Diffuse Pulmonary Uptake of Indium-111-Labeled Leukocytes in Drug-Induced Pneumonitis

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Indium-111-labeled-leukocyte scintigraphy was performed on three febrile patients, two of whom had no signs or symptoms referable to the respiratory tract. The third patient had dyspnea on exertion, unchanged over two months. Their past histories were remarkable in that all three had recently undergone chemotherapy for malignancy (2 lymphoma, 1 malignant thymoma). Diffuse pulmonary uptake of labeled leukocytes was observed in all three individuals. As a direct result of leukocyte imaging, all three underwent fiberoptic bronchoscopy and transbronchial biopsy. The final diagnosis in each of these patients was drug-induced pneumonitis, which responded to treatment with corticosteroids. This entity should be added to the group of conditions, both infectious and noninfectious, that cause diffuse pulmonary uptake on labeled leukocyte images. Moreover, in the appropriate clinical setting, even in the absence of pulmonary signs or symptoms, diffuse pulmonary uptake of labeled leukocytes should alert the physician to the possibility of drug-induced pneumonitis.

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Although ^{111}In-labeled leukocyte scintigraphy is useful to diagnose pyogenic infection, there is limited data available on its utility for diagnosis of pulmonary infection (*1–9*). This may be not only because chest radiographs and sputum cultures are both easily obtained and generally diagnostic, but also because pulmonary uptake of labeled leukocytes is relatively nonspecific and is associated with conditions other than infection (*2,4,6,7,10*). Few leukocyte studies therefore are performed specifically for pulmonary infection (*7*). We recently observed diffuse pulmonary uptake of labeled leukocytes in three patients with antineoplastic drug-induced pneumonitis.

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CASE REPORTS

All three patients underwent labeled leukocyte scintigraphy 24 hr after injection of ~18.5 MBq (500 μCi) of mixed autologous leukocytes labeled with ^{111}In-oxine according to the method of Thakur et al. (*11*). Whole-body images, including 6-min static images of the chest were obtained on a large field of view gamma camera (Omega 500, Technicare Corp., Solon, OH) equipped with a medium-energy, parallel-hole collimator, using 20% windows centered over the 174 and 247 keV photopeaks of ^{111}In.

Case 1

A 68-yr-old man presented with a fever of 39°C, but with no other signs or symptoms. He had undergone multiple cycles of chemotherapy with bleomycin, doxorubicin, cisplatin and prednisone for a malignant thymoma diagnosed 9 mo previously. His most recent treatment had been completed 4 wk prior to admission. On admission, his peripheral leukocyte count was 2700/mm^3 (NI = 4,800-10,800/mm^3). Admission chest x-ray revealed right hilar enlargement and multiple pleural based masses suggestive of metastatic disease. The patient remained febrile but otherwise asymptomatic over the next 10 days. Repeated blood, sputum, and urine cultures were reported as no growth. Whole-body computed tomography was negative for infection. Leukocyte scintigraphy performed 11 days after admission demonstrated diffuse bilateral pulmonary parenchymal uptake of labeled cells, more intense on the left. Chest x-ray performed after the leukocyte study revealed bilateral interstitial infiltrates (Fig. 1). The patient was empirically placed on prednisone and trimethoprim/sulfamethoxazole (Septra). Fiberoptic bronchoscopy and transbronchial biopsy performed three days later revealed acute interstitial pneumonitis. No viral inclusions or malignant cells were seen. Special stains for acid-fast bacilli and *pneumocystis carinii* organisms were negative and Septra was discontinued. The patient continued to receive prednisone, his symptoms abated, and he was discharged home 20 days after admission. The final diagnosis was drug-(probably bleomycin) induced pneumonitis.

Case 2

A 61-yr-old man with non-Hodgkin's lymphoma diagnosed 6 mo previously was admitted with a fever of 38.5°C and occipital headache. He complained of dyspnea on exertion which had been unchanged over the past 2 mo. He had been treated with four cycles of methotrexate, bleomycin, doxorubicin, cisplatin, vin-

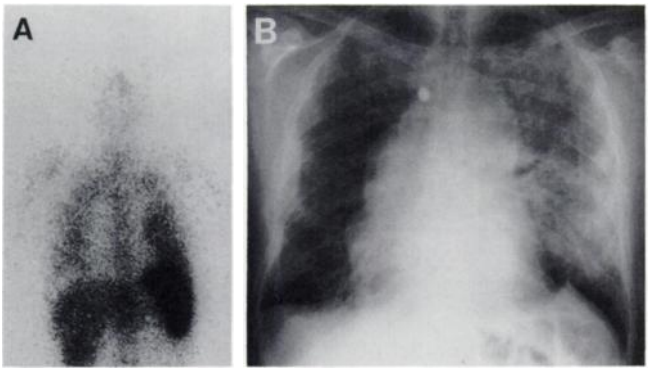

FIGURE 1. (A) Diffuse bilateral pulmonary uptake of labeled leukocytes more intense on the left, is seen on this 24-hr anterior image of the chest. The relatively photopenic area centrally corresponds to the widened mediastinum seen on the chest x-ray in Figure 1B. (B) Posteroanterior chest radiograph performed on the same day as Figure 1A shows prominent mediastinal widening with lobulated masses on the right and a large mass extending into the left upper chest. A large plaque-like tumor mass along the lateral margin of the left chest wall is also noted. Bilateral interstitial infiltrates, more extensive on the left (corresponding to distribution of activity in Fig. 1A), are also evident.

cristine and dexamethasone, completing his last cycle 6 days before admission. Admission laboratory values, lumbar puncture and computed tomography of the head were all unremarkable. Repeated blood, urine and sputum cultures were reported as no growth. Leukocyte imaging performed 1 wk after admission revealed diffuse bilateral pulmonary activity. A chest x-ray performed the same day as the leukocyte study revealed bilateral infiltrates (Fig. 2) and the patient was placed on prednisone and Septra. Fiberoptic bronchoscopy with transbronchial biopsy, performed 24 hr later, revealed poorly developed granulomata, without lymphocytic reaction. The adjoining lung parenchyma showed septal edema. Special stains for acid-fast bacilli, fungi, and *pneumocystis carinii* organisms were negative. The findings were interpreted as consistent with methotrexate pneumonitis.

Case 3

A 53-yr-old man, receiving his third cycle of cyclophosphamide, prednisone, procarbazine, bleomycin, vincristine and doxorubicin for large-cell lymphoma diagnosed 4 mo previously, was admitted with a fever of 41°C, shaking chills, and a left sixth cranial nerve palsy. Admission chest x-ray was without evidence of infiltrates or effusions. Blood, urine and sputum cultures were negative. Leukocyte scintigraphy, performed seven days after admission, showed intense diffuse, bilateral pulmonary uptake. A chest x-ray obtained 2 days later revealed no definite infiltrates (Fig. 3). On fiberoptic bronchoscopy and transbronchial biopsy performed the same day as the chest x-ray, the lung parenchyma showed extensive diffuse alveolar wall fibrosis with focal chronic inflammation and alveolar macrophage proliferation. Moderate numbers of small to medium sized lymphocytes were seen. No malignant cells were identified. Special stains for acid-fast bacilli and *pneumocystis carinii* organisms were negative. Despite the negative bronchoscopy, the patient was placed on Septra. The patient remained febrile and after 3 days, Septra was discontinued, prednisone was instituted, and he defervesced within 24 hr. The final diagnosis was drug-(probably bleomycin) induced pneumonitis.

DISCUSSION

Pulmonary uptake of labeled leukocytes in drug-induced pneumonitis is not surprising in view of the fact that this entity is accompanied by an intense, acute, inflammatory reaction characterized by migration of neutrophils and other inflammatory cells into the lung (*12*). Leukocyte imaging has been used, in fact, to monitor neutrophil migration in the lungs of bleomycin-treated rabbits (*13*).

Regardless of the etiology, pulmonary uptake of leukocytes is presumably due to nonspecific inflammatory responses that stimulate leukocyte accumulation in the lungs through increased vascular permeability due to complement activation or endothelial damage, or pulmonary vascular bed vasodilatation (*4*). Lung activity on leukocyte images therefore is not specific for infection. Cook et al. (*4*) reported pulmonary uptake of labeled leukocytes in 16% of 306 leukocyte studies performed for occult infections. While infection was associated with focal pulmonary uptake 52% of the time, it was associated with diffuse lung uptake only 10% of the time. McAfee et al. (*6*) identified pulmonary uptake of labeled leukocytes in 14% of 154 leukocyte studies performed for possible bacterial infec-

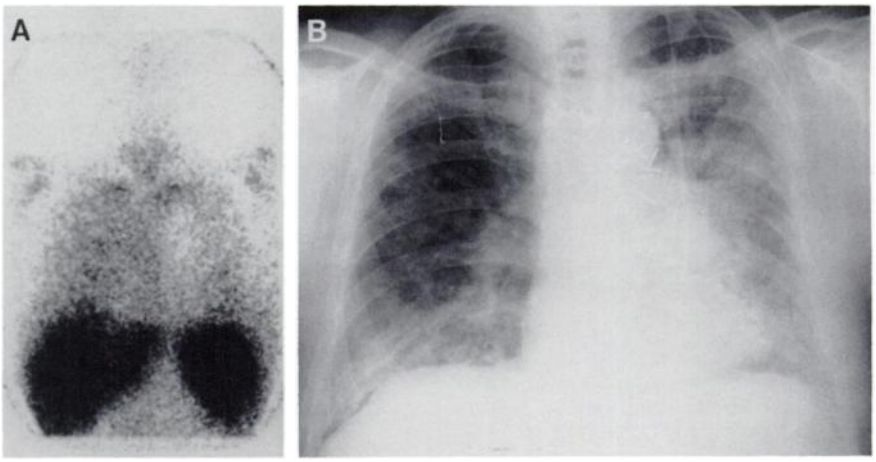

FIGURE 2. (A) Mild diffuse bilateral pulmonary uptake, somewhat patchy on the left, is appreciated on this 24-hr anterior chest image. (B) There are bilateral hilar masses, larger on the left. A diffuse haziness involving the lower two-thirds of the left lung is present. Bilateral interstitial infiltrates are also seen in this posteroanterior chest x-ray performed the same day as Figure 2A.

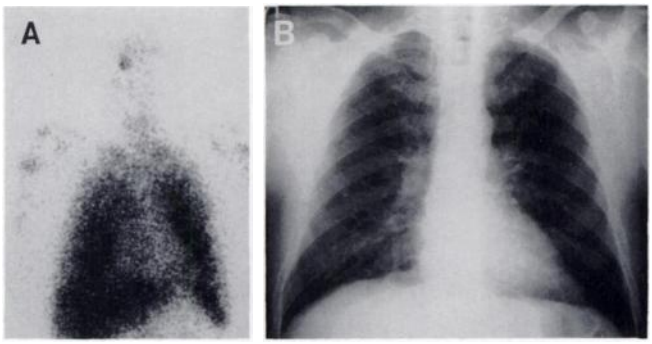

FIGURE 3. (A) Twenty-four hour anterior leukocyte image of chest demonstrates intense, homogeneous, bilateral lung uptake of labeled leukocytes. (Nasal uptake was attributed to rhinitis.) (B) Minimally increased interstitial markings in both lungs are present on this posteroanterior chest radiograph obtained 48 hr after (A). There are no definite infiltrates.

tion. In their series, while focal pulmonary uptake was always associated with infection, only one of nine cases of diffuse pulmonary uptake was associated with infection. In reviewing 162 leukocyte scans, Segall et al. (*7*) found that intensity of pulmonary uptake correlated better with infection than did (focal versus diffuse) pulmonary uptake patterns. They found that pulmonary activity (focal or diffuse), at least as intense as hepatic activity, was highly specific for infection.

Noninfectious causes of diffuse lung uptake of labeled leukocytes include congestive heart failure (*4,6*), atelectasis (*4*), adult respiratory distress syndrome (*2,4,10*), aspiration (*4*), and tumor (*4,6*). Diffuse pulmonary uptake following radiation therapy (*6*), cardiopulmonary resuscitation (*6*), and hemodialysis (*14*) has also been described. Recently, diffuse lung uptake associated with increased numbers of circulating immature leukocytes has been observed (*15*). To this group can be added another noninfectious cause of diffuse pulmonary uptake of labeled leukocytes: drug-induced pneumonitis.

The ideal diagnostic procedure is both sensitive and specific. While the sensitivity of leukocyte imaging for detecting drug-induced pneumonitis cannot be ascertained on the basis of these three cases, the diffuse pulmonary uptake we observed is clearly not specific for this entity. Even using the criteria of Segall et al. (*7*), two of the three patients we are reporting would have been incorrectly classified as having pulmonary infection. Further complicating the interpretation of these images is the fact that in addition to noninfectious causes, diffuse pulmonary uptake of labeled leukocytes has been observed in opportunistic infections to which individuals receiving antineoplastic agents may be predisposed (*3,8,9,16*).

The nonspecificity of the pulmonary findings in these patients does not, however, diminish the importance of leukocyte imaging in the diagnosis of their ailments. Of all the noninvasive studies performed, leukocyte imaging was the first to localize the site of an active pathologic process: the lungs, thus identifying a fruitful site for biopsy. While the ability of leukocyte imaging to specifically identify pulmonary infection may be limited, the incidental finding of pulmonary activity on leukocyte images, as these cases of drug-induced pneumonitis illustrate, may be of considerable importance in the management of the patient.

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