Thymic Localization of Gallium-67 in Pediatric Patients with Lymphoid and Nonlymphoid Tumors

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To determine the significance of ^{67}Ga localization in the thymus of children, 142 ^{67}Ga photoscans from 45 children with various tumors were studied. Sixty-nine photoscans were taken for 17 cases of lymphoma, 73 photoscans were made for 28 cases of nonlymphoid tumors. Thymic localization of ^{67}Ga was positive in 16 (36%) of the 45 patients and in 30 (21%) of the 142 photoscans. Positive thymus scans were seen in five (29%) of the 17 cases of lymphoma and 11 (39%) of the 28 solid tumors. The positive incidence was highest (90%) in ages 1–2 yr old. Of the eight grade 2 (strong positive) patients, the thymus in one case of Hodgkin's disease was diagnosed as malignant and the other seven solid tumor cases were nonmalignant. Most of the latter seven cases became positive after beginning of treatment (surgery and/or chemotherapy). Although the precise mechanism is not well understood, thymic localization of ^{67}Ga may represent immunologic response to tumors, especially in infants with nonlymphoid neoplasms.

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Gallium-67 (^{67}Ga) citrate is widely used for visualization of tumors and infectious lesions (*1–4*), but caution must be exercised that it normally accumulates in the liver, spleen, long bones, nasopharynx, and gastrointestinal tract (*5*). In children, ^{67}Ga also accumulates in the thymus. However, in contrast to the other organs, the thymus is not consistently visualized by ^{67}Ga. According to the reviews of ^{67}Ga photoscan (*6–8*), thymic images in pediatric patients are stated to be normal and no specific conditions of thymic visualization have been defined, except for definite tumors of the thymus. At our pediatric clinic, however, we often encounter patients with lymphoid or nonlymphoid malignant tumors who show a positive thymus by ^{67}Ga scintigraphs. Since the mechanism, frequency and significance of thymic visualization are not well understood, we have had difficulties in evaluating the thymic uptake of ^{67}Ga, as to whether the image is normal or malignant, especially in cases of lymphoid malignancy. In this paper, we report our studies on the frequency of positive thymic images in children with lymphoid and nonlymphoid tumors.

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PATIENTS AND METHOD

Whole-body [^{67}Ga]citrate photoscans were taken of 45 children with various tumors between January 1, 1984 and August 31, 1985 (Table 1). The patients were 15 cases of non-Hodgkin's lymphoma (NHL), two of Hodgkin's disease (HD), 16 of neuroblastoma and 12 of other solid tumors. A total of 142

TABLE 1
Patients' Profile

	No. of patients	No. of ^{67}Ga scans
Total	45	142
Male	24	85
Female	21	57
Types		
Malignant lymphoma	17	69
Non-Hodgkin's lymphoma	15	50
Hodgkin's lymphoma	12	19
Neuroblastoma	16	48
Wilms' tumor	2	12
Others	10	13
Soft-tissue sarcoma	3	4
Adrenal cortical tumor	2	2
Histiocytosis X	2	3
Retinoblastoma	1	2
Testicular tumor	1	1
Teratoma	1	1

