolar opacities in the lingula and the right lower lobe on December 23, 1993. This late relapse was again very sensitive to oral corticosteroids. In May 1994, 20 months after the first pneumonitis episode, the patient was doing well, on 6 mg-day^{-1} of methylprednisolone, with only small residual linear opacities in the left middle lobe.

Patient No. 2

The patient was a 55 year old female smoker. On October 10, 1991 she was treated by means of breast-conserving surgery for an invasive adenocarcinoma of the left breast. Receptors for oestradiol and progesterone were positive and axillary lymph nodes were normal. Using a photon X source, an external radiation therapy was given from November 12, 1991, for 5 weeks. The total irradiation dose received by the left breast was 50 Gy. In December 1991, the patient received a 20 mg-day^{-1} dose of ciproteron acetate, continuing to the present time. On June 6, 1992, she presented with fever and a dry cough, associated with an alveolar opacity in the left lower lobe on chest roentgenogram (fig. 2a). Antibiotics, introduced for 10 days, induced a partial improvement. However, cough persisted, and one month later, a chest roentgenogram and lung CT scan showed extension of alveolar opacities to the left upper lobe, then migrating to the right lower lobe on August 24, 1992 (fig. 2b and c). Lung function tests and arterial blood gases were within normal ranges: VC 92% pred; FEV_1 103% pred; FEV_1/VC 93%; TLC 104% pred; Kco 124% pred; Pao_2 11.9 kPa (89 mmHg); Paco_2 4.5 kPa (34 mmHg). ESR was 22 mm-h^{-1} . No significant abnormality was found on serum globulins, blood cell counts, CEA and carbohydrate antigen 15-3 levels. No infectious disease was identified. Neither thrombosis, connective tissue disease, inhalation injury, neoplastic or drug-induced pulmonary disease was detected. Histological study of the TBLB, performed in the right lower lobe, showed the presence of many intra-alveolar buds of organizing granulation tissue supporting the diagnosis of COP. Treatment of 48 mg-day^{-1} methylprednisolone was started on August 27, 1992, resulting in rapid cough resolution. Steroid doses were then progressively tapered. Whilst on 8 mg-day^{-1} of methylprednisolone, a chest roentgenogram

