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Research Article

Bronchiolitis Obliterans Organizing Pneumonia after Breast Cancer Radiotherapy and letrozole: A Case Report and Literature Review

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Abstract

Objectives:
Bronchiolitis obliterans organizing pneumonia occurs with prevalence rate 1–3% after breast conservative treatment in series. In response to radiation of a lung or surrounding tissues, an inflammatory reaction can affect both lungs and is located within the radiation field. Characteristic imaging features include multiple alveolar opacities and diffuse ground-glass shadows. Letrozole may induce iatrogenic organizing pneumonia.

Materials and methods: we report the case of a 76-year-old female who underwent conservative treatment for an invasive ductal carcinoma of the left breast. Hypofractionated radiotherapy was delivered with a total dose of 42.5 Gy in 16 sessions of 2.65 Gy using a three-dimensional technique. After the radiotherapy ended letrozole was indicated.

Results: Several weeks after the radiotherapy ended and letrozole was introduced, she described a flu-like syndrome. Samples were negative, and there was no improvement after four courses of antibiotics. Imaging suggested bronchiolitis obliterans organizing pneumonia. Her symptomatology lessened after the letrozole was discontinued, and 11 months after radiotherapy finished, her imaging results were clear.

Conclusion: Physicians must consider bronchiolitis obliterans organizing pneumonia. Cases may increase with hypofractionated radiation treatment and new drugs. Letrozole may potentiate the risk. Dosimetry may be adapted to the lung and subpleural areas for patients with risk factors and taking adjuvant or concurrent drugs with potential pneumotoxicity.

Keywords: bronchiolitis obliterans organizing pneumonia; organizing pneumonia; radiation therapy; breast cancer; letrozole

INTRODUCTION

Bronchiolitis obliterans organizing pneumonia occurs with prevalence rate 1–3% after breast conservative treatment in series [1–5]. Organizing pneumonia is not a common complication after radiation exposure. In response to radiation of a lung or surrounding tissues, an inflammatory reaction can affect both lungs, in contrast to radiation-induced pneumonitis, which is located within the radiation field and it's distinct from radiation pneumonitis, also because of the migratory characteristic. A first case was described in France by Crestani et al in 1995 [6]. After he defined criteria to characterize the organizing pneumonia after radiation therapy from 15 cases after tumorectomy or mastectomy and breast irradiation: radiation therapy to the breast within 12 months, general or respiratory symptoms lasting for at least 2 weeks, lung infiltrates outside the radiation field, and no specific cause. Patients experience fever, dry cough, and dyspnea. Imaging characteristics include multiple alveolar opacities and diffuse ground-glass shadows with a migratory pattern. Organizing pneumonia has mainly been reported in a Japanese series after whole-breast radiotherapy. A few cases were reported after conventional and stereotactic radiotherapy in lung cancer [7,8] and one case after liver radioembolization [9]. Organizing pneumonia is caused by various pulmonary infections, systemic diseases and several drugs. Endocrine therapy with an aromatase inhibitor (AI) is the standard for postmenopausal women with hormonal receptor-positive large clinical trials [10–12]. A study showed the incidence of BOOP in the patients who received tamoxifen and anastrozole (1.6%) was higher than the group without (0.8%) [13–15]. Letrozole may induce iatrogenic organizing pneumonia.

Case report

We report the case of a 76-year-old female. She had three pregnancies, menopause at age 49 years, and was on no treatment. She self-palpated a nodule of the left breast leading to the diagnosis of a tumor in the upper-inner quadrant. Tumorectomy found a grade 1, invasive ductal adenocarcinoma (axis 0.9 cm) that tested positive for hormone receptor and negative for human epidermal growth factor receptor 2. The tumor resection margins and sentinel lymph-node biopsy were negative. She

