Gallium-67 Citrate Imaging in Acquired Immunodeficiency Syndrome

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This is the first in a series of four continuing education articles on AIDS patient management and care. This article is designed to present an overview of complications due to the AIDS virus and the use of nuclear medicine techniques to assist in patient management. Upon completion of this article the technologist will be able to: 1) identify complications due to the AIDS virus; 2) recognize the usefulness of gallium imaging for follow-up of these complications; and 3) recognize the importance of gallium imaging for early detection of complications.

Acquired immunodeficiency syndrome (AIDS) has rapidly become one of the leading causes of morbidity and mortality, both in the United States and abroad (*1–5*). This disease is due to infection by the human immunodeficiency virus (HIV), resulting in progressive loss of cellular immunity and greatly increased susceptibility to infection. In addition to typical infections by high-grade pathogens, these patients also are susceptible to infection by a variety of low-grade or opportunistic organisms. These acute infections are the major cause of morbidity and mortality in AIDS (*2,6–9*). The signs and symptoms of various complications of AIDS often may be clinically indistinguishable. Prompt diagnosis and institution of appropriate therapy is vital to maximize survival.

Acute onset of fever and/or respiratory symptoms is a common clinical presentation leading to a workup for infection. Chest radiographs are frequently normal or equivocal early on in many of the more common pulmonary infections seen in these patients, such as *pneumocystis carinii* pneumonia (PCP) and mycobacterium avium intracellulare (MAI) infection, an atypical form of tuberculosis. Definitive diagnosis of these conditions may require bronchoscopy and biopsy, which are expensive and invasive procedures.

Gallium-67 citrate (^{67}Ga) imaging is well established as a sensitive means of detecting infectious processes, particularly in the absence of clear-cut localizing signs or symptoms (*9–15*). Specifically, ^{67}Ga imaging may provide important clues in the differential diagnosis of these infections, and can permit earlier institution of appropriate therapy. In addition, a negative gallium study can obviate the need for more costly and invasive procedures such as bronchoscopy. Diffuse pulmonary activity strongly suggests the presence of an acute pneumonic process such as PCP or viral pneumonia. Focal nodal activity most often is associated with MAI infection or lymphoma. Increased colonic activity is associated with inflammatory processes in the large bowel. Indium-111 (^{111}In) white blood cell imaging may be complementary to gallium in certain instances, and may be particularly useful in the evaluation of infections involving the oropharynx, bowel, sinuses, and central nervous system. This paper will review the role of gallium scintigraphy in the evaluation of patients with AIDS. In addition, the sometimes complementary role of ^{111}In white blood cell imaging also will be mentioned.

TECHNIQUE

The utility of gallium scintigraphy in any clinical setting can be maximized by careful attention to technique. Gallium imaging in adults is performed most often using doses in the range of 5–10 mCi of ^{67}Ga citrate given intravenously, representing an increase in dose compared to earlier use. Increasing the dose improves count statistics and spatial resolution, at some cost in terms of increased patient radiation dose. Triple photopeak imaging is advantageous for the same reasons, and imaging of the three lower energy peaks (93 keV, 185 keV, and 300 keV) should be performed if the gamma camera used has this capability. A medium-energy parallel-hole collimator is used. Either spot imaging or whole-body imaging may be used, and tomography may be helpful in selected cases, by means of SPECT imaging or using a dedicated tomographic device such as an Anger tomoscanner.

In the case of suspected acute inflammatory processes, the usual situation in imaging AIDS patients, at least one set of early images should be obtained. We routinely obtain the initial images at 24 hr postinjection, although uncommonly imaging as early as 6 hr postinjection may be indicated such as in the case of suspected life-threatening acute abdominal abscess. These early images are of great importance in order to diagnose potentially life-threatening infections as quickly as possible. In addition, delayed images also should be obtained at 48–72 hr or later. The delayed images frequently are superior because of greater clearance of background activity in the blood pool and soft tissues, resulting in improved lesion contrast. In the case of assessment of pulmonary activity, this factor is particularly important, as up to half of normal individuals may appear to have mild diffuse pulmonary activity at 24 hr (*16*).

