철운반단백질 포화정도에 따른 Gallium-67 체내분포의 변화: 증례보고

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= Abstract =

Altered Biodistribution of Gallium-67 in a Patient with Multiple Factors Influencing Iron-transport Protein Saturation

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We present a case of a young female patient with fulminant hepatitis who showed an altered biodistribution of Ga-67, after being scanned twice at 10 month intervals. On initial scan, uptake of Ga-67 was increased in the liver, kidneys, and skeletons. Increased hepatic Ga-67 uptake may be explained by increased transferrin unbound Ga-67 that was taken up by the inflamed liver. The saturation of iron-binding proteins due to multiple transfusions may lead to increased renal and skeletal Ga-67 uptake. On follow-up scan hepatic Ga-67 uptake was markedly increased. Also increased Ga-67 uptake in the axial skeleton and normalized renal uptake were shown. The findings were consistent with iron deficiency anemia. This case demonstrates altered Ga-67 biodistribution associated with multiple transfusions, fulminant hepatitis, and iron deficiency anemia. **(Korean J Nucl Med 1998;32:114-9)**

Key Words: Gallium-67, Fulminant hepatitis, Iron deficiency anemia, Transfusion

Since Edwards and Hayes first described the localization of Ga-67 in human tumors in 1969[1], Ga-67 has been used for the localization of some human tumors and inflammatory lesions[2,3]. The mechanism of Ga-67 uptake in vivo, though it is still a subject of controversy in spite of many investigations, is usually explained in association with iron-transport proteins or carrier molecules such as transferrin, lactoferrin, ferritin and siderophore[4-7].

The biodistribution of Ga-67 is affected by various physiological or pathological factors including iron metabolic status. Many experimental and several human studies have reported that alterations in iron levels resulted in modified Ga-67 localiza-

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tion[8-10]. Altered distribution of Ga-67 by saturated iron-binding sites after repeated transfusion of red blood cells is a well known example[11,12]. However, there are few human reports about Ga-67 scan findings regarding iron deficient state.

We present a case of a young female patient who showed altered biodistribution of Ga-67, after being scanned scan twice at 10 months intervals, in which increased hepatic Ga-67 uptake was found to be associated with various factors including multiple transfusions, fulminant hepatitis, and iron deficiency anemia. The implications of the findings are discussed.

Case Report

A thirty-two year old female was admitted to the hospital because of jaundice that developed 10 days before admission. She had been taking antituberculous medications including isoniazid, rifampicin and pyrazinamide for the past 8 months due to pulmonary tuberculosis and had consumed a medicinal broth of black goat 1 month prior to admission. Physical examination revealed splenomegaly and ascites. Laboratory data included hemoglobin, 12.5 g/dl(normal, 12.0-16.0 g/dl); platelet, 42000/mm^3(150,000-400,000/mm^3); total/direct bilirubin, 23.8/15.0 mg/dl(0-1.6/0-0.5 mg/dl); serum albumin, 2.6 g/dl(3.5-5.5 g/dl); AST/ALT, 253/289 units/L(0-40/0-40 units/L); prothrombin time, 6.58 INR; serum alpha-fetoprotein, 310 ng/ml(< 20 ng/ml); negative hepatitis B surface antigen, and positive hepatitis B surface antibody. She was diagnosed as having acute fulminant hepatitis, most likely caused by antituberculous medications.

During admission, she received multiple transfusions including 10 units of red blood cells and 32 units of fresh frozen plasma over 2 months preceding Ga-67 scan, because laboratory data showed normochromic, normocytic anemia, thrombocytopenia and consumptive coagulopathy.

Computed tomography(CT) scan showed spenomegaly, ascites, and a small contracted liver, particularly in the right lobe, with multiple nodules which were consistent with the findings of hepatic cirrhosis(Fig. 1). The microscopic examination of the ascites revealed no evidence of malignant cells.

On the 44th day after admission, fever developed. Blood, urine and ascites culture failed to disclose the cause of fever. Bone marrow aspiration and biopsy showed slightly increased cellularity with increased early granulocytic precursors. A

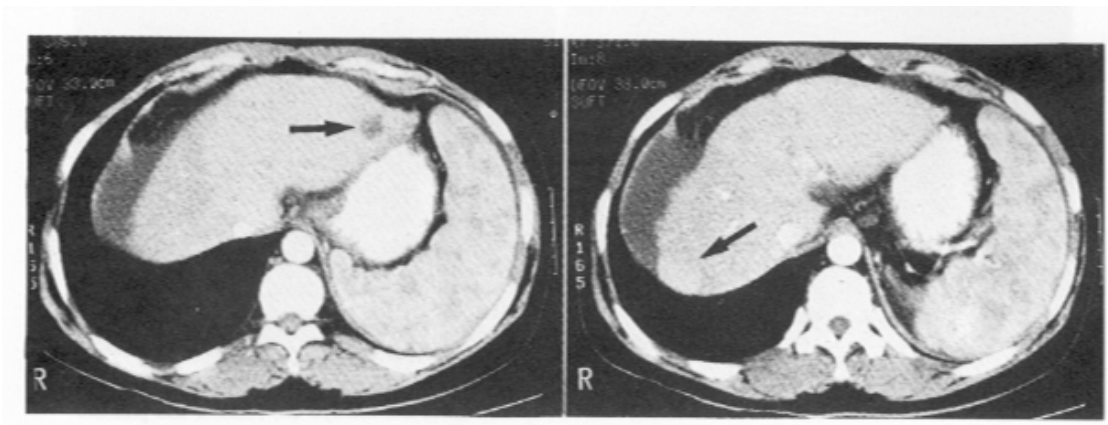

Fig. 1. Enhanced CT images showing a hypodense mass(arrow) in the left lobe (A) and an isodense mass(arrow) in the right lobe (B). Note the small contracted liver, especially in the right lobe, with a nodular surface, ascites and massive splenomegaly. These findings are consistent with hepatic cirrhosis.

Ga-67 scan was performed to evaluate the fever of unknown origin. Images obtained 48 hrs after injection of 111 MBq of Ga-67 showed increased radioactive accumulation in the left lobe of the liver, mimicking diffuse hepatoma(Fig. 2A). Ga-67 accumulation was also increased in the kidneys and whole skeleton. At this time, laboratory data included serum iron(Fe), 102 g/dl(50-130 g/dl); serum total iron-binding capacity(TIBC), 201 g/dl(280-400 g/dl); serum transferrin saturation, 50.7%(20-50%); and serum ferritin, 228.6 ng/ml(10-290 ng/ml). Fever subsided after intravenous antibiotic therapy and the patient was discharged in a much improved state.

Ten months after the initial Ga-67 scan, there were no significant changes in the liver on follow-up CT. Sono-guided needle biopsy showed disarrayed lobular structure with partly nodular formation, macrovesicular fatty change and focal piecemeal necrosis without malignant cells. These findings were consistent with active post-necrotic cirrhosis. Follow-up laboratory data included hemoglobin, 9.9 g/dl; Fe, 24 g/dl; TIBC, 376 g/dl; serum transferrin saturation, 10.1%; ferritin, 7 ng/ml; and serum alpha-fetoprotein, 9 ng/ml. Follow-up Ga-67 scan and Tc-99m phytate liver scan were performed. Ga-67 accumulation was increased in the liver and axial skeleton corresponding to the red marrow distribution. Renal accumulation which was higher on the initial scan was normalized(Fig 2B). The Tc-99m phytate liver scan showed splenomegaly, atrophy of the right lobe and a hypertrophic

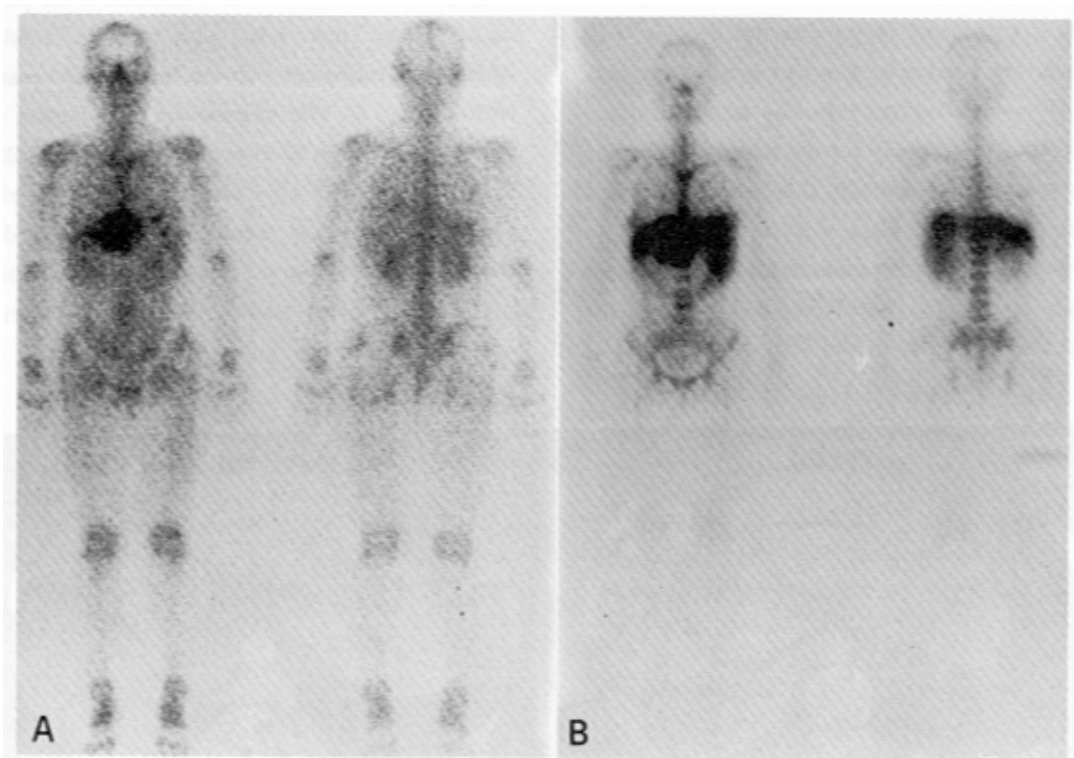

Fig. 2. (A) Anterior and posterior images obtained 48 hrs after intravenous Ga-67 administration. Note the increased accumulation of Ga-67 in the left lobe of the liver, whole skeleton, and kidneys. (B) Anterior and posterior Ga-67 images obtained 10 months after the initial scan, showing markedly increased Ga-67 uptake in the liver and axial skeleton corresponding to the red marrows. Also, note the normalized Ga-67 uptake in the kidneys.

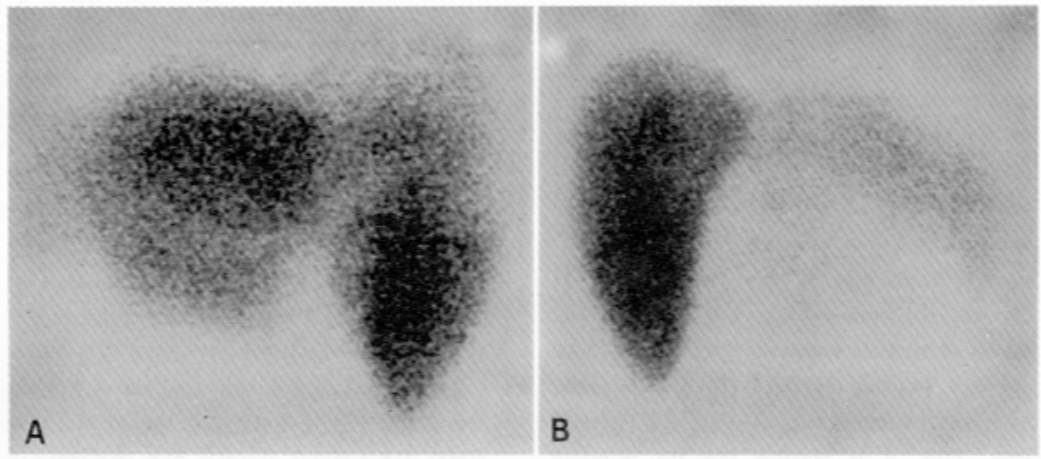

Fig. 3. Anterior (A) and posterior (B) images of Tc-99m phytate liver scan showing inhomogeneous radioactive uptake without focal defect. Also, note atrophy of the right lobe with an enlarged left lobe and increased splenic uptake. These findings are compatible with hepatic cirrhosis.

left lobe without focal defect(Fig. 3).

Discussion

Physiologically, 10-25% of Ga-67 is excreted via the kidneys over the first 24 hrs. Thereafter, the principle route of excretion is the colon, and the kidneys and the urinary bladder may normally be visualized faintly. At 48 hrs after injection about 75% of the injected dose remains in the body and is equally distributed among the liver, bone and bone marrow, and soft tissues[13].

The uptake mechanism of Ga-67 in vivo is usually explained in association with iron-transport proteins or carrier molecules such as transferrin, lactoferrin, ferritin and siderophore[4-7]. The majority of intravenously injected Ga-67 is bound to these proteins, mostly transferrin[4]. Ga-67-protein complex is taken up by endocytosis into cells such as the hepatocytes, and leukocytes via receptors on the surface and Ga-67 is bound to acceptor molecules such as ferritin or heparan sulfate in lysosomes[13-16].

Modification in iron metabolism can alter Ga-67 distribution because Ga-67 competes with iron for the iron binding sites. When desferoxamine, an iron chelating agent or several forms of iron(e.g. iron dextran, ferric chloride, ferric citrate etc.) was administered before or concurrently with Ga-67, tumor and tissue localization was inhibited and urinary excretion increased in some experimental models[8-10]. In iron overload from multiple transfusions, Ga-67 scan shows prolonged, increased renal, skeletal and bladder radioactivity and decreased hepatic and bowel uptake due to relative saturation of iron binding sites by exogenous iron[11,12].

In our patient, we believe that three factors were involved in the alterations of the Ga-67 biodistribution: fulminant hepatitis, multiple transfusion and iron deficiency anemia. On initial examination, increased hepatic and renal uptake was found. Although there are only a limited number of reports describing Ga-67 uptake in hepatitis, Ga-67 uptake(in a transferrin-bound form) in the inflamed liver was usually not increased[17]. Also, increased hepatic Ga-67 uptake has been reported in only a few cases with regenerating nodules[17-19]. In the

present case, increased Ga-67 uptake in the left lobe of the liver, could not be explained by regenerating nodules alone. Recent reports suggested the presence of a transferrin independent gallium and iron uptake mechanism, especially in hepatocytes[20-22]. A report showed Ga-67 of transferrin-unbound form was taken up more by acute inflamed liver of mice treated with CCl4 than the transferrin-bound form[23]. In our case, history of multiple transfusions and initial laboratory data including decreased TIBC and increased transferrin saturation suggested an iron overload state. Thus, it is possible that the increased transferrin-unbound Ga-67 due to iron overload caused increased Ga-67 uptake by the inflamed liver in the present case. Increased uptake in the kidneys and whole skeleton could also be explained by saturation of iron binding sites and redistribution of Ga-67 due to multiple transfusions[11].

On follow-up Ga-67 scan when laboratory data was also consistent with iron deficiency anemia, markedly increased hepatic uptake was shown, which may be explained by the iron deficiency. Several experimental studies revealed that hepatic uptake of Ga-67 was increased in an iron deficient state[24,25]. Increased skeletal Ga-67 uptake corresponding to red marrow distribution could also be explained by increased RBC production due to chronic anemia[26].

This case demonstrated Ga-67 biodistribution altered by various factors including fulminant hepatitis, multiple transfusions, and iron deficiency anemia. The interpretation of Ga-67 scan must be done with careful consideration of various factors including iron status, underlying disease, drug, and physiological status because they can influence the biodistribution of Ga-67 and lead to misinterpretation of the Ga-67 scan.

요 약

반복적인 수혈을 받은 급성전격성간염 환자에서 Ga-67 체내분포의 양상을 추적하였다. 급성기에 시행한 갈륨스캔에서 간의 악성종양을 의심하게 하는 간섭취증가와 신장, 뼈섭취증가가 관찰되었다. 간섭취증가는 철운반단백질에 결합하지 않은 Ga-67이 염증이 일어난 간세포에 섭취되었기 때문으로 해석되었다. 신장과 뼈섭취증가는 반복적인 수혈에 의한 철운반단백질의 포화에 따른 Ga-67의 세포내운반저하에 의한 것으로 생각되었다. 10개월 후에 다시 시행한 갈륨스캔에서 간섭취는 더욱 증가되었으며 골수섭취의 증가가 관찰되었다. 반면 신장섭취는 정상화되었다. 이러한 소견은 철결핍성 빈혈에 의한 것으로 해석되었다. 이 증례는 체내 철의 양과 이에 따른 철운반단백질 포화도의 변화에 의한 Ga-67의 체내분포의 변화를 예시해 준다.

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