

## The role of Gallium-67 imaging in the detection of foci in recent cases of fever of unknown origin

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We have assembled data from patients with fever of unknown origin who underwent gallium scintigraphy during the past 5 years in order to obtain a more current sampling of patients, and evaluated the role of gallium scintigraphy retrospectively. Of the 36 patients studied, gallium scintigraphy was positive and contributed to the detection of the foci or fever origins in 17 (47.2%). The ratio of neoplastic diseases with myeloproliferative and with lymphoproliferative disorders was relatively high compared with previous reports. However, gallium scintigraphy did not contribute to the diagnosis of collagen disease. With the ability to detect both inflammatory and neoplastic lesions, gallium scintigraphy was useful in detecting the foci of fevers of unknown origin.

**Key words:**  $^{67}\text{Ga}$ -scintigraphy, fever of unknown origin, inflammatory lesions, neoplastic disease

### INTRODUCTION

RADIOACTIVE gallium citrate has been widely used to investigate sources of neoplasms or inflammatory lesions in cases with fever of unknown origin (FUO).<sup>1-7</sup> Recently, various excellent means such as computed tomography, ultrasound, and magnetic resonance imaging have served as diagnostic procedures in investigating the sources of fever in FUO. In this situation, the role of scintigraphy with radioactive gallium citrate may be altered. In this report, we have assembled data from FUO cases in order to obtain a more up-dated sampling of patients, and evaluated the role of gallium scintigraphy retrospectively.

### MATERIALS AND METHODS

We collected the records of patients who had undergone gallium scintigraphy to detect the source of FUO during the five years from August, 1985. The selection criteria for FUO cases were: illness of more than 3 weeks duration, documented fever higher than 37.5°C, uncertain diagnosis after more than 3 weeks of hospitalized observation, and they had been followed up for more than 6 months. Of 41 patients who had undergone gallium scintigraphy to detect the foci of the fever, 36 had sufficient laboratory and clinical assessment. Therefore, these patients (age 3 months-80 years, 21 male and 15 female) were reviewed retrospectively. Gallium scintigraphy was performed 48-72 hours after the intravenous administration of 111 MBq (3 mCi) gallium-67 citrate, using a gamma camera (TOSHIBA-GCA901 and GCA-401-5) fitted with a midrange energy collimator with two 10% windows of 93, 185 and 300 keV. Whole body planar images were routinely obtained, and additional spot images were added when necessary for localization.

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## RESULTS

Of the 36 patients studied, gallium scintigraphy demonstrated abnormalities in a total of 17 (47.2%). Further examinations were undertaken regarding these sites, and final diagnoses were achieved. Table 1 lists the final diagnoses of 17 positive gallium scans. The percentage of cases with neoplastic disorders was 47.0%, which was a relatively high incidence. Moreover, the incidence of tuberculous lesions (pulmonary 1, extrapulmonary 2) was also high among inflammatory lesions. No false positive findings were observed in the present series. However, 5 (13.8%) patients exhibited no abnormal accumulation in spite of inflammatory and malignant disorders, and the source of the fever was undetermined in the remaining 9 (25.0%) until discharged, with only conservative treatment being administered (Table 2).

## CASE REPORTS

### Case 1 Gastric cancer with multiple bone metastasis

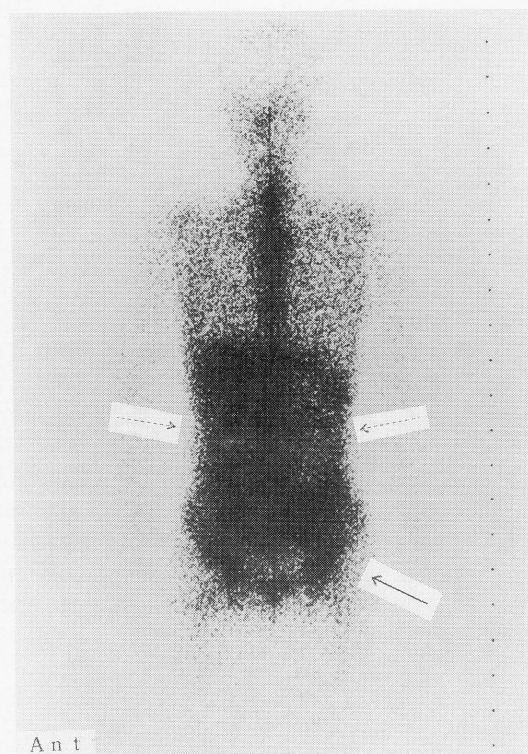
**Table 1** Final diagnoses of 17 cases with positive Ga scans

Inflammatory or Infectious lesions (Total 8)	Abnormal accumulation sites
Pericarditis (bacterial)	1 Pericardium
Bronchiectasis	1 Lung
Pyrogenic arthritis	1 Rt-knee joint
Cytomegalovirus pneumonia	1 Bil-lung (diffuse)
Liver abscesses (tuberculous)	1 Liver, Spleen, Abdominal L.N. (multiple)
Sinusitis	1 Paranasal
Peritonitis due to tuberculosis	1 Lower abdomen (diffuse)
Pleuritis due to tuberculosis	1 Rt-thorax (diffuse)
Neoplastic diseases (Total 8)	
Gastric cancer with bone metastasis	1 Bones (multiple)
Prostate cancer with bone metastasis	1 Bones (multiple)
Cholangiocarcinoma	1 Liver
Malignant lymphoma	1 Neck (multiple)
	1 Neck and Inguinal (multiple)
	1 Cheek, Paranasal, Neck (multiple)
	1 Neck (multiple)
Myelodysplastic syndrome	1 Systemic bone marrow, Liver, Spleen (multiple)
Autoimmune diseases (Total 1)	
Erythema elevatum diutinum	1 Bil-hand joint
<b>Total</b>	<b>17</b>

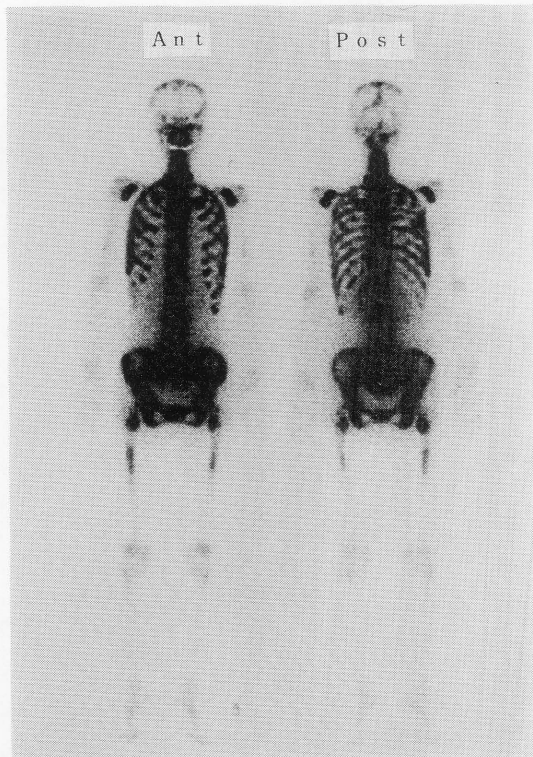
A 49-year-old, female presented with a 1-month history of a low grade fever of 37.2°–38°C and complaining of lumbago. She was diagnosed as having urinary tract infection due to WBC and E. Coli detected upon urinary examination. The fever persisted in spite of antibiotic treatment. Laboratory data revealed increased ALP and CRP as well as anemia. Gallium scintigraphy revealed diffuse ab-

**Table 2** Final diagnoses of 19 cases with negative Ga scans

Inflammatory or Infectious lesions (Total 4)	
Liver abscess (pyrogenic)	1
Chronic pyelonephritis	1
Aseptic meningitis	1
Lymphadenitis	1
Autoimmune diseases (Total 5)	
Polymyositis	1
Adult Still's syndrome	3
Systemic vasculitis	1
Neoplastic diseases (Total 1)	
Ovarian cancer	1
Undetermined	9
<b>Total</b>	<b>19</b>



**Fig. 1A** Anterior view of whole-body gallium scan of a case of gastric cancer with multiple bone metastasis (Case 1). Abnormal accumulations were seen diffusely in vertebrae, pelvis (→) and sternum. In addition, increased diffuse activity in the abdomen was observed (↔).



**Fig. 1B** Whole-body bone scan with  $^{99m}\text{Tc}$ -HMDP revealed findings resembling "super bone sign" and "absent kidney sign".

normal accumulations in the spine and pelvic bones, and also increased diffuse gallium activity in the abdomen (Fig. 1A). Because of the abnormal gallium scintigram, bone marrow biopsy of the sternum was performed, and adenocarcinoma cells were found. Subsequent bone scintigraphy with  $^{99m}\text{Tc}$ -HMDP resulted in the finding of likely a "super bone sign" and "absent kidney sign" (Fig. 1B). Because X-rays revealed osteolytic changes in the thoracic and lumbar vertebra ( $\text{Th}_{12}$ ,  $\text{L}_4$ ), metastatic bone lesions were considered. Gastroscopy demonstrated IIc-like advanced gastric cancer. Abdominal ultrasound demonstrated slight ascites, and the increased radioactivity in the abdomen on gallium scintigraphy was thought to be due to malignant ascites.

*Case 2 Myelodysplasia syndrome with an acute leukemic change*

A 52-year-old female with high grade fever and arthralgia for 1 month was admitted to our hospital. The laboratory data revealed anemia, thrombocytopenia and hypercalcemia. Because a malignant lesion was suspected, a systemic survey made by computed tomography and ultrasound revealed only splenomegaly. Gallium scintigraphy demonstrated multiple sites of abnormal accumulation along the spine and proximal limbs as well as hepatosplenomegaly (Fig. 2). Bone scintigraphy with  $^{99m}\text{Tc}$ -

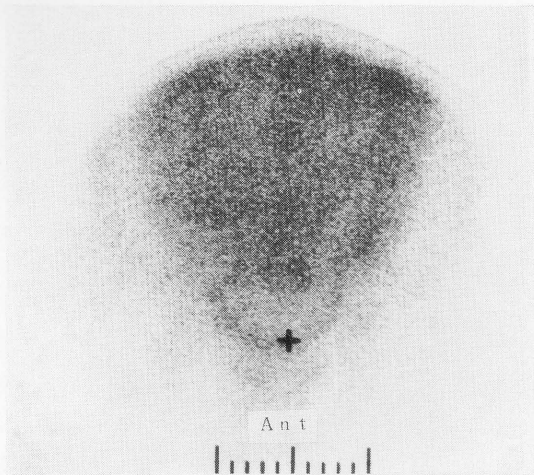


**Fig. 2** Anterior view of a whole-body gallium scan of a patient with myelodysplastic syndrome (Case 2). Abnormal accumulations were seen in the bilateral shoulders ( $\rightarrow$ ), spine, pelvis and upper portion of the thigh bones ( $\rightarrow$ ).

HMDP was positive in the same bone foci, while radiography failed to provide clear abnormal findings. The characteristics and unusual distribution of the bone lesions indicated a hematologic disorder. Bone marrow biopsy revealed myelodysplasia syndrome with an acute leukemic change.

*Case 3 Tuberculous peritonitis*

A 21-year-old male was admitted to our hospital with prolonged low grade fever. A chest X-ray revealed right pleural effusion. A sputum culture was tubercule positive, leading to a diagnosis of pulmonary tuberculosis with pleuritis. The patient responded to anti-tuberculous medications (SHR therapy), and the chest X-ray confirmed improvement in these lesions. Despite this and other improvements indicated by laboratory data, the fever continued, and a gallium scintigram was ordered upon suspicion of an extrathoracic lesion. Gallium scintigram revealed increased diffuse activity in the lower abdomen (Fig. 3), but no ascites or mass lesion was identified by ultrasound and computed tomography. The origin of the fever remained undiagnosed, but he was operated on for inguinal herniation. Miliary tuberculous nodules were found



**Fig. 3** Anterior view of an abdominal gallium scan of tuberculous peritonitis (Case 3). Diffuse abnormal activity was seen in the lower abdomen.

in the sac which extruded into the intra-abdominal cavity, and these were identified from a specimen of a nodule.

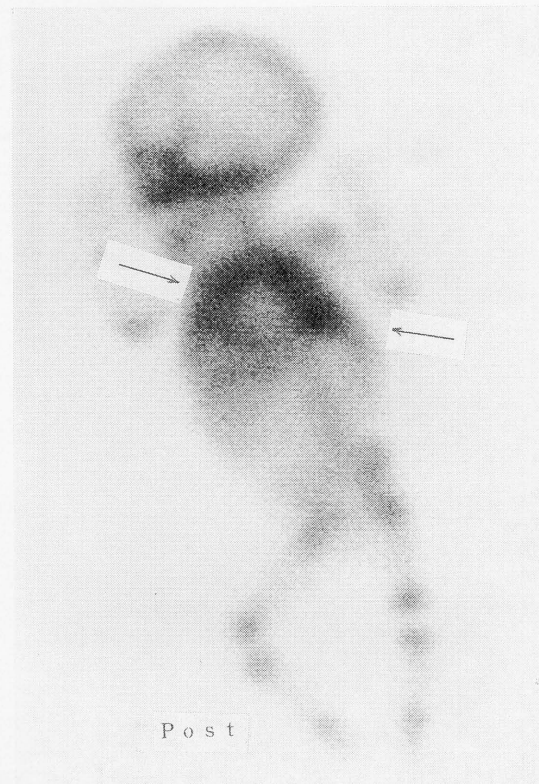
#### Case 4 *Cytomegalovirus pneumonia*

This patient, a 5-month-old male, at birth was a small-for-date infant (SFD) and had a rupture of the abdominal wall. After abdominal surgery, tracheotomy and intravenous hyperalimentation were performed for dyspnea because of massive ascites with hypoalbuminemia. During this course and after tracheotomy, he had a 1 month history of intermittent high grade fever. Systemic survey by means of radiography and ultrasound revealed nothing abnormal. However, a gallium scintigram revealed a diffuse uptake in both lungs (Fig. 4). The follow up chest X-ray revealed a diffuse interstitial shadow in the right lung field, and pneumocystis carinii or cytomegalovirus infection was suspected. However, pneumocystis carinii was not found in bronchial lavage. Cytomegalovirus pneumonia was diagnosed by IgG and IgM antibody. The chest X-ray results and fever were both improved 1 month later.

## DISCUSSION

### *Neoplastic diseases*

In cases with F.U.O., fever is often caused not only by occult inflammatory lesions but also malignant processes and autoimmune or collagen diseases. Moreover, systemic myeloproliferative and lymphoproliferative diseases remain uncommon but important causes of F.U.O.<sup>4,7</sup> In the present study, neoplastic disease accounted for 9 of 36 (25.0%) F.U.O. cases, and the ratio of those except for inflammatory diseases causing F.U.O. accounted for more than other



**Fig. 4** Posterior view of whole-body gallium scan in a case of cytomegalovirus pneumonia (Case 4). Diffuse abnormal accumulation was seen in both lungs (→).

previous reported series.<sup>5,6,8</sup> This may reflect the routine use of other imaging methods. Larson EB et al. and Misaki T et al.<sup>4</sup> also pointed out this recent tendency.

Radioactive gallium citrate is known to accumulate and show a similar affinity for both tumor tissues and inflammatory lesions. The exact mechanisms related to the uptake of this radiopharmaceutical in neoplasms and inflammatory lesions have not been fully elucidated.<sup>9-13</sup> However, possible mechanisms are increased vascularity, uptake by inflammatory and tumor cells and increased permeability of capillaries. Thus, gallium scintigraphy cannot distinguish between infectious and non-infectious inflammatory lesions and neoplastic lesions. This fact, although perhaps a disadvantage in usual clinical situations appears to be an advantage in elucidating the foci of fever in F.U.O. cases, which include both inflammatory and neoplastic disorders. In the present study, gallium scintigraphy detected both inflammatory and neoplastic lesions in 17 of 36 patients and therefore played an important diagnostic role.

In the two cases with systemic bone metastasis (gastric cancer, prostatic cancer), gallium scintigraphy revealed the distribution of bone metastasis

and thus gave diagnostic clues. Metastases should be considered when multiple foci of bone are observed.

Myelodysplastic syndrome encompasses a broad spectrum of bone marrow disorders characterized by peripheral blood cytopenia despite adequate to increased cellularity.<sup>14</sup> An interesting finding obtained with gallium scintigraphy was the characteristic accumulation at the proximal femora, which suggested a myeloproliferative disease.<sup>4,15</sup> In all of 4 cases with malignant lymphoma, multiple and intense abnormal accumulations were found. The systemic distribution and intense nature seemed to be characteristic features of lymphoma.<sup>16</sup> In the present study, the gallium scintigraphy provided the first indications of systemic disease in these myelo-proliferative and lymphoproliferative diseases, and moreover was useful in obtaining an idea of their distribution.

#### *Inflammatory disease*

Pyrogenic abscesses were found in only 2 cases in the present study, though common in previous reports of FUO, as mentioned above.<sup>5,6,8,17,18</sup> This seemed to be due to earlier detection of affected sites by other imaging means. The false negative factor in gallium scintigraphy in a liver abscess in this study was thought due to the small size ( $2 \times 2.5$  cm), and antibiotic therapy was undertaken for the prolonged fever.<sup>17</sup> On the other hand, in the case with multiple liver abscesses, gallium scans detected these lesions even though they were less than 1 cm in diameter. In this case, ultrasound failed to find these lesions, and only later they were detected by computed tomography. In this case, after follow up chemotherapy for acute myeloblastic leukemia, it was difficult to differentiate between recurrent and inflammatory lesions without biopsy.

In this study, the ratio of tuberculous lesions was relatively high compared with other inflammatory or infectious lesions. In a case of tuberculous peritonitis, diffuse abnormal localization of gallium was found. Diagnosis of peritoneal tuberculosis is often difficult because the clinical findings may not be obvious and the laboratory examination may be misleading.<sup>19-21</sup> Peritonitis, a diffuse inflammatory process typically cannot be visualized by computed tomography, as at present this method is anatomic rather than functional in orientation. Moreover, repeated bacteriologic examination of ascitic fluid and cultures may generally give negative results.<sup>7</sup> The incidence of tuberculosis has decreased recently and likewise, general awareness of the disease, since extrapulmonary disease represents an increasing proportion of cases reported in literature.<sup>7</sup> Therefore, clinicians must increase their awareness of this disease, especially in patients with prolonged fever.

In a 5-month-old male with cytomegalovirus pneu-

monia, diffuse lung uptake of gallium citrate was observed without concurrent abnormal findings in chest X-ray. Later chest X-rays however revealed an infiltrative shadow in the bilateral lung field, so that gallium scintigraphy was useful in detecting this lung disorder. Cox F and Hughes WT<sup>23</sup> emphasized the reliability of gallium scans in diagnosing infection in children as a non-invasive method. In the patient described above, gallium scintigraphy successfully demonstrated affected sites before hematologic diagnosis.

#### *Autoimmune disease*

The ratio of collagen diseases was decreased compared with previous reports,<sup>6,7</sup> perhaps because the improvement and routine use of immunological tests served to prevent these from becoming FUOs. In support of this hypothesis is the observation that the diagnosis of adult Still's syndrome was observed in three cases in spite of the lack of a diagnosis of SLE or rheumatic fever.<sup>7</sup> False negative cases in autoimmune disease were relatively high in this study, so that gallium scintigraphy could not play a significant role in this disease. Hiraki Y, et al.<sup>24</sup> reported that abnormal accumulation was obtained only in 3 of 11 patients with dermatomyositis and polymyositis, and that abnormal accumulations seemed unusual in this disease, especially when therapy had already started. Nakamura R, et al.<sup>5</sup> pointed out that abnormal accumulations in bone marrow were important findings in collagen disease because anemia is closely related. They reported that 7 of 38 cases with abnormal accumulation in bone marrow were diagnosed as having collagen disease. In the present retrospective study, two cases with adult Still's syndrome had a relatively intense accumulation in the bone marrow. However, a more definitive radiopharmaceutical for detecting systemic autoimmune or collagen disease is necessary.

Recently, besides gallium citrate, a new radiopharmaceutical for detecting inflammatory lesions such as In-111-labeled leukocytes,<sup>25-27</sup> Tc-99m-hexamethylpropyleneamine oxime-labeled leukocytes,<sup>28</sup> Tc-99m-labeled proteins,<sup>29</sup> In-111 nonspecific polyclonal IgG<sup>30</sup> and Tc-99m human immunoglobulin (HIG).<sup>31</sup> Of these agents, leukocyte scintigraphy has been introduced routinely in some hospitals, and is a reliable method for locating inflammation in patients with infections with a duration of less than two weeks. However, it may be falsely negative for more prolonged infections.<sup>27</sup> In contrast, gallium citrate accumulates even in subacute or chronic infectious lesions, so that gallium scintigraphy could be a superior method for detecting the sites of subacute or chronic infections in cases with a prolonged fever.<sup>32</sup> These other agents are more specific

for inflammatory lesions than gallium citrate. However, gallium scintigraphy, which can detect both inflammatory and neoplastic lesions will be a more useful screening investigator in cases of FUO for the reasons outlined above, even when these radiopharmaceuticals are used routinely.

In summary, our results reconfirmed that Ga-67 scintigraphy should form an integral part of the management of FUO, as these patients have diseases of various origins, not only to inflammations.

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