Delayed images also may be of great value in differentiating between normal colonic excretion of ^{67}Ga citrate and inflam-

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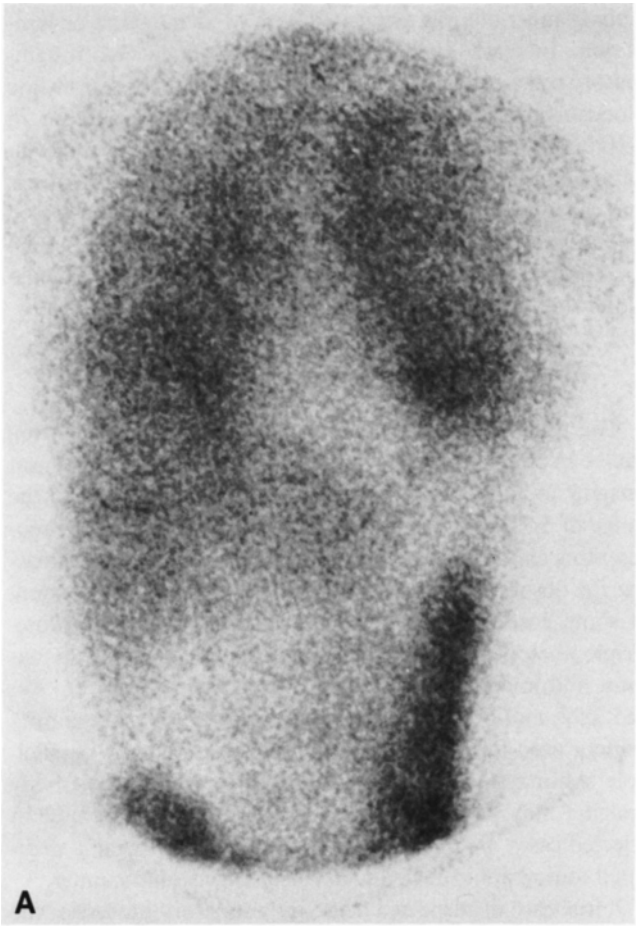
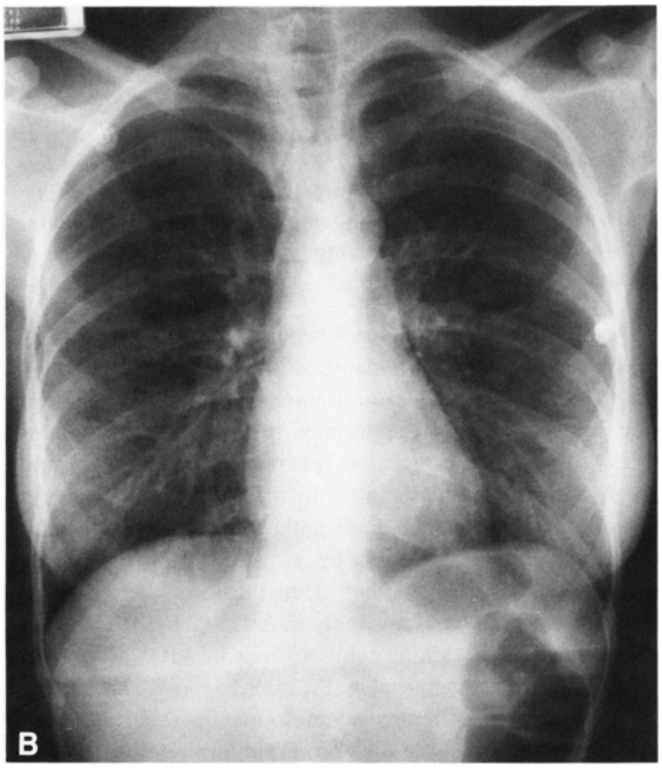
matory processes in the colon, which are common in AIDS, as already mentioned. The use of bowel preparation is controversial, but it is sometimes used to minimize colonic activity (*17–19*). We prefer not to use bowel preparation routinely, since it is time-consuming, inconvenient, and not always successful. Bowel preparations only remove stool from the lumen of the bowel and do not prevent activity from remaining within the mucosa of the colon. Furthermore, vigorous bowel preparation may actually increase colonic activity by irritating the bowel wall. In most cases, movement of bowel activity on serial images will identify it as nonpathologic. Selective use of enemas may be helpful in some cases, such as retention of activity in the rectosigmoid region.

