Bronchoalveolar Lavage in Amiodarone Pneumonitis*

Cellular Abnormalities and their Relevance to Pathogenesis

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To investigate the contribution of direct cytotoxicity and immune-mediated hypersensitivity to the pathogenesis of amiodarone pneumonitis, we evaluated cells recovered by bronchoalveolar lavage from 13 patients with amiodarone pneumonitis. Alveolar macrophages from all patients contained two types of abnormal inclusions: small clear vacuoles and large phagolysosomes containing phospholipid in lamellar structures, abnormalities previously attributed to direct cytotoxicity from amiodarone. However, these changes were always associated with abnormalities in the numbers and types of immune and inflammatory cells present in the lower respiratory tract, which closely resemble those seen in hypersensitivity pneumonitis associated with inhaled antigens. Following discontinuation of amiodarone and institution of corticosteroid therapy, clinical improvement correlated with a return toward normal in the pattern of inflammatory cells present in the lung, although alveolar macrophages continued to display evidence of drug-induced cytotoxicity. These findings support the possibility that a cell-mediated immune response usually plays a role in the pathogenesis of amiodarone pneumonitis, although direct cytotoxicity may predispose these patients to the development of this abnormal immune response.

Amiodarone has been used extensively since 1967 in the treatment of angina pectoris and cardiac arrhythmias.1,2 Pulmonary toxicity associated with amiodarone therapy was first reported in 1980,3 and since that time numerous articles have appeared describing the clinical, radiologic, and pathologic features of this disease.4-9

The pathogenesis of amiodarone pneumonitis remains controversial. Several authors have suggested that amiodarone pneumonitis results from direct toxic effects of the drug on the lung. This conclusion is based on the findings that amiodarone produces characteristic lamellar inclusions in a variety of cell types including alveolar macrophages and lung parenchymal cells,5,6,26 and that amiodarone can directly injure lung tissue in vitro.25 The predilection for localized pulmonary injury has been attributed to the selective accumulation of amiodarone within the lung parenchyma.17,27,28 However, others have suggested that amiodarone pneumonitis represents a drug-induced hypersensitivity reaction. Evidence in favor of this hypothesis includes the low frequency of pulmonary toxicity,4,12,19-31 the poor correlation observed in some (but not all) series between the dose of amiodarone and the appearance of toxicity,12,19,20,31-33 the presence of immune and inflammatory cells or their products in lung tissue and liquid recovered by bronchoalveolar lavage,4,19,34-36 and the demonstration of drug-induced lymphokine release and basophil degranulation in peripheral blood of a patient with amiodarone pneumonitis.36

Prior studies have evaluated a single case or a small number of patients, and have usually sought evidence either of direct cytotoxic effects or immune abnormalities associated with amiodarone therapy. Therefore, it remains unclear whether two independent mechanisms can produce lung disease, or whether evidence of direct cytotoxic effects and evidence of abnormalities in the immune system co-exist in these patients. Therefore, to clarify the pathogenesis of amiodarone pneumonitis, we have evaluated cells recovered by bronchoalveolar lavage from a large series of patients and characterized the frequency and nature of the changes in immune and inflammatory cells, as well as the direct cytotoxic effects produced by amiodarone therapy.

Materials and Methods

Study Populations

The diagnosis of amiodarone pneumonitis was established by the following criteria. 1) Patients had been receiving amiodarone prior to the onset of illness on a long-term basis. 2) New bilateral infiltrates, consistent with amiodarone toxicity, appeared on chest x-ray film. 3) Absence of congestive heart failure determined by clinical evaluation (ten cases), failure of infiltrates to improve following forced diuresis (two cases), or normal pulmonary artery and wedge pressures during right heart catheterization (one case) were noted. 4) Exposure to environmental agents or other drugs known to be...
associated with pulmonary disease was absent. 5) No other known etiology of interstitial lung disease after appropriate diagnostic evaluation could be demonstrated. 6) Rapid and obvious clinical and/or radiologic improvement followed discontinuation of amiodarone therapy (seven patients) or discontinuation of amiodarone and institution of corticosteroid therapy (0.5 mg prednisone/kg/day, five patients); or autopsy findings were consistent with amiodarone pneumonitis (one case).

