

Gallium-67-Citrate Imaging in the Detection of Focal Lesions for Anemia, Proteinuria, and Prolonged Fever

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CASE PRESENTATION

A 41-yr-old woman was found to have anemia, proteinuria, and microhematuria at a health checkup as a new employee. She had had a history of severe toxemia of pregnancy at age 27, but apparently had been healthy since that time, and was asymptomatic at the time of her job application. The anemia did not respond to i.v. injections of an iron compound at a private clinic. Over a period of 2 mo, there was dyspnea on effort, loss of appetite, and dull discomfort of her lower legs occurred. She was then referred to our hospital. On admission she had edema of her face and legs, pale conjunctivae, and wheezing over both her lungs. Temperature was 38.4°C, blood pressure 178/100 mmHg, and pulse rate 110/min. Her Hct was 29%, WBC 8,600/ μ l, platelet count 299,000/ μ l, ESR 91 mm/hr, and CRP 3+. Her serum protein was reduced to 5.0 g/dl, with an albumin of 3.3 g/dl. She lost 2.5-3.5 g protein per day in her urine. Initial chest roentgenogram revealed areas of hazy infiltration in both the middle and lower lung fields. Antibiotic therapy achieved disappearance of these pneumonic shadows but only partial and transient relief of the fever. At this point, ESR was still elevated at 89 mm/hr with a CRP of 2+. To determine the site of possible focal lesion responsible for the fever and other symptoms, scintigraphy with 74 MBq (2 mCi) of gallium-67- (^{67}Ga) citrate was performed on the 14th hospital day. From the result of the gallium study, a bone scan and roentgenograms of thoracic spine were ordered.

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Radiographic and Nuclear Medicine Findings

The ^{67}Ga -citrate scan taken 72 hr postinjection demonstrated multiple sites of abnormal accumulation at thoracic spine and roots of neighboring ribs (Fig. 1). Bone scintigraphy with 555 MBq (15 mCi) of technetium-99m- ($^{99\text{m}}\text{Tc}$) methylenediphosphonate was also positive in the same loci (Fig. 2). Radiography confirmed compression fractures and osteopenia at vertebrae and lytic foci at ribs (Fig. 3).

Final Diagnosis and Treatment Course

Due to the unusual distribution of bone lesions, atypical for metastases, a hematologic disorder was suspected. The subsequent bone marrow aspiration revealed malignant plasmacytes. Bene-Jones protein, tested by heating urine was negative, but repeat electrophoreses of concentrated urine reproducibly showed an abnormal peak at β -globulin locus, which was later identified as κ chain of immunoglobulin. Chemotherapy for the multiple myeloma was started, which she tolerated well. As of this writing, the patient has shown partial hematologic improvement, but her nephrotic syndrome persists despite doses of oral prednisolone.

DISCUSSION

It has been well established that ^{67}Ga accumulates at the site of inflammation as well as neoplasms (1,2), and thereby can serve as an useful agent to localize clinically suspected abscess and other forms of focal infection (3,4). In the clinical situation of "fever of unknown origin (FUO)," when physical examination failed to disclose the source of prolonged fever, gallium citrate scans may play an important diagnostic role. There have been numerous reports about the high sensitivity and the accuracy of this procedure for detecting pyogenic foci such as abscesses, urinary tract infection, and osteomyelitis (3-6), but they have rarely mentioned cases of malignant diseases causing fever. In 58 consecutive cases of FUO studied with ^{67}Ga scans, unusual



FIGURE 1
Posterior spot image of the chest with ^{67}Ga citrate. There are two horizontal bands of increased accumulation at lower dorsal spine, with multiple hot spots at both sides of the vertebral column.

patterns of abnormal accumulation suggested systemic illness in six patients. Three of these patients had systemic autoimmune diseases, and another three, including the case described above, had hematologic malignancies.

