EDITORIAL

Radiation-induced injury in the "nonirradiated" lung

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Does radiation injure "nonirradiated" lung?

An unqualified answer to the above question is "yes". A qualified response, however, requires that the word, "nonirradiated", be defined. A truly nonirradiated lung represents the pulmonary parenchyma that is not exposed to any type or amount of radiation. Currently, there is sufficient scientific basis to consider that this nonirradiated normal lung parenchyma can suffer injury caused by radiation therapy aimed at malignant disease. There have been several reports of pathological processes occurring outside the field of radiation, including the contralateral lung [1–5]. These abnormalities have been demonstrated by a diffuse increased gallium uptake on lung scan, lymphocytosis in the bronchoalveolar lavage (BAL) fluid of nonirradiated lung [5], and a histological pattern consistent with bronchiolitis obliterans-organizing pneumonia (BOOP) in biopsy specimens from nonirradiated lung. BOOP, however, remains less well known among clinicians. The type of injury sustained by the lung that is not exposed to radiation is different from either the acute radiation-induced pneumonitis or the chronic radiation-induced pulmonary fibrosis. These two well known types of lung pathology indicate a direct physical insult of radiation on the lung.

The "classic" radiation pneumonitis has been recognized in patients receiving radiation treatment for nonpulmonary (*i.e.* breast) as well as pulmonary malignancies [6, 7]. In most cases, radiographic findings are confined to the field of radiation. However, bilateral lymphocytic alveolitis develops in both lung fields in most patients after unilateral breast irradiation [5]. When external beam radiation therapy is contemplated for the treatment of cancers of the lung, breast, oesophagus, or other organs adjacent to or in the vicinity of the lungs, great effort is undertaken to avoid radiation injury to lung parenchyma uninvolved in the neoplastic process. While this effort is theoretically sound, it is practically impossible to prevent normal pulmonary parenchyma (that is closely adjacent to the radiated area) from some exposure to radiation. This normal lung exposed to direct radiation thus suffers radiation injury. Furthermore, normal pulmonary parenchyma in the path of the tangential radiation field can also suffer injury. Some have argued that "radiation scatter" over areas away from those intended can cause radiation lung injury. All of these represent direct radiation insult to the lungs. The effects are well-recognized in clinical medicine as acute radiation-induced lung injury and chronic radiation-induced lung

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fibrosis. The pulmonary damage caused by radiation in these entities is dependent on the total dosage, fractionation protocol, dose rate, type of radiation used, and the volume of lung exposed to the radiation.

What is the mechanism of injury?

Accumulating scientific data suggest that immunological reactions, mediated by lymphocytes, lead to lung injury in the nonirradiated lung parenchyma. In this issue of the *European Respiratory Journal*, the prospective study by MARTÍN *et al.* [8] further clarifies the notion that diffuse lymphocytic alveolitis is one of the mechanisms of lung damage. Specifically, they demonstrate that lymphocytic alveolitis induced by unilateral thoracic radiation therapy is indeed diffuse and bilateral. Their study consisted of a group of females scheduled to undergo radiation therapy for the management of breast cancer. These patients underwent BAL before and twice after the radiation therapy. A control group consisting of healthy females also underwent BAL studies. The first important observation was the presence of a significantly elevated percentage of lymphocytes ($29.5\pm15.7\%$) in radiated patients compared to the control group of patients ($6.2\pm3.3\%$) ($p<0.01$). Although bilateral alveolar lymphocytosis developed in 22 of 26 (85%) patients, only eight (31%) patients developed radiological evidence of pneumonitis 15–90 days after completion of radiation therapy; none had involvement of the contralateral (nonirradiated) lung. Secondly, the lymphocyte counts showed no statistically significant difference between irradiated and nonirradiated lung. Thirdly, even though patients with active radiation-induced pneumonitis had significantly higher ($24.8\pm10.2\%$) CD4 subset T-cells than asymptomatic patients ($15.2\pm8.9\%$), the percentages of lymphocytes in the BAL fluid did not significantly differ between those who eventually developed radiation pneumonitis ($24.5\pm13.5\%$) and those without pneumonitis ($32.8\pm16.5\%$). Another finding was that patients who developed radiation pneumonitis were younger than those who did not.

