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Bilateral lymphocytic alveolitis: a common reaction after unilateral thoracic irradiation

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Bilateral lymphocytic alveolitis: a common reaction after unilateral thoracic irradiation. C. Martín, S. Romero, J. Sánchez-Payá, B. Massutí, J. M. Arriero, L. Hernández. ©ERS Journals Ltd 1999.

ABSTRACT: The main aim of the present study was to assess the early diagnostic value of bronchoalveolar lavage (BAL) in radiation-induced lung injury in patients with breast carcinoma.

Twenty-six females receiving postoperative radiotherapy for breast cancer were evaluated before and 0, 15, 30, 60, and 180 days after radiotherapy. History, physical examination, chest radiographs, and pulmonary function tests were obtained. BAL, including lymphocyte subsets analysis, was limited to the second evaluation after radiotherapy. A group of 21 healthy females were used as control. Findings after radiotherapy in asymptomatic patients were compared with findings in a group of patients with radiation pneumonitis.

Irradiated patients showed a significantly ($p<0.01$) greater percentage (29.5±15.7%) of BAL lymphocytes than controls (6.2±3.3%). No statistical differences existed in BAL findings between the irradiated and unirradiated sides of the chest. Percentages of BAL lymphocytes did not differ significantly between patients who developed subsequent pneumonitis (24.5±13.5%) and those who did not develop pneumonitis (32.8±16.5%). Patients with pneumonitis at the time of BAL had significantly higher ($p<0.05$) alveolar CD4 subset cells (24.8±10.2%) than asymptomatic patients (15.2±8.9%). Maximal reductions in total lung capacity ($p<0.01$), and residual volume ($p<0.05$) occurred 60 days after irradiation.

The early lymphocytic alveolitis induced by unilateral thoracic radiotherapy in most patients with breast cancer is always bilateral and does not predict the subsequent development of radiological evidence of pneumonitis.

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Thoracic radiotherapy is limited by its adverse effects on normal lung tissue [1–3]. The volume of irradiated lung, total radiation dose delivered, dose rate, fractionation applied, and the type of energy used all influence the subsequent appearance of radiation lung injury [4]. In up to 15% of patients, an early acute pneumonitis develops 6–12 weeks after radiotherapy [5]. Lung changes induced by thoracic radiation were thought to be confined to only that part of the lung included in the radiation window [1–4]. However, ROBERTS *et al.* [6] have recently demonstrated that in most patients a lymphocytic alveolitis develops in both lung fields 4–6 weeks after strictly unilateral thoracic irradiation, and this was more pronounced in patients who developed pneumonitis. The mechanism whereby limited irradiation produces a severe generalized process has not been established [6, 7]. The present prospective study was designed to confirm the existence of an early bilateral alveolitis following unilateral radiation and, since the presymptomatic finding of these changes could lead to a more effective management of radiation pneumonitis, to assess whether its presence or intensity could bear any relationship with the subsequent development of pneumonitis.

For editorial comments see page 715.

Patients and methods

The prospective study group consisted of 26 females referred for postoperative radiotherapy for breast cancer. The mean age was 50.9±11.2 yrs (range 29–68 yrs). Six patients were current or former smokers with a mean of 7±4.9 pack-yrs.

Mastectomy, partial in 13 patients, and axillary dissection had been performed in all 26 patients.

Twenty-four premenopausal females received six cycles of adjuvant chemotherapy. In 12 patients, adriamycin, cyclophosphamide and 5-fluorouracil were given before radiotherapy, and in the 12 remaining patients, radiotherapy was given between the third and fourth cycles of cyclophosphamide, methotrexate, and 5-fluorouracil. Two postmenopausal patients received tamoxifen, 20 mg daily.

All patients gave their informed consent for the study. Before radiotherapy, the following studies were performed: detailed medical history and examination, posteroanterior and lateral views of chest radiograph, and pulmonary function tests (PFT). All these procedures were repeated just after completing radiotherapy, and 15, 30, 60, and 180 days after. Bronchoalveolar lavage (BAL) was performed 15 days after the completion of radiotherapy.

