Thymic Gallium-67 Localization in Pediatric Patients on Chemotherapy: Concise Communication

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Localization of Ga-67 in the thymus has been reported to occur in children. In our control group of 87 patients, 15% of children under 5 yr and 11% of children over 5 yr demonstrated thymic localization. In contrast, in our study group of seven children with acute lymphocytic leukemia or malignant lymphoma, lymphocytic diffuse, treated on a modified non-Hodgkin's lymphoma protocol, Sloan-Kettering LSA_2-L_2, thymic localization occurred during treatment in five of the seven. We conclude that increased thymic gallium localization in children under chemotherapy for a known malignancy may reflect increased activity of thymic medullary epithelial cells and regeneration of thymic lymphocytes during recovery from involution induced by certain chemotherapeutic agents.

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Gallium (Ga-67) citrate is widely used for tumor (*1–4*) and abscess (*2,5,6*) location. Thymic localization of Ga-67 has been reported in children (*7–10*) and has generally been considered a normal finding, although the mechanism is unexplained. In this paper, we report on seven patients having acute lymphocytic leukemia (ALL) or malignant lymphoma, lymphocytic diffuse (ML), with a high frequency of thymic localization of Ga-67. All patients were being treated according to a modified Sloan-Kettering lymphoma protocol (*11*). These patients are in contrast to a larger number evaluated for neoplastic or inflammatory processes in an attempt to place thymic Ga-67 uptake in its proper perspective. Speculations concerning the mechanism of localization will be presented.

PATIENT POPULATION AND METHODS

The seven study patients, 2–14 yr old, with ALL and ML, had a total of 25 Ga-67 scintigraphic studies at intervals during their clinical course. They will be referred to as the "study group." An additional 87 patients, from less than 1 yr to 21 yr old, had gallium scintigraphy during evaluation of inflammatory or neoplastic processes. They constitute the "control group."

Based on age and weight, patients received 0.5–3.0 mCi of gallium Ga-67 citrate intravenously. Whole-body and high-resolution images were obtained 24–48 hr after injection, using a large-field-of-view gamma scintillation camera and a medium-energy collimator.

All studies were reviewed by one of the authors (JCL) without the benefit of history. Studies were considered positive if thymic (anterior mediastinal) uptake was present, and negative in the absence of thymic uptake. For the purposes of this paper, abnormal gallium localization in other regions did not constitute a positive study.

Additional studies available for review in the study group and positive controls include high-kilovoltage chest radiographs and, in four study patients (5 studies), computerized transmission tomography (TCT). Tomographic sections were obtained at 1-cm intervals from the lung apex to the diaphragm. An interpretation of "pathologic mass" was made if the tissue in the region of the thymus extended in a convex manner beyond the mediastinal confines.

The clinical status of a study patient was categorized as "active" if bone-marrow aspiration, cerebrospinal fluid analysis, or biopsy data revealed evidence of disease. All results were categorized by age, arbitrarily using 5

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TABLE 1. PATIENT DATA AT THE TIME OF Ga-67 SCINTIGRAPHY

Patient	Age (yr)	Sex	Diagnosis	Ga	Chest radiograph	Chest TCT	Clinical status	Drugs*
1	3	M	Malignant lymphoma	+	+		A	None
				+	+		A (bone marrow)	MTX, BCNU, TG
				+	−		I	ARA-C, VCR, MTX, TG, CP
				+	−		I	MTX, BCNU, ARA-C
				+	−		I	CP, HU, DM
				+	−		I	HU, MTX, BCNU, DM
				−	−	+	I	MTX, BCNU
				+	−		I	MTX, BCNU, TG
				−	−		A (CNS)	MTX, VCR, PRED, HC, ARA-C
2	2	F	Malignant T-cell lymphoma	+	+		A (thymus)	None
				−	−		I	L-ASP, MTX, BCNU
				−	−		I	Off therapy for 5 mo
3	9	F	Acute lympho-cytic leukemia	+	−	−	I	MTX, BCNU
				−	−		A (bone marrow)	Off therapy for 12 mo
4	11	M	Malignant lymphoma	+	−	−	A (testicle)	CP, BLEO, 6-MP, PRED
				−	−		I	L-ASP, PRED
				+	−		A (bone marrow)	CP, BLEO, 6-MP, PRED
5	17	F	Acute lympho-cytic leukemia	−	−		I	MTX, CP, TG, DM
				−	−		I	HU, ARA-C, MTX
6	12	M	T-cell leukemia	+	+	+	A (thymus)	ARA-C, MTX, VCR
				−	−		I	ADR, PRED, MTX, ARA-C
				−	−	−	I	MTX, ARA-C, TG
7	14	F	Malignant lymphoma	−	−		A (bone marrow)	None
				−	−		I	L-ASP, MTX, BCNU, CTR
				−	−		I	TG, MTX, HU, DM