The most intriguing aspect of BOOP occurring in nonirradiated lung is its propensity to appear almost exclusively in patients who have undergone breast surgery and radiation therapy for the treatment of breast cancer. Even though a large number of patients undergo surgery followed by radiation therapy to treat lung cancer, the occurrence of BOOP outside the radiation field in these patients is exceedingly uncommon. The presence of activated CD4+ T-cells in BAL fluid suggests that an initial radiation-induced injury "primes" the lymphocytes, ultimately leading to development of BOOP. Radiation-induced

gene transcription and pro-inflammatory cytokine release may also play a role [9]. The role of adjuvant chemotherapy as a possible "primer" has been considered but not substantiated. Other factors, including the mode of radiation (tangential *versus* scatter) and genetic predisposition, may all contribute to the occurrence of BOOP. The tangential lung radiation that occurs during breast irradiation tends to be low dose. This low-dose or indirect radiation exposure may initiate lymphocyte stimulation, which in turn leads to immunological and hyperrsensitivity reactions in the "nonirradiated lung". Based on this theory, the concept of the truly "nonirradiated lung" becomes untenable. On the other hand, if "radiation scatter" is the only mechanism of damage outside the radiation field, clinicians should have encountered many more cases. The uncommon occurrence of damage outside the radiation field indicates the possibility of individual susceptibility [10].

What are the pathological features?

Classic acute radiation pneumonitis begins as an acute exudative phase, followed by an organizing phase with interstitial infiltration by neutrophils and other inflammatory cells in the irradiated lung parenchyma. Chronic radiation-induced pulmonary fibrosis produces typical interstitial fibrotic processes. However, the occurrence of BOOP in the radiated lung is uncommon. BOOP occurs much more commonly in the nonirradiated lungs of females after radiation therapy for breast cancer. Lung biopsy specimens in the latter group of patients have shown a pattern of organizing pneumonia consistent with BOOP: polypoid plugs of proliferating fibroblasts set in a mucopolysaccharide-rich stroma within terminal airspaces (bronchiolitis obliterans), alveolar ducts and alveolar spaces (organizing pneumonitis). A mild chronic interstitial inflammatory cell infiltrate composed predominantly of macrophages and lymphocytes, and occasionally a small number of eosinophils may be seen [10]. Changes noted in chronic radiation-induced fibrosis, such as hyaline membranes, giant cells, thrombi, vascular hyalinization, intimal thickening, or significant interstitial fibrosis are lacking.

How common is the entity?

Both acute radiation-induced pneumonitis and chronic radiation-induced pulmonary fibrosis occur more commonly than the BOOP that occurs in nonirradiated lung. Indeed, radiographic changes, without overt clinical symptomatology, are often discovered after radiation therapy [11]. The uncommon occurrence of BOOP, however, has led to wrong diagnoses. As noted by MARTIN *et al.* [8], bilateral lymphocytic alveolitis appears to occur in the overwhelming majority of patients who receive radiotherapy for breast cancer. However, clinical presentation with respiratory symptomatology and radiological infiltrates is unusual. Even when lung infiltrates develop in the nonirradiated lung, the possibility of radiation-induced organizing pneumonia is often not considered. Presence of fever usually leads to the diagnosis of an infectious pneumonia. In the largest series of patients with BOOP occurring in the nonirradiated lung, the mean time from symptoms to diagnosis was 18 weeks [12].

Indeed, only a handful of cases of BOOP occurring in the nonirradiated lung have been described in the literature [1–5]. The Groupe d′Etudes et de Recherche sur les Maladies Orphelines Pulmonaires from Lyon, France have described their experience with BOOP occurring in 15 females after radiation therapy for breast cancer [12]. All 15 females, mean age 60 ± 6 yrs, had the following features: radiation therapy to the breast within 12 months, general and/or respiratory symptoms lasting for ≥2 weeks, lung infiltrates outside the radiation port, and no other specific cause for lung changes. All patients had localized breast carcinoma and had undergone breast surgery (limited lumpectomy in 13 patients and total mastectomy in two patients) and axillary dissection of lymph nodes. The primary tumour was in the right breast in eight patients and the left breast in seven. Data on radiotherapy in 14 patients showed that 45–55 Gy were given to the affected breast using tangential fields in all cases and an additional boost to the primary tumour site of 10–20 Gy in five patients using tangential fields. Ipsilateral radiotherapy was administered to the axilla in three patients, to the supraclavicular region in seven patients, and to the internal mammary chain in nine patients. Two patients had received concomitant chemotherapy (epirubicin, cyclophosphamide, and 5-fluorouracil) and nine patients were receiving tamoxifen at the time of lung disease diagnosis. All patients were symptomatic and the symptoms appeared between 3 and 47 weeks (14 ± 13) after the completion of radiotherapy. The mean time from symptoms to diagnosis was 18 weeks (2–48). Fever (>37.5°C) was noted in all patients. Other symptoms included asthenia (13 patients) and weight loss (six patients). A persistent cough was noted in 13 patients, nine had dyspnoea, and wheezing was noted in one patient. Localized crackles were heard in nine patients. Chest radiographs revealed peripheral alveolar infiltrates with migratory pattern. The erythrocyte sedimentation rate ranged 45–140 mm^{-1} in 14 patients. BAL in 10 patients revealed lymphocytosis (>20%) in all, neutrophilia (>5%) in eight, and eosinophilia (>5%) in five. BOOP was identified in lung biopsies from five patients. All patients demonstrated dramatic improvements with corticosteroid therapy. However, relapses occurred in 12 patients while tapering or after stopping corticosteroid therapy [12].