DIFFUSE PULMONARY ACTIVITY

The most common abnormal pattern seen in AIDS patients presenting with acute fever and/or respiratory symptoms is the presence of diffusely increased pulmonary activity (DPA), as shown in Figure 1. This finding may be strongly suggested





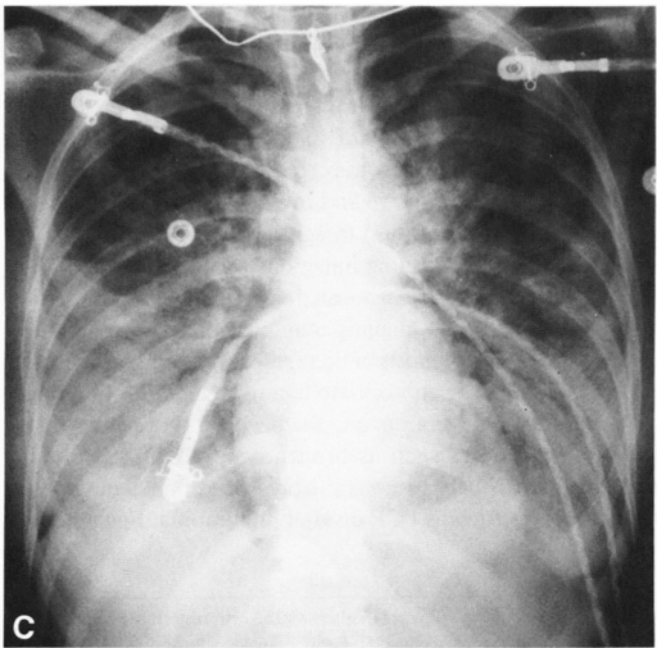


FIG. 1. Diffuse pulmonary activity due to *pneumocystis carinii* pneumonia (PCP). (A) 96-hr anterior chest and abdomen image with marked diffuse lung uptake bilaterally. Normal activity is also seen in the liver and colon. (B) Chest radiograph at the time of the gallium scan, demonstrating only slightly prominent interstitial lung markings at the bases. (C) A follow-up chest radiograph several days later demonstrates interval development of bilateral alveolar infiltrates, typical of advanced PCP. Subsequent bronchoscopy confirmed the diagnosis of PCP.

on 24-hr images but should always be confirmed on delayed images if possible. In many instances, the presence of a relatively photopenic or negative defect in the region of the cardiac silhouette will help distinguish DPA from blood-pool activity (Fig. 2).

The presence of DPA strongly suggests an acute pulmonary infection by an opportunistic organism. The most common infection is PCP, a potentially life-threatening infection caused by a small protozoan that may be present in normal individuals without causing illness (*7,9,20*). A definitive diagnosis of PCP requires direct visualization of the organism, either in sputum samples or on biopsy. In patients without productive cough, aggressive efforts to diagnose this infection should be made by means of bronchoscopy with transbronchial or brush biopsy, or by open lung biopsy. The chest radiograph is frequently normal early in this disease. Gallium-67 citrate imaging is more sensitive than the chest x-ray for the detection of PCP, detecting ~ 90% of cases overall and up to 86% even with a negative chest radiograph (*10,13,20–27*). If untreated, the chest radiograph eventually will demonstrate perihilar infiltrates that may rapidly progress to diffuse alveolar infiltrates. The absence of increased pulmonary activity is strong evidence against the presence of PCP, and can preclude the necessity of bronchoscopy or open lung biopsy (*28*). In some instances, the findings in PCP may be somewhat atypical, with asymmetric lung uptake or even focal lung or lymph node activity, as illustrated in Figure 3 (*29*).

While a common cause of DPA in these patients, PCP is by no means the only etiology of this finding (*10,13, 15,20,24,25,27,30*). DPA can be caused by other opportunistic infections, such as viral or fungal pneumonias, of which cytomegalovirus (CMV) is common. Typical bacterial infections or tuberculosis can also result in DPA. Noninfectious inflammatory processes can also mimic these infections on gallium scans, including pulmonary vasculitis, drug toxicity (e.g., bleomycin, cytoxan, etc.), prior radiation therapy, lymphangitic carcinomatosis and even lymphoma. As a result, DPA should be considered as a sensitive but nonspecific finding, which always warrants further workup to determine its cause. Specificity can be improved by using a grading system for intensity of uptake (*23*), since faint pulmonary uptake may be physiologic. Specificity also is higher in cases having a normal chest radiograph (*24*).