+ = thymic uptake of Ga-67, mediastinal widening (x-ray), or pathologic mass (TCT).
− = no abnormality by imaging modality.
A = active; I = inactive.
* Drugs received in the month before Ga-67 scintigraphy:

ADR = adriamycin
ARA-C = arabinoside-C
L-ASP = l-asparaginase
BLEO = bleomycin
BCNU = 1,3-bis (2-chlorethyl)-1-nitrosourea
CP = cyclophosphamide
DM = daunomycine
HC = hydrocortisone
HU = hydroxyurea
6-MP = 6-mercaptopurine
MTX = methotrexate
PRED = prednisone
TG = thioguanine
VCR = vincristine

TABLE 2. RESULTS OF GALLIUM SCINTIGRAPHY IN ALL PATIENTS

		≤ 5 years		>5 years	
		Infection	Malignancy	Infection	Malignancy
Control patients	Ga +	4 (4)	2 (2)	0	5 (6)
	Ga −	23 (23)	12 (14)	22 (24)	19 (48)
Study patients*	Ga +	0	2 (8)	0	3 (4)
	Ga −	0	2 (4)	0	5 (9)

* Patients appear in both Ga + and Ga − groups.
Ga + = thymic Ga-67 localization.
Ga − = no thymic localization.
( ) = number of studies.

yr as a separation point for analysis. The U-test for sampling from a binomial population was utilized to determine whether a significant difference existed between age groups (*12*). A p value of less than 0.05 was considered significant.

RESULTS

A summary of patient data is presented in Tables 1 and 2. Table 1 correlates the clinical status, the presence or absence of thymic Ga-67 localization, the radiological findings, and the chemotherapy in the month before scintigraphy for the seven study patients. In Table 2 the results of Ga-67 scintigraphy in both patient groups are presented, divided on the basis of clinical indication for the study and the age category.

In the control group, thymic localization of Ga-67 was noted in 15% (6/41) of patients 5 yr or younger, four being studied because of a known or suspected inflammatory process. Over 5 yr of age, 11% (5/46) of the patients, all with a known malignancy, showed thymic localization. Of the seven patients with a known malignancy, four were imaged at the time of diagnosis. One patient with Hodgkin's disease had the only abnormal chest radiograph in this group. The remaining three patients had normal chest radiographs and had received vincristine, cyclophosphamide, or prednisone in the month preceding scintigraphy.

Thymic localization of Ga-67 was seen in five of the seven study-group patients. The 48% incidence of positive studies (12/25) in these patients contrasts with 10% (12/121) of the control group studies ($p < 0.01$). Both study patients 5 yr or younger had positive studies, whereas only 15% of age-matched control patients had a positive study ($p < 0.01$). In the older study patients, 60% (3/5) had Ga-67 positive studies, compared with 11% of the control patients ($p < 0.05$).

In the study group thymic localization of Ga-67 was associated with mediastinal widening on chest radiography in three patients who had four studies (Fig. 1). Two patients had biopsy-proven malignant lymphoma, lymphocytic diffuse, within the thymus. The remaining two studies were in a patient with malignant lymphoma in a cervical lymph node and bone marrow. Of the four studies, two were performed before initiation of therapy and the other two after the patient had received either vincristine or 1,3-bis(2-chlorethyl)-1-nitrosourea (BCNU) in the month before study (Table 1).