Radiotherapy technique

Eighteen patients received both a direct anterior field to the supraclavicular fossa angled to the ipsilateral axilla with the medial edge at midline, as well as medial-lateral opposed tangential beams for the chest wall or residual breast tissue. Eight patients received only the latter type of radiotherapy. Doses used were 45–50 Gy in 1.8–2-Gy fractions to the supraclavicular fossa and to the breast. All treatments were given 5 days·week^{-1} using a Cobalt-60 machine (Theratron 80; AELC, Ottawa, Canada).

Bronchoalveolar lavage

The BAL results from 21 healthy females, with a mean age of 20.2±3.6 yrs were used as controls. Seventeen of these females were smokers of 2.4±1.0 pack-yrs.

For comparative reasons, BAL results from three females with clinical radiation pneumonitis who were not included in the prospective study were also used. BAL was carried out using an Olympus fibreoptic instrument (Olympus Optical Company, Hamburg, Germany) under local anaesthesia. The bronchoscope was wedged into the anterior segment of both upper lobes, beginning with the unirradiated one. In the five patients who presented with radiation infiltrates, the BAL samples were taken from the more affected segment. Room-temperature normal saline (150 mL) was instilled into each segment, in three 50-mL aliquots, each aspirated gently with syringe after instillation. The first aliquot was exclusively used for bacteriological studies, including *Mycobacterium tuberculosis* and *Pneumocystis carinii*. The fluid was collected in a siliconized vessel and immediately transported to the laboratory.

The fluid was homogenized with a Pasteur pipette, and a sample of the lavage was counted in a Neubauer chamber. Cell counts were expressed as cells per 100 mL. The analysis of differential cell counts and lymphocyte subsets of BAL cells was performed using a flow cytometer (Cytoron Absolute Ortho; Ortho Diagnostic System, New Jersey, USA). BAL cells were washed with phosphate-buffered saline (PBS) and centrifuged for 10 min at $600 \times g$. An aliquot (100 µL) at 5×10^6 cells·mL^{-1}, was incubated with 10 mL of fluorochrome-conjugated monoclonal antibody for 20 min at 4°C, and gating was checked using a flow cytometer. The following antibodies were used: CD3, CD4, CD8, CD20, CD56, CD36, CD15, CD-11b and human leukocyte antigen (HLA)-DR (Ortho Diagnostic System, Neckargemünd, Germany). A lymphocyte percentage >15% was considered indicative of alveolar lymphocytosis [8, 9].

Pulmonary function tests

The initial evaluation was performed several weeks after mastectomy when the scar had healed, and incisional pain was no longer present. The following PFT were performed using a Master-Lab Jaeger equipment (Würzburg, Germany): maximum expiratory flow–volume curve, including forced vital capacity (FVC), forced expired volume in one second (FEV_1), and the FEV_1/FVC ratio; single breath diffusing capacity, and lung volume studies, including total lung capacity (TLC) and residual volume (RV). Each PFT was expressed as a percentage of predicted values based on age, sex, race and height according to European Community for Coal and Steel reference values [10].

Chest radiographs

Posteroanterior and lateral radiographs of the chest were evaluated independently by three observers (C. Martín, S. Romero, L. Hernández), and agreement of at least two was required.

Any new interstitial or alveolar infiltrate with or without simultaneous loss in lung volume in the absence of another evident cause was considered indicative of radiation pneumonitis.

Statistical analysis

To compare pulmonary function parameters between intervals, the Wilcoxon rank test for paired data in the SPSS statistical package (SPSS Inc., Chicago, IL, USA) was used. The Mann–Whitney U-test was used to compare changes in pulmonary function between groups.

To compare BAL findings between groups, the Student′s t-test for unpaired data was used. Differences in BAL between both lungs were assessed by the paired Student′s t-test. Values of $p<0.05$ were considered as significant.