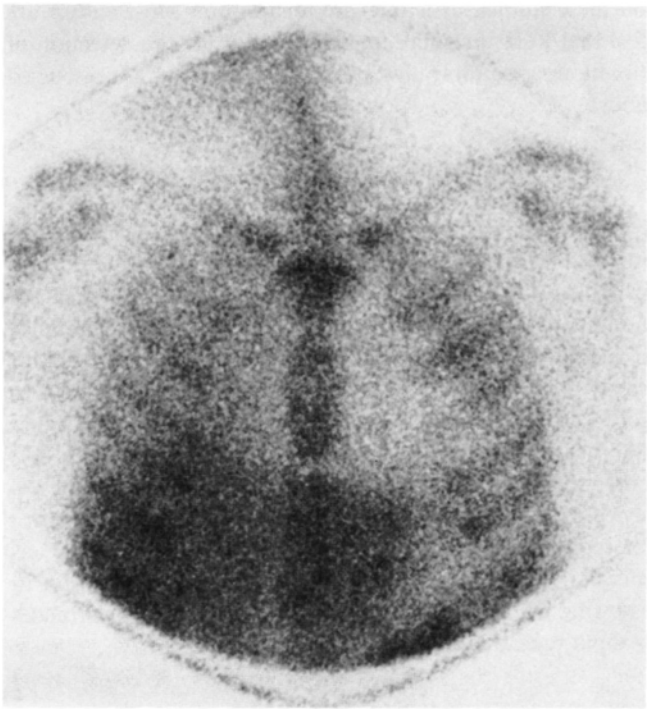


FIG. 2. Anterior gallium image of the chest in a 26-yr-old male with AIDS presenting with high fever, shaking chills, and shortness of breath. Note the "negative cardiac silhouette," indicating that the activity in the lungs is greater than that of the blood pool and therefore pathologic.

Gallium-67 imaging is very useful for the follow-up of patients subsequently proven to have PCP or other pulmonary infections. The DPA will resolve as the infection is successfully treated and may precede resolution of abnormalities on the chest radiograph. Gallium-67 may also be helpful in the early detection of recurrences, which are common. With the advent of therapeutic agents, including azidothymidine (AZT), ^{67}Ga imaging may play a role in the selection of patients for treatment and assessment of the efficacy of therapy. Finally, the finding of DPA in an HIV-positive patient with AIDS-related complex (ARC) may lead to reclassification of the patient as having full-blown AIDS (*26*).

FOCAL NODAL ACTIVITY

Another common abnormality seen on gallium images in AIDS patients is the presence of focal adenopathy. This finding may be seen anywhere in the body, but it is most commonly found in the pulmonary hilar or mediastinal nodes, cervical, or paraaortic nodes (Fig. 4). Nodal uptake is not usually seen in HIV-positive patients having adenopathy without other infectious or neoplastic processes. This finding also is not pathognomonic for any entity, but it is seen most often in cases of lymphoma, typical tuberculosis or atypical tuberculosis, such as MAI (*20,26,27*). AIDS patients have an increased incidence of lymphoma secondary to decreased immunity to the development of neoplasms. MAI is a less common form of tuberculosis, which is less pathogenic than typical mycobacterium tuberculosis, and therefore more prone to occur in immunocompromised hosts. MAI is usually more resistant to therapy than typical mycobacterium tuberculosis infection. These entities can be differentiated only by biopsy and are not surprisingly treated very differently. Either condition can present with fever or respiratory symptoms indistinguishable from PCP or other infections. Uncommonly, PCP itself may present with focal nodal uptake. Another common cause of adenopathy in AIDS, Kaposi's sarcoma, does not accumulate gallium, and will result in a negative study (*20,27*).

FOCAL PULMONARY UPTAKE

Focal pulmonary uptake is nonspecific, but it is most often due to focal inflammatory processes such as bacterial pneu-