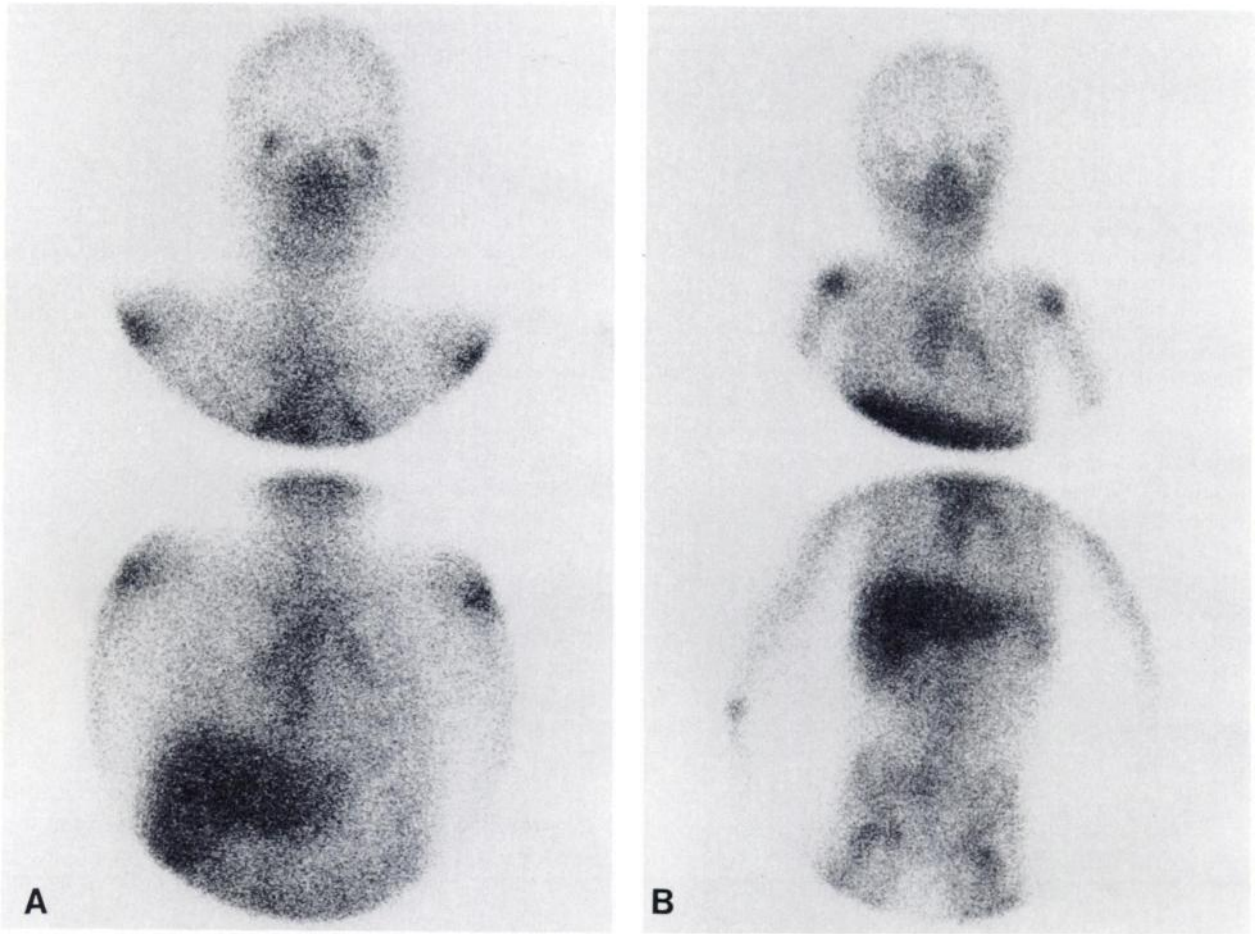

FIGURE 1
Grading of ^{67}Ga thymic localization: (a) grade 1; (b) grade 2 (see text).

photoscans, an average of three scans for each patient, were examined. Gallium-67 citrate (1–4 mCi) was administered i.v. 72 hr before scanning. Patients were given a cleaning enema a few hours before scanning. Each child was scanned from head to foot by a Shimazu-Searle Pho/ Gamma LFOV in anterior and posterior projections. The left lateral view was also obtained when necessary.

We classified thymic localization of ^{67}Ga into three grades as shown in Figure 1. Grade 0 indicates no definite uptake; grade 1 is a clearly discernible thymus-shaped uptake at the antero-superior mediastinum, but its intensity is less than that of the liver; grade 2 is an intense thymus-shaped uptake at the upper mediastinum, with intensity equal to or more than that of the liver.

