

## Short reports

### Early neutrophil alveolitis after rechallenge in drug induced alveolitis

SERGIO SALMERON, LAURENT BROCHARD, BERNADETTE RAIN,  
PHILIPPE HERVE, FRANCOIS BRENOT, GERALD SIMONNEAU, PIERRE DUROUX

*From the Service de Pneumologie et Réanimation and Département d'Anatomo-Pathologie, Hôpital Antoine Bécélère, Clamart, France*

**ABSTRACT** A patient with drug induced alveolitis due to an antidepressant drug, nomifensine, is described. After an inadvertent rechallenge by the patient sequential bronchoalveolar lavage was carried out. Twenty four hours after the rechallenge the lavage fluid contained a high cell count with neutrophils predominating. Seven days after challenge the cells were predominantly lymphocytes.

Bronchoalveolar lavage is frequently performed as an aid to diagnosis in drug induced pulmonary disease. There are few data, however, concerning the early and delayed lavage findings in acute drug induced alveolitis. We report a case of alveolitis due to the antidepressant drug nomifensine, in which changes in alveolar cell populations were assessed by sequential lavage after an inadvertent rechallenge test by the patient. A transient neutrophil alveolitis occurred soon after the rechallenge; the findings suggest that an immediate hypersensitivity reaction played a part.

#### Case report

A 56 year old woman was admitted to hospital, acutely ill, with a three day history of fever and dyspnoea. She had had surgery for a benign thymoma in 1967. Before the present illness she had been in good health except for a recent bout of depression, for which she had been taking nomifensine 100 mg daily for four weeks before admission and diazepam. Nomifensine, an isoquinoline derivative, is an antidepressant drug that was widely used in Europe until it was recently withdrawn from the market. On admission she was febrile (39.5°C) with a dry cough. Physical examination disclosed sinus tachycardia, dyspnoea at rest, cyanosis, and scattered crepitations over both lungs. The chest radiograph showed diffuse interstitial infiltrates and a previously known post-operative raised left hemidiaphragm.

Haematological indices were normal apart from a raised white blood cell count ( $20.3 \times 10^9/l$ ) with 97% polymorphonuclear neutrophils. She was treated with erythromycin 2 g daily and nomifensine was discontinued on admission. The patient improved, becoming afebrile after 48 hours, and her white cell count returned to normal. Bacterial and serological

Address for reprint requests: Dr Sergio Salmeron, Service de Pneumologie et Réanimation, Hôpital Antoine Bécélère, 157 rue de la Porte de Trivaux, 92141 Clamart, France.

Accepted 25 March 1988

#### *Changes in cell profiles and total counts in bronchoalveolar lavage fluid and blood*

<i>Time after rechallenge</i>	<i>24 h</i>	<i>7 days</i>
<i>Bronchoalveolar lavage fluid</i>		
Total number of cells (/ml)	$14.6 \times 10^5$	$6.9 \times 10^5$
Polymorphonuclear neutrophils (%)	80	2
Lymphocytes (%)	5	70
Eosinophils (%)	—	4
Alveolar macrophages (%)	15	24
<i>Blood</i>		
White blood cell count ( $10^9/l$ )	24.6	6.2
Polymorphonuclear neutrophils (%)	96	45
Lymphocytes (%)	3	37
Eosinophils (%)	—	12

studies, including tests for mycoplasma, gave negative results. The patient was discharged after 12 days, with normal findings from clinical examination and clear lung fields on the chest radiograph. As the suspected diagnosis was infectious pneumonitis, erythromycin was continued for a further week.

On the day after discharge she was readmitted with dyspnoea, which occurred a few minutes after she had taken nomifensine (50 mg). She was febrile (39.8°C) and physical examination yielded the same abnormal findings as at her previous admission. The chest radiograph again showed diffuse interstitial infiltrates. The white cell count was  $24.6 \times 10^9/l$  with 96% neutrophils. While she was breathing air her arterial oxygen tension (PaO<sub>2</sub>) was 6.8 kPa, carbon dioxide tension (Paco<sub>2</sub>) 4 kPa, and pH 7.49. Nomifensine was withdrawn and with no additional treatment (erythromycin was discontinued on admission) her temperature fell to normal and respiratory improvement occurred after 48 hours. No evidence for the presence of other potential antigens—for example, avian protein—was found in the patient's home.

Bronchoalveolar lavage was performed 24 hours and seven days after this rechallenge with nomifensine, four aliquots of 50 ml 0.9% saline being instilled into the middle lobe. The cell populations in the lavage fluid and blood are shown in the table. At 24 hours there was an increased total number of cells in the lavage fluid ( $14.6 \times 10^5/ml$ ) with 80% neutrophils. At seven days lymphocytes constituted 70% of the total cells with only 2% neutrophils and 4% eosinophils. At 7 days the peripheral white blood cell count was  $6.2 \times 10^9/l$  with 45% neutrophils, 37% lymphocytes, and 12% eosinophils. The lung fields on the chest radiograph had returned to normal.

The basophil degranulation test gave a positive result

(54%) in the presence of nomifensine and the lymphoblastic transformation test a negative result. The results of microbiological and serological studies and serum precipitin tests were negative. The patient was discharged after 10 days, in good health, with normal lung fields on her chest radiograph. She was informed of the danger of taking further nomifensine.

### Discussion

Our report documents a case of drug induced alveolitis. The role of nomifensine was suggested by the clinical course, the rechallenge performed by the patient herself, and the complete recovery after withdrawal of the drug.<sup>1</sup> The absence of any other cause and the positive result of the basophil degranulation test provide further support.

Lymphocytosis is the classical feature of lavage fluid in allergic alveolitis.<sup>2</sup> Our patient showed an early alveolar neutrophil influx concomitant with peripheral neutrophilia. Subsequently there was a parallel decrease in neutrophils and increase in lymphocytes in both lavage fluid and blood. A similar early neutrophil alveolitis has been reported after antigen inhalation<sup>3</sup> but, to our knowledge, not in drug induced alveolitis.

In a guinea pig model of allergic alveolitis an acute neutrophil alveolitis was followed 48–96 hours later by a rapid increase in T lymphocytes.<sup>4</sup> Interestingly, the immunisation procedure (100 µg ovalbumin with adjuvant) has also been shown to induce the reaginic antibodies concerned in the guinea pig anaphylactic reaction.<sup>5</sup> In our patient an

immediate (type I) hypersensitivity reaction was suggested by the early onset after rechallenge, the presence of eosinophils in lavage fluid<sup>6</sup> and blood, and the positive result in the basophil degranulation test.<sup>7</sup>

Although the clinical role of lavage in drug induced alveolitis is still not clear,<sup>8</sup> the information obtained from early and delayed lavage may increase knowledge of the mechanisms concerned in acute drug induced alveolitis.

### References

- 1 Hamm H, Aumiller J, Böhmer R, Missmahl HP, Füllbrandt U, Frenzel H. Alveolitis associated with nomifensine. *Lancet* 1985;i:1328–9.
- 2 Daniele RP, Elias JA, Epstein PE, Rossman MD. Bronchoalveolar lavage: role in the pathogenesis, diagnosis, and management of interstitial lung disease. *Ann Intern Med* 1985;102:93–108.
- 3 Fournier E, Tonnel AB, Gosset Ph, Wallaert B, Ameisen JC, Voisin C. Early neutrophil alveolitis after antigen inhalation in hypersensitivity pneumonitis. *Chest* 1985;88:563–6.
- 4 Bernardo J, Hunninghake GW, Gadek JE, Ferrans VJ, Crystal RG. Acute hypersensitivity pneumonitis: serial changes in lung lymphocyte subpopulations after exposure to antigen. *Am Rev Respir Dis* 1979;120:985–94.
- 5 Anderson P. Antigen-induced bronchial anaphylaxis in actively sensitized guinea-pigs. *Allergy* 1980;35:65–71.
- 6 Butterworth AE, David JR. Eosinophil function. *N Engl J Med* 1981;304:154–6.
- 7 Benveniste J. The human basophil degranulation test as an in vitro method for the diagnosis of allergies. *Clin Allergy* 1981;11:1–11.
- 8 Reynolds HY. Bronchoalveolar lavage. *Am Rev Respir Dis* 1987;135:250–63.