These patients (ten men and three women) had an average age of 73 ± 5 years. None had a history of tobacco use. All had been receiving a maintenance dose of 200 mg amiodarone/day. The period of treatment was 41 ± 45 mo (range five to 156 mo) and the total cumulative dose was 180 ± 192 g amiodarone (range 23 to 702 g). Ten patients presented with dyspnea on exertion, low grade fever, and/or moderate-to-marked weight loss. Three asymptomatic patients were identified on the basis of new abnormalities present on routine chest roentgenographic examination. In all patients, chest x-ray film disclosed interstitial and/or alveolar shadows, usually diffuse and bilateral, with no particular topographic predilection. In 12 of 13 patients, pulmonary function tests demonstrated a restrictive syndrome (vital capacity 73 ± 11 percent predicted; total lung capacity 75 ± 12 percent predicted; FEV, 72 ± 8 percent predicted; diffusing capacity CO, single breath, 60 ± 18 percent predicted). None of the patients had evidence of air flow obstruction, and all were hypoxemic (PaO₂, 59 ± 12 mm Hg).

Nine patients receiving amiodarone therapy but without evidence of amiodarone pneumonitis were also evaluated. These patients (six men and three women) had an average age of 63 ± 12 years. None had a history of tobacco use. All had been receiving a maintenance dose of 200 mg amiodarone/day (total cumulative dose 185 ± 146 g). None of these patients had experienced recent symptoms suggestive of amiodarone pneumonitis, and a recent chest x-ray film was unchanged from prior films.

Forty-three normal volunteers were used as control subjects. None had clinical evidence of present or prior pulmonary disease, and none had a history of tobacco use.

All patients and control subjects gave informed consent before inclusion in the study protocol.

Bronchoalveolar Lavage

Bronchoalveolar lavage was performed as previously described by topical anesthesia of the nasal mucosa (5 percent lidocaine spray). Following fiberoptic examination, the bronchoscope (BF-TT, Olympus, Tokyo, Japan) was wedged into a subsegment of the right middle lobe and a total of 300 ml of sterile, warm saline solution was instilled in six aliquots of 50 ml each. The fluid was recovered by gentle aspiration in a siliconized flask kept at 4°C. The lavage fluid was filtered through sterile surgical gauze to remove the mucus, resuspended, and the total cell count was determined on an aliquot of fluid using a hemocytometer. A differential cell count was performed on cytocentrifuge preparations prepared from uncentrifuged lavage fluid and stained with May-Grunwald-Giemsa (MGG) stain. The lavage fluids were then centrifuged (200 g, 4°C, 10 min) to obtain a cell pellet. In all patients, radiologically-apparent abnormalities were present in the subsegment lavaged.

Morphologic Evaluation of Alveolar Cells

Cytocentrifuge preparations were stained with MGG and examined by light microscopy to study the cytologic features of lavage cells. For electron microscopic examination, a cell pellet containing 5 x 10³ cells was fixed for one hour with 2.5 percent glutaraldehyde in cacodylate buffer (0.2 M, pH 7.4, 360 mOsm) and washed in cacodylate buffer containing 1 percent saccharose. The cells were subsequently post-fixed in 1 percent osmium tetroxide solution, dehydrated in absolute ethanol and propylene oxide, and embedded in Epon (Balzers, Meudon, France). Semithin sections of 10 μm were prepared, stained with methylene blue-azur II, and examined by light microscopy to identify representative regions. Ultrathin sections were subsequently prepared and examined using an Elmiskop electron microscope (Siemens) after staining with uranyl acetate and lead citrate. One patient underwent an open lung biopsy and the tissue obtained was prepared for optical and electron microscopic examination according to the procedures described for the lavage cells.

In order to assess the composition of lipids present in alveolar macrophages, cytocentrifuge preparations were stained using three different histochemical techniques: the oil red 0 technique, specific for unsaturated triglycerides; the Baker technique, used for identification of phospholipids; and the Sudan black technique, also used to detect phospholipids.