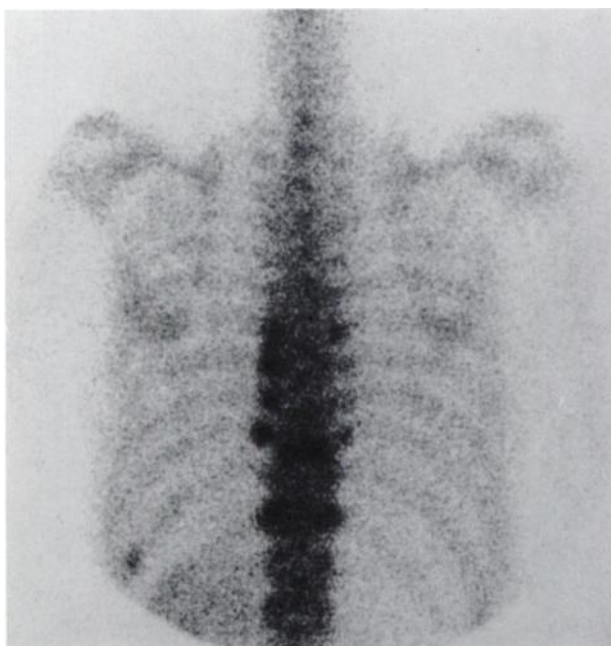


FIGURE 2
Posterior spot image of the chest with $^{99\text{m}}\text{Tc}$ -MDP. A hot spot at left 11th rib was noticed besides lesions demonstrated in the gallium study.

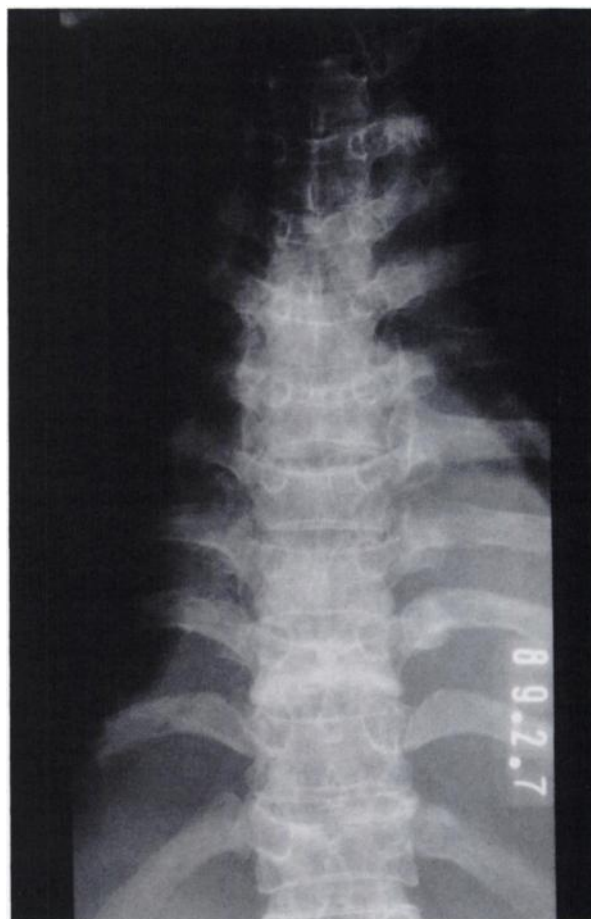


FIGURE 3
X-ray film of thoracic spine, showing pathologic compression fractures of vertebral bodies and osteolytic lesions at roots of some ribs. These correspond to the hot bands and spots seen in gallium and bone scans.

The latter three all had fever and anemia, but lacked clinical features typical of their respective disease at the initial presentations, so that they were labeled as F.U.O.

