The Effects of Inadvertent Administration of Antineoplastic Agents Prior to Ga-67 Injection: Concise Communication

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Alteration of the gallium-67 (Ga-67) distribution after administration of chemotherapeutic agents has been demonstrated in experiments on both normal and tumor-bearing animals. We have encountered eight patients who had Ga-67 scintigrams in which the findings were similar to those in the animals experiments: markedly increased uptake in bone, with suppressed uptake in liver, muscle, and tumor. Five of the patients had hematologic neoplasms, and three had solid tumors, and each had received one or more chemotherapeutic agents during the 24 hr preceding Ga-67 administration. In three patients while not on antineoplastic medication subsequent Ga-67 images showed a return to the usual Ga-67 distribution pattern. The altered Ga-67 distribution may result from inhibition of protein synthesis or of a serum-binding agent for Ga-67, or from competitive blockage of specific Ga-67 organ receptors by the antineoplastic agents.

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Deviations from the normal pattern of body distribution of Ga-67 must be assessed carefully during interpretation of a Ga-67 citrate image from a patient receiving antineoplastic medication. Normal animals given chemotherapeutic agents have a marked decrease in the total-body retention and in the soft-tissue distribution of injected Ga-67 citrate, with a significant increase in its deposition in bone and increased urinary excretion (*1*). Similar alterations in Ga-67 distribution, along with decreased tumor uptake, were observed in tumor-bearing mice following their treatment with methotrexate (*2*). It is not feasible to reproduce experimental protocols like these in a clinical setting, but antineoplastic agents could happen to be administered before Ga-67 injection.

This retrospective study was prompted by the finding of a Ga-67 scintigram showing suppressed uptake by liver, muscle, and tumor, with increased uptake in bone and kidneys, in a patient who had widespread metastatic disease.

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MATERIALS AND METHODS

Eight patients were included in the study on the basis of the following criteria: (a) Ga-67 citrate image in which the findings were similar to those in the animal experiments, namely, markedly increased uptake in bone and kidneys, with suppressed uptake in liver, muscle, and tumor; (b) clinical, radiologic, and laboratory evidence of active neoplastic disease; (c) no clinical or biochemical evidence of liver and/or renal disease.

Patients meeting these criteria included five men and three women ranging in age from 12 to 64 yr. Their histologic and clinical diagnoses are listed in Table 1. Each was injected intravenously with 6–8 mCi of Ga-67 citrate for imaging. The usual preparation of patients included administration of oral laxatives each day, starting on the day of radionuclide injection and continuing until imaging was completed; or of 60 ml of castor oil by mouth; or of administration of an enema on the evening before the initial image. The Ga-67 image was performed 48 hr (in two patients) or 72 hr (in six patients) after tracer injection.

In six patients the image was performed with a rectilinear scanner with dual 12.85-cm (5-in.) detectors. Three independent pulse-height analyzers for each detector permitted simultaneous recording of the 93-, 184-,

TABLE 1

Classification	Patient	Sex	Age (yr)	Histologic diagnosis
Hematologic neoplasms	1	F	46	Hodgkin's Disease, MCT*: P.S. IV (M+)
	2	M	48	Hodgkin's Disease, LD†: P.S.‡ IV (M+)§
	3	M	64	Acute Myelogenic Leukemia
	4	M	12	Acute Lymphoblastic Leukemia
	5	F	33	Acute Lymphoblastic Leukemia
Solid tumors	6	M	62	Lung Carcinoma (left): squamous cell
	7	F	71	Lung Carcinoma (right): small cell, undifferentiated
	8	M	17	Alveolar Rhabdomyosarcoma (metastatic)

* MCT: mixed-cell type
† LD: lymphocyte-depleted
‡ P.S.: pathologic stage
§ M+: bone marrow

and 296-keV photon emissions of Ga-67. The medium-energy collimator used (38H) had a focal depth of 9 cm. The other two patients were imaged with a multiplane imaging system.* Simultaneous anterior and posterior images were made with the patient in the supine position. In all patients the area covered reached from the level of the head to below the knee. Information density of at least 400 counts/cm^2 was obtained in all images.

RESULTS

All of the Ga-67 citrate images in the eight patients showed a remarkable similarity. In each case, there was increased uptake of Ga-67 in bone and kidneys, whereas uptake in the liver and soft tissues was suppressed.

In spite of clinical, radiologic, and laboratory evidence of active neoplastic disease, the uptake of Ga-67 by soft-tissue tumors was suppressed entirely, except for uptake in a skeletal lesion in each of three patients (e.g., Fig. 1).

Analysis of the patients' records revealed a strikingly similar sequence of events. All had received an injection of one or more chemotherapeutic agents within the 24 hr before Ga-67 administration. Table 2 lists the antineoplastic agents used, the interval between chemotherapy and Ga-67 injection, and Ga-67 study findings.

Each of three patients in this group had a follow-up image (at intervals of 2, 3, and 4 wk, respectively) after chemotherapy had been discontinued. All scintigraphs showed a return to the usual Ga-67 distribution pattern. (e.g., Fig. 2).

DISCUSSION

Since its introduction by Edwards and Hayes (*3*), Ga-67 citrate scintigraphy has been widely used for the imaging or detection of a large variety of epithelial and lymphoreticular neoplasms or inflammatory diseases. The efficacy of this examination has also been the subject of many reviews (*4–9*). The normal organ localization of Ga-67 at 48 or 72 hr after i.v. injection, and variations in its distribution related to age and sex, have been described in detail (*10–11*). Deviations from the normal

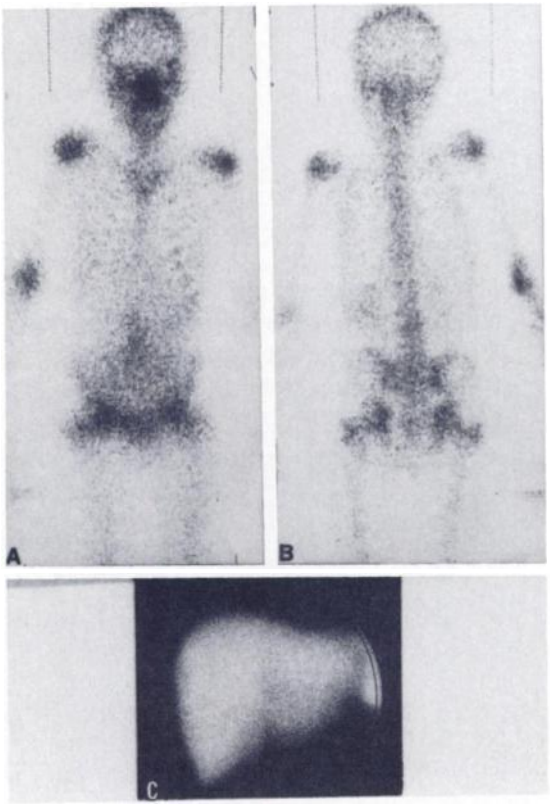

FIG. 1. Twelve-year-old boy (Patient 4) with acute lymphoblastic leukemia. Gallium-67 citrate scintigram, (A) anterior and (B) posterior views, show increased uptake by bone and kidneys, diminished uptake by liver, and area of increased activity in right distal humerus. (C) Normal Tc-99m sulfur colloid liver study, anterior view, of same patient.

TABLE 2

Interval (hr) between chemotherapy & Ga-67 injection		Chemotherapeutic agents received <24 hr before Ga-67	Time interval (hr) between Ga-67 injection and imaging	Ga-67 image results
Patient				
1	<24	Vincristine Cyclophosphamide Prednisone Procarbazine	72	↑↑ Bone and kidneys ↓↓ Soft tissue No liver visualization
2	<24	Vincristine Prednisone Procarbazine	72	↑↑ Bone and kidneys ↓↓ Soft tissue No liver visualization
3	<24	Cytosine arabinoside 6-Thioguanine Doxorubicin	48	↑↑ Bone and kidneys ↓↓ Soft tissue No liver visualization Sternal lesion
4	<24	Vincristine L-asparaginase Prednisone	72	↑↑ Bone and kidneys ↓↓ Soft tissue No liver visualization Rt. humerus lesion
5	<24	Cytosine arabinoside Prednisone	72	↑↑ Bone and kidneys ↓↓ Soft tissue No liver visualization
6	<24	5-Fluorouracil	72	↑↑ Bone and kidneys ↓↓ Soft tissue No liver visualization
7	<24	VP-16-213 Cyclophosphamide Doxorubicin	48	↑↑ Bone and kidneys ↓↓ Soft tissue No liver visualization Rt. rib lesion
8	<24	DTIC	72	↑↑ Bone and kidneys ↓↓ Soft tissue No liver visualization

pattern of Ga-67 distribution due to prior administration of scandium (*12–14*), stable gallium (*15*), lymphangiographic contrast agents (*16*), or radiation therapy (*17*), have also been reported. More recently, several investigators have described the effects of whole-body irradiation and chemotherapy (e.g., with vincristine, mechlorethamine, and methotrexate) in normal and tumor-bearing animals (*1,2,18*).

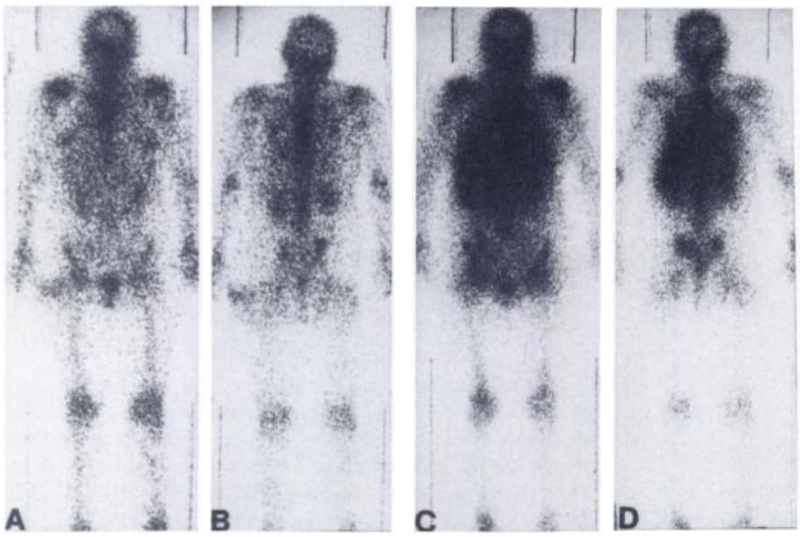

FIG. 2. Forty-six-year old woman (Patient 1) with Hodgkin's disease, pathologic Stage IV according to bone-marrow biopsy. (A) and (B): Ga-67 citrate image, anterior and posterior views, showing increased bone and renal uptake, diminished in liver and tumor. Tracer was injected less than 24 hr after administration of vincristine, cyclophosphamide, prednisone, and procarbazine. (C) and (D): Ga-67 citrate image, anterior and posterior views, 4 wk after course of chemotherapy had ended.

After whole-body irradiation or chemotherapy, there is a significant decrease in total-body and soft-tissue retention of Ga-67 citrate, with a significant increase in the deposition in bone and augmented urinary excretion. The inadvertent administration of antineoplastic agents before Ga-67 injection has occurred in random cases. The unusual appearance of the Ga-67 citrate scintigram as a consequence of such events, and the significance of such a finding, have been commented on by us and by other investigators (*18*).

Each Ga-67 image for the eight patients in this series, had a remarkably similar appearance: suppressed liver, soft-tissue, and tumor uptake and increased uptake in bone and kidneys. Faint or absent Ga-67 liver uptake often results from hepatic failure or from competing uptake by tumor or inflammatory lesions (*11*). None of our patients had evidence of parenchymal liver disease, as indicated by normal liver-function tests and normal Tc-99m sulfur colloid liver studies. Except for one osseous lesion in each of three of the patients, none of the images showed uptake in the area of tumor involvement; such uptake could have competed with uptake of Ga-67 by the liver.

The distribution of Ga-67 as seen on the image depends to some extent on the interval between injection of the radionuclide and imaging. During the first day there is rapid renal excretion, which results in increased renal radioactivity. In studies performed 48 to 72 hr after injection, however, renal activity is rarely detectable (*10*). The Ga-67 images in this series were obtained at 48 hr in two patients and 72 hr in six patients. Intense bilateral, diffuse uptake of Ga-67 by the kidneys has been reported in conditions such as pyelonephritis (*20*), acute interstitial nephritis (*21*), renal amyloidosis (*22*), and renal involvement by lymphoreticular or hematologic neoplasms (*4–9*). Infection or neoplasms in the kidneys of these patients was excluded on the basis of urinalysis, urine culture, and radiographic examinations.

In animal studies on the normal distribution of radiogallium, the highest concentration of Ga-67 was observed in bone; this was followed by liver, spleen, and kidneys (*23*). The bone-seeking properties of Ga-67 may be enhanced by prior injection of scandium (*12–14*) or by addition of stable gallium (*15*). At the same time, these elements greatly decrease the deposition of Ga-67 in normal soft tissues, whereas they increase its renal excretion (*12*). Failure by radiopharmaceutical companies to supply a carrier-free solution of Ga-67 citrate could have explained the appearance of the Ga-67 image in our patients. However, a review of the images of other patients injected with the same solution on the same day showed the usual pattern of radionuclide distribution.

Many fundamental aspects of Ga-67 transport, normal localization, and mechanisms of uptake in inflammatory lesions or tumors, are not completely understood. After i.v. administration, the distribution of Ga-67 depends on its migration from plasma proteins—mainly transferrin and other alpha and beta serum globulins—to organs, tissues, or microorganisms that have a stronger affinity for the radionuclide. Gallium-67 acts somewhat like an iron analog, but its affinity for transferrin is lower than that of iron, and gallium is not incorporated into heme or other biologically important proteins. Transferrin and the other serum globulins appear to act primarily as carrier proteins for Ga-67, transporting it from the site of injection to the site of cellular localization (*25*).

An increased blood supply, hyperpermeability of the capillary endothelium, and the presence of lactoferrin-rich leukocytes in areas of inflammation may explain the localization of Ga-67 (*25*). Normal tissues and secretions, neutrophilic leukocytes, and certain tumors with high concentrations of lactoferrin, ferritin, or a specific 40,000-dalton protein, avidly bind Ga-67 (*26,27*).

The existence of specific Ga-67 organ receptors, although not proved, cannot be dismissed in discussions of the localization of Ga-67 in normal tissues and in sites of inflammation or tumor. A small fraction of Ga-67 transferrin may interact with a specific transferrin receptor on the tumor cell (*28–30*).

The intracellular localization of Ga-67 occurs in lysosomes or lysosome-like granules of the cell. Gallium may also bind to nuclear, mitochondrial, and microsomal cell components of viable tissue (*31*), or to intracellular lipoproteins, nucleoproteins, phospholipids, and nucleic acids (*32*). It is possible that Ga-67 displaces calcium and magnesium from intracellular sites that bind divalent cations (*33*).

Blocking of transferrin-binding sites for Ga-67 by administration of scandium, stable gallium, and iron—or saturation of the binding sites by endogenous iron (e.g., in hemochromatosis)—explains the decreased localization of radiogallium in the liver and in soft-tissue tumors, as well as its increased uptake by bone and its more rapid renal clearance (*34*). Ionizing radiation, antineoplastic drugs, antimetabolites, and some antimicrobial compounds, are known to cause hypoplastic or aplastic anemia that is associated with an elevated level of serum iron. The exact mechanisms for this induced hyperferremia are not completely clear (*35*). Methotrexate, an antimetabolite, is known to cause temporary inhibition of the incorporation of iron by erythrocytes, and it prolongs the disappearance time of plasma iron. Thus, iron that is normally removed from the plasma builds up, saturating the plasma iron-binding capacity (*36*). Gallium-67-binding sites in serum are therefore reduced in number, and more unbound Ga-67 is initially present in serum; this enhances the uptake by bone.

Other antimetabolite drugs, such as 5-fluorouracil, cytosine arabinoside, and 6-thioguanine, may have an effect like that of methotrexate on the kinetics of iron.

The chemotherapy-induced hyperferremia would therefore explain the changes in Ga-67 distribution in the images of three patients who had received the antimetabolites before the injection of radiogallium. Unfortunately, no determinations of the status of serum iron and of the unsaturated iron-binding capacity were made in these patients at the time of injection of the chemotherapy agents and of Ga-67.

Five patients received antineoplastic agents that belong to different categories: alkylating agents, antibiotics, carbamylators, enzymes, hormones, and microtubulin inhibitors. Although all of these may also induce hyperferremia, a different mechanism of action, such as chemical damage, could be considered. These drugs may damage the sites where a carrier molecule for Ga-67 is synthesized, or they may disturb the synthesis of transferrin. Alternatively, they may damage the specific cellular organelles (e.g., lysosomes) that either accumulate gallium or act directly on the Ga-67 carrier molecule (*1*). A competitive blockade of specific Ga-67 organ-tumor receptors by the antineoplastic agents cannot be totally ruled out.

Regardless of whether the changes in the biodistribution of Ga-67 are due to induced hyperferremia, chemical damage, or competitive blockade, they are short-lived. Chilton et al. (*2*) demonstrated that, when the interval between the last dose of methotrexate and the injection of Ga-67 was increased from 24 hr to 7 days, the tissue levels of Ga-67 in tumor-bearing mice were the same as those in the group that had not received methotrexate. One patient in our series had a Ga-67 image showing normal distribution only 2 wk after the chemotherapy had been discontinued.

In summary, a highly specific and consistent pattern of Ga-67 distribution was seen in patients who had inadvertently received a Ga-67 citrate injection less than 24 hr after the injection of one or several chemotherapeutic agents. This pattern was characterized by suppressed uptake of Ga-67 by soft tissues and tumor, increased deposition in bone, and increased renal radioactivity. A transient hyperferremia, temporary chemical damage of cellular organelles or of Ga-67 carrier proteins, or temporary blockade of membrane receptors caused by the antineoplastic drugs, may explain these changes in the Ga-67 distribution.

The likelihood of false-negative findings in Ga-67 citrate tumor imaging of patients receiving chemotherapy could be diminished by measurement of serum iron and unsaturated iron-binding capacity before Ga-67 injection. False-negative results will be reduced further if the injection of Ga-67 is delayed for at least a week after the last chemotherapy dose has been given.

FOOTNOTE

* Pho/Con, Searle Radiographics, Inc.

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A fund has been established in the ERF by friends of Marc Tetalman, M.D., who was a tragic homicide victim while attending the SNM meeting in Atlanta in June 1979. This fund will permit an award of $3,000 to be made in June, 1984 to a young investigator (35 years of age or younger) who is pursuing a career in Nuclear Medicine. This award is to be repeated annually. It is possible that additional contributions to our fund will permit the stipend to be increased in future years. Applicants should submit prior to March 1, 1984 a curriculum vitae together with data supporting current research efforts.

All letters and applications should be addressed to:

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