Phenotyping of Lymphocytes

Monoclonal antibodies used to identify cell surface antigens expressed on lymphocytes were: OKT3 (pan T-lymphocytes, Ortho Diagnostics, Raritan, New Jersey, USA); OKT4 (helper/inducer T-lymphocytes, Ortho); OKT8 (suppressor/cytotoxic T-lymphocytes, Ortho); and OK-1a (HLA-DR + cells, Ortho). Cells obtained by BAL were washed twice in Hank's balanced salt solution (Eurobio, Paris, France) and adjusted to a concentration of 2 x 10⁶ cells/ml. For each assay, 100 μl of this cell suspension was placed into a 75 x 13 tube, and 10 μl of the monoclonal antibody at the proper dilution was added. Cells were incubated at 4°C for 30 min, washed three times in phosphate-buffered saline solution (pH 7.4) containing 0.1 percent sodium azide (PBS-azide). Ten μl of fluorescein-conjugated goat antimouse IgG (Dyanech, Paris, France) was added. Cells were incubated for 30 min at 4°C, washed three times in PBS-azide, and subsequently resuspended in RPMI-1640 (Eurobio); they were then examined using a fluorescence microscope (Olympus BHB, Tokyo, Japan) equipped with phase contrast optics. The percentage of fluorescein-labeled lymphocytes was calculated after counting a minimum of 200 lymphocytes per slide.

Statistical Methods

All results are expressed as mean ± standard deviation. Statistical comparisons were made using Student's two-tailed t-test.

RESULTS

Bronchoalveolar Lavage in Amiodarone Pneumonitis

The number of cells recovered by lavage from patients with amiodarone pneumonitis was significantly increased (Table 1). This increased cellularity was largely explained by a dramatic increase in the numbers of lymphocytes present. Significantly increased numbers of neutrophils, eosinophils and mast cells were also present. In contrast, the number of alveolar macrophages recovered by lavage from patients with amiodarone pneumonitis and normal subjects was not significantly different. The number and types of cells recovered by lavage from patients receiving amiodarone therapy but without signs or symptoms suggesting amiodarone pneumonitis (amiodarone control subjects) were not significantly different from those observed in normal volunteers (Table 1).

Interestingly, two distinct patterns of lavage were seen in patients with amiodarone pneumonitis. In nine patients, lavage was characterized by a large increase in the number of lymphocytes (197 ± 109 x 10⁶ lymphocytes/ml) and a moderate increase in the number of

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Table 1—Numbers and Types of Cells Recovered by Bronchoalveolar Lavage from Patients with Amiodarone Pneumonitis, Amiodarone Control Subjects and Normal Volunteers

<table>
<thead>
<tr>
<th></th>
<th>Amiodarone pneumonitis</th>
<th>Amiodarone controls</th>
<th>Normal subjects</th>
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<tbody>
<tr>
<td></td>
<td>Cells/ml* %</td>
<td>Cells/ml* %</td>
<td>Cells/ml* %</td>
</tr>
<tr>
<td>Total cells</td>
<td>393.1 ± 221.3*</td>
<td>197.8 ± 80.2</td>
<td>163.1 ± 119.5</td>
</tr>
<tr>
<td>Alveolar macrophages</td>
<td>191.0 ± 197.6 47.2 ± 22.7*</td>
<td>180.3 ± 80.7 90.4 ± 5.2</td>
<td>144.6 ± 113.6 87.0 ± 7.5</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>142.3 ± 123.1 37.3 ± 22.9</td>
<td>136.3 ± 7.8 7.6 ± 4.3</td>
<td>150.0 ± 9.3 7.2 ± 6.8</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>54.0 ± 114.8* 13.8 ± 20.0</td>
<td>3.1 ± 3.3 1.9 ± 1.8</td>
<td>3.2 ± 3.9 2.0 ± 1.4</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>5.7 ± 9.4* 1.6 ± 2.3*</td>
<td>0.5 ± 1.1 0.2 ± 0.4</td>
<td>0.5 ± 1.2 0.3 ± 0.6</td>
</tr>
<tr>
<td>Mast cells</td>
<td>0.6 ± 1.0* 0.2 ± 0.3*</td>
<td>&lt;0.1 &lt;0.1</td>
<td>&lt;0.1 &lt;0.1</td>
</tr>
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neutrophils (21 ± 25 × 10⁴ neutrophils/ml) recovered by lavage. Increased numbers of eosinophils (seven of nine patients; 8 ± 11 × 10⁴ eosinophils/ml) and mast cells (four of nine patients; 1 ± 1 × 10⁴ mast cells/ml) also were frequently observed in this group.