In the index case featured in this report, the malignant plasmacytes were secreting light chains but not whole immunoglobulin molecules usually seen in multiple myeloma as an *M* peak in γ globulin fraction of serum protein. In fact, most of the paraprotein in this patient was being excreted to the urine. The concomitant nephrotic syndrome made it even more difficult to analyze the relative balance between components of protein in serum and urine. In the literature, radionuclide imaging is said to be relatively insensitive and of limited use compared to conventional radiographs (7,8). Still, Waxman et al. reported that the ^{67}Ga scans were positive in 10 out of 18 patients studied, and was useful in detecting a fulminant subtype of the disease when combined with radiophosphonate bone scan (9). In the patient described here, both scans successfully demonstrated affected sites before the hematologic diagnosis was known.

One of the other two patients with hematologic malignancies was a 70-yr-old female who first presented with prolonged fever, flu-like symptoms, and dyspnea on effort. Her final diagnosis was chronic myelomonocytic leukemia, but she had normal peripheral leukocyte and thrombocyte counts and no significant splenomegaly on admission. Moreover, the initial bone marrow aspiration demonstrates mild reticulocytosis and no definite malignant change, with a normal nucleated cell count. After vigorous antibiotic therapy failed to normalize body temperature, a ^{67}Ga scan was performed to determine the cause of fever (Fig. 4). The pattern of scintigraphic abnormality and an emerging splenomegaly prompted physicians to perform the second bone marrow tap, which revealed abnormal monocytoid proliferation with erythrophagia. Retrospectively, she may have been in a smoldering phase of the leukemia when admitted. With characteristic accumulation at proximal femora as described in textbooks (10,11), her gallium scan strongly suggested a myelo-proliferative disease.

The remaining patient was a 71-yr-old housewife, who first presented with high fever and various neuro-

logic symptoms. She later was found to have non-Hodgkin's lymphoma, but there was no palpable surface lymph adenopathy on admission. Since the cranial and peripheral nerve signs were diverse and florid, diagnostic efforts were mainly concentrated on neurologic examinations like electrophysiologic studies, peripheral nerve biopsy, and repeat brain computed tomographs. All showed normal or only nonspecific findings. In retrospect, she may have had paraneoplastic peripheral neuropathy (12) or, alternatively, compression of nerves by rapidly enlarging lymphnodes. Radiogallium scans showed multiple sites of intense accumulation in the whole body (Fig. 5), before superficial lymphnode swelling became evident. The systemic distribution and intense nature of abnormal accumulation seemed pathognomonic of lymphoma as widely acknowledged (10,11,13). An excisional biopsy of left inguinal node gave a definite histological diagnosis.

FUO is often due to occult infectious lesions, but sometimes is caused by malignant processes, autoimmune or collagen diseases, or cerebrovascular accidents