Results

Eight patients (31%) developed radiological signs of pneumonitis 15–90 days after completing radiotherapy. The infiltrates, interstitial or alveolointerstitial, were always limited to the upper lobes of the irradiated side. Signs of volume loss were evident in two patients. Together with the radiographic signs, four patients presented symptoms consisting of cough (four), dyspnoea (three) and fever (one). Four patients remained asymptomatic. No patient developed progressive symptomatic radiation fibrosis.

Patients who developed radiation pneumonitis were younger (46.8±10.9 yrs) than patients without pneumonitis (52.6±11.7 yrs). Seven out of eight patients who developed radiation pneumonitis had received direct irradiation.

BAL results

Differences in mean BAL data between patients and controls are given in table 1. When compared with healthy females, total lavage cell numbers, the percentages of neutrophils, lymphocytes, and CD4 and CD8 lymphocyte subsets were significantly higher in patients (table 1).

In 22 of 26 patients (85%), radiotherapy induced an alveolar lymphocytosis. Alveolar lymphocytosis was always bilateral and of a similar intensity in the irradiated (29.5±15.7% lymphocytes) and unirradiated lung (29.1± 13.6% lymphocytes) (table 2).

Two patients presented with radiographic pneumonitis when the BAL was carried out. The BAL data from these patients, together with those of the three patients not prospectively studied, are shown in table 3, and compared with those of the 24 patients without evident pneumonitis in table 4. The mean age of the five patients with radiation pneumonitis was 51.2±5.3 yrs, and all were nonsmokers and had been treated with adjuvant cyclophosphamide, methotrexate and 5-fluorouracil.

Table 1. – Bronchoalveolar lavage findings: differences between patients (irradiated side) and healthy female controls

	Patients n=26	Controls n=21	p-value
Volume mL	66.9±12.7	80.8±12.4	0.01
Total cells*	34.5±11.1	23.7±14.6	0.001
Macrophages %	61.5±19.5	91.9±4.1	0.001
Neutrophils %	4.6±3.6	1.5±1.7	0.001
T-lymphocytes %	29.5±15.7	6.2±3.3	0.001
CD4 %	15.1±8.6	3.1±1.5	0.001
CD8 %	12.9±8.2	3.2±1.9	0.001
CD4/CD8 ratio	1.7±1.3	1.1±0.4	0.05

Results are expressed as mean±SD. *: expressed as 10^6 cells·100 mL lavage fluid^{-1}.

No significant differences between lungs were found in the lavage material of patients with pneumonitis (table 3).

Patients with pneumonitis at the time of BAL had a higher percentage of CD3 lymphocytes (39.0±8.0%) than patients without pneumonitis (30.0±16.4%) and a significantly higher percentage ($p<0.05$) of CD4 (table 4).

Early inflammatory lymphocytic alveolitis in both irradiated (21.3±14.1 *versus* 32.8±16.5% lymphocytes) and unirradiated sides (25.7±16.2 *versus* 30.8±13.6% lymphocytes), was of a similar degree in patients who ultimately, but not at the time of BAL, developed pneumonitis than in those who did not develop pneumonitis (tables 5 and 6). Two out of the six patients who later developed pneumonitis did not present with lymphocytic alveolitis.

No observable effect was found for surgical lumpectomy *versus* mastectomy or for methotrexate *versus* adriamycin on the percentage of alveolar lymphocytes, although the total number of cells was significantly lower in patients treated with methotrexate or by lumpectomy (data not shown). The two patients who did not receive chemotherapy developed bilateral alveolar lymphocytosis (40 and 27% on the irradiated side, and 37 and 38% on the unirradiated side).

The bacteriological studies were always negative.

Lung function

Maximal and significant reductions in TLC ($p<0.01$), and RV ($p<0.05$), with respect to basal values, occurred 60 days after radiotherapy. A significant recovery ($p<0.04$), 4 months later, was only evident in RV (table 7). The reduction was not more pronounced in those patients who developed pneumonitis.