In four patients, a different pattern was observed. Lavage fluid contained a normal number of lymphocytes (20 ± 3 × 10⁴/ml) but a greatly increased number of neutrophils (128 ± 201 × 10⁴/ml). Lavage fluid was macroscopically hemorrhagic in two of these four patients. Increased numbers of eosinophils and mast cells were not observed. The large increase in neutrophils could not be attributed to infection, since none of the patients showed clinical evidence of infection, and bacteriologic evaluation of lavage samples was negative. Furthermore, the neutrophilia could not be accounted for by the lung hemorrhage observed in these cases. Subsequent evaluation of two of the four patients in this second group was possible. In both cases, subsequent evaluation demonstrated abnormalities similar to those observed in the first group of patients. One individual was relavaged 15 days later while still receiving amiodarone therapy but prior to receiving corticosteroid treatment, at which time lavage samples demonstrated a dramatic increase in the number of lymphocytes (from 17 to 239 × 10⁴/ml), a fall in the number of neutrophils (from 429 to 5 × 10⁴/ml), and the appearance of increased numbers of eosinophils and mast cells. The second patient underwent open lung biopsy 20 days after the first lavage while still receiving amiodarone but prior to receiving corticosteroid therapy. Lung biopsy sample demonstrated alveolitis rich in lymphocytes, eosinophils and mast cells but containing only a small percentage of neutrophils (described in more detail later).

Analysis of lavage fluid from asymptomatic patients with amiodarone pneumonitis revealed results similar to those observed in symptomatic patients. Two asymptomatic patients had markedly increased numbers of lymphocytes and moderately increased numbers of neutrophils, eosinophils and/or mast cells among cells recovered by lavage. The third asymptomatic patient had an isolated increase in neutrophils.

Morphologic and Histochemical Evaluation of Alveolar Macrophages

Although the number of alveolar macrophages recovered by lavage from patients with amiodarone pneumonitis was similar to that recovered from normal subjects, alveolar macrophages from all patients demonstrated striking morphologic abnormalities. Numerous foamy macrophages were present, which were not encountered in control lavage samples. This foamy appearance resulted from the presence of large numbers of intracytoplasmic vacuoles (Fig 1). Two types of vacuoles were observed. The first type was small, numerous, and appeared to be empty at the light microscopic level. Evaluation of semithin sections stained with methylene blue-Azur II and electron microscopic examination of ultrathin sections further confirmed that these small vacuoles were actually devoid of any organized inner substance.

The second type of vacuole was less numerous, larger and appeared light green after MGG staining. When evaluated in semithin sections, these larger granules exhibited morphologic features of phagolysosomes, present throughout the cytoplasm although frequently concentrated in the perinuclear regions. They were optically dense, and most had a homogeneous appearance. Electron microscopic evaluation confirmed the presence of numerous intracytoplasmic phagolysosomes which, at this level, displayed a lamellar structure (Fig 1). Because of the presence of large numbers of these two types of vacuoles, few areas of normal cytoplasm were present and the number of other intracellular organelles was reduced. Overall, the cells appeared globally distended and had few cytoplasmic extensions.

The lamellar structure of the phagolysosomes suggested that they contained lipidic material. In order to further characterize this material, a variety of histochemical staining procedures were used. The oil red O stain was either negative, or gave a weakly positive result in some macrophages. Even when positive, only diffuse cytoplasmic staining was observed, indicating that the dense vacuoles contained little or no triglyceride. In contrast, the Baker technique intensely

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stained most of the macrophages from patients with amiodarone pneumonitis. Dark blue staining was concentrated in the numerous, large and dense inclusions, some of which displayed the characteristic lamellar organization observed on the semithin sections. Sudan black stain results were also positive, confirming the phospholipidic nature of these inclusions.

