The Role of Gallium-67-Citrate in the Detection of Phenytoin-Induced Pneumonitis

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A patient with a history of cardiac transplant presented with a fever of undetermined etiology. The patient had been on multiple medications, including phenytoin, which can occasionally cause allergic or hypersensitivity pneumonitis. A chest x-ray and CT scan of the chest revealed no active disease. A ^{67}Ga study was obtained after intravenous administration of 377.4 MBq (10.2 mCi) of ^{67}Ga-citrate. The images showed diffuse intense lung uptake bilaterally. Bronchoscopic biopsy revealed hypersensitivity pneumonitis. Phenytoin was withdrawn and corticosteroid was started in therapeutic doses. A follow-up gallium study obtained 25 days after the baseline demonstrated marked improvement in the lungs with concurrent clinical recovery. This case illustrates the usefulness of ^{67}Ga in the detection of drug-induced pneumonitis and in the follow-up of response to therapy.

Key Words: phenytoin; pneumonitis; gallium-67.

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Patients with lung inflammation due to drug-induced pneumonitis can be identified by the avid accumulation of ^{67}Ga. The medications which have been identified by gallium scintigraphy include amiodarone, busulfan, bleomycin, procarbazine, nitrofurantoin, pentazocine, cephalosporin, cyclophosphamide and cocaine (*1,2*).

We present a case of a 49-yr-old male, postcardiac transplantation, who was diagnosed with phenytoin-induced hypersensitivity pneumonitis. Gallium scintigraphy was used not only as an aid in the diagnosis of the disease process, but also to evaluate the response of the patient after discontinuation of the offending agent and treatment with corticosteroid.

CASE REPORT

A 49-yr-old white male who had a heart transplant 1 yr ago, secondary to end-stage idiopathic hypertrophic subaortic stenosis and severe congestive heart failure, presented to the emergency room of Hahnemann University Hospital with a 2-wk history of intermittent fevers and chills. Associated symptoms were shortness of breath, nonproductive cough and yellowish discoloration of the sclera. His past medical history also included cardiac arrest 2 yr ago, cerebrovascular accident, subarachnoid bleeding associated with a single episode of seizure 1 yr ago, chronic renal failure, hypertension, insulin-dependent diabetes mellitus and immunosuppression. On presentation, his medications included azathioprine (imuran), cyclosporine, prednisone, phenytoin (dilantin), clonidine, ranitidine (zantac), labetolol, quinine, nicardipine (cardene), ferrous sulfate, furosemide (lasix), metolazone (zaroxylin) and insulin. He had no known drug allergies.

On physical examination at the time of admission, the vital signs were within normal limits. There was evidence of mild jugular venous distention, mild icterus, few bilateral basilar rales and occasional wheezes. Cardiac examination revealed an end-systolic murmur grade 3/6. The remainder of the exam was unremarkable.

Initial laboratory values revealed leucopenia (WBC 2.8 K/Ul), anemia (hemoglobin 11.3 gm/dl), platelet count of 191 K/Ul, blood urea nitrogen and creatinine were elevated up to 88 mg/dl and 3.3 mg/dl, respectively. Blood, urine and sputum cultures were negative. A chest x-ray (Fig. 1) revealed chronic parenchymal and pleural scarring at the right base and cardiomegaly. There was no radiographic evidence of active disease or CHF. Unenhanced CT of the chest showed right basal pleural calcification.

Gallium scintigraphy was requested to detect occult infection. The patient received 377.4 MBq (10.2 mCi) of ^{67}Ga intravenously. Images of the head, neck and trunk were obtained 72 and 120 hr postinjection using a LFOV gamma scintillation camera equipped with a medium-energy collimator and calibrated for three ^{67}Ga photopeaks (93, 184 and 296 KeV), and a 20% energy window. One million counts per view were obtained for the chest and abdomen, which demonstrated abnormal, increased concentration of ^{67}Ga throughout both lungs (Figs. 2A and B). The patient's subsequent work-up included cytology, antibody titer and culture for cytomegalovirus and special stains for *pneumocystis carinii* (PCP), legionella and toxoplasmosis, all of which were negative.

Broncho-alveolar lavage revealed an increased number of lymphocytes and histiocytes. There was no evidence of malignant cells, CMV or PCP. Bronchoscopic biopsy was performed, which demonstrated bronchiolitis obliterans, mild eosinophilia, loosely formed organizing exudate and granulomas (Fig. 3). Stains for AFB, PCP and fungi were all negative. These findings were most suggestive of an allergic or hypersensitivity reaction.

At this point, the possibility of a phenytoin-induced pulmonary reaction was strongly entertained and the medication was withdrawn. The patient was started on higher doses of corticosteroids

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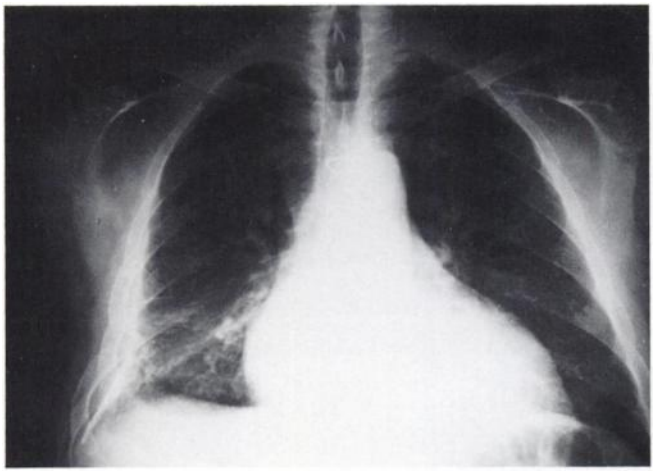

FIGURE 1. Chest x-ray demonstrates cardiomegaly with no evidence of active disease or CHF. Parenchymal and pleural changes at the right base represent chronic scarring.

50 mg prednisone b.i.d. for 3 days and then was tapered down to the 20 mg b.i.d., when he was discharged.

A repeat ^{67}Ga scan was obtained 25 days later to evaluate the response to the therapy. This demonstrated a marked improvement in the previously noted abnormal pulmonary activity (Figs. 2C and D).

The patient improved clinically and was discharged from the hospital 1 wk later.

DISCUSSION

Acute pulmonary disease may occur as part of the hypersensitivity angiitis caused by phenytoin sodium (*3*). The clinical features of the pulmonary involvement are fever, dyspnea and cough. Radiographic features have been found to be variable. These may show diffuse pulmonary infiltrates, occasionally with mediastinal and hilar adenopathy, or may be totally unremarkable (*3*). Lung biopsies in these cases have shown diffuse, subacute inflammatory exudate consisting of scattered neutrophils, lymphocytes, macrophages and a few eosinophils with the alveolar spaces filled with an organizing exudate (*3,4*). In our case, the biopsy findings were similar to the above but the cellular response was not too impressive. This can be explained by the fact that the patient was immunosuppressed.

This pathological process is believed to be reversible on cessation of the offending agent and treatment with corticosteroids, if necessary. However, it can have potentially serious complications if left untreated. Gallium-67 scanning has been used for the past two decades for the detection of inflammation. Currently, gallium scintigraphy is one of the most sensitive imaging tests for the diagnosis of inflammation in the lungs (*1,5–9*). Multiple factors contribute to the accumulation and retention of ^{67}Ga in inflammatory lesions. Gallium-67 almost exclusively bound to transferrin, enters inflammatory lesions due to increased capillary permeability. Some gallium is taken up by leukocytes by binding to the plasma membrane and entering the cytosol when the membrane is disrupted. In addition, ^{67}Ga may also bind to lactoferrin secreted by the secondary granules present within the neutrophils (*10–12*).

The clinical utility of ^{67}Ga in cases of drug-induced lung disorders includes detection of the disease activity in the lungs when chest radiographs may still be normal or inconclusive, determining the activity of the disease and demonstrating response to therapy (*13*). Abnormal gallium scans have been reported with amiodarone, cephalosporin, busulfan, bleomycin, procarbazine, nitrofurantoin, pen-

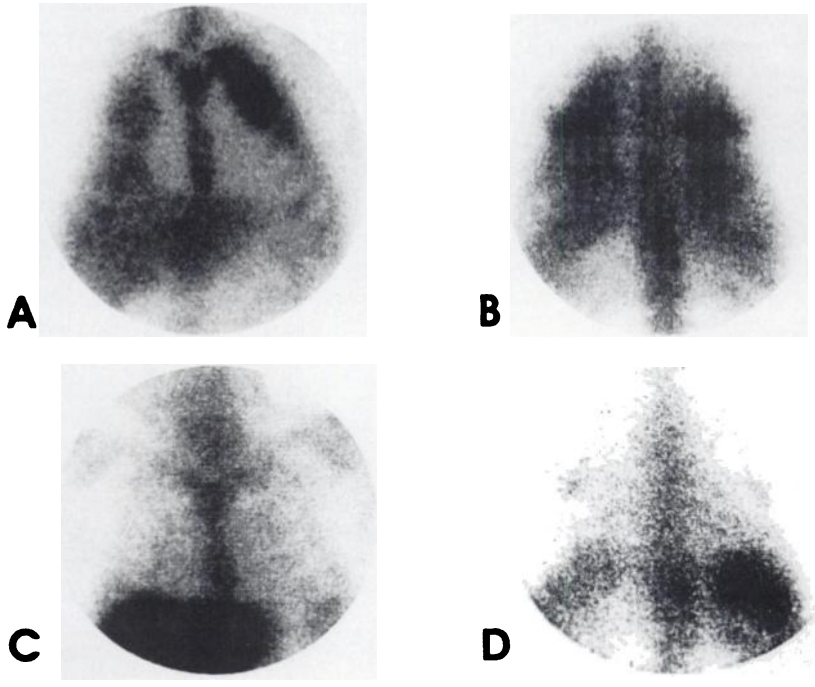

FIGURE 2. (A and B) Initial ^{67}Ga-citrate images of the anterior and posterior chest, respectively, demonstrating diffuse increased uptake. In the right lung, it is equal to the hepatic activity, whereas the left lung uptake is greater than the hepatic activity. A photopenic cardiac silhouette is also present. (C and D) Post-therapy ^{67}Ga-citrate images of the anterior and posterior chest demonstrate normal isotope uptake in both lung fields, indicating complete resolution of the inflammatory lung disease.

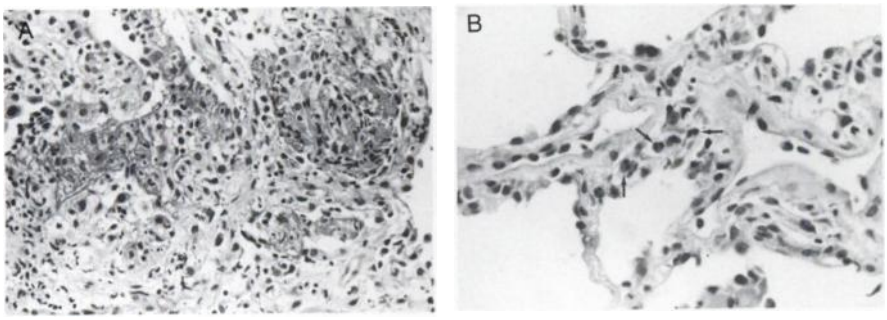

FIGURE 3. (A and B) Transbronchial biopsy shows lung parenchyma with an acute inflammatory infiltrate, including eosinophils (arrows), which is consistent with hypersensitivity pneumonitis.

tazocine, cyclophosphamide and cocaine (*14–17*). Lentle et al. (*18*) have described altered biodistribution of radiogallium in patients receiving dilantin which resulted in abnormal uptake of ^{67}Ga in mediastinal and hilar lymph nodes.

In our patient, gallium scintigraphy proved to be most valuable in the diagnosis of phenytoin-induced hypersensitivity pneumonitis. Gallium-67 scintigraphy was also useful in evaluating the response to therapy. In conclusion, we would like to emphasize that ^{67}Ga should be utilized in the early evaluation of suspected drug-induced hypersensitivity pneumonitis, especially when changes are not manifest on chest radiographs or CT scan since the pathological process is believed to be reversible with early treatment.

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