Table 2. – Bronchoalveolar lavage findings: comparison between the irradiated and unirradiated sides of the chest in 26 patients

	Irradiated	Unirradiated	p-value
Volume mL	66.9±12.7	62.6±16.7	0.28
Total cells*	34.5±11.1	36.3±12.4	0.59
Macrophages %	61.5±19.5	62.2±18.2	0.67
Neutrophils %	4.6±3.6	4.8±4.0	0.64
T-lymphocytes %	29.5±15.7	29.1±13.6	0.79
CD4 %	15.1±8.6	15.0±7.8	0.96
CD8 %	12.9±8.2	13.0±7.7	0.89
CD4/CD8 ratio	1.7±1.3	1.6±1.2	0.064

Results are expressed as mean±SD. *: expressed as 10^6 cells·100 mL lavage fluid^{-1}.

Table 3. – Bronchoalveolar lavage findings: comparison between the irradiated and unirradiated sides of the chest in five patients with radiation pneumonitis

	Irradiated	Unirradiated	p-value
Volume mL	72.2±8.4	69.6±19.7	0.77
Total cells*	34.1±9.6	34.0±10.0	0.98
Macrophages %	50.0±8.6	56.8±9.3	0.052
Neutrophils %	6.6±6.9	4.6±2.7	0.46
T-lymphocytes %	39.0±8.0	34.6±10.4	0.08
CD4 %	24.8±10.2	25.2±13.2	0.36
CD8 %	16.2±6.8	12.0±5.2	0.28
CD4/CD8 ratio	2.2±1.8	2.8±1.9	0.38

Results are expressed as mean±SD. *: expressed as 10^6 cells·100 mL lavage fluid^{-1}.

Discussion

There is usually a delay, ranging 1–3 months, from the completion of radiotherapy to the development of acute pneumonitis [3, 11]. Although symptoms may develop before apparent radiographic change, the number of patients who show radiological abnormalities is significantly higher than the number of patients with symptoms [3]. It was for this higher sensitivity that the radiographic changes were considered in this study as the markers of acute lung injury. Compared with the routine chest radiographs, computed tomography (CT) has been considered to be more sensitive for radiation-induced lung injury in that changes may be observed as early as 4 weeks post-irradiation [5]. Because, in the present study, two patients showed radiographical evidence of pneumonitis only 2 weeks post-irradiation, such an early detection does not, however seem exclusive to CT.

The development of lymphocytic alveolitis in the lung exposed to radiation in patients with lung as well as breast cancer has been previously demonstrated [12–15]. The first well-documented study of bilateral lymphocytic alveolitis after unilateral radiotherapy in patients with breast cancer was published by GIBSON *et al.* [7] in 1988, and more recently, they have expanded upon their prior investigation

Table 4. – Differences in bronchoalveolar lavage (BAL) findings between five patients with radiation pneumonitis and 24 patients without any evidence of pneumonitis at the moment of BAL (irradiated side)

	With pneumonitis	Without pneumonitis	p-value
Volume mL	72.2±8.4	66.5±13.1	0.36
Total cells*	34.1±9.6	34.9±10.5	0.62
Macrophages %	50.0±8.6	61.5±19.9	0.22
Neutrophils %	6.6±6.9	4.8±3.6	0.61
T-lymphocytes %	39.0±8.0	30.0±16.4	0.24
CD4 %	24.8±10.2	15.2±8.9	0.04
CD8 %	16.2±6.8	12.3±8.0	0.32
CD4/CD8 ratio	2.2±1.8	1.8±1.3	0.56

Results are expressed as mean±SD. *: expressed as 10^6 cells·100 mL lavage fluid^{-1}.

Table 5. – Bronchoalveolar lavage findings (irradiated side): differences between six patients ultimately developing radiation pneumonitis (DRP) and 18 patients without any evidence of pneumonitis (NDRP)

	DRP	NDRP	p-value
Volume mL	67.7±11.6	66.1±13.8	0.86
Total cells*	39.0±12.5	33.7±11.6	0.55
Macrophages %	73.5±17.3	57.4±19.5	0.12
Neutrophils %	3.5±2.1	5.2±4.0	0.44
T-lymphocytes %	21.3±14.1	32.8±16.5	0.12
CD4 %	13.5±9.3	15.7±9.0	0.62
CD8 %	7.8±5.9	13.9±8.3	0.11
CD4/CD8 ratio	1.9±0.7	1.7±1.4	0.29

Results are expressed as mean±SD. *: expressed as 10^6 cells·100 mL lavage fluid^{-1}.