Morphologic evaluation of alveolar macrophages from amiodarone control subjects revealed findings similar to those observed in patients with amiodarone pneumonitis. In particular, the quantity and type of intracytoplasmic vacuoles appeared similar in the two groups, although morphometric comparisons were not made. However, alveolar macrophages from most patients with amiodarone pneumonitis had fewer cytoplasmic extensions and had a more generally distended appearance than macrophages recovered from amiodarone control subjects.

Characterization of Lymphocytes Recovered by BAL

As previously discussed, the number of lymphocytes recovered by lavage was markedly increased in nine of 13 patients evaluated. As in normal subjects, most of these lymphocytes were T-lymphocytes (amiodarone pneumonitis patients, 84 ± 13 percent T3+ lymphocytes; normal subjects 87 ± 8 percent, p > 0.2). The total number of both T4+ and T8+ lymphocytes recovered/ml lavage was increased in patients with amiodarone pneumonitis (Fig 2). However, the lymphocytosis resulted from a predominant expansion of T8+ (suppressor/cytotoxic) lymphocytes, (66 ± 15 percent T8+ lymphocytes, 17 ± 9 percent T4+ lymphocytes). Consequently, the T4/T8 ratio was considerably lower in patients with amiodarone pneumonitis compared to that observed in normal subjects, amiodarone pneumonitis patients 0.5 ± 0.2; normal subjects 2.0 ± 0.5 (p < 0.05).

Not only were the lymphocytes increased in number, but these lymphocytes also demonstrated evidence of activation. All patients had a high percentage of large lymphocytes which contained increased amounts of basophilic cytoplasm and had irregularly shaped nuclei, features characteristic of activated lymphocytes. Furthermore, in the two patients evaluated, both of whom had an increased proportion of lymphocytes (65 and 66 percent), the percentage of lymphocytes expressing HLA-DR antigens was considerably increased (27 and 60 percent, respectively). Although HLA-DR surface antigens are expressed on B-lymphocytes as well as activated T-lymphocytes, more than 85 percent of lymphocytes recovered from these individuals were T-lymphocytes, indicating that an increased proportion of HLA-DR+ T-lymphocytes was present.

Effect of Discontinuation of Amiodarone Therapy

In two cases, bronchoalveolar lavage was repeated two months after discontinuing amiodarone and instituting corticosteroid therapy (0.5 mg prednisone/kg body weight). In both cases, this therapy was associated with dramatic improvement in clinical status and nearly complete resolution of radiologic abnormalities. Interestingly, both patients demonstrated an increase in the number of alveolar macrophages to clearly abnormal levels (131 to 399 and 107 to 492 × 10^6 alveolar macrophages/ml). Consistent with the knowledge that amiodarone has a long half-life, 48 two months after discontinuing therapy alveolar macrophages still contained large numbers of abnormal lipid inclusions. At the light and electron microscopic level, both the

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21555/)  
**Figure 1.** Electron micrograph of an alveolar macrophage recovered by lavage from a patient with amiodarone pneumonitis. Two types of abnormal inclusions are present: small, empty vacuoles (arrows), and large phagolysosomes containing lamellar structures. (14,400 × original magnification)

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21555/)  
**Figure 2.** Surface phenotype of T-lymphocytes recovered by lavage from patients with amiodarone pneumonitis. Shown are the absolute number of T4+ and T8+ lymphocytes/ml lavage fluid (left) and the T4/T8 ratio (right) for patients lavaged while receiving amiodarone (solid symbols), and one patient lavaged two months after amiodarone was discontinued and prednisone therapy (0.5 mg/kg body weight) started (open symbols). The shaded areas represent the mean ± SD for normal volunteers.
number and type of intracytoplasmic vacuoles present two months after beginning therapy appeared similar to those observed prior to treatment. However, morphometric comparisons were not made, and therefore more subtle differences may have been missed. In both cases, therapy was associated with a fall in the number of lymphocytes (292 to 66 and 188 to $133 \times 10^3$/ml respectively). However, in spite of the dramatic fall in the number of lymphocytes observed in the first of these two patients, the remaining lymphocytes were predominately $T^\uparrow$ $T$-lymphocytes (72 percent $T^\uparrow$ lymphocytes, 11 percent $T^4$ lymphocytes), and therefore the $T^4/T^8$ ratio remained lower than that observed in normal subjects (Fig 2). In both cases, a fall in the number of neutrophils recovered by lavage was also observed (47 to 8 and 39 to $8 \times 10^3$ neutrophils/ml respectively). One patient was evaluated nine months following discontinuation of amiodarone therapy, at which time the numbers and types of cells recovered by lavage were normal.

