CLINICAL FORUM

Chronic eosinophilic pneumonia after radiation therapy for breast cancer

V. Cottin*, R. Frognier*, H. Monnot[#], A. Levy[†], P. DeVuyst⁺, J-F. Cordier*,
and the Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P)

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ABSTRACT: The priming of bronchiolitis obliterans organising pneumonia by radiation therapy (RT) to the breast is now a well recognised syndrome.

This study describes the occurrence of chronic eosinophilic pneumonia following RT after surgery for breast cancer in five female patients, with a mean age of 68 yrs (range 49–77).

All patients had a history of asthma and/or allergy. At the onset of eosinophilic pneumonia, all patients were symptomatic. Chest radiograph showed pulmonary infiltrates, unilateral and limited to the irradiated lung in three patients, and bilateral in two. Pulmonary opacities were migratory in one patient. All patients had blood eosinophilia $>1.0 \times 10^9 \cdot L^{-1}$ and/or eosinophilia $>40\%$ at bronchoalveolar lavage differential cell count. The median time interval between the end of radiation therapy and the onset of eosinophilic pneumonia was 3.5 months (range 1–10). All patients rapidly improved with oral corticosteroids without sequelae. Relapse occurred in two patients after treatment withdrawal.

Priming of alveolitis by radiation therapy to the breast might promote either bronchiolitis obliterans organising pneumonia or chronic eosinophilic pneumonia, with the latter depending on genetic or acquired characteristics of patients and/or further stimulation that may trigger a T-helper cell type 2 form of lymphocyte response, especially in patients with asthma or other atopic manifestations.

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*Service de Pneumologie, Hôpital Cardiovasculaire et Pneumologique Louis Pradel, Université Claude Bernard, Lyon, [#]Centre Hospitalier Régional, Saint-Omer, [†]Centre Hospitalier Général Jacques Cœur, Bourges, France, and ⁺Hôpital Universitaire Erasme, Bruxelles, Belgique.

Correspondence: J-F. Cordier, Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires, Hôpital Cardiovasculaire et Pneumologique Louis Pradel, 69394 Lyon Cedex 03, France.

Fax: 33 472357653

E-mail: germop@univ-lyon1.fr

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Radiation therapy (RT) to the chest may cause acute and chronic radiation pneumonitis. The authors have previously described the occurrence of bronchiolitis obliterans organising pneumonia as a complication of RT for breast cancer [1, 2], a disorder defined by the characteristic presence of granulation tissue within the lumen of distal pulmonary airspaces, with nonspecific clinical manifestations including fever, nonproductive cough, mild dyspnoea, weight loss, and multiple patchy alveolar opacities on chest radiograph.

Chronic eosinophilic pneumonia is a distinct syndrome often associated with atopic manifestations including asthma [3], characterised by nonspecific pulmonary symptoms, peripheral alveolar opacities on chest imaging, with alveolar and usually peripheral blood eosinophilia [4]. Chronic eosinophilic pneumonia may be idiopathic [5], or be related to various causes, such as parasitic infections or drug-induced toxicity. The current study describes the occurrence of chronic eosinophilic pneumonia following RT for breast cancer in females.

Methods

Case recruitment

This retrospective multicenter study was conducted by the Groupe d'Etudes et de Recherche sur les Maladies "Orphelines"

Pulmonaires (GERM"O"P). A letter was sent to participating physicians asking them to report cases of chronic eosinophilic pneumonia in patients with a recent history of RT to the breast. Reports to the GERM"O"P registry were nominative for patients who gave their written consent, or anonymous otherwise. The clinical data were collected through a detailed questionnaire.

The GERM"O"P is a French-speaking collaborative group founded in 1993 for study and research on rare (so-called "orphan") pulmonary diseases. The group includes >200 French chest physicians and 40 university hospitals nationwide. Members keep in regular contact through newsletters and an annual meeting, and thus constitute a motivated group.

Study population

Cases were included in the study if the following criteria were met: 1) time interval between the end of RT and the onset of eosinophilic pneumonia <12 months; 2) diagnostic criteria for chronic eosinophilic pneumonia including pulmonary alveolar infiltrates on chest radiograph, blood eosinophilia $>1 \times 10^9 \cdot L^{-1}$ and/or eosinophils $>40\%$ at bronchoalveolar lavage differential cell count, and symptoms present for >2 weeks [5]; 3) presence of radiographic lung infiltrates outside

the radiation port; 4) no evidence of a specific cause of eosinophilic pneumonia. Six cases were reported to the GERM"O"P registry. One case was excluded from the study because not all the diagnostic criteria for eosinophilic pneumonia were met. Five cases were included in this series.

Results

Patient characteristics and associated conditions

The patients were five females, with a mean age of 68 yrs (range 49–77). Two patients were former smokers (smoking stopped for 31 and 33 yrs), and three had never smoked. Patient no. 3 had been treated for tuberculosis in 1960. Patient no. 1 had a familial history of asthma. Patients no. 1–4 had a history of asthma since 1, 2, 12, and 24 yrs respectively, leading to chronic obstructive lung disease with forced expiratory volume in one second (FEV1) of 56% predicted and FEV1/forced vital capacity of 56% in patient no. 4. Patients no. 1–3 had been receiving inhaled corticosteroids for asthma within a year prior to the diagnosis of eosinophilic pneumonia; all three had a history of nasal polyposis. In addition, patient no. 4 had positive skin tests for cockroach and house dust mite; patient no. 5 was allergic to strawberries. Patients no. 1, 2, and 4 had undergone surgery for chronic sinusitis.

Potential triggering factors of eosinophil pneumonia

Drugs taken within 6 months prior to the onset of eosinophilic pneumonia are shown on table 1. Eosinophilic pneumonia of parasitic origin was excluded by stool smears and serological methods. None of the patients met the criteria for Churg-Strauss syndrome or idiopathic hypereosinophilic syndrome. None had occupational exposure to inhaled antigens.

Several diagnostic criteria for allergic bronchopulmonary aspergillosis were present in patient no. 4, including asthma, peripheral blood eosinophilia ($1.1 \times 10^9 \cdot L^{-1}$), immediate cutaneous reactivity to *Aspergillus* and *Penicillium*, precipitating antibodies against *Aspergillus* antigen (with four precipitin arcs by double gel diffusion method, presence of the catalase arc), elevated serum total immunoglobulin E (IgE) and IgE specific for *Aspergillus fumigatus*, and presence of *A. fumigatus* in sputum; however, no bronchiectasis was seen on computed tomography of the chest. It was considered that *Aspergillus* may have contributed to the eosinophilic pneumonia, and this patient was treated with itraconazole in addition to corticosteroids.

Breast cancer and radiotherapy

All five patients had been treated by surgery for localised breast carcinoma, left-sided in four cases and right-sided in one case. Surgery consisted in tumorectomy (four patients) or mastectomy (patient no. 4), and axillary lymph node dissection (patients no. 1 and 4). No patient received adjuvant chemotherapy. Four patients were receiving tamoxifen at the onset of the lung disease. In all patients, breast surgery was followed by RT (50 Gy to the affected breast by tangential fields, with a daily dose of 2.5 Gy). The treatment also included a boost of 10 Gy to the tumour site (three patients), irradiation of the ipsilateral supraclavicular region (one patient), and of the internal mammary chain (two patients).

Clinical and functional respiratory manifestations

The onset of respiratory symptoms followed the completion of RT by a median time of 3.5 months (range 1–10). At the onset of chronic eosinophilic pneumonia, all patients were symptomatic, with dyspnoea (class I of the New York Heart Association, three patients; class II, one patient; class III, one patient), cough in four, bronchorrhea in three, chest pain in two, and haemoptysis in one patient. Fever and asthenia were present in four patients each. Two patients had lost 6 kg each. Localised crackles were heard in three patients, and wheezing in two patients with previous asthma. Upper respiratory tract manifestations were present only in patient no. 1, who had uncomplicated chronic sinusitis. Extrathoracic manifestations were present in two patients (patient no. 2 presented chest pain related to acute pericardial effusion; patient no. 4 complained of transient arthralgias). No neurological, gastrointestinal, cutaneous, or renal involvement was observed.

At lung function testing, a mild restrictive ventilatory defect was found in patient no. 3. An obstructive defect was present only in patient no. 4, with a history of chronic obstructive pulmonary disease. Transfer factor for carbon monoxide and transfer coefficient were decreased in the two tested patients.

Chest imaging

The initial chest radiograph showed pulmonary opacities in all patients, which consisted of alveolar consolidation in four patients, and localised infiltrates of both upper lobes predominating on the left side in patient no. 4. Thus, opacities were strictly unilateral and limited to the irradiated lung in three of five patients, and bilateral in two. Patient no. 3 also had contralateral localised bronchiectasis and infiltrates as sequelae of lung tuberculosis at the age of 26 yrs. Pulmonary opacities were migratory only in patient no. 5 (fig. 1).

Table 1. – Overview of clinical characteristics

Patient no.	Age yrs	Time interval between RT and respiratory manifestations months	Irradiated breast side	Location of pneumonia	Blood eosinophilia $\times 10^9 \cdot L^{-1}$	Alveolar eosinophilia %	Drugs during the preceding 6 months	Relapse
1	49	1	Left	Left, lower lobe	5.3	N/A	Tamoxifen, Montelukast, Loratadine, Salmeterol, Fluticasone	Yes
2	56	3.5	Left	Left, upper lobe	18.5	70	Paroxetine, Salmeterol, Fluticasone	No
3	67	1.5	Left	Left, lingula	3.4	59	Tamoxifen, Fluticasone	Yes
4	91	10	Right	Bilateral, upper lobes	1.1	N/A	Itraconazole	No
5	77	4	Left	Bilateral, migratory	3.6	N/A	Trimetazidine	No

RT: radiation therapy; N/A: not available.

Chest computed tomography scans performed at the time of the diagnosis were available in three of five patients. Air-space consolidation present in each patient represented the main finding. Ground glass opacities (one patient), localised bronchiectasis (one patient), and small pleural effusions (two patients) were also found.

Biology

The median blood eosinophilia was $3.6 \times 10^9 \cdot L^{-1}$ (range 1.04–18.7), with blood eosinophilia $>1.0 \times 10^9 \cdot L^{-1}$ in all patients. Bronchoalveolar lavage was performed at the time of diagnosis and before any corticosteroid treatment in two patients, with eosinophils representing $>40\%$ of the bronchoalveolar lavage differential cell count in both (59 and 70%).

A raised percentage of neutrophils was also present at bronchoalveolar lavage cell count (10 and 24% respectively). The search for infectious pathogens was negative.

IgE levels were strongly elevated in the four patients tested ($>1240 IU \cdot L^{-1}$, normal <175). None of the patients had proteinuria or renal failure. No antineutrophil cytoplasmic antibodies or antinuclear antibodies were present in the three tested patients. Circulating immune complexes were negative in both cases tested.

Lung biopsy

A video-assisted thoracoscopic lung biopsy was performed in patient no. 2, in whom pleurodesis was indicated for iatrogenic pneumothorax after pleural effusion puncture. The

Fig. 1.—Chest radiographs in patient no. 5 (radiation therapy to the left breast), showing migratory alveolar opacities in a) April 9, 2001; b) May 11, 2001; c) May 29, 2001; and d) June 25, 2001.

biopsy showed typical eosinophilic pneumonia, with an interstitial infiltrate and alveolar exudate with predominating eosinophils.

Treatment and outcome

All patients were treated with oral corticosteroids, with a starting dose of $0.4\text{--}0.8\text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ of prednisone. Three patients also received inhaled corticosteroids. A complete resolution of clinical symptoms was obtained within 2 days in two patients, and within 2 weeks in the remaining three patients. Pulmonary opacities resolved in all patients, without significant sequelae (minimal residual opacities in two patients). Oral corticosteroids could be stopped in all patients; the mean duration of treatment was 12.4 ± 7.5 weeks.

A relapse occurred in patients no. 1 and 3, 4 weeks after corticosteroid withdrawal, and despite continued use of inhaled steroids. Pulmonary opacities were present in both cases, and were migratory in patient no. 3. The eosinophilic pneumonia again completely resolved after corticosteroids were resumed.

Median follow-up was 14.6 months after the diagnosis (range 6–17). None of the patients were still receiving oral corticosteroids at the last visit. Peripheral eosinophilia ($0.8\times 10^9\cdot\text{L}^{-1}$) was still present in two of four patients tested.

Discussion

This study reports five cases of females who presented with chronic eosinophilic pneumonia following RT for breast cancer, suggesting that radiation to the lung may promote the development of chronic eosinophilic pneumonia similar to that described for organising pneumonia [2]. All patients had a history of asthma and/or atopic manifestations. All presented with a characteristic clinical syndrome of chronic eosinophilic pneumonia that followed after 1–10 months from the completion of RT to the breast. The main manifestations included dyspnoea of subacute onset, cough, alveolar and/or infiltrative pulmonary opacities, and marked alveolar and peripheral eosinophilia, in the absence of any identifiable cause of eosinophilic pneumonia. A dramatic and rapid resolution of clinical and radiological manifestations was obtained with corticosteroid therapy in all cases. A relapse was observed in two patients within weeks after stopping oral corticosteroids. A migratory pattern of radiological opacities characteristic of idiopathic chronic eosinophilic pneumonia was present at initial presentation or at relapse in two cases.

The clinical and radiological manifestations of chronic eosinophilic pneumonia and organising pneumonia may be almost similar, with an excellent response to corticosteroid therapy in both cases. Therefore, the differential diagnosis between the two entities is based on the presence of a marked peripheral blood and alveolar eosinophilia in chronic eosinophilic pneumonia, and on histopathological analysis in organising pneumonia; however, pulmonary biopsy is rarely performed in chronic eosinophilic pneumonia [4]. There is occasional pathological overlap between these entities, with the possible presence of foci of intraluminal granulation tissue in otherwise typical eosinophilic pneumonia, and possible eosinophilic interstitial infiltrates in organising pneumonia [6, 7]. Similarly, mild alveolar eosinophilia may be present in cryptogenic [4] and RT-induced organising pneumonia [1, 2, 8]. In the present series, the diagnosis of chronic eosinophilic pneumonia was based on the combination of typical clinical, radiological, and biological features [4]. Eosinophilia was pronounced, with blood eosinophil count $>1.0\times 10^9\cdot\text{L}^{-1}$ in all cases, and alveolar differential cell count $>40\%$ in the two

cases where bronchoalveolar lavage was performed at diagnosis. In addition, the diagnosis of eosinophilic pneumonia was confirmed pathologically in a patient who underwent video-assisted thoracoscopic pleurodesis.

A strong association between idiopathic chronic eosinophilic pneumonia and asthma is now well established [3]. The present observation further suggests that RT to the breast may predispose to the development of chronic eosinophilic pneumonia, especially in patients with a history of asthma or atopy. A causal relationship between RT and chronic eosinophilic pneumonia in patients from the current study is supported by the appearance of pulmonary opacities in the irradiated area, with subsequent spreading to the ipsilateral lung, then to the contralateral lung, as occurs in radiation-induced organising pneumonia [2]. In three of the five cases, the lung opacities remained strictly unilateral, a feature that is unusual in idiopathic chronic eosinophilic pneumonias [5], further suggesting that RT may have contributed to the development of this syndrome. The time course of the chronic eosinophilic pneumonia was compatible with a role of RT, since previous studies have demonstrated that radiation-induced organising pneumonia may develop within a year after the completion of RT [1, 2]. A careful search identified no parasitic infection that could have caused eosinophilic pneumonia. *Aspergillus* may have contributed to the development of eosinophilic pneumonia in one patient. Diagnostic criteria of allergic bronchopulmonary aspergillosis were not fulfilled in this patient without proximal bronchiectasis on chest computed tomography. However, "allergic bronchopulmonary aspergillosis-seropositive" [9] may be considered despite the lack of relapse with steroid taper. One patient received montelukast, a drug which has been suspected to induce chronic eosinophilic pneumonia [10], and to trigger the onset of formes frustes of Churg-Strauss syndrome [11]; however, this is controversial and the responsibility of the drug has not been established. As in the published series of organising pneumonia primed by RT [2], several patients had also received tamoxifen in the months preceding the eosinophilic pneumonia, an agent which may enhance radiation-induced lung fibrosis [12], but is not recognised as a definite cause of eosinophilic pneumonia. Interestingly, the incidence of idiopathic chronic eosinophilic pneumonia is higher in females [5].

The authors hypothesise that chronic eosinophilic pneumonia may be facilitated by lung irradiation. Indeed, a slightly elevated number of eosinophils in bronchoalveolar lavage cell count has been reported in patients receiving RT following breast cancer surgery [13]. RT induces a diffuse bilateral and persistent lymphocytic alveolitis [14]. The development of chronic eosinophilic pneumonia may then be triggered by other factors such as drugs, *Aspergillus* infection, and environmental exposures. The hypothesis that *Aspergillus* may have contributed to the development of the eosinophilic pneumonia in one patient is consistent with the proposed model of pathophysiology, where priming by RT is followed by antigenic stimulation (in this particular case *Aspergillus* may have provided the antigen). Diffuse bilateral lymphocytic alveolitis develops in most patients after unilateral breast irradiation [15], even in the absence of radiological evidence of pneumonitis [16]. Lymphocytes recruited to the lung mainly consist of activated CD4+ helper T cells, which may be "primed" by RT [14]. T-helper cells can be divided into two subsets, T-helper cell type 1 (Th1) cells, which secrete interferon- γ and lymphotoxin, and T-helper cell type 2 (Th2) cells, which secrete interleukin (IL)-4, IL-5, and IL-13. Interestingly, Th1 and Th2 lymphocyte clones are not equally sensitive to irradiation [17]. Lymphoid irradiation and ultraviolet B radiation have been shown in animal models to shift the allospecific memory response

toward a Th2 cytokine profile [18, 19]; Th2-like functions recover rapidly after lymphoid irradiation, whereas a selective deficit in the Th1-like functions persists for several weeks [20]. The authors speculate that antigenic stimulation may trigger a Th2-type of lymphocyte response when occurring in the weeks following lymphocyte priming by RT, thus leading to the occurrence of chronic eosinophilic pneumonia. The Th2-type immunological response may also be further facilitated by individual susceptibility and genetic factors, which were indeed suggested by a history of asthma or allergy in patients in the current study. In contrast, a Th1 response might predispose to radiation-induced organising pneumonia [21]. RT-induced organising pneumonia may occur several years after the completion of RT [22, 23], consistent with the persistence of alveolitis for a prolonged period of time. It is thus conceivable that eosinophilic pneumonia may be primed by RT, and then triggered by antigenic stimulation several months thereafter.

In conclusion, these observations suggest that chronic eosinophilic pneumonia may be included in the spectrum of potential pulmonary changes secondary to radiation therapy to the chest. Although a causal relationship between radiation therapy and chronic eosinophilic pneumonia cannot be definitively established from this descriptive study, the authors hypothesise that priming of alveolitis by radiation therapy to the breast may result in either chronic eosinophilic pneumonia or organising pneumonia, depending on the genetic or acquired characteristics of patients and/or further triggering factors. A history of asthma or allergy may thus predispose to the development of this condition.

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