My colleagues and I recently described six cases of radiation-induced BOOP occurring outside the radiation port [10]. All patients were female, mean age 62.8 yrs, range 50–75 yrs, who had received radiation therapy (mean dose 65 Gy) for breast cancer. From 6–17 months (mean 8.8 months) after the completion of radiotherapy, these patients developed recurrent and migrating lung infiltrates outside the radiation field. Three had significant respiratory symptoms whereas the remainder were minimally symptomatic or asymptomatic. Thoracic computed tomography (CT) showed dense alveolar infiltrates with air bronchograms in all patients. BAL in two patients revealed lymphocytosis (25% and 19%), and lung biopsy in five patients demonstrated a histological pattern consistent with bronchiolitis obliterans with organizing pneumonia. Even though the symptomatic patients showed prompt resolution of their symptoms and radiographic abnormalities following systemic corticosteroid therapy, the lung infiltrates recurred once corticosteroid therapy was stopped.

What are the clinical manifestations?

BOOP occurring in the nonirradiated lung exhibits clinical features akin to those in acute radiation pneumonitis. Almost all patients are those with carcinoma of the breast treated by surgery and postoperative radiation therapy. Clinical features appear within 12 months of the completion of radiation therapy, although some patients develop respiratory illness within 3 weeks after the completion of radiotherapy [12]. However, recurrent episodes of migratory BOOP can be seen. When symptoms occur, dyspnoea is the commonest complaint. Fever, present in almost all patients, can range from low-grade to high and spiking. Nonproductive cough is also common. The most common laboratory findings are a polymorphonuclear leukocytosis and an elevated erythrocyte sedimentation rate. This sedimentation rate can be very high, up to 140 mm·h^{-1} [10, 12]. Extrapulmonary symptoms are uncommon.

The first radiographic change is usually a diffuse haze in the treatment zone, which progresses to patchy alveolar infiltrates with air bronchograms [13]. A migratory pattern of dense alveolar infiltrates in both radiated and non-irradiated lung zones can be seen [1, 2, 10, 12]. Computed chest tomography (CT), while not indicated in all patients, usually confirms plain radiographic findings. Among the 15 patients described by CRESTANI et al. [12], a migratory pattern of the lung infiltrates was noted in 11 patients prior to corticosteroid treatment, with the infiltrates beginning in the irradiated area, then spreading to the nonirradiated areas of the ipsilateral lung and then to the contralateral lung. In three patients, the migratory pattern of infiltrates was noted only after corticosteroid treatment when relapses occurred in previously unaffected areas, involving both lungs. Among the six patients in the Mayo series, the radiological features varied from solitary nodular infiltrate to migratory, bilateral diffuse and dense alveolar infiltrates with well-defined air bronchograms [10].

In the 15 patients of CRESTANI et al. [12], pulmonary function tests in 10 patients showed a mild restrictive ventilatory defect in two and a decrease in the transfer coefficient for carbon monoxide (<80% of predicted) in six of the eight patients tested; mild hypoxaemia was noted in four of 10 patients.

What is the treatment?

Classic radiation pneumonitis is often reversible with corticosteroid therapy whereas fibrosis is usually not reversible. Corticosteroid dosages in the range 5–60 mg·day^{-1}, with rapid tapering, have been given. BOOP occurring in nonirradiated lung promptly responds to systemic corticosteroid therapy. The resolution of respiratory symptoms is dramatic. Complete resolution of symptoms can be expected within 1 week and radiological resolution within 2–4 weeks. Short-term therapy, however, leads to recurrence of migratory BOOP with significant respiratory symptoms [10, 12]. In such patients, long-term, low-dose corticosteroid therapy should be considered. Among the 15 patients described in CRESTANI et al. [12], 21 relapses occurred in 12 patients (one relapse in five patients, two relapses in five patients, three relapses in two patients). Most relapses occurred 1–6 weeks after steroid withdrawal (17 relapses in 10 patients). The mean total duration of steroid treatment was 49 weeks (range 17–100 weeks).

The long-term outcome appears excellent, based on the follow-up available on the limited number of cases. Development of chronic or progressive pulmonary fibrosis in these cases has not been observed.

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