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# The Bronchoalveolar Lavage Pattern in Radiation Pneumonitis Secondary to Radiotherapy for Breast Cancer

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**ABSTRACT**

***Background and purpose:*** *Radiotherapy in breast cancer patients is limited by lung tissue tolerance. Two complications involving the lung are known: radiation pneumonitis (RP) and radiation fibrosis. The aim of the study was to evaluate the pattern of bronchoalveolar lavage (BAL) in patients with RP after radiotherapy for breast cancer in symptomatic and asymptomatic patients.*

***Material and methods:*** *Sixty-five female patients (mean age 58.3 yrs) with RP after radiotherapy for breast cancer were included in the study. The majority of patients had previous breast surgery (mastectomy or lumpectomy and axillary dissection) and received doses of radiations of 45-50Gy. All patients had adjuvant chemotherapy with cyclophosphamide, 5-fluoro-uracil, and epirubicin or methotrexate.*

***Results:*** *All patients had an infiltrate or consolidation on chest radiography confined to the upper lobe of the irradiated lung, as marker of RP. Based on the presence or absence of symptoms, we divided the patients in 2 groups: 49 patients (75.4%) with symptomatic RP (fever, cough, dyspnea, chest pain and fatigue) and 16 patients (24.6%) without any symptom. Symptomatic RP patients had a BAL with significant increase in total cells (18.0±12.2 $x10^6$ cells•100mL-1) when compared to BAL in asymptomatic patients (11.9±6.2 $x10^6$ cells•100mL-1), p=0.01. Lymphocytosis in BAL was significantly increased in symptomatic group, compared with asymptomatic one (35.4±18.7% vs. 26.1±14.3%, p=0.045), with predominance of T lymphocytes (CD3). It was also a predominance of CD4 lymphocytes in all patients, but the CD4/CD8 ratio was inside normal range in the majority of cases. Five patients had clinical features of bronchiolitis obliterans organizing pneumonia (BOOP) secondary to irradiation with increased percentages of lymphocytes, neutrophils, eosinophils, and mast cells in BAL and one patient without history of atopic disease had a percentage of 40% eosinophils. Only a mild reduction in diffusing capacity for carbon monoxide was seen in both groups on pulmonary function tests. The lung volumes were normal in all patients.*

***Conclusions:*** *Lymphocytic alveolitis was the marker of radiation pneumonitis in all patients. The degree of the inflammatory reaction of the lungs was correlated with the presence of symptoms. The lymphocytic alveolitis consisted mainly of T lymphocytes, with a predominance of CD4 subset in both groups, but the CD4/CD8 ratio remained mostly into normal range.*

**Keywords:** radiation pneumonitis, breast cancer, bronchoalveolar lavage, lymphocytosis

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## BACKGROUND

The combined use of surgery, chemotherapy and radiotherapy increased the efficacy of breast cancer treatment. The use of radiotherapy is limited by its complications, especially involving the lung (1,2). Lung tissue tolerance to radiation therapy often requires treatment breaks or dose reductions that limit the success of the therapy.

Radiation-induced lung injury comprises two syndromes: radiation pneumonitis and radiation fibrosis. Radiation pneumonitis (RP) usually becomes apparent after 1 to 6 months after the completion of radiotherapy and radiation fibrosis after at least 6 months to one year (3,4). Pathogenesis is uncertain, but involves direct lung toxicity and an inflammatory response of the lung to irradiation (2,5).

The diagnosis of radiation pneumonitis is based on radiographic image associated with nonspecific clinical appearance with or without abnormalities in pulmonary function tests. The clinical appearance of radiation pneumonitis could consist of fever, cough, and dyspnea and the radiological pattern consists of infiltrates or alveolar consolidation, usually corresponding to the irradiated side (2,3). The challenge in this issue lies in the differential diagnosis of RP with infections and cancer relapse. BAL proved to be a useful tool in the investigation of inflammatory reactions in the lung interstitium (6-9). A retrospective analysis in 451 patients found early radiologic changes compatible with radiation pneumonitis in 29.7% and clinical symptoms associated with radiological image in only 5.5% of breast cancer patients (10). ❑

## OBJECTIVES

In the last years bronchoalveolar lavage (BAL) was frequently used in the diagnosis of RP (11-15) and the purpose of this study is to evaluate the inflammatory reaction in the lung parenchyma using BAL technique in patients with radiation pneumonitis after radiotherapy for breast cancer. ❑

## MATERIAL AND METHODS

A prospective study group of 65 consecutive women with suspected radiation pneumonitis after radiotherapy for breast cancer diagnosed in "Marius Nasta" Institute of Pneumology between 2001 and 2009 were included in this study. The age of the patients was 58.3±12.3 yrs (range 29-79 yrs). Eleven patients were smokers or former smokers (23.9±17.5 pack-years) and 54 were non-smokers. All patients included in the study had a newly discovered chest radiological image consisting of an infiltrate or consolidation corresponding to the radiation field.