RESULTS

In a view of 142 [^{67}Ga]citrate photoscans from 45 patients, patients were considered positive if they showed a thymic ^{67}Ga uptake at least once in serial repeated photoscans. The results disclosed that 16 (36%) of the 45 cases and 30 (21%) of the 142 scans were positive (grade 1–2) for thymic visualization [Table 2 (a and b)]. Eight of the 16 positive cases were grade 2 (strong positive). Of the 30 positive scans, 13 were grade 1 and 17 showed grade 2. In 15 cases of NHL, only four cases (a total of five out of 50 scans) revealed grade 1 positive. Out of 19 photoscans from two cases of HD, thymus was positive only once, showing grade 2. Among solid tumors, neuroblastoma showed the highest positive. Six cases were grade 2 and 2 cases were grade 1 (a total of ten grade 2 and seven grade 1 out of 48 scans). A case of Wilms' tumor was also grade 2 positive. Seven of the eight patients, except a case of Hodgkin's disease, with grade 2 positive thymus were on chemotherapy. For practical purposes, the grade 2 positive thymus detected in eight cases should have been differentiated from a malignant invasion. The grade 2 thymic visualization in a patient with Hodgkin's disease, which occurred 9 mo after completion of six courses of COPP therapy, was interpreted as malignant, although not confirmed by biopsy. Treatment by irradiation to the upper mediastinum was followed by a relapse in cervical nodes, suggesting the preceding recurrence at the thymus. As for the other seven patients, the grade 2 positive thymus was interpreted as nonmalignant, because the thymus was con-

TABLE 2
Summary of Thymic ^{67}Ga Uptake in 45 Pediatric Patients with Lymphoid and Nonlymphoid Tumors

(a) Incidence of positive thymus in 45 cases

Type	Grade 2	1	0
Non-Hodgkin's lymphoma (15)	0	4	11
Hodgkin's disease (2)	1	0	1
Neuroblastoma (16)	6	2	8
Wilms' tumor (2)	1	1	0
Others (10)	0	1	9

(b) Incidence of positive thymus in 142 photoscans

Type	Grade 2	1	0
Non-Hodgkin's lymphoma (50)	0	5	45
Hodgkin's disease (19)	1	0	18
Neuroblastoma (48)	10	7	31
Wilms' tumor (12)	2	4	6
Others (13)	0	1	12

sidered to be a highly unlikely site of metastasis in these nonlymphoid tumors. Follow-up of these patients have not disclosed any tumor progression at the thymus.

Frequency of the positive scans in relation to age is shown in Figure 2. A clear relationship between patient's age and thymic accumulation of ^{67}Ga was present. Positive scans were 61% (11/18) in infants less than 2 yr old versus 15% (19/124) in children over 2 yr old. One- to two-year-old infants showed the highest positive rate (90%). None of the patients over 11 yr old was positive. The 11 positive scans in infants younger than 2 yr of age were all in neuroblastoma patients.

The fact that NHL had a low incidence may be caused by the effect of adrenocorticoids on thymic ^{67}Ga uptake. It is well known that the size of the thymus decreases after adrenocorticoids are administered (*9–10*) and a rebound hypertrophy takes place within 2 wk of cessation of the drugs (*11–12*). Therefore, the 142 scans were divided into two groups, "no administration" and "administration" of adrenocorticoids within the one month prior to ^{67}Ga scanning (Fig. 2). The positive incidence in the administration group was 5/47 (11%) and 25/95 (26%) in the no administration group. Grade 2 uptake was seen only in the latter group. However, as seen in Figure 2, the age distribution for the two groups was quite different (median age; 10 yr versus 3 yr). In lymphoid malignancies alone, age distribution and the positive thymus rate were not significantly different between the two groups ($p > 0.05$, by Fisher's exact probability test). Accordingly we assume that adrenocorticoids did not cause a significant effect on thymic uptake of ^{67}Ga in our patients.

Serial follow-up studies of the 16 cases which were positive for thymic uptake at least once are summarized in Figure 3. Only two cases were already positive at the onset. However, nine out of 11 cases (five cases were not studied on admission) were initially negative and became positive after beginning of therapy (surgery and/or chemotherapy). In addition, in six out of these nine cases, a positive thymus appeared within 6 mo.