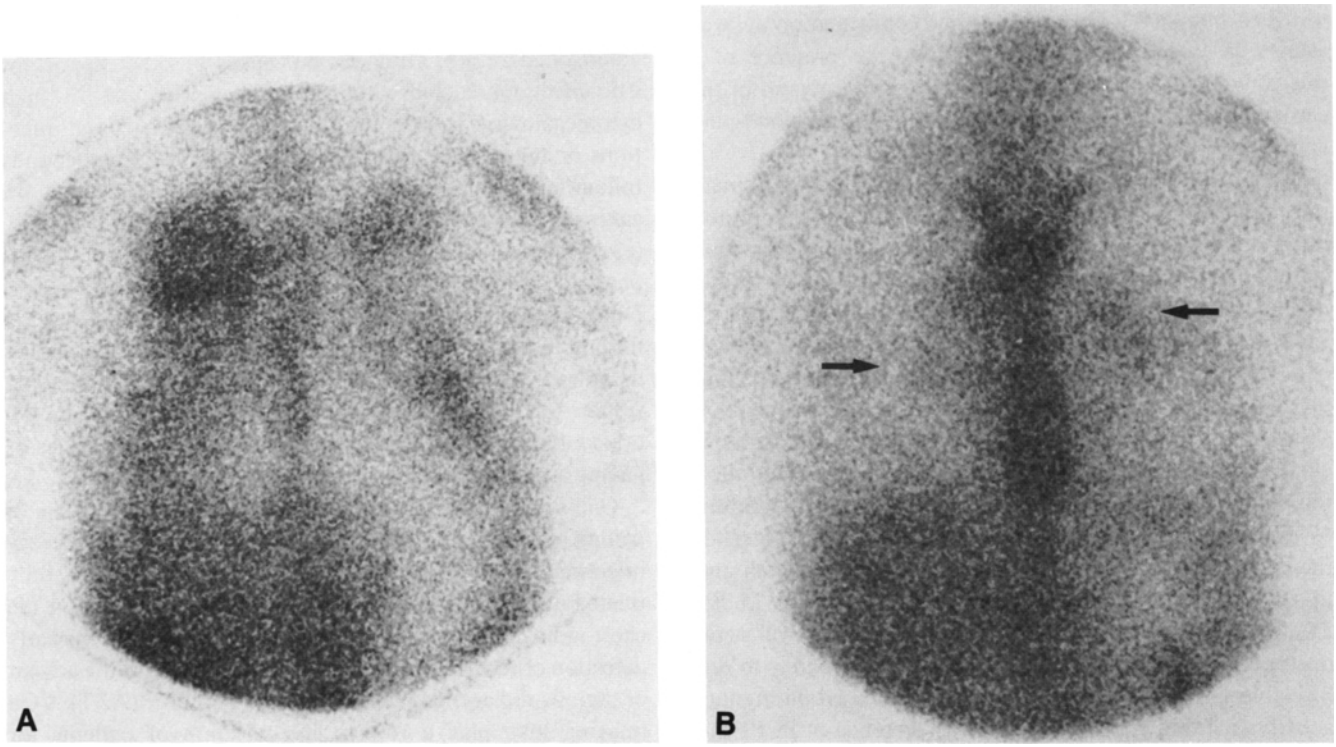


FIG. 3. Atypical patterns of abnormality in PCP. (A) 72-hr anterior chest image demonstrating bilateral increased, inhomogeneous pulmonary uptake with a negative cardiac silhouette. Greater uptake is seen in the right upper lobe, with some sparing of the left mid-lung field. (B) Anterior chest image showing faint bilateral perihilar activity (arrows). This finding mimics the early radiographic finding of patchy perihilar infiltrates. Focal perihilar activity more often is associated with hilar adenopathy due to tuberculosis or lymphoma.

monias and lung abscesses or neoplasms (*20,27*). An example is shown in Figure 5. As previously mentioned, uncommonly, focal patterns may be seen with PCP, but in such cases the findings are usually bilateral, even if asymmetric (Fig. 3). The finding of focal lung uptake requires correlation with clinical findings and the chest radiograph.

OTHER FINDINGS

One of the benefits of ^{67}Ga imaging is that it affords the opportunity to evaluate the entire body for the presence of infection. As in other cases of fever of unknown origin without localizing symptoms, AIDS patients may demonstrate focal abnormalities on ^{67}Ga imaging at unexpected sites. As previously mentioned, inflammatory processes in the colon are common in AIDS and may result in persistent increased bowel activity that does not change configuration over time (Fig. 6). The 72-hr images are useful because of improved lesion-to-background contrast and the ability to detect changing patterns of colonic activity, which are indicative of normal colonic gallium excretion. Fungal infections involving the oral cavity and/or esophagus, such as candidiasis (thrush) are common in AIDS, but are not often detected by ^{67}Ga imaging. One recent report has suggested that ^{111}In-labeled white blood cell imaging may be more sensitive for the detection of this infection, as well as infections involving the sinuses and central nervous system (*31*). Furthermore, ^{111}In studies may be preferable for the evaluation of suspected bowel infections, since there is no potentially confusing normal bowel activity on these studies, as is the case for gallium. Most authorities feel that ^{67}Ga imaging remains superior for the detection of the more common pulmonary infections in AIDS discussed above.