[6], confirming the previous results. Although the lymphocytic alveolitis was more intense in patients who developed clinical pneumonitis, a similar but less intense reaction was also seen in the lavage of asymptomatic patients who received radiotherapy.

Despite differences in BAL technique, with respect to these latter studies [6, 7], the present study confirms their results. The cytocentrifuge preparations used herein, compared with millipore filter preparations, may underestimate the percentage of lymphocytes in the BAL fluid [16, 17]. However, due to its relative simplicity, it has been common practice to use the cytocentrifuge method for quantifying BAL cells in most laboratories [8, 9, 18]. Although in the patients studied by ROBERTS *et al.* [6], using millipore filter preparations, the percentages and absolute number of alveolar lymphocytes were much higher than in the patients in the present study, the differences with controls in both studies were equivalent, allowing similar conclusions to be drawn.

The present study demonstrates that the lymphocytic alveolitis occurs within 15 days after completion of radiotherapy in a proportion of patients almost identical to that found by ROBERTS *et al.* [6] 2–4 weeks post-irradiation, and as in their patients, the intensity of the lymphocytic alveolitis was higher in those with pneumonitis. In the present study these differences were only significant in the CD4 subset, but this higher percentage of CD4 cells, together with evident overactivation of these cells, was also found by ROBERTS *et al.* [6] in the only patient in whom lymphocyte subsets were determined.

Table 6. – Bronchoalveolar lavage findings (unirradiated side): differences between six patients ultimately developing radiation pneumonitis (DRP) and 18 patients without any evidence of pneumonitis (NDRP)

	DRP	NDRP	p-value
Volume mL	68.5±12.2	59.0±17.7	0.23
Total cells*	34.4±8.3	38.2±13.3	0.84
Macrophages %	69.2±19.4	58.9±18.4	0.37
Neutrophils %	2.8±1.8	5.6±4.4	0.15
T-lymphocytes %	25.7±16.2	30.8±13.6	0.44
CD4 %	14.7±9.3	15.8±7.8	0.97
CD8 %	11.0±8.0	13.5±7.9	0.46
CD4/CD8 ratio	1.5±0.6	1.6±1.4	0.53

Results are expressed as mean±SD. *: expressed as 10^6 cells·100 mL lavage fluid^{-1}.

Microcapillary vascular damage together with damage to type I and II pneumocytes results in ischaemic tissue injury, altered surfactant production, atelectasis and secondary vascular atrophy within the radiation treatment window [11, 19]. These changes result from the interaction of radiotherapy with genetic or environmental factors, such as concurrent therapy [20], degree of lymphoid irradiation [21], and age [22]. ROBERTS *et al.* [6] postulated that because this mechanism cannot adequately explain either the degree of respiratory distress after the irradiation of a relatively small volume of lung tissue, or the resolution of symptoms with time without significant sequelae in most patients, another mechanism, possibly a lymphocytic-mediated hypersensitivity reaction, could participate in the process. It is possible that direct tissue damage from radiotherapy, known to cause antigen release [3], produces sensitization of autoreactive lymphocyte clones, which then migrate to the lung and react with pulmonary tissues.

Scattering of irradiation outside the intended radiation field may occur. However, the dose that the unirradiated lung would receive is usually well below the tolerance dose for lung tissue and the dose received by the irradiated lung. Although lung infiltrates outside the radiation field may occur [23–25], most patients, as in the present study, show involvement confined to the irradiation window. Thus, scattering of irradiation appears an unlikely explanation for the lymphocytic alveolitis demonstrated in BAL of the contralateral lung, which is of similar intensity to that seen in the irradiated lung.