received adjuvant whole-breast irradiation with a three-dimensional conformal technique. Hypofractionated radiotherapy was delivered with a total dose of 42.5 Gy in 16 sessions of 2.65 Gy. Treatment was well tolerated. Letrozole was introduced when radiotherapy ceased [10,16]. At the third-month evaluation, she described side effects of letrozole, with hot flashes, and weight gain of 2.5 kg associated with increasing dyspnea grade 2 (Medical Research Council [17], dry cough, and intermittent low-grade fever. No other drug had been introduced. Physical examination did not find signs of heart failure or venous thromboembolic disease. Chest X-ray showed a pneumopathy in the left lobar base. Chest tomography revealed a post-radiation appearance of consolidation in the left lung (**Figure. 1A**). All serologies were negative. Symptoms progressively worsened despite four courses of antibiotic therapy (amoxicillin and clavulanate, cephalosporin, macrolide [18,19]. Bronchial endoscopy found a normal bronchial tree and the absence of secretions. Bronchioalveolar lavage was negative for pathogens but identified lymphocytic alveolitis with no eosinophilic disorder. Computed tomography showed bilateral pneumopathy with alveolar consolidation, and a diffuse ground-glass appearance, in keeping with a diagnosis of bronchiolitis obliterans organizing pneumonia (**Figure. 1B**). She received low-dose corticotherapy (<1 mg/kg per day), but adverse effects led to this being discontinued 8 days later.

With the chronology and the interstitial lung disorder, we considered drug-induced pneumonia due to letrozole. One month after letrozole was discontinued, and nine months after radiotherapy ceased, computed tomography revealed a partial regression of the opacities, with clinical improvement. Eleven and 5 months after radiotherapy and letrozole ended, respectively, computed tomography revealed disappearance of the abnormalities (**Figure. 1C**), and the patient had fully recovered without permanent sequelae. Regarding dosimetry, lung and subpleural areas received radiation (Dmax: 43 Gy) with the tangential field (**Figure 2A**). The mean dose received by the ipsilateral lung was 8.7 Gy, with the volume receiving 20 Gy equal to 17% (**Figure. 2B**).