NEGATIVE STUDY

While the sensitivity of ^{67}Ga imaging is obviously of great importance in the early diagnosis of opportunistic infections in AIDS, the value of a negative study is no less great. A negative gallium study is strong evidence against the presence of a clinically significant infection, and obviates the need for costly and potentially invasive workup (*20,23,24,27,28*). In such cases, fever may be related to drug reactions or other noninfectious etiologies. Hattner, et al. have estimated a 36% potential cost-savings provided by using the presence or absence of DPA as a criterion for referring patients to bronchoscopy and biopsy to detect PCP (*28*). In addition, as mentioned above, follow-up ^{67}Ga imaging can be useful in assessing the response to therapy and excluding recurrences without repeating invasive studies.

SUMMARY

Gallium-67 citrate scintigraphy is a sensitive examination for the evaluation of fever or acute respiratory symptoms in patients with AIDS, allowing for earlier diagnosis and treat-

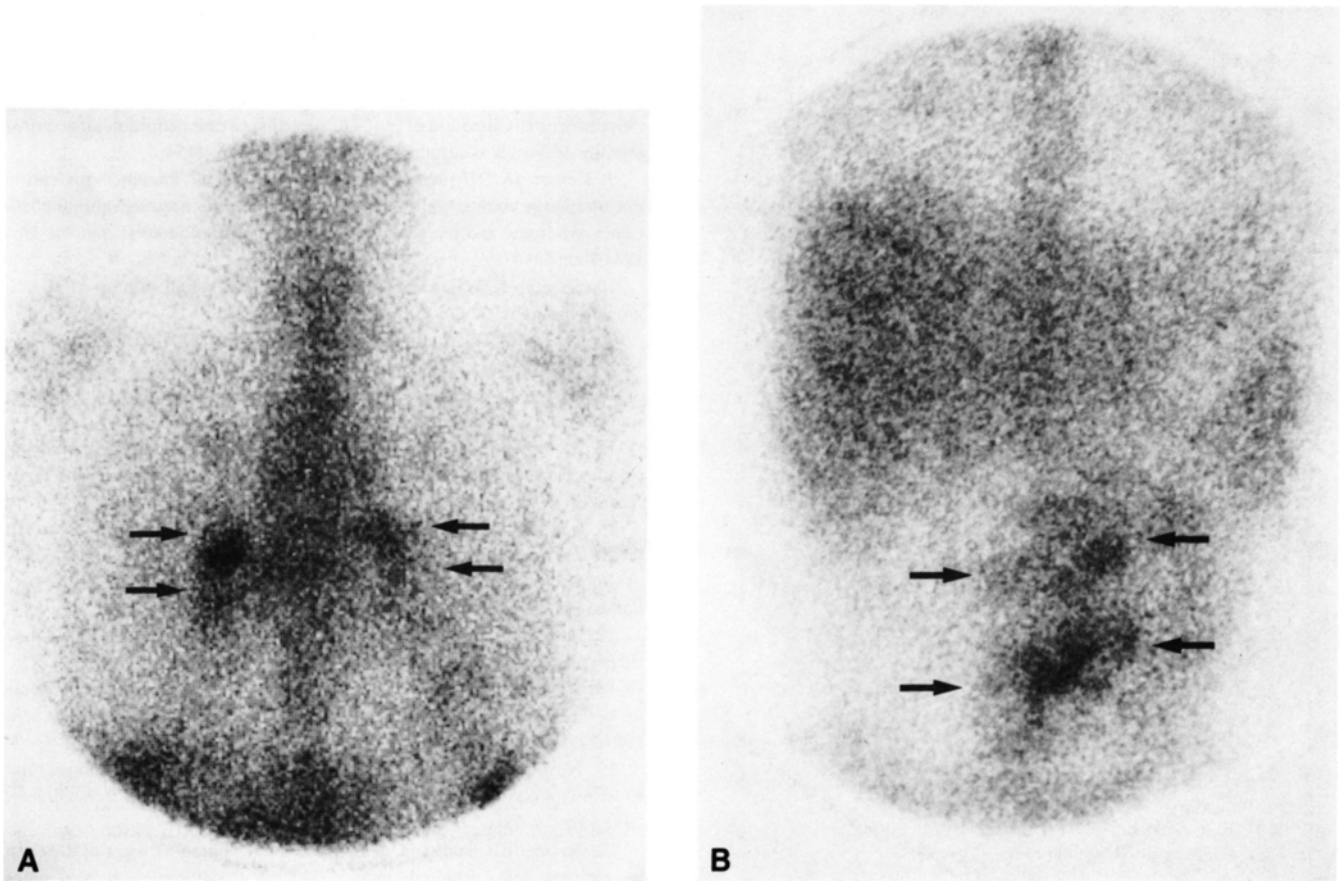


FIG. 4. Focal lymph node uptake. (A) Anterior chest image demonstrating focal increased activity noted in both hilar regions (arrows). The patient was diagnosed as having atypical tuberculosis due to mycobacterium avium intracellulare (MAI). (B) 72-hr anterior abdomen image in a different patient. Note the focal increased activity in the paraaortic region (arrows), compatible with adenopathy. This finding was unchanged from 24 hr images (not shown). The final diagnosis proved to be lymphoma.

