Gallium-67 Distribution in a Man with a Decrease in Both Transferrin and Hepatic Gallium-67 Concentration

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A patient with reduced transferrin concentration had a ^{67}Ga scintigram that showed uptake in a peritoneal abscess, pericarditis and pleural effusion but only faint liver uptake. Gallium-67 activity was measured in liver, lung, muscle and plasma samples obtained at autopsy. The percent injected dose/kg for liver and plasma samples was considerably lower than previously reported while that in muscle and lung tissues values were comparable to prior data. In this patient, sites on transferrin available to bind ^{67}Ga were reduced from the normal 40 μM to 5.2 μM; this in turn increased the concentration of radiogallate from 1% to 7%. This elevated free activity increased ^{67}Ga excretion and reduced the amount of ^{67}Ga•transferrin species. These results and those of previous studies suggest that liver uptake is slower than abscess uptake and more sensitive to concentration of ^{67}Ga•transferrin. Iron status is an important facet of the interpretation of ^{67}Ga scintigrams.

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The role of transferrin (TF) in ^{67}Ga localization in an abscess or normal tissues is somewhat controversial (*1–5*). Results in the few patients that have been reported so far have implied an important role for TF in the distribution of ^{67}Ga (*6*). Liver uptake of ^{67}Ga was substantially reduced and body excretion was increased following transfusions which saturated the TF with iron and reduced the number of iron binding sites on TF. We report a case where the available TF concentration had been reduced; several tissue specimens were obtained in order to quantify distribution of ^{67}Ga and its relationship to TF.

CASE REPORT

A 77-yr-old diabetic male with a history of congestive heart failure and a stroke with left hemiparesis was admitted because of progressive confusion. Chest x-ray showed no acute infiltrate and no pulmonary edema. His white blood cell count was elevated at 18,800 cells/μl, total iron (Fe) was 17 μg/dl (normal 86–180 μg/dl), TIBC was 128 μg/dl (normal 280–400 μg/dl), transferrin concentration was 116 mg/dl (normal 240–355 mg/dl), hemoglobin was 12.6 and hematocrit was 38.

Head CT demonstrated an old CVA but not a new one. Lumbar puncture and abdominal ultrasound were negative. He developed atrial fibrillation and episodic hypotension which responded to medications. Gram-negative rods were cultured from his sputum. He was placed on antibiotic therapy but his clinical course did not improve. On Day 5 after admission, because his hematocrit was drifting downward, he was transfused with 1 unit of packed red cells.

A radiogallium study was ordered on Day 7 to search for occult sites of infection. After intravenous administration of 6.14 mCi (227 MBq) of ^{67}Ga-citrate, imaging was performed at 48 hr. The most revealing image (Fig. 1A) was an anterior view which demonstrated reduced hepatic uptake of radiogallium with increased concentration in the lungs, pericardial area and along the diaphragm. Because the patient's hematocrit remained low, the values for Fe and TIBC were again determined and despite the transfusion remained low, 19 and 48 μg/dl, respectively.

Antibiotic therapy was continued, but the patient did not improve and died on Day 12 from cardiopulmonary arrest. Autopsy indicated severe coronary atherosclerosis with a recent thrombus in the LAD and an extensive acute myocardial infarct. There was fibrous pericarditis with fibrinous fluid and a perforated duodenal ulcer with 1000 ml of hemorrhagic fluid in the peritoneal cavity. Pulmonry edema with bilateral pulmonary effusion was also evident.

DISCUSSION

To correlate the role of TF in ^{67}Ga localization with scintigrams and actual tissue concentration, it is necessary to determine the percentage of the main nonprotein bound ^{67}Ga species, the radiogallate $[^{67}Ga(OH)_4]^-$, in the blood as a function of TF saturation. This percentage can be estimated from a set of equations that describe this equilibrium system:

$$T_{Ga} = \alpha_{Ga}[Ga] + [Ga{\bullet}TF] + 2[Ga_2{\bullet}TF] \quad \text{Eq. 1}$$

$$T_{TF} = [TF] + [Ga{\bullet}TF] + [Ga_2{\bullet}TF] \quad \text{Eq. 2}$$

$$K_1^* = [Ga{\bullet}TF]/[Ga][TF], \quad \text{Eq. 3}$$

where T_x = total analytical concentration of ^{67}Ga or TF, α_{Ga} = pH-dependent function which accounts for the

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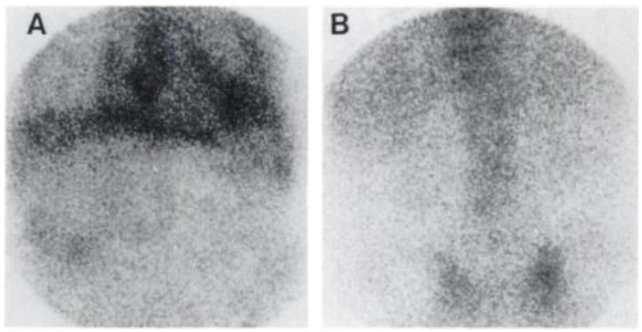

FIGURE 1. (A) Anterior view (top) of the lower chest and abdomen at 48 hr after radiogallium administration. The sternum can be seen in the midline, with intense activity around the heart and along the diaphragm. (B) Posterior view (bottom) of lower abdomen at 24 hr. The spine and sacro-iliac joint are identified with the liver barely visible.

various Ga hydrolysis species, [Ga] = concentration of unchelated and unhydrolyzed ^{67}Ga, [TF] = concentration of uncomplexed TF, [Ga*TF] and [Ga_2*TF] = concentration of ^{67}Ga bound to one and to both sites on TF, respectively, and log K_1^* = conditional affinity constant for binding of ^{67}Ga to one site on TF. Since the concentration of ^{67}Ga is at least 1000-fold lower than TF concentration, the [Ga_2*TF] terms can be neglected and $T_{TF} \approx$ [TF]. The equations are solved for α_{Ga}[Ga], which at pH 7.4 $\approx$ [$^{67}Ga(OH)_4^-$, $\alpha_{Ga} = 1.02 \times 10^{13}$ and log $K_1^* = 19.7$ (*7*). The final expression for the percentage of gallate is:

$$\alpha_{Ga}[Ga]/T_{Ga} = \alpha_{Ga}/\{TF_{TF}K_1^* + \alpha_{Ga}\} \times 100. \quad \text{Eq. 4}$$

Reduction of the concentration of available ^{67}Ga sites on TF from the normal value of 40 to 5.2 μM (29 μg/dl) in this patient on the day of the ^{67}Ga study would increase the radiogallate concentration ~7-fold, from 1% to 7% of the total blood activity. While the values of α_{Ga} and K_1^* are subject to some error, ±10% (*7,8*), this would change only slightly the absolute percent of gallate. These estimates suggest that while a majority of blood ^{67}Ga is usually TF-bound, in this patient the increase in free ^{67}Ga would allow a concomitant increase in the ^{67}Ga excreted over time. The free activity would readjust to the equilibrium value after each passage through the kidney. Much less activity would then be available to be distributed internally.

Both scintigrams and the concentration of free TF sites have been reported in two other cases (*6*). In Case 1, the available TF concentration was 2 μM, which would yield a 17-fold (17% free) increase in gallate concentration. In Case 3, the increase could be 29-fold (29% free). Even though both the Fe and TIBC values were identical, given experimental error, the TF site concentration could be as much as 1 μM. This analysis is consonant with the scintigrams which both show marked increase in bladder and kidney activity. In comparison, the kidneys of our patient were barely visible at 24 hr (Fig. 1B), which suggests a much lower amount of free activity. Normally only 8%–12% of injected activity is excreted through the urinary tract in the first 24 hr and the kidneys are only faintly visualized at 48 hr (*9,10*).

Both values for liver uptake and plasma binding are close to the low end of each data range from previous autopsy data (*9*) and represent about a 4–5-fold diminution from the mean values (Table 1). This decline is in the same range as might be expected from the increase in free ^{67}Ga and confirms what is seen on the scintigrams. In contrast, the %ID/kg for muscle and lung are comparable to older data. Therefore, muscle and lung tissue uptake in this patient might be considered normal. The appearance of increased lung activity is probably due to pleural effusion and not augmented tissue uptake.

This analysis implies that in patients liver uptake is more sensitive to the available concentration of ^{67}Ga*TF than uptake by inflammatory processes. In a rat abscess model (*3*), uptake for liver tissue and the abscess appeared equally sensitive since the %ID/g of ^{67}Ga was reduced in both with the saturation of TF with iron. In patients, abscess uptake may be a more rapid process in comparison to liver incorporation and this could mean that both ^{67}Ga*TF and free ^{67}Ga can easily pass through an abscess wall or disrupted endothelial barrier and bind to siderophores or lactoferrin present at the site. In contrast, the liver may depend on partially catabolized TF for its slower uptake (*1,11*). In addition, the medications (dopamine and norepinephrine) used to maintain blood pressure in this patient could slow liver uptake by decreasing mesenteric blood flow. Propranolol, which also causes peripheral vasoconstriction, does reduce ^{67}Ga uptake in the liver but not in muscle tissue in mice (*12*).

Whether TF site concentration influences inflammatory lesion detection is unsettled. In this patient and in the two previously reported (*6*), large abscesses were easily identified. However, in Case 3, cited above, with the greatest

TABLE 1
Tissue Concentration of ^{67}Ga in a Patient Who Died Five Days After Intravenous Administration

Tissue*		Mean			Nelson et al.†	
		μCi/kg	μCi/kg	%ID/kg‡	%ID/kg	Range
Liver	(1)	18.3				
	(2)	16.7	17.7	0.72	2.8	(0.6–5.2)
	(3)	18.1				
Muscle	(arm)	7.5	7.5	0.31	0.2	(0.03–1.1)
Lung	(1)	42.8	44.1	1.79	1.3	(0.3–3.0)
	(2)	45.4				
Plasma		1.4	1.4	0.057	0.3	(0.02–1.8)

* Radioactivity in tissue samples measured immediately after autopsy from noninfected areas and injected dose was decay-corrected to time of autopsy.

† Mean values and range for tissues from autopsy data of Nelson et al. (*9*).

‡ Normalized to a body weight of 70 kg. Patient's weight = 81.8 kg.

amount of free ^{67}Ga (~29%), Hodgkin's disease involving lymph nodes and a small renal abscess went undetected. It appears from this limited number of patients that as the number of available TF sites is reduced the egress of ^{67}Ga from the body is increased. Therefore, only small abscesses, near the detection limit of 1–2 cm, might be affected and then only when the increase in free ^{67}Ga is very high (~29%). In ^{67}Ga scan interpretation, it seems prudent to consider the iron status of patients as an important factor until a study in a larger number of patients can provide more definitive information.

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