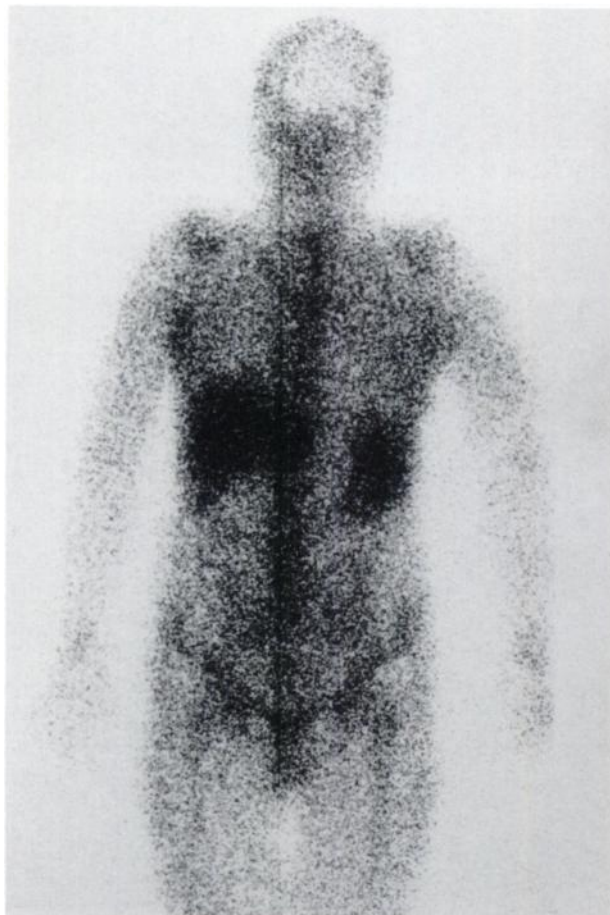


FIGURE 4
Anterior view of whole-body gallium scan of a patient with chronic myelomonocytic leukemia. Abnormal uptake was seen at bilateral shoulders, armpits, and upper halves of thigh bones.

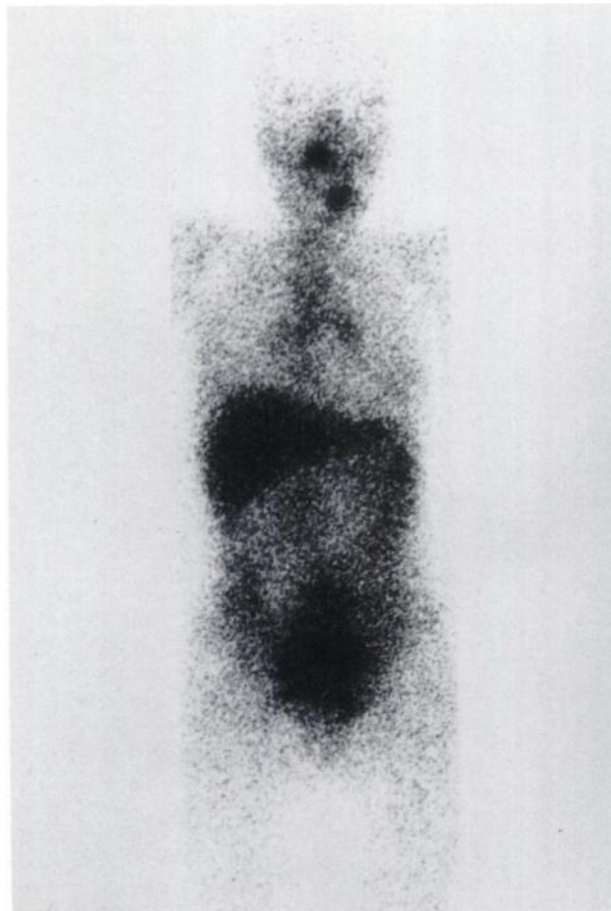


FIGURE 5
Anterior view of whole-body gallium scan of a patient with non-Hodgkin's lymphoma. Intense hot spots were found at right nasal, left submandibular, and minor pelvic regions, together with moderate accumulation at bilateral hili and around aortic bifurcation.

(14,15). Solid tumors tend to be diagnosed rapidly with modalities such as ultrasonography, computed tomography and radionuclide imaging, and with measurement of various tumor markers. Hence, they are infrequent causes of puzzling fever. On the contrary, myeloproliferative and lymphoproliferative diseases still constitute uncommon but important causes of FUO. Their prognoses are generally poor and often fatal, and delay in diagnosis could aggravate the situation.

Besides gallium citrate, indium-labeled leukocytes also have been shown to detect inflammatory foci (16–18). In spite of its advantages, e.g., lower intestinal background and more rapid results as compared to radiogallium, the cumbersome procedures needed to separate and label blood cells seems to hinder its wide use in routine clinical practice. Moreover, its significance in locating malignant lesions is yet to be tested, despite a few reports of occasional tumor uptake (18,19). A similar argument may apply to the new method of labeled-leukocyte scintigraphy with technetium hexamethylpropyleneamine oxime (20,21). With its established ability to detect both inflammatory and neoplastic lesions, ⁶⁷Ga-citrate scan still appears quite useful as a diagnostic screening test in cases of puzzlingly prolonged fever.

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