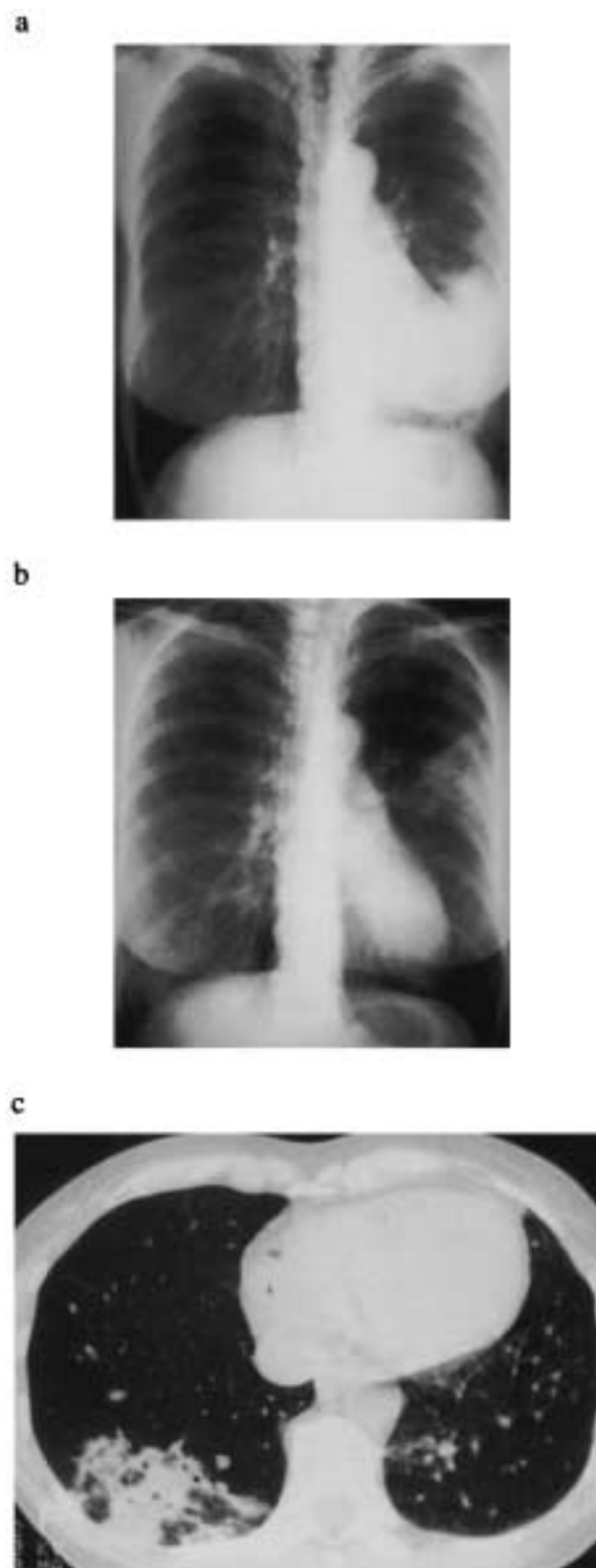


Fig. 2. — Radiological findings in patient No. 2: a) In June 1992, 6 months after completion of radiation therapy, an alveolar opacity in the left lower lobe is seen on chest roentgenogram. In August 1992, despite treatment with antibiotics, there was a migration of pulmonary opacities to the left upper and right lower lobes as displayed: b) on the anteroposterior chest roentgenogram; and c) on lung computed tomographic (CT) scan.

was normal on October 6, 1992, with only linear sequelae in the previously affected segments on CT-scan. Two weeks after withdrawal of corticosteroids, on December 8, 1992, cough relapsed, associated with an increased ESR ($40 \text{ mm}\cdot\text{h}^{-1}$), and the appearance of an axillary pulmonary infiltrate on the left side. Steroid treatment was restarted, with $16 \text{ mg}\cdot\text{day}^{-1}$ of methylprednisolone for 10 days, and then tapered, with a complete clinical response. The chest roentgenogram was normalized on January 29, 1993. Corticosteroids were withdrawn for six weeks. A second relapse occurred on April 5, 1993, characterized by cough recurrence and a new alveolar opacity in the right upper lobe. Again, clinical and radiological signs cleared quickly after reintroduction of methylprednisolone at $24 \text{ mg}\cdot\text{day}^{-1}$. In October, 1993, corticosteroids were withdrawn. On August 23, 1994, the patient was doing well and her chest roentgenogram was normal.

Discussion

The pathological findings of intra-alveolar fibrosis (associated or not with "proliferative" bronchiolitis obliterans) is not pathognomonic of any condition. This pathological process has been identified in a number of settings, including infections, connective tissue disorders, toxin exposure, drug therapy, and other miscellaneous causes [10]. However, the majority of cases have no known cause and are classified as idiopathic. Both of our patients presented with the most typical clinical and imaging signs of COP. They had a preceding flu-like syndrome, nonproductive cough, and, in one case, also progressive dyspnoea on exertion, associated with peripheral alveolar opacities on chest roentgenogram later migrating to previously unaffected areas [11–13]. Bronchoalveolar lavage performed in patient No. 1, showed a mixed cellular pattern (with increased lymphocytes, neutrophils and eosinophils), as reported previously in this condition [13, 14]. Alveolar eosinophilia was mild and lower than the lymphocyte percentage, as is usual in cryptogenic organizing pneumonia [14]. Even though controversy exists regarding the utility of TBLB in making the specific diagnosis of COP, the presence of intraluminal granulation tissue on TBLB, associated in both cases with typical clinical and imaging features, allowed a final diagnosis of migratory, steroid sensitive and relapsing organizing pneumonia [9].