Previous breast surgery, performed in 63 cases (96.9%), consisted of total mastectomy in 55 cases (34 on the right side and 21 on the left side), lumpectomy in 8 cases (2 on the right side and 6 on the left side), plus axillary dissection in all of them. Two patients had no surgical intervention.

All patients received radiotherapy with direct anterior field to the supraclavicular fossa angled to the ipsilateral axilla with the medial edge at midline, and medial-lateral opposed tangential beams for the chest wall and/or residual breast tissue. The doses used were 45-50Gy in 2Gy fractions. Sequential adjuvant chemotherapy was added to all patients and included cyclophosphamide, 5-fluoro-uracil, and epirubicin (58 cases, 89.2%) or methotrexate (7 cases, 10.8%).

Patients with hormone-receptor-positive breast cancer (45 cases, 69.2%) received tamoxifen, 20mg daily for 5 years.

At entry into the study the following were performed: detailed medical history, physical examination, chest radiography and CT-scan, respiratory function tests, and fiber optic bronchoscopy with BAL. All patients gave informed consent for study procedures, including bronchoscopy and bronchoalveolar lavage (BAL).

Posteroanterior and lateral radiographs and CT-scans of the chest were evaluated for new infiltrates, consolidations or other lesion considered indicative of radiation pneumonitis.

The following lung function tests were performed using a Master-Screen Body Jaeger equipment: maximum expiratory flow-volume curve, including forced vital capacity (FVC), forced expired volume in one second (FEV1), the FEV1/FVC ratio, and maximal expiratory flow at 50% of vital capacity (MEF50); lung volume studies, including total lung capacity (TLC) and residual volume (RV); single breath diffusing capacity (DL,co) and single breath diffusing capacity/alveolar ventilation ratio (DL,co/AV). Each parameter 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 (16-18).

Bronchoscopy and BAL were carried out using a fiberoptic instrument under local anesthesia with lidocaine. The bronchoscope was wedged into the segment of the lobe with the most prominent radiologic lesion. Bronchoalveolar lavage was performed with 120-160mL of room-temperature normal saline instilled into segmental bronchi corresponding with the involved area on the chest radiography in 20mL aliquots, each being aspirated immediately after instillation. Identification and enumeration of different cell types was performed on smears after May-Grünwald-Giemsa staining. Lymphocyte subsets were identified by monoclonal antibodies using a peroxidase-antiperoxidase method (19,20). A lymphocyte percentage >15% was considered indicative of alveolar lymphocytosis (21).

Results were compared using Student t-test for independent samples. ❑

## RESULTS

All patients included in the study were diagnosed with radiation pneumonitis with a delay of 2.9±2.1 months (range 0-9 months) after completing radiotherapy. The latent period was shorter in the symptomatic group (2.5±1.9 months) comparative to the asymptomatic group (4.5±2.3 months). All patients had chest radiological image consisting of infiltrates (fig.1) or alveolar consolidation with air bronchogram (fig.2) confined to the upper lobe of the irradiated lung. The radiological abnormalities were considered markers of radiation pneumonitis. It is known that the number of patients with radiological changes in RP is higher than those with both clinical symptoms and radiological image (2).

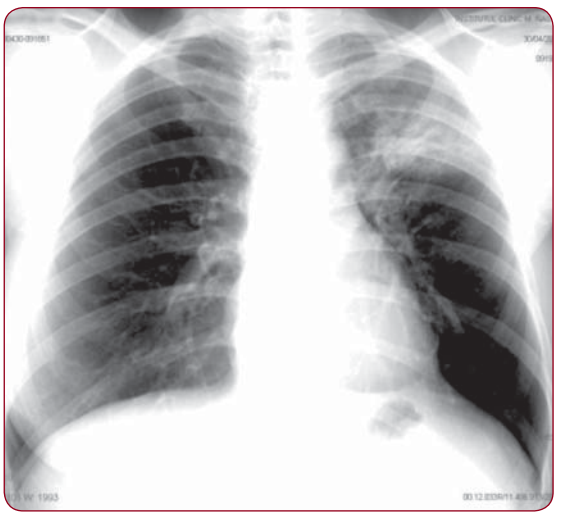

**FIGURE 1.** Chest radiography with left upper lobe infiltrate

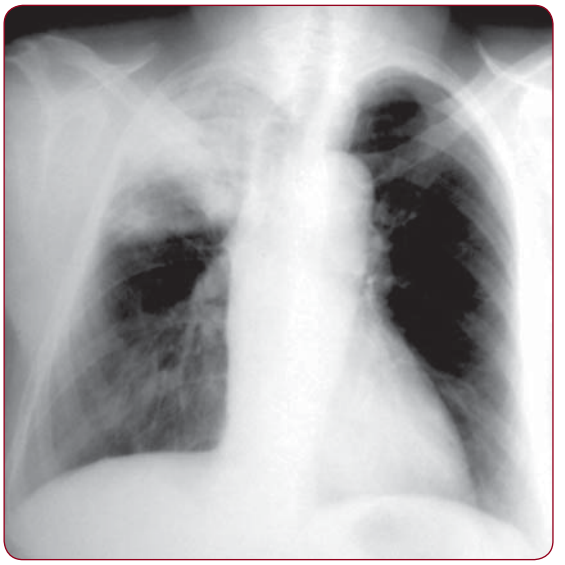

**FIGURE 2.** Chest radiography with right upper lobe consolidation

Based on the presence or absence of radiation pneumonitis symptoms patients were included in 2 groups: symptomatic radiation pneumonitis group and asymptomatic group. Symptomatic pneumonitis group had 49 patients (75.4%) with symptoms consisting of: cough (40 patients), dyspnea (25 patients), chest pain (6 patients), fever (16 patients), and fatigue (9 patients). Asymptomatic pneumonitis group consisted of 16 patients (24.6%) with radiological signs of RP and no health complaints (fig. 3). There were no significant differences neither in age (58.7±12.5 yrs in symptomatic RP and 57.1±12.2 yrs in asymptomatic RP) nor in the extension of radiological lesions. The symptomatic patients seek medical advice after a period of 4.6±3.9 weeks since symptoms occurred.

The differences in mean BAL data between patients with symptomatic RP and asymptomatic RP are given in table 1.

The number of total cells recovered from BAL fluid was significantly increased in symptomatic group ($18.0\pm12.2 \times 10^6$ cells•$100mL^{-1}$) in comparison with asymptomatic patients ($11.9\pm6.2 \times 10^6$ cells•$100mL^{-1}$), p=0.01.

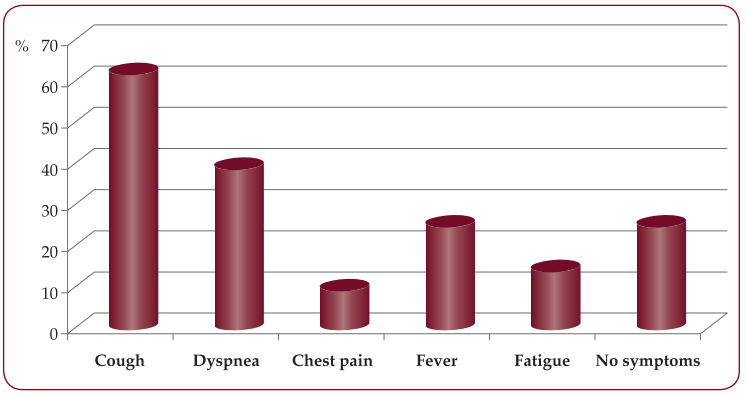


**FIGURE 3.** Patients with symptoms of radiation pneumonitis and asymptomatic patients (n=65 patients)

| | Symptomatic RP n=49 (mean ±SD) | Asymptomatic RP n=16 (mean ±SD) | p-value |
|---|---|---|---|
| Total cells (x $10^6$ cells • 100 $mL^{-1}$) | 18.0±12.2 | 11.9±6.2 | 0.01 |
| Macrophages (%) | 51.4±21.7 | 69.1±15.4 | 0.0001 |
| Lymphocytes (%) | 35.4±18.7 | 26.1±14.3 | 0.045 |
| Neutrophils (%) | 8.9±12.6 | 3.3±2.3 | 0.005 |
| Eosinophils (%) | 2.6±6.0 | 1.2±2.4 | 0.2 |
| Mastocytes (%) | 0.4±0.9 | 0.2±0.3 | 0.12 |
| Plasmocytes (%) | 0.0 | 0.0 | - |

**TABLE 1.** Bronchoalveolar lavage findings in symptomatic and asymptomatic patients with radiation pneumonitis (RP)
SD – standard deviation

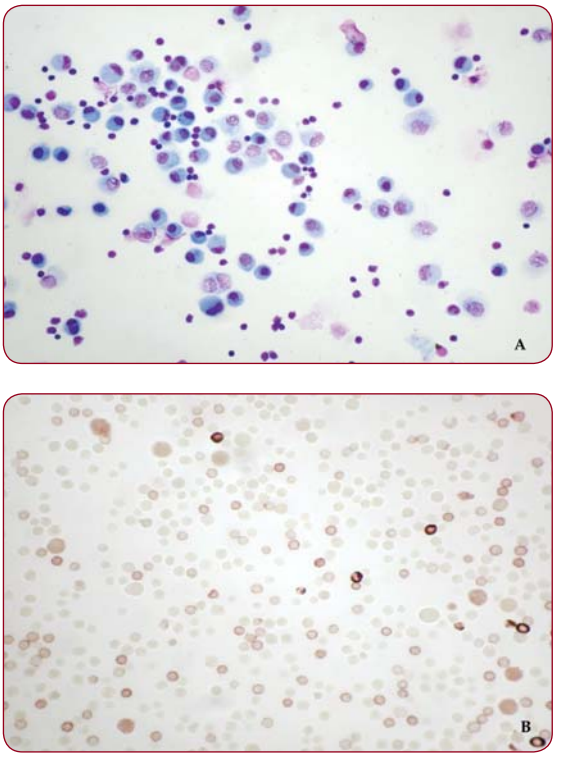


**FIGURE 4.** Bronchoalveolar lavage in radiation pneumonitis: a. Lymphocytic alveolitis (May-Grünwald-Giemsa stain); b. T lymphocytes (CD4) subtype (peroxidase-antiperoxidase method using monoclonal antibodies).

The increase in total lavage cell numbers in symptomatic patients appeared to be mostly attributable to the increase in lymphocyte count. The percentages of lymphocytes were higher than 15% in both symptomatic and asymptomatic patients which is indicative of alveolar lymphocytosis (fig. 4) (21). In symptomatic patients the percentage of lymphocytes was significantly higher (35.4±18.7%) than in asymptomatic patients (26.1±14.3%), p=0.045. The lymphocyte predominance was associated with a reciprocal decrease in the percentage of lavage macrophages in both groups, with a statistical significant lower level in symptomatic patients.

Neutrophils were significantly increased in symptomatic patients (8.9±12.6%) in comparison with asymptomatic group (3.3±2.3%), p=0.005. The percentages of eosinophils were not different in symptomatic group (2.6±6%) and in asymptomatic group (1.2±2.4%).

All patients with RP (symptomatic or not) had a lymphocytic alveolitis with high percentages of T lymphocytes, CD3 positive (table 2). In both groups there was predominance of CD4 lymphocytes, with a higher level in symptomatic patients. The CD4/CD8 ratio was inside the normal range, but it was decreased in asymptomatic RP in comparison with the symptomatic group. In the symptomatic group, 6 patients had a CD4/CD8 ratio above 3.5 and 2 patients had a CD4/CD8 ratio below one. None of the patients had an increased number of B lymphocytes (CD20).

Five patients had clinical aspect of secondary to radiotherapy bronchiolitis obliterans organizing pneumonia (BOOP), with migratory infiltrates on chest radiography initially inside the radiated field but spread out to the ipsilateral non irradiated areas. All 5 patients had symptoms consisting of: fever, cough and dyspnea. BAL features in these patients showed: total cells 14.6±7.4 x$10^6$ cells•100$mL^{-1}$, macrophages 49±14.5%, lymphocytes 36.8±6%, neutrophils 10.9±10.4%, eosinophils 1.88±2.6% and mast cells 1.32±2.6%. In compari-

| | Symptomatic RP n=18 (mean ±SD) | Asymptomatic RP n=3 (mean ±SD) | p-value |
|---|---|---|---|
| CD3 (%) | 87.6±9.4 | 88.7±1.5 | 0.85 |
| CD4 (%) | 59.6±15.6 | 46.3±15.0 | 0.19 |
| CD8 (%) | 26.1±9.8 | 38.7±16.0 | 0.07 |
| CD4/CD8 | 2.8±1.5 | 1.5±1.2 | 0.19 |
| CD20 (%) | 0.5±0.8 | 0.7±1.2 | 0.9 |

**TABLE 2.** Analysis of lymphocyte subsets in bronchoalveolar lavage in radiation pneumonitis

SD – standard deviation

| Population | Symptomatic RP n=49 (mean ±SD) | Asymptomatic RP n=16 (mean ±SD) | p-value |
|---|---|---|---|
| VC (% predicted) | 92.4±15.9 | 94.7±17.2 | NS |
| FEV1 (% predicted) | 93.6±16.1 | 96.0±13.8 | NS |
| FEV1/VC (%) | 84.3±6.8 | 84.3±9.9 | NS |
| MEF50 (% predicted) | 76.8±22.5 | 78.3±29.3 | NS |
| TLC (% predicted) | 102.6±16.2 | 107.5±24.1 | NS |
| RV (% predicted) | 130.7±36.1 | 130.9±49.3 | NS |
| DL,co (% predicted) | 66.8±14.8 | 71.7±20.8 | NS |
| DL,co/AV (% predicted) | 87.4±17.1 | 86.0±15.8 | NS |

**TABLE 3.** Lung function tests in symptomatic and asymptomatic radiation pneumonitis

SD – standard deviation; NS = not significant

son with the other patients only mast cells were increased. The percentages of lymphocytes, eosinophils, and neutrophils were at the same level.

One patient without history of asthma or atopy had an eosinophilia of 40% in BAL.

The smoking group (11 patients) had a slightly increased percentage of macrophages in BAL, but there were no statistically significant differences with the non-smokers group.

The bacteriological studies (cultures for Gram positive and Gram negative bacteria), and cultures for Mycobacterium tuberculosis, were negative in all patients. The cytology for cancer cells was also negative in all patients.

Lung function tests (table 3) showed only mild reduction in diffusing capacity for carbon monoxide in all patients with a slightly lower level in symptomatic patients (66.8±14.8%) in comparison with asymptomatic patients (71.7±20.8%), p=NS). The other lung function parameters were inside the normal range. ❑

## DISCUSSION

Radiation pneumonitis is a well-recognized potential complication of radiotherapy for breast cancer (3). Two mechanisms are involved in radiation-induced lung damage: *direct lesion of type I and II pneumocytes* with increased vascular permeability which results in altered surfactant production, atelectasis, reduced ventilation, and secondary vascular atrophy and *microcapillary vascular damage* producing ischemic tissue injury that eventually results in fibrotic healing (22-24). These mechanisms may explain direct tissue damage from radiotherapy within the radiation treatment portal but do not adequately explain the lung inflammatory reaction that occurs after irradiation. Previous histological studies were limited by the invasive methods required to obtain samples, but a series of open-lung biopsies taken from within the field of irradiation in patients with clinical pneumonitis has suggested a lymphocytic infiltration as the dominant finding in acute-phase pneumonitis (25). The investigation of radiation pneumonitis was difficult until the widespread use of bronchoalveolar lavage. Marked unilateral lymphocytic alveolitis was found in the bronchoalveolar lavage in the irradiated segments of the lungs in patients with clinical pneumonitis, demonstrating the

occurrence of lung inflammatory reaction after radiotherapy (26-28).

The degree of the lymphocytic alveolitis suggests an immunologic process that could be involved in the pathogenesis of radiation pneumonitis. Classically, the lymphocytic alveolitis is confined to the irradiated area, but there are studies that suggest a widespread inflammation in the lung. It is possible that antigen released by direct tissue damage (2) from radiotherapy produces a sensitization of the lymphocytes clones which migrate to the lung. After irradiation it is well known that lymphocytopenia may occur, due to the destruction of the lymphocytes in adjacent lymphoid structures or migration through the lung at the time of irradiation (29).

The present study, performed on 65 female patients with radiation pneumonitis after radiotherapy for breast cancer confirms the marked lymphocytic alveolitis described in previous studies (26,27). This inflammatory process was suggested by the marked increase in the absolute number and percentage of lymphocytes recovered from bronchoalveolar lavage performed in the lung segments with radiological evidence of RP. This lymphocytic alveolitis was more prominent in patients with clinical symptoms of RP, but it was also present on a lesser degree in patients with no symptoms of RP.

Lymphocytic alveolitis seems to be a reaction of both lungs, as suggested by previous studies. Gibson et al. provided evidence that radiation pneumonitis was not confined to the field of irradiation. Four patients with severe bilateral radiation pneumonitis after strictly unilateral chest irradiation had a severe lymphoid interstitial pneumonitis, with a marked increase in the total cell count and percentage of lymphocytes in BAL (60% to 75% of the recovered cells) (30). Another study published by the same group showed a severe bilateral lymphoid interstitial process in patients with unilateral thoracic irradiation. The number and the percentage of the lymphocytes recovered from BAL were increased both in the irradiated and non irradiated sides at practically the same level (65.1% and 67.6% respectively) (12). These studies suggest that a lymphocyte-mediated hypersensitivity phenomenon may account for the generalized patho physiologic changes. The analyses of lymphocyte subsets made by the same study in one patient with RP showed that virtually all lymphocytes were identified as T lymphocytes (CD2, CD3), and almost all were CD4. No B lymphocytes (CD20) and few NK cells (CD56) were found. Martin et al. confirm the lymphocytic alveolitis that occur within 15 days after completion of radiotherapy and the intensity of it was higher in patients with pneumonitis. They also found that patients with pneumonitis had a higher percentage of CD3 lymphocytes than patients without pneumonitis and a significantly higher percentage of CD4 subset (13).

In our study we found that almost all lymphocytes were T lymphocytes (CD3) in both symptomatic and asymptomatic patients. It was a predominance of CD4 lymphocytes in both groups with a CD4/CD8 ratio into normal range in almost all patients in both groups. Only 6 patients had a CD4/CD8 ratio above 3.5 and 2 patients had a CD4/CD8 ratio below one in the symptomatic group.

The degree of lymphocytosis observed in this study is found in few respiratory conditions and implies an immunologic process. The main differential diagnoses to consider are sarcoidosis, tuberculosis, and hypersensitivity pneumonitis. No other environmental, clinical or radiologic features suggested these diagnoses in our patients, and the bronchoalveolar lavage fluid culture was negative for Mycobacterium tuberculosis.

Similar findings of lymphocytosis with T lymphocytes CD4 in bronchoalveolar lavage specimens have been reported in methotrexate-induced pneumonitis, which is now recognized as a hypersensitivity phenomenon (31). In our study there were only 7 patients who received methotrexate based chemotherapy. They had radiological lesion confined to the irradiated territory of the lung and the BAL aspect showed no differences with that from the patients without methotrexate based chemotherapy.

Classically radiological abnormalities appeared inside the radiation field (2,3). In the last years case reports with lung infiltrates outside the radiation field were described on the irradiated side and even in the contralateral lung. In these cases patients developed bilateral migratory infiltrates with histological proven bronchiolitis obliterans organizing pneumonia (32-38). BAL performed in these cases demonstrated a significant increase in the percentage of lymphocytes, neutrophils, eosino-

phils, and mast cells with a significant decrease in the percentage of macrophages (15,32,34).

In the present study only 5 patients had infiltrates outside the radiation field but only on the irradiated side, with a clinical pattern of BOOP secondary to radiotherapy. No biopsy was performed. In these patients BAL demonstrated increased percentages of lymphocytes, neutrophils, eosinophils and mast cells.

Chronic eosinophilic pneumonia with eosinophils greater than 40% in BAL was described after radiation therapy for breast cancer in 5 female patients with a history of asthma and/or allergy (39). In the present study only one patient without history of asthma or atopy had a percentage of eosinophils in BAL of 40%.

In previous studies of radiation pneumonitis lung function tests showed a decrease in lung volumes and diffusing capacity, typical for alveolar-based disease (13,33,40). In the present study lung volumes were inside the normal range. Only the diffusing capacity was mildly decreased both in symptomatic and asymptomatic groups. ❑

## CONCLUSIONS

In summary, BAL remains an important diagnostic technique in radiation pneumonitis, especially in differentiating it from infection and cancer relapse. The results of this study confirm the presence of marked lymphocytic alveolitis in a group of 65 female patients who developed radiation pneumonitis after radiotherapy for breast cancer. The degree of the inflammatory reaction of the lungs was correlated with the presence of clinical symptoms. The level of lymphocytosis from BAL fluid was significantly increased in symptomatic in comparison with asymptomatic patients. The lymphocytic alveolitis consisted mainly of T lymphocytes, with a predominance of CD4 subset in both groups, but the CD4/CD8 ratio remained mostly into normal range. From the perspective of pulmonary function tests, there were no statistical significant differences between symptomatic and asymptomatic patients. ❑

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