**Histologic Evaluation of Lung Tissue**

As discussed above, one patient underwent open lung biopsy. Biopsy sample demonstrated an important intraluminal and intramural alveolitis dominated by foamy macrophages and lymphocytes. The lymphocytes demonstrated the morphologic criteria of activation described above, and occasionally were present in nodular clusters. Increased numbers of plasma cells, neutrophils, eosinophils, and mastocytes were also present in the alveolar structures, but these cells represented 10 percent of the inflammatory cells present. In most areas, thickening of the alveolar walls was associated with the presence of increased numbers of inflammatory cells, although some areas of the specimen also demonstrated variable degrees of fibrosis. Electron microscopic examination of this specimen disclosed the presence of numerous and dense lamellar bodies in alveolar macrophages, type 2 pneumocytes and endothelial cells. Finally, immunofluorescent microscopy demonstrated the presence of kappa light chains along some alveolar and endothelial walls, but evaluation for complement was negative.

**Discussion**

To clarify the pathogenesis of amiodarone pneumonitis, we evaluated cells recovered by bronchoalveolar lavage from 13 patients for evidence of direct cytotoxic effects and abnormalities in the types of immune effector cells present on the surface of the lower respiratory tract. All patients demonstrated a marked accumulation of phospholipids within phagolysosomes of alveolar macrophages, indicating the presence of drug-induced cytotoxicity. However, this was always accompanied by changes in the profile of immune and inflammatory cells which closely resembled those seen in hypersensitivity pneumonia associated with inhaled antigens. These findings support the hypothesis that a cell-mediated immune response contributes to the pathogenesis of amiodarone pneumonitis, although direct cytotoxic effects of amiodarone may contribute to the appearance of this abnormal immune response.

A variety of abnormalities in the immune and inflammatory cells recovered by lavage were demonstrated in amiodarone pneumonitis. Although the number of alveolar macrophages recovered from patients with amiodarone pneumonitis was normal, these cells demonstrated marked morphologic abnormalities. Alveolar macrophages from all patients contained two types of abnormal vacuoles, small optically empty vacuoles, and larger phagolysosomes containing phospholipid material organized into lamellar structures. These cytoplasmic vacuoles were also observed in macrophages obtained by lavage from amiodarone control subjects. In the single lung biopsy sample examined, abnormal numbers of phospholipid-containing phagolysosomes were also observed in capillary endothelial cells and type 2 pneumocytes. These inclusions are similar to those described in the lung and other tissues of patients receiving amiodarone therapy,

Second, in patients with amiodarone pneumonitis these cytotoxic effects were always associated with abnormalities in the types of immune and inflammatory cells present in the lung. Finally, in two patients studied two months after discontinuing amiodarone and instituting steroid therapy (which resulted in a dramatic improvement in clinical and x-ray abnormalities), alveolar macrophages continued to demonstrate cytopathic effects.