ment of various opportunistic infections, avoidance of unnecessary invasive procedures and improved follow-up of the response to therapy. The pattern of abnormality may provide strong clues in the differential diagnosis of these infections, and may also reveal noninfectious disorders, such as lymphoma. Gallium-67 citrate imaging has limited sensitivity for the detection of candidiasis and inflammatory processes of the sinuses and central nervous system. In these instances, ^{111}In white blood cell imaging may play a useful role. The management of fever in AIDS is difficult, and requires a multidisciplinary approach. Radionuclide imaging with ^{67}Ga and ^{111}In provides useful information, but the results of these studies must be correlated with other clinical and laboratory data. The abnormalities detected on these studies are relatively nonspecific and require confirmation prior to institution of definitive therapy.

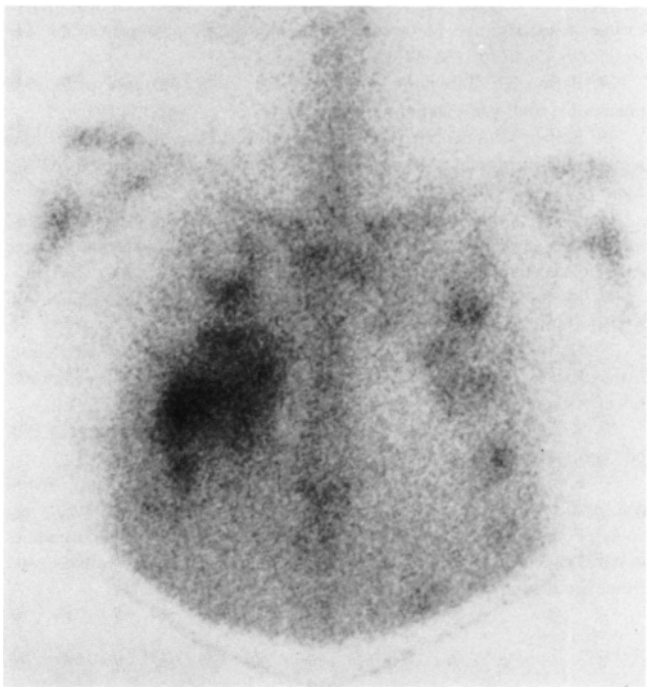


FIG. 5. Anterior chest image with multiple focal areas of increased lung uptake noted bilaterally, most striking in the right lung base. These areas corresponded to focal masses on the chest radiograph (not shown), and were found to represent lymphomatous involvement of the lungs. Solitary focal areas of increased lung uptake are nonspecific but are often caused by bacterial pneumonias.

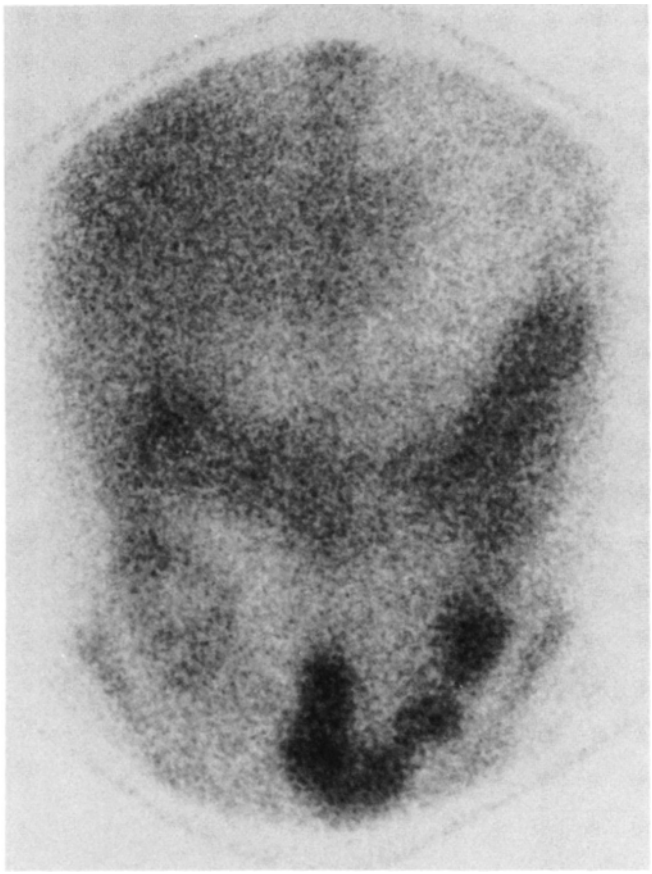


FIG. 6. 96-hr anterior image of the abdomen and pelvis in an AIDS patient with a 1-wk history of profuse diarrhea, night sweats, and weight loss. Note the diffusely increased colonic activity, which was unchanged from earlier images at 24 and 48 hr (not shown). Stool cultures demonstrated Entamoeba hartmanni infection, a form of amebiasis caused by an opportunistic pathogen. Other infections, such as cryptosporidium, and less commonly, colonic lymphoma, can result in a similar appearance. Bowel infections may be more readily detected by ^{111}In WBC imaging (see text).

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GALLIUM IMAGING IN ACQUIRED IMMUNODEFICIENCY SYNDROME

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A. *The percentage of normal individuals with mild diffuse pulmonary gallium activity at 24 hr is:*
144. <25%.
145. up to 50%.
146. up to 75%.
147. up to 95%.

B. *The most common abnormal pattern seen in AIDS patients presenting with acute fever and/or respiratory symptoms is:*
148. focal pharyngeal activity.
149. focal pulmonary activity.
150. diffuse pulmonary activity.
151. diffuse gastric activity.

C. *Diffuse pulmonary activity may be distinguished from blood-pool activity by the presence of:*
152. decreased cardiac activity.
153. increased cardiac activity.
154. increased hepatic activity.
155. decreased hepatic activity.

D. *Diffuse pulmonary activity may be caused by:*
156. *pneumocystis carinii pneumonia* (PCP).
157. cytomegalovirus pneumonia (CMV).
158. tuberculosis.
159. all of the above.

E. *An advantage of gallium imaging in AIDS patients is the ability to demonstrate focal abnormalities at unexpected sites.*
160. True
161. False

F. *Infection is a major cause of morbidity and mortality in patients with AIDS.*
162. True
163. False

G. *Dose ranges of _____ mCi of ^{67}Ga citrate are commonly used for imaging adult patients.*
164. 1–3
165. 3–5
166. 5–10
167. 10–20

H. *A "negative cardiac silhouette" on an anterior chest gallium image indicates*
_____
168. decreased heart activity.
169. increased lung activity.
170. decreased blood-pool activity.
171. increased heart activity.

I. *The value of a negative gallium study is that it*
_____.
172. provides strong evidence against infection.
173. eliminates the need for additional costly procedures.
174. both of the above are correct.
175. neither of the above are correct. A negative gallium study is of little diagnostic use.

J. *Chest radiographs are frequently normal in early stages of the more common pulmonary infections seen in AIDS patients.*
176. True
177. False

K. _____ *may be a useful imaging agent for detection of inflammatory processes of the sinuses.*

178. Gallium-67
179. Indium-111 leukocytes
180. Indium-111 platelets.
181. Technetium-99m-labeled RBCs.

L. *Gallium imaging should be performed with a:*

182. PET camera.
183. medium-energy parallel-hole collimator.

M. *Gallium imaging for suspected acute inflammatory process should begin at:*

184. 6 hr.
185. 24 hr.
186. 72 hr.
187. 184 or 185.

N. *Improved lesion contrast is achieved:*

188. during early imaging.
189. during delayed imaging.
190. only in AIDS infections.

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