Several factors suggest that radiation therapy was responsible for the occurrence of the pulmonary syndrome in our patients. No other cause was identified (to the best of our knowledge, no case of anti-oestrogen-associated pneumonia has been reported) even though infection could be debated in patient No. 2, as antibiotics initially induced a partial but transient clinical improvement. The disease-free interval between the end of radiation therapy and the onset of first symptoms was 3 and 6 months, respectively, in our patients. This is consistent with the delay in the onset of a radiation-triggered alveolitis after the period of irradiation [1, 2]. The first episode of pneumonia in each patient, was homolateral to the

irradiated breast. In patient No. 1 the lung received up to 40% of the total irradiation dose, just at the site where the first pulmonary infiltrate was located. The probability of developing a clinical pneumonia with such a dose is far from negligible [1, 15]. Pathological abnormalities characterizing radiation pneumonia share some similarities with cryptogenic COP: both are associated with damage to the alveolar epithelium [3, 16] and endothelial cells [16–19], a denuded basement membrane, and an increase of the microvascular permeability, causing firstly interstitial oedema then an intra-alveolar exudate [1, 3, 17]. In radiation pneumonia the alveolar fluid is rich in proteins (including high-molecular weight proteins) [20]. The subsequent intermediate phase consists of progressive organization of the intra-alveolar exudate and interstitial infiltration with mononuclear cells, and other inflammatory cells [3, 5, 17, 19]. Furthermore, intra-alveolar fibrosis has been reported as a prominent feature in radiation pneumonia [21].

Strictly unilateral pulmonary irradiation may occasionally result in bilateral pneumonia [6, 7, 22, 23]. Bronchoalveolar lavage in radiation pneumonia shows a lymphocytic alveolitis, and cell cycle analysis in one patient has shown that alveolar lymphocytes had a marked increase in their ribonucleic acid (RNA) content, suggesting that they were activated (blood lymphocytes were not) [20]. A recent prospective BAL study in 22 women, unilaterally irradiated for breast carcinoma, demonstrated bilateral lymphocytic alveolitis in most cases, without significant differences between irradiated and nonirradiated sides [24]; the alveolitis intensity was just more pronounced in patients who developed a clinical pneumonia. Activated CD4 T-cells were the most numerous lymphocytes found among BAL cells [24], instead of the CD8 T-cells classically observed in BOOP [14] (we did not study the phenotype of T-cell subpopulations in BAL in our cases). Similarly, gallium lung scan studies have shown an increased gallium uptake in both lungs in patients with acute radiation pneumonia after unilateral irradiation of the thorax [24, 25]. Thus, a focal lung injury caused by irradiation can result in a lymphocyte alveolitis involving both lungs. The mechanism by which radiation injury induces lymphocytic alveolitis is unknown. Radiation might induce the activation of pulmonary lymphocytes that recognize autoantigens released and unmasked after the initially local lung tissue damage. Whether this phenomenon is sufficient by itself, or whether a second and unrecognized triggering factor - the causal agent(s) of cryptogenic organizing pneumonia - acting on "radiation-primed" lymphocytes is necessary to produce a pneumonia is unknown.

The two cases reported are clearly distinct from usual radiation pneumonia, especially because of the migratory character of the alveolar opacities on chest imaging, which completely resolved under corticosteroid treatment and relapsed on corticosteroid withdrawal. Furthermore, radiation pneumonia usually progresses to radiation fibrosis, the imaging feature of which is rather characteristic. This was not present in our patients. Two previous reports related the onset of BOOP to radiation therapy [21, 26]. In one case, it occurred 2 weeks after the

completion of the chest irradiation for small cell lung carcinoma in a 61 year old man, and was limited to the area of the radiation field, suggesting that it was just a peculiar pathological aspect of radiation pneumonitis [21]. In the second case of a 63 year old woman, it occurred after 18 years [26]. This seems to us rather long to establish a reliable relationship between COP and the radiation therapy.

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