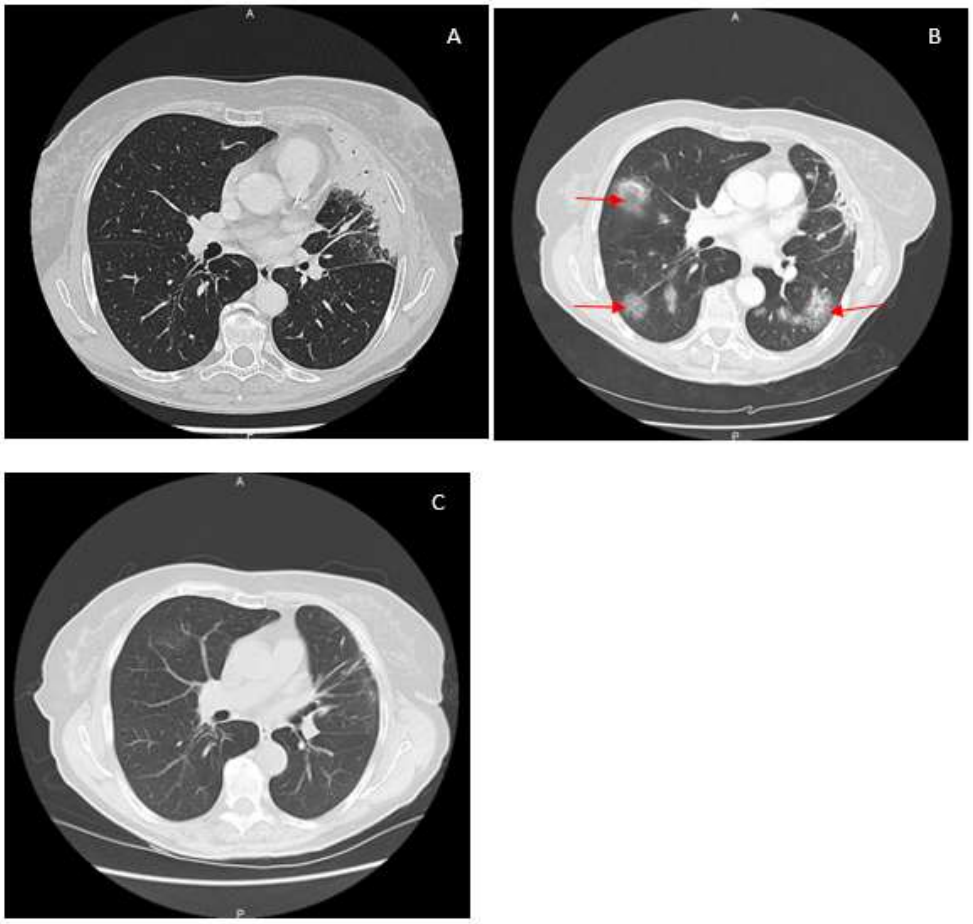

Figure 1: Chest computed tomography after radiotherapy three months (A), six months (B), eleven months (C)

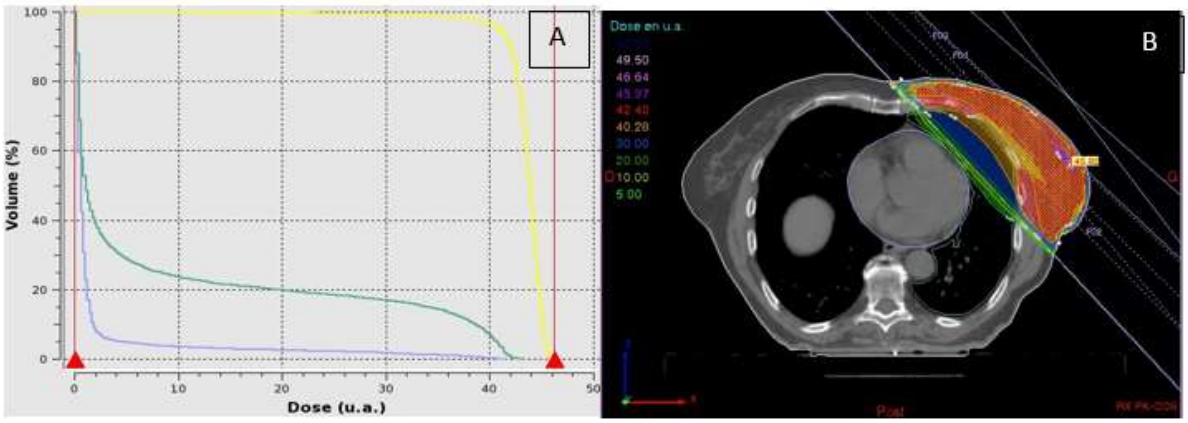

Figure 2: Transverse plane. PTV (blue) coverage with 95% isodose (orange) (A) - Dose volume histogram: left lung (green curve), left breast (yellow curve), heart (blue curve) (B)

Methods

The patient was diagnosed and followed-up at the Dupuytren University Hospital Centre in Limoges, France. A postmenopausal female who underwent conservative treatment for an invasive ductal carcinoma of the left breast that tested positive for hormone receptor. Hypofractionated radiotherapy was delivered with a total dose of 42.5 Gy in 16 sessions of 2.65 Gy by a Clinac 2300 linear accelerator, using a three-dimensional technique. The prescribed dose of 42.5 Gy was delivered to the planned target volume (PTV) (whole mammary gland with a margin of 5mm) and it received 95% of the prescribed dose (Figure. 2B). After the radiotherapy ended letrozole was started 2.5 mg per day for 5 years.

Discussion

Conventional whole-breast or chest-wall radiotherapy is the standard treatment after breast cancer surgery. Adjuvant radiation improves local control, disease-free survival, and mortality rates [20]. However, radiotherapy can induce early and late pulmonary toxicity. Organizing pneumonia is rarely described, but cases of bronchiolitis obliterans organizing pneumonia after radiation therapy have increased in literature. Radiation therapy or letrozole are the least-described triggering factors. The tangential radiation field generally spares the parenchyma but causes inflammation of the subpleural region, rich in lymphoid tissue, inducing lymphocyte recruitment and alveolitis. In addition, part of patients irradiated for breast neoplasia have discrete pleural effusion [21]. Radiation of one lung can create inflammation in both lungs [22,23], highlighted by bilateral lymphocytic alveolitis and biopsy [24,25]. Cottin et al. reported five cases of eosinophilic pneumonia in atopic patients caused by whole-breast radiotherapy [26]. Pneumopathy occurs within 3 weeks to 12 months after radiation and can disappear within a year. Symptoms appear within several weeks to more than a year after radiotherapy ceases. As our case, shortness of breath or dry cough during radiotherapy may be an early sign of a pulmonary reaction and further toxicity. Patients experience a flu-like syndrome: dry cough, increasing dyspnea, persistent low-grade fever, and sometimes chest pain [6,25,27]. There is a lack of clinical response to antibiotic therapy with no pathogen found. Pulmonary function test results can be normal. Bronchioalveolar lavage can show no abnormalities or hypercellularity [24,25,27]. Computed tomography reveals diffuse ground-glass opacities with air–space consolidation. Patchy opacities occur more frequently in the periphery and lower-lung zones. Varying abnormalities are characteristic, in the radiation-exposed lung and extending into the contralateral lung, outside the radiation fields, which distinguish it from radiation pneumonitis [1,25]. With this suggestive radiological and clinical presentation, biopsy is not mandatory [24]. A literature review identified some recurrent risk factors: age > 50 years [13], chemotherapy and concurrent endocrine therapy. A preclinical study has shown Letrozole can be a radiosensitiver, but the association with normofractionated radiotherapy is considered as safe [28,29] and incidence of lung fibrosis is similar between concurrent and sequential introduction of aromatase inhibitors [29]. One case suggested that trastuzumab had induced organizing pneumonia after breast irradiation [30]. It may occur with genetic mutations and an individual response of hypersensitivity to radiation [31]. Oie et al. suggested a link between organizing pneumonia and radiation pneumonitis [2]. They concluded that opacities spread from the site of radiation pneumonitis to the hilum and often to the contralateral lung. In a meta-analysis, radiation pneumonitis risk factors were hypofractionation (dose > 2.5 Gy), the volume of irradiated lung, and several concomitant drugs. By contrast, organizing pneumonia is not associated with irradiated lung volume [13], one study showed a correlation with central lung distance > 1.8 cm [4]. Cases have been reported after hypofractionation [30,32], partial breast [13] and chest-wall irradiation [33,34]; with three-dimensional radiotherapy. In our case no biopsy was realised and corticotherapy was too brief. We cannot exclude letrozole a cause. To our knowledge this is the first case in which there is the temporal correlation between Letrozole initiation and symptoms emergence, and both scanner normalization and symptomatic improvement after discontinuation of letrozole without immunosuppressive treatment. Cough, dyspnea, and interstitial pneumonitis are rare sides effects of Letrozole [35–37]. Several cases of pneumopathy with anti-aromatase have been reported [35,38,39] and the time to start adjuvant hormonotherapy in patients who will receive post-operative radiotherapy remain controversial moreover with hypofractionnated scheme in which dose per fraction can rise 2.67 to 6 Gy [40,41]. A study shown mild to moderate toxicity but not designed for assessment of lung toxicity [42]. Treatment should depend on the severity of clinical conditions, and considering the adverse effects of prolonged corticosteroids and risk of relapse [43]. A few deaths have been reported.

Conclusion

Physicians must consider bronchiolitis obliterans organizing pneumonia. Cases may increase with hypofractionated radiation treatment and new drugs. Letrozole could potentiate the risk. Dosimetry may be adapted to the lung and subpleural areas of patients with risk factors and taking adjuvant or concurrent drugs with potential pneumotoxcity.

ETHICS

The patient kindly provided her informed consent at the time of hospital admission to the publication of personal data.

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DECLARATION OF COMPETING INTEREST

The authors declare that they have no conflicts of interest.

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