Provocation Test Coupled with Bronchoalveolar Lavage in Diagnosis of Drug (Nilutamide)-Induced Hypersensitivity Pneumonitis*

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A 79-year-old man was given a cumulative dose of 16.5 g of nilutamide for treatment of prostate cancer. He then presented with a respiratory illness having clinical, radiologic and functional characteristics of interstitial pneumonitis. No other cause of pneumonitis was found. Bronchoalveolar lavage showed a lymphocytic alveolitis with an inverted lymphocyte subset ratio. After an 11-week period of drug withdrawal, clinical, radiologic and functional improvement was observed along with a normal alveolar lymphocytosis. Nilutamide therapy was then resumed for five weeks and induced the recurrence of clinical, functional and alveolar abnormalities. Nilutamide treatment was finally stopped and two months later, clinical and functional abnormalities resolved. This observation seems to exemplify the possible diagnostic value of coupling provocation test with BAL cell data in hypersensitivity pneumonitis induced by drugs. In addition, these data support the role of a cell-mediated immunologic mechanism in the pathogenesis of nilutamide-induced pneumonitis.

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The case we are reporting here is that of a patient whose interstitial pneumonitis seemed to be induced by nilutamide, a newly available active drug for prostate cancer treatment.† The correlation between variations of BAL cell data sequentially evaluated and the provocation test with this drug would appear to exemplify the possible diagnostic interest in this procedure. In addition, these BAL data support the role of a cell-mediated immunologic mechanism in the pathogenesis of this nilutamide-induced pneumonitis.

CASE REPORT

A 79-year-old man, an ex-shopkeeper who gave up smoking 40 years prior to seeing us, was referred to us by late July 1987. He had a gastrectomy at the age of 50 years and a myocardial infarction at the age of 73 years. Since then, he had been taking isosorbide dinitrate orally and diprydamole for angina pectoris and methyl-dopa for mild hypertension. Six years later, bone investigations revealed defects consistent with malignant deposits in the fifth and sixth right ribs, pelvis and vertebral column; a chest roentgenogram showed normal lung parenchyma. The ESR was 20 mm at first hour. A transrectal biopsy demonstrated a prostatic adenocarcinoma. In late April 1987, he underwent a surgical castration and was given

REFERENCES


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radiotherapy (45 grays) over two months to the right ribs along with prednisone (first 25 and then 10 mg daily). Treatment with nilutamide was begun (300 mg daily for 34 days, then 150 mg daily for 42 days).

At the end of the second month of this treatment, bone pain had improved but he developed a slight fever (38°C) and exertional dyspnea. On admission, his general condition was good. Crepitations were heard in both lungs. A chest roentgenogram showed metastases on fifth and sixth right ribs and small opacities of an interstitial type spread throughout both lungs (Fig 1). A few days after admission this patient's respiratory assessment was suddenly interrupted by the occurrence of thromboembolic disease with diffuse chest pain, increased dyspnea, signs of right ventricular failure and left lower limb phlebitis. Systemic blood pressure was normal. Chest roentgenogram displayed a blunted right costophrenic angle, an elevated right diaphragm; PaO2 was 45 mm Hg and PaCO2 25 mm Hg on room air. The thromboembolism was confirmed by pulmonary angiography which showed multiple pulmonary emboli; deep vein thrombosis of the left leg was obvious on phlebography film. Treatment was commenced with heparin and a filter (Gunter No. 30) was placed in the inferior vena cava through the right femoral vein.

Fifteen days later, all thromboembolic signs had subsided. Clinically, and while still on nilutamide, he remained breathless with crepitations audible in both lungs. A chest x-ray film showed an interstitial process throughout both lungs, a similar appearance to that seen prior to thromboembolism. Peripheral blood cell count was 9,250 with 70.4 percent neutrophils, 2.3 percent eosinophils, 20.9 percent lymphocytes and 6.4 percent monocytes; ESR was increased to 60 mm at first hour. Pulmonary function tests showed results consistent with a restrictive syndrome (vital capacity: 76 percent predicted) with PaO2 of 60 mm Hg on room air and an alveolo-arterial oxygen gradient greatly increased to 54 mm Hg. Gas-diffusing capacity was decreased to 0.8 mmol/min/kPa/L (normal value: 1.9 to 2.4). All tests of sputum and serum for bacterial, viral or fungal infection were negative. Tuberculin skin test was negative. Serum IgE level was normal as were serum levels of C3 and C4 complement fractions and circulating immune complexes (Raji-cell technique). A search for rheumatoid factor, cryoglobulin and antinuclear antibodies was negative. A migration inhibition test on peripheral blood leukocytes in the presence of different concentrations of nilutamide showed an inhibition of 31.3 percent at the 72nd hour of a cell culture containing 10⁻¹ µg nilutamide/ml, with the same concentration, no significant inhibition (10 percent) was observed in a healthy control. Fiberoptic bronchoscopy (Olympus BF B3) was negative as was bronchial tumor cytology. In BAL fluid using a conventional technique, there was alveolar lymphocytosis with disturbed lymphocyte subset ratio (Table 1). By contrast, T-lymphocyte subsets in peripheral blood were normal (CD4 = 48 percent; CD8 = 30 percent; CD4/CD8 = 2.4). Diagnosis of nilutamide-related hypersensitivity pneumonitis was then considered likely. Thus, the drug was withdrawn (cumulative dose: 16.5 g) and prednisone daily dosage was increased to 30 mg for one month and progressively reduced before its withdrawal the next month.

Eleven weeks after nilutamide was stopped, exertional dyspnea and lung crepitations had disappeared. Chest roentgenogram and chest CT-scan showed complete clearing of interstitial opacities. The ESR fell to 24 mm. Pulmonary function returned to normal. The PaO2 had risen to 89 mm Hg; alveolo-arterial oxygen gradient was 16 mm Hg. In BAL fluid, lymphocytosis was normal (8 percent) with a rise in CD4/CD8 ratio (0.55).

Two months later, because of recurrence of bone pain and an elevated serum-specific prostatic antigen (165 ng/ml), nilutamide administration was resumed for five weeks (150 mg daily) with the patient's informed consent. By the end of this time, exertional dyspnea and crepitations at both bases reappeared and PaO2 decreased (62 mm Hg). No change was seen on chest x-ray film, but in BAL fluid, lymphocytosis was present (33 percent) with accentuation of lymphocyte subset imbalance (0.35). Finally nilutamide treatment was stopped. Two months after the second nilutamide withdrawal, the patient's respiratory condition remained satisfactory.

**Table 1—Bronchoalveolar Lavage Cell Populations (%)**

<table>
<thead>
<tr>
<th></th>
<th>On Admission</th>
<th>11 Weeks after Nilutamide Cessation</th>
<th>5 Weeks after Nilutamide Resumption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophages</td>
<td>38</td>
<td>86</td>
<td>62</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>1</td>
<td>6</td>
<td>4.8</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>3</td>
<td>0</td>
<td>0.4</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>58</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>CD4 lymphocytes*</td>
<td>13</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>CD4 lymphocytes†</td>
<td>67</td>
<td>54</td>
<td>70</td>
</tr>
<tr>
<td>CD4/CD8 lymphocytes ratio</td>
<td>0.19</td>
<td>0.55</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*OK-T, and OK-T4A monoclonal antibodies (Ortho, Raritan, NJ).
†TOT8 monoclonal antibody (Immunotech, France).
DISCUSSION

Nilutamide is a nonsteroidal anti-androgen newly available for the treatment of prostatic cancer. In a case recently reported, it has been considered responsible for an interstitial pneumonitis occurring after a treatment of two months (cumulative dose: 12.5 g) and disappearing three months after the drug was withdrawn; in BAL fluid, there was a lymphocytosis (55 percent) with a low CD4:CD8 T lymphocyte ratio (0.25). In another case, the role of nilutamide is controversial because another drug, busereline, a LHRH analog, was given simultaneously.

In our patient, nilutamide-induced interstitial pneumonitis seems likely. Although no pulmonary biopsy has been performed because the patient was on anticoagulant treatment, metastatic lung disease could be ruled out because interstitial lung opacities disappeared. In the same way, lung reaction to radiotherapy could not be considered: radiation was administered exclusively to the right rib metastases and pneumonitis involved both lungs. No other infectious cause was found, nor was there evidence of systemic diseases such as sarcoidosis or collagen vascular diseases. On the other hand the other drugs (isosorbide dinitrate, dipyridamole, methylprednisolone) this patient had been receiving have never been reported to induce pneumonitis; furthermore, despite continuation of these drugs, pneumonitis disappeared when nilutamide was discontinued.

In fact, this pneumonitis had all the clinical, radiologic and functional features of hypersensitivity pneumonitis. Cessation of nilutamide treatment was followed by disappearance of the disease and its resumption caused reappearance of symptomatic and functional abnormalities. The BAL cell analysis provided data (lymphocytosis and lymphocyte subset imbalance) similar to those recorded in hypersensitivity pneumonitis due to inhalation of organic dusts or to treatment with other drugs such as amiodarone, gold salts, methotrexate, nitrofurantoin and propranolol. Furthermore, drug cessation for 11 weeks caused a return to normal of BAL lymphocytosis and an increase of lymphocyte subset ratio; subsequently, drug resumption for five weeks was associated with a rise in alveolar lymphocytosis while lymphocyte subset ratio decreased. This provocation test had previously been found informative in some cases of extrinsic allergic alveolitis; if coupled with sequential BAL cell analysis, it has seemed demonstrative in two cases of drug-induced pneumonitis due to acebutolol and propranolol. Nevertheless, this procedure could be potentially harmful when certain drugs like methotrexate are used. Thus, it should always be performed with caution with the patient being monitored in an intensive care unit.

Finally, in this case, reduction of clinical, radiologic and functional abnormalities after withdrawal of the drug would be in favor of an immunologic hypersensitivity pathogenesis; this hypersensitivity would seem predominantly cell-mediated from the evidence of cell data in the BAL. Additionally, in our patient, secretion of a lymphokine (leukocyte inhibitory factor) by blood sensitized T lymphocytes was detected in the presence of nilutamide by the leukocyte migration inhibition test; this was also the case in other patients with interstitial pneumonitis induced by amiodarone, methotrexate, nitrofurantoin and gold salts.

In summary, this case would seem to represent an immune lung reaction of the cell-mediated type triggered by nilutamide. It exemplifies the possible diagnostic value of coupling provocation test with cell variations noted in sequential BAL. However, such a procedure needs to be further evaluated in many other patients with drug-induced hypersensitivity pneumonitis unless the suspected drug is well known to induce sudden and severe respiratory disorders (eg, methotrexate).

If this coupling test turns out to be valid, it would allow early confirmation or exclusion of the diagnosis of this iatrogenic lung disease and so consideration of its therapeutic consequences. Clearly, the withdrawal of a very active drug not responsible for pneumonitis would be detrimental to some patients. On the other hand, if a very active drug is definitely responsible for pneumonitis, one should consider reducing by half the drug dosage together with the addition of corticosteroid therapy: this seemed beneficial in some cases of pneumonitis due to drugs other than nilutamide; nonetheless, in such a clinical setting if pneumonitis does progress, the drug has to be totally withdrawn and an alternate therapy instituted. Otherwise lung disease will inevitably evolve toward irreversible pulmonary fibrosis which is the natural endpoint of all granulomatous lung process.

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Unilateral Diaphragmatic Paralysis Secondary to Carbon Monoxide Poisoning*

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Complications of carbon monoxide poisoning include peripheral neuropathy, which is usually confined to the lower extremities. We report a case of carbon monoxide-associated neuropathy resulting in unilateral diaphragmatic paralysis. Possible mechanisms of injury are described.

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Carbon monoxide poisoning accounts for 3,500 deaths per year in the United States, nearly half of the deaths from all poisonings. Nonlethal complications include pulmonary edema, central nervous system dysfunction with psychomotor difficulties, and neuropathy. Peripheral neuropathy has been described but is almost exclusively confined to the lower extremities. We report a case of transient unilateral diaphragmatic paralysis associated with carbon monoxide poisoning.

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FIGURE 1. Admission chest x-ray film revealing an elevated right hemidiaphragm.

CASE REPORT

A 56-year-old white man was admitted to our hospital after having been found unconscious in his automobile which had been left in operation in a closed garage. He had a previous history of depression with a past medical history of hypertension, non-insulin-dependent diabetes mellitus and a cerebrovascular accident. Initial physical examination revealed that he was afebrile, had spontaneous but labored respirations and was unresponsive to painful stimuli. His initial arterial blood gas values on 5 L of oxygen by nasal cannula revealed mild hypoxemia but no acidosis. His carboxyhemoglobin level, measured approximately 2 h after being found, was 10.2 g percent (Instrumentation Laboratories CO-oximeter model 282). The white blood cell count was 15,200/cu mm with a normal differential cell count. Serum glucose level was 283 mg percent and serum electrolyte values were normal. Chest x-ray film showed an elevated right hemidiaphragm (Fig 1) while a comparison film taken 22 months previously was normal (Fig 2).

He was treated with high flow oxygen. Within 24 h his carboxyhemoglobin level had fallen to 1.3 g percent and his neurologic examination was normal. Fluoroscopy revealed paradoxic motion of the right hemidiaphragm and an abdominal ultrasound did not reveal any mass in the right upper quadrant of his abdomen. On day 4 he was considered medically stable and was transferred to

FIGURE 2. Normal chest x-ray film of patient taken 22 months prior to admission.