Eight positive Ga-67 studies were associated with a normal chest radiograph in three patients. Biopsy revealed thymic hyperplasia in one patient (Fig. 2). The second patient had evidence of active disease at the time of two studies. The remaining patient had several positive studies following induction therapy (*5*). Biopsy at a time when the gallium study was negative revealed thymic hyperplasia, although the cortex was found to be slightly depleted of lymphoid tissue and phagocytes while me-

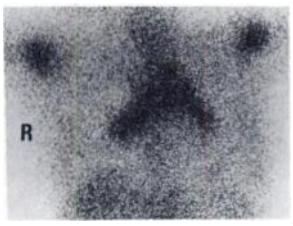

FIG. 1. From a 12-yr-old male with T-cell leukemia and mediastinal widening by chest radiograph. Note thymic uptake of Ga-67. Biopsy revealed tumor infiltration.

FIG. 2. From 9-yr-old female with acute lymphocytic leukemia and normal chest radiograph. Note thymic uptake of Ga-67 on 48-hr postinjection image (arrows). Biopsy showed thymic hyperplasia.

TABLE 3. CORRELATION OF DIAGNOSTIC STUDIES AND SURGICAL PATHOLOGY

Patient	Age (yr)	Ga	Chest radiograph	Chest TCT	Clinical status	Thymus biopsy
1	3	−	−	+	I	Hyperplasia
3	9	+	−	−	I	Hyperplasia
6	12	+	+	+	A	Leukemia
6	12	−	−	−	I	Not done
4	11	+	−	−	A	Not done
2	2	+	+	Not done	A	Malignant lymphoma

− = No evidence of mediastinal abnormality.
+ = Mediastinal abnormality.
I = Inactive.
A = Active.

dullary tissue was normal. All patients had received cyclophosphamide, prednisone, vincristine, or BCNU, alone or in combination, in the month preceding scintigraphy (Table 1).

Thirteen studies, at least one in every study patient, were negative for thymic localization of gallium. Three patients had evidence of active disease at the time of the Ga-67 study. One patient was newly diagnosed as having ML, the second had recurrence of null-cell ALL after being off therapy for one year, and the third had leukemia of the central nervous system. All had negative chest radiographs, and seven studies were associated with antecedent prednisone, cyclophosphamide, BCNU, or vincristine therapy. Only one patient in the group, previously mentioned, underwent surgical biopsy, with a final diagnosis of thymic hyperplasia.

Although the number of patients studied with all three imaging modalities is small, the results are summarized in Table 3. Abnormal TCT scans were noted in both thymic hyperplasia and neoplastic involvement. Of note, however, is that patients with proven tumor involvement of the thymus had evidence of a thymic abnormality by at least two modalities. Patients with thymic hyperplasia, on the other hand, had an abnormality demonstrated by no more than one modality.

DISCUSSION

Thymic localization of gallium Ga-67 citrate has been previously reported as a normal variant in children, although no specific age limits or frequency have been stated (*7–10*). In the present series we found Ga-67 localization in 15% (4/27) of studies in patients 5 yr old or younger when the indication for the examination was suspected inflammatory process. In the same age group, on the other hand, 36% (10/28) of studies in patients with a known malignancy showed thymic localization. No patient over age 5 who was studied because of an infectious process had thymic localization of Ga-67. However, in this age group, 15% (10/67) of the studies in patients with a known malignancy had evidence of thymic localization.

The exact mechanism for uptake of Ga-67 in the thymus is unknown. While the epithelial membrane in the active, intact, normal thymus of children should prevent the passage of macromolecules (*13*), the development of a tumor within the thymus (*14*), or a change in its size, may result in loss of membrane integrity and the passage of Ga-67-bound macromolecules. A change in thymic size may be caused by chemotherapy (*15–17*) or an immunologic response to a stress situation (*5,8*). For instance, thymic enlargement has been described after recovery from severe burns (*18*), corrective surgery for transposition of the great vessels (*19*), cessation of orally administered corticosteroids (*20*), and during and after chemotherapy (*21*). Such an enlargement has been referred to as a "rebound phenomenon" (*21*).

The positive Ga-67 studies in our patients with leukemia or lymphoma may have resulted from tumor replacement or a drug-induced alteration in thymic size. Tumor invasion was demonstrated by biopsy in two patients and was inferred in one patient (2 studies), not previously treated, with known cervical lymph node involvement as well as other evidence of disseminated disease. These three patients (four studies) had associated mediastinal widening by chest radiography.

Eight positive Ga-67 studies in three patients were associated with a normal chest radiograph and uptake was most likely secondary to increasing thymic size and metabolic activity during recovery from the toxic effects of chemotherapy. Histologically proven thymic hyperplasia was observed in one patient (1 study). One patient had numerous positive Ga-67 studies (five studies) but at the time of the thymic biopsy that revealed hyperplasia, only the TCT study was abnormal. We speculate that the cause of the positive Ga-67 studies was thymic hyperplasia in this patient and in another (2 studies) who did not undergo thymic biopsy.

It is noteworthy that these eight studies (ave. = 23 days, range 9–34 days) were performed on the patients within one month of their having received one or more

of the following drugs: vincristine, cyclophosphamide, prednisone, and/or BCNU. All of these agents have been reported to produce involution of the rat thymus (*15–17*). Not all patients receiving these agents, however, had positive studies, and seven of the thirteen negative studies were performed within an average of 16 days (range 7–26 days) following administration of these drugs.

We conclude that during thymic recovery, enhanced localization of Ga-67 may occur. Gad (*22*) found a rapid proliferation of thymic lymphocytes and increased medullary epithelial-cell activity associated with the presence of rough-surfaced endoplasmic reticulum, presumably lysosomes, during recovery from thymic involution. Taheda (*23*) has reported the subcellular localization Ga-67 within the lysosomal fraction in normal liver cells. While the exact role of ferritin in gallium localization (*24*) is unsettled, note that Clark (*13*) identified ferritin within endothelial cells, perivascular macrophages, and macrophages deep within thymic parenchyma following intravenous ferritin injection in rats, suggesting a relative inability of the thymus epithelial basement membrane to exclude ferritin. Such a defect might enhance gallium localization during periods of rapid proliferation and growth, and may relate to the absence of uptake in Patient 1 just before surgery that showed a relative depletion of macrophages.

Cohen et al. (*21*) recently described seven patients being followed for known malignancies who had an anterior mediastinal mass by chest radiography. Six of the seven were under 5.4 yr of age, and three had been off therapy 1–9 mo. Of the four on therapy, two were receiving vincristine and actinomycin D. The chemotherapy of the other two patients was not stated. These authors concluded that widening of the mediastinum in an otherwise healthy patient was most likely due to "rebound phenomenon" and should be observed closely. They did not report the use of Ga-67 scintigraphy. Our experience differed significantly from theirs. Thymic hyperplasia was not associated with radiographic mediastinal widening, and TCT was abnormal in only one of the two patients in whom the diagnosis was surgically confirmed. Both abnormal chest radiographs and the other abnormal TCT scan were indicative of a malignant invasion of the thymus.

In conclusion, we found thymic uptake of Ga-67 to occur with a higher frequency in children with a variety of neoplastic disorders, especially within our study population. We speculate that this uptake may be related to enhanced localization of Ga-67 in the thymus as a result of tumor invasion or regeneration following chemotherapeutically induced involution. We feel that patients with leukemia or lymphoma, and possibly those with other malignancies, who show mediastinal widening by chest radiography or thymic localization of Ga-67 on routine imaging, should be appropriately evaluated by noninvasive techniques, e.g., Ga-67 scintigraphy and chest radiography, and a review of the patient's chemotherapy. Surgical biopsy seems warranted in the patient with an abnormal chest radiograph or TCT study and thymic localization of Ga-67, since this combination was found in the two patients who had proven malignant infiltration of the thymus. When only one modality is abnormal in a clinically healthy child with a known malignancy, benign thymic hyperplasia, possibly reflecting recovery from the effects of chemotherapy, is the most likely diagnosis, and clinical observation seems preferable to biopsy.

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