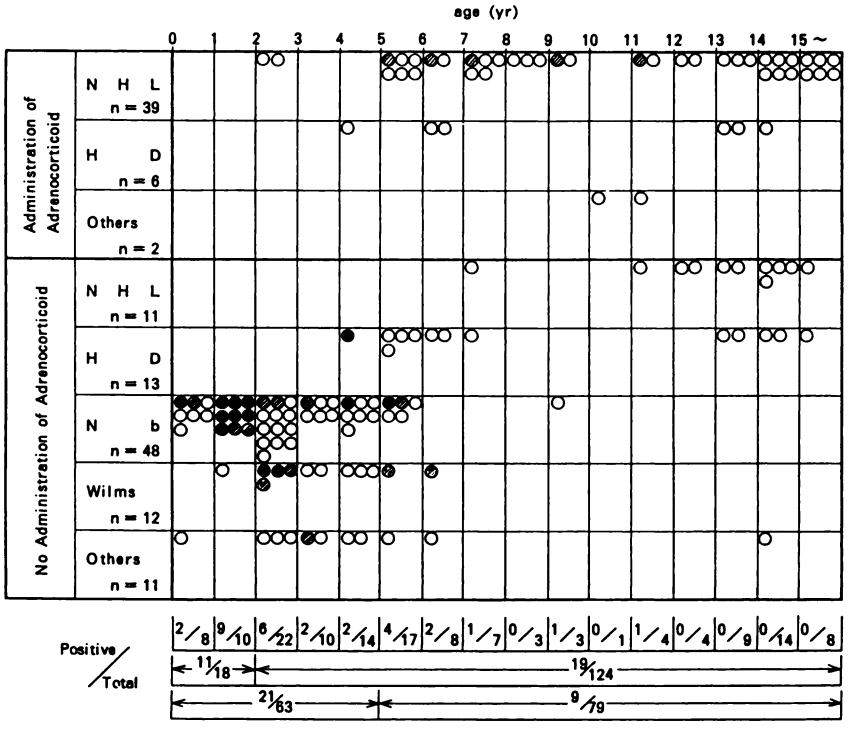

FIGURE 2
Distribution of ^{67}Ga positive photoscans, in relation to age, types of tumors, an adminisration of adrenocorticoids. (●) grade 2; (◍) grade 1; (○) grade 0; NHL = non-Hodgkin's lymphoma; HD = Hodgkin's disease; Nb = neuroblastoma.

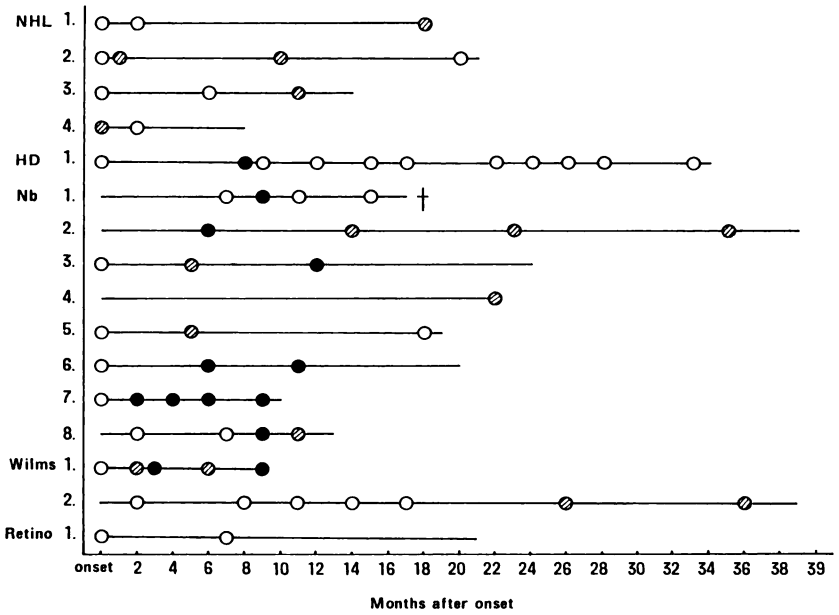

FIGURE 3
Serial follow-up of thymic ^{67}Ga localization in the 16 positive cases. (●) grade 2; (◉) grade 1; (○) grade 0; (†) expired. NHL = non-Hodgkin's lymphoma; HD = Hodgkin's disease; Nb = neuroblastoma; Retino = retinoblastoma.

DISCUSSION

Edward and Hayes (*13*) first described a localization of ^{67}Ga in human tumors in 1969 and it is now known that intravenously administered ^{67}Ga accumulates in neoplastic and inflammatory lesions. A possible explanation of ^{67}Ga accumulation is that ^{67}Ga weakly binds to transferrin in plasma and circulates through the body. Gallium-67 then translocates to lactoferrin at tumor or inflammatory sites, where leukocytes and tumor cells such as HD, Burkitt's lymphoma, and melanoma contain lactoferrin. Lactoferrin, which is normally present in the spleen, gastrointestinal tract mucosa, bone marrow and nasal secretions as well as in milk, binds ^{67}Ga more actively than does transferrin. Therefore, these normal tissues and secretion as well as tumor and inflammatory sites are the major sites of ^{67}Ga accumulation (*14–18*).

In terms of the thymus, the situation is different from such organs normally visualized by ^{67}Ga. In children with infectious diseases, the thymus was reported to accumulate ^{67}Ga without direct involvement (*6–8,19*). In addition, in young children, ^{67}Ga accumulation in the thymus may represent a "normal variation" or a result of some purely physiologic variables. It is possible that the thymus in children may take up ^{67}Ga under the stress of illness or the effects of chemotherapy etc.

In this study, we reviewed 142 ^{67}Ga photoscans of 45 children with various tumors and found the positive rate 21% (Table 2, Fig. 2). Whether this rate indicates a specific high incidence in children with tumors remains to be determined by comparing the incidence of thymic visualization in a similar age group of children without neoplasms. The fact that the thymus was visualized in 61% (11/18) of scans in patients below 2 yr in contrast to 15% (19/124) in patients over 2 yr of age, clearly indicates that younger infants show a positive thymus more frequently. Donahue reported that 36% of ^{67}Ga studies in patients less than 5 yr old with various malignancies showed thymic localization (*19*). This is compatible with the 33% (21/63) of scans in the same age group in our series. Normally, the volume of human thymus is 0.27% of total-body weight and decreased to 0.02% between the ages of 5 and 15 yr (*20*). It is interesting that in our series it was not the youngest (0-1 yr) age group but the older infants (1–2 yr) who showed the highest positive rate (90%). Based on these observations, it is unlikely that tumor types influence the positive incidence of thymic ^{67}Ga uptake, and age must be a key factor for the thymic visualization.

Adrenocorticoids reduce size and weight of the thymus by killing thymic lymphocytes in the cortex within 48 hr after its administration (*9–10*). On cessation of adrenocorticoids, the thymus begins to re-expand within a few days (*11–12*). This shrinkage and re-expansion is well observed in chest x-rays. So, we suspected the influence of adrenocorticoids on thymic ^{67}Ga uptake, especially in lymphoid malignancies. Although five out of 45 scans were positive in the administration group and only one out of 24 scans was positive in the no administration group, it was not statistically different (Fig. 2).

We divided positive thymus into grade 1 (mild uptake) and grade 2 (strong uptake) and concentrated our attention to the grade 2 cases. One case of HD who showed the only grade 2 uptake among lymphoid malignancies was diagnosed to be a true thymic involvement of malignancy. All of the other seven cases of solid tumors with grade 2 uptake were interpreted to be nonmalignant. In addition, all of the seven young infants showed a strongly positive thymus 2-12 mo after the initiation of therapy. The possibility that such

thymic ^{67}Ga uptake in these patients might have been a malignant infiltration was highly unlikely. Another possible explanation could be a thymic visualization that takes place as a rebound phenomenon after chemotherