Indium-111-Leukocyte Imaging in Gaucher's Disease

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A 29-yr-old man with Gaucher's disease and fever of unknown origin underwent ^{111}In-labeled mixed autologous leukocyte scintigraphy. Although no focus of infection was identified, the resulting images were most unusual and were characterized by massive hepatomegaly, lack of central marrow activity and extensive lymph node uptake of labeled leukocytes. All of these findings could be explained on the basis of the patient's underlying disease. Hepatomegaly and absent central marrow activity correlated with extensive infiltration of these organs by Gaucher cells, while the lymph node findings were attributed to the presence of extramedullary hematopoiesis.

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Indium-111-labeled leukocyte scintigraphy is useful for localizing sites of infection. The normal distribution of labeled leukocytes is limited to the liver, spleen and bone marrow, and any activity outside these three organs is usually equated with infection (*1*). Local or systemic conditions, as well as selective labeling of subpopulations of white cells, i.e., lymphocytes, even in the absence of infection, can alter normal scan appearance. The unusual labeled leukocyte images of a patient with Gaucher's disease form the basis of this report.

CASE REPORT

A 29-yr-old man was admitted to the hospital complaining of fevers and night sweats, epistaxis, gingival bleeding, diffuse bone pain and right ankle swelling. His past history was remarkable for Gaucher's disease diagnosed at five years of age. He underwent splenectomy for hypersplenism at age 15 and subsequently became severely anemic and transfusion-dependent. On admission he was febrile to 38.5°C. Physical examination revealed multiple ecchymoses, massive hepatomegaly and a swollen, nontender right ankle. Laboratory results were remarkable for a hemoglobin of 7 g/dl (nl: 14–18 g/dl) and a hematocrit of 20% (nl: 42%–52%). Peripheral leukocyte count was 2200 per mm^3 (nl: 4,000–10,500 per mm^3), with 33% polymorphonuclear leukocytes, 57% lymphocytes, 4% monocytes and 6% bands. The platelet count was 14,000 per mm^3 (nl: 130,000–400,000 per mm^3). Blood and urine cultures were reported as no growth. Bone marrow biopsy revealed marrow replacement by Gaucher cells with large areas of coagulative necrosis. Increased reticulin was noted. No granulomata or tumor cells were identified.

Labeled leukocyte imaging was ordered to search for the cause of his fever. Twenty-four hours after injection of ~18.5 MBq (500 μCi) of mixed autologous leukocytes, labeled with ^{111}In according to the method of Thakur et al. (*2*), imaging was performed on a large field of view gamma camera (Omega 500, Technicare Corp., Solon, OH) equipped with a medium-energy, parallel-hole collimator with 20 percent windows centered over the 174 keV and 247 keV photopeaks of ^{111}In. Images demonstrated marked hepatomegaly, absent splenic activity and nearly absent central marrow activity. Asymmetric irregular marrow expansion into the distal femurs was present. There was intense disseminated lymph node uptake involving posterior cervical, supraclavicular, axillary, mediastinal, iliac, inguinal and femoral lymph node groups (Fig. 1). Computed tomography (CT) of the abdomen performed three days after the leukocyte study demonstrated massive hepatomegaly and retroperitoneal lymphadenopathy. Twenty-four hours later, because of the labeled leukocyte and CT findings, the patient underwent right scalene and internal jugular lymph node biopsy. Histologic analysis of the nodes demonstrated nonspecific hyperplasia, sinus histiocyte proliferation and scattered clusters of Gaucher cells. Extramedullary hematopoiesis was also identified. Special stains for acid-fast bacteria and fungi were negative.

Following lymph node biopsy, the patient developed dyspnea. A chest x-ray was reported as without evidence of infiltrates. Although he was seronegative for the HIV virus, the patient underwent fiberoptic bronchoscopy with bronchoalveolar lavage three days after lymph node biopsy because of a history of multiple blood transfusions. Special stains for acid-fast bacilli, fungi and *pneumocystis carinii* organisms were negative. No malignant cells were seen. Numerous hemosiderin-laden macrophages were present, indicating extensive pulmonary involvement by Gaucher's disease. Over the next several days, the patient continued to run low-grade fevers. He refused any additional procedures and was discharged three weeks after admission with diagnoses of severe anemia, thrombocytopenia and multisystemic involvement by Gaucher's disease. No source of infection was identified.

DISCUSSION

The normal distribution of activity on ^{111}In-labeled leukocyte images is confined to the liver, spleen and bone marrow; any activity outside these three organs is generally equated with infection (*1*). Local or systemic condi-

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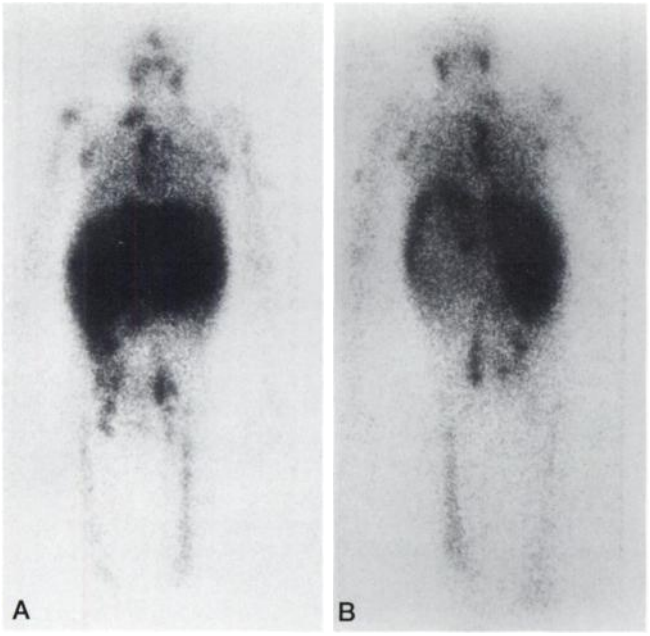

FIGURE 1. Anterior (A) and posterior (B) whole body images performed ~24 hr after injection of ^{111}In-labeled mixed autologous leukocytes. A massively enlarged liver with heterogeneous distribution of activity occupies most of the abdomen in this splenectomized 29-yr-old man with Gaucher's disease. The axial skeleton is virtually devoid of functioning bone marrow; residual functioning marrow is seen in the right humerus and both femurs. Intense, disseminated lymph node uptake is seen in posterior cervical and right supraclavicular lymph nodes, both axillae, the right paratracheal region and the mediastinum. Extensive lymph node uptake is also identified in the para-aortic, iliac, inguinal and femoral lymph node groups.

tions and selective labeling of subpopulations of leukocytes can, even in the absence of infection, alter normal scan appearance. Accurate interpretation of the study therefore requires that individuals interpreting these images be cognizant not only of any underlying condition in a particular patient, but also of the manner in which such a condition(s) could affect scan appearance.

Gaucher's disease is a chronic, hereditary disorder characterized by a deficiency in the activity of beta-glucocerebrosidase, a catabolic enzyme responsible for cleavage of glucose from ceramide. As a result of this deficiency, the uncleaved glycolipid, glucocerebroside, accumulates in the monocyte-macrophage cell system. These large glycolipid-containing cells, known as Gaucher cells, can be found in virtually every organ system of an affected individual, but are most prominent in the liver, spleen, bone marrow and lymph nodes (*3*).

Gaucher cells, invariably present in the liver of patients with this disease, are confined to the sinusoids; hepatocytes are never involved. The extent of liver disease reflects the severity of the overall illness, and in the most severe cases fibrosis, cirrhosis, and portal hypertension are present. Splenomegaly, generally present, is often massive. One-half of all Gaucher's patients undergo splenectomy, primarily because of thrombocytopenia. Following splenectomy, a relative, if not absolute, lymphocytosis is frequently present for reasons that are not well understood. Microscopically, Gaucher bone marrow demonstrates groups of macrophages replacing normal marrow cells, which results in peripheral expansion of hematopoietically active marrow. Extensive replacement of normal marrow may be accompanied by extramedullary hematopoiesis (*4,5*).

The labeled leukocyte images of this patient are the visual correlates of the pathologic effects of Gaucher's disease on the reticuloendothelial/hematopoietic system. The massive hepatomegaly and paucity of functioning marrow illustrate the extensive infiltration of these organs by Gaucher cells. Lymph node uptake can also be attributed to the consequences of Gaucher's disease in this young man.

In general, the frequency and significance of lymph node visualization on labeled leukocyte images varies with the population of cells labeled. When only granulocytes or mixed leukocytes are labeled, lymph node uptake is infrequent and has been attributed to inflammation and infection (*6*), tumor uptake (*7–9*) and, particularly in children, a normal variant (*10*). None of these conditions, however, were present in this patient. In contrast, in patients studied with selectively labeled lymphocytes, nodal visualization is routinely present and is considered a normal finding (*11–14*). In animals, nodal uptake of labeled lymphocytes is enhanced following splenectomy (*15*). Although the majority of this patient's labeled leukocytes were lymphocytes, it is unlikely that lymphocytosis (even in the presence of a previous splenectomy) can explain the extensive lymph node activity seen. This lymphocytosis was more relative than absolute, in as much as the patient's total peripheral leukocyte count was only 2200/mm^3 at the time of labeling. Consequently, the total number of lymphocytes labeled was not significantly different from the number labeled in a patient with a normal peripheral leukocyte count (and a normal differential) in whom lymph node visualization would not be expected.

The most plausible explanation for lymph node activity in this patient was the presence of extramedullary hematopoiesis. Extramedullary hematopoiesis, the formation of blood in tissues other than bone marrow, is a compensatory mechanism and represents a reversion of the involved tissues to their fetal blood-forming function. Although extramedullary hematopoiesis can occur anywhere in the body, it is most frequently encountered in those structures concerned with hematopoiesis during intrauterine life: liver, spleen and lymph nodes. Since sites of extramedullary hematopoiesis are histologically indistinguishable from bone marrow (*16*) and bone marrow activity is normally present on labeled leukocyte images, it is likely that the lymph node uptake on these images simply reflects extramedullary "bone marrow."

In summary, even grossly abnormal leukocyte images cannot be automatically equated with infection. A knowl-

edge of underlying disease processes and their effects on the hematopoietic system in general and on leukocytes in particular is mandatory if these studies are to be interpreted in a meaningful fashion.

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