Very large numbers of lymphocytes were present on the surface of the lower respiratory tract in most patients. In these individuals, lymphocytosis was characterized by a disproportionate expansion of $T^\uparrow$ $T$-lymphocytes and evidence of lymphocyte activation. Moderately increased numbers of neutrophils, eosinophils and mast cells were also observed in this group. However, bronchoalveolar lavage did not always demonstrate a lymphocytic alveolitis. In a minority of patients, the number of lymphocytes recovered by lavage was normal, but large numbers of neutrophils were present and lavage fluid was frequently hemorrhagic. However, when two patients who initially presented with an alveolitis dominated by neutrophils were reevaluated less than one month later and prior to receiving corticosteroid therapy, the alveolitis was

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characterized by increased numbers of lymphocytes, eosinophils, and mast cells and the proportion of neutrophils had decreased. Thus, the two patterns observed in amiodarone pneumonitis appear to reflect two stages in the evolution of the same disorder. The increased numbers of lymphocytes, neutrophils, eosinophils and mast cells observed in our patients is clearly associated with the appearance of amiodarone pneumonitis, since such abnormalities were not observed in patients receiving amiodarone therapy but without evidence of pulmonary involvement.

Previous studies evaluating cells recovered by lavage have also demonstrated increased numbers of neutrophils and lymphocytes in the lower respiratory tract of patients with amiodarone pneumonitis. The failure of Liu et al. to find abnormalities in all patients may be due to their failure to lavage subsegments demonstrating radiographic involvement or other technical factors. The present study underscores the fact that an alveolitis can be demonstrated by lavage in most patients with amiodarone pneumonitis, although the nature of the alveolitis appears to evolve over time.

The abnormalities observed in amiodarone pneumonitis are strikingly similar to those seen in hypersensitivity pneumonitis associated with inhaled antigens. In hypersensitivity pneumonia, exposure of sensitized individuals to antigen results in the early appearance of hemorrhagic lavage fluid containing large numbers of neutrophils. Later, the alveolitis evolves into one dominated by large numbers of lymphocytes and containing moderately increased numbers of neutrophils, eosinophils and mast cells. As in amiodarone pneumonitis, the lymphocytosis associated with hypersensitivity pneumonia is characterized by large numbers of activated T8+ lymphocytes. These similarities suggest that the pathogenesis of amiodarone pneumonitis and hypersensitivity pneumonia may be closely linked.

Two limitations of this study should be emphasized. First, although our results suggest that amiodarone pneumonitis represents a hypersensitivity reaction, our study does not identify the antigen(s) involved. Prior studies, demonstrating amiodarone-induced proliferation of blood lymphocytes from a patient with amiodarone pneumonitis suggest that the drug itself may serve as a hapten. Consistent with this hypothesis, patients with amiodarone pneumonitis are susceptible to allergic reactions against radiographic contrast agents, possibly due to the fact that both amiodarone and contrast agents are iodine-containing compounds. However, the release of sequestered autoantigens resulting from direct cytotoxic effects of amiodarone could also play a role in the development of the local immune response observed. Our finding that alveolar macrophages from patients with amiodarone pneumonitis appeared somewhat more distended than those observed in amiodarone control subjects would be consistent with this possibility.

Second, these studies do not demonstrate whether or not the cytotoxic effects observed in the alveolar macrophages are important in the pathogenesis of amiodarone pneumonitis. Alveolar macrophages can both stimulate and suppress immune responses, and alterations in macrophage maturity and activation are known to alter this balance. Although the number of alveolar macrophages recovered by lavage was normal in amiodarone pneumonitis, macrophage turnover (and therefore the proportion of immature alveolar macrophages) may be increased. Consistent with this hypothesis, the number of alveolar macrophages recovered by lavage increased dramatically following discontinuation of amiodarone therapy. Similarly, the alterations in macrophage morphology observed in this study may be associated with changes in the ability of these cells to initiate immune responses. In this context, it is interesting to note that foamy alveolar macrophages containing numerous phagolysosomes are often present in hypersensitivity pneumonitis, although the morphologic features of these phagolysosomes are distinct from those seen in patients receiving amiodarone therapy. Therefore, it is possible that alterations in alveolar macrophage function associated with amiodarone-induced cytotoxicity predispose these individuals to drug-induced hypersensitivity reactions.

Thus, the changes in immune and inflammatory cells recovered by bronchoalveolar lavage from patients with amiodarone pneumonitis demonstrated in this study support the possibility that a cell-mediated immune response usually plays a role in the pathogenesis of this disorder. Further studies are required to directly demonstrate the antigen(s) involved and to study the role of drug-induced alterations in macrophage function in this disease.

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