In the present study patients were not used as their own control, and this does not rule out the presence of a previous lymphocytic alveolitis. Methotrexate pneumonitis [26] or toxicity from another chemotherapeutic agent [27], or allergic alveolitis related to a humidifier system or to another antigen in the local environment [28] could be associated with similar findings in the BAL. However, patients receiving methotrexate without evidence of pulmonary toxicity had a normal percentage of alveolar lymphocytes, and no patient in this series presented any distinctive signs related to methotrexate pneumonitis [26, 29]. Furthermore, 12 patients, included herein, free from chemotherapy with methotrexate, also demostrated bilateral alveolar lymphocytosis. Also, against the possible influence of chemotherapy is the fact that two patients in the present study and 10 patients in the study by ROBERTS *et al.* [6], who did not receive chemotherapy, developed bilateral alveolar lymphocytosis. A selective allergic alveolitis was not clinically evident in any patient, and was considered unlikely in females who, while in hospital, were not exposed to any environmental agents known to induce lung disorders, and were later treated as outpatients.

The present study was designed to evaluate whether an early inflammatory alveolitis was associated with the subsequent development of radiation pneumonitis. Contrary to the study by LAFFITE *et al.* [12], which showed a significantly more intense lymphocytic alveolitis in those patients who later on developed pneumonitis, it was not possible from the initial intensity of the alveolitis to anticipate the subsequent course of the disease. It is difficult to assess the methodological differences responsible for this interstudy discrepancy because to our knowledge, the study by LAFFITE *et al.* [12] was only published as an abstract. However, chronological differences could explain the differences in the results from both studies. In fact, a

Table 7. – Changes in pulmonary function tests after radiotherapy

Time	FVC %	TLC %	RV %	$D_{L,CO}$ %	$P_{A\text{-}a,O_2}$
BRT	108 (99–116)	102 (92–111)	96 (87–115)	97 (87–107)	11 (6–18)
ART	108 (99–119)	105 (96–113)	101 (89–113)	98 (89–105)	13 (6–18)
Day 14	111 (100–118)	103 (92–112)	103 (88–112)	97 (87–105)	7 (4–14)
Day 30	111 (97–118)	106 (100–110)	100 (84–115)	97 (85–106)	8 (4–12)
Day 60	110 (92–120)	96 (90–105)	90 (73–106)	94 (88–101)	11 (4–18)
p-value*	0.36	0.007	0.019	0.73	0.67
Day 180	106 (92–121)	101 (86–113)	92 (84–108)	95 (88–108)	10 (4–17)
p-value**	0.64	0.23	0.035	0.51	0.18

Results are expressed as the median (25–75th percentiles). BRT: before radiotherapy; ART: after radiotherapy; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; $P_{A\text{-}a,O_2}$: alveolar–arterial tension difference for oxygen; *: denotes the difference between values before radiotherapy and values 60 days after its completion; **: denotes the difference between values 60 and 180 days after the completion of radiotherapy.

heralding alveolitis 4 weeks post-irradiation, as the results of LAFFITE *et al.* [12] seem to indicate, but not evident only 2 weeks post-irradiation, cannot be ruled out. However, a lymphocytic alveolitis has been previously shown in patients with Crohn′s disease [30, 31], dairy farmers [32, 33] and individuals exposed to asbestos [34]. In all of these, as in the present population, lavage lymphocytosis *per se* did not predict lung disease, deterioration of pulmonary function, or radiological changes over the time span studied.

In radiation pulmonary lung injury, PFT are typical for an alveolar-based disease, with a decrease in lung volumes and diffusing capacity usually being detected within 11 weeks after the completion of radiotherapy [35]. In this limited series of patients with irradiated breast cancer, significant changes were revealed by TLC and RV. The maximal decrease was 60 days after completion of radiotherapy and occurred, as reported previously [36–38], without any apparent relationship with radiographic changes. These findings suggest that the reduction in pulmonary volume depends more on the diffuse lymphocytic alveolitis than on the extension of the localized lung damage.

In summary, the results of the present study confirm that in most patients, an early lymphocytic alveolitis develops in both lung fields after strictly unilateral thoracic irradiation. However, the early cytological changes in bronchoalveolar lavage do not add any valuable information to that provided by routine chest radiographs for the better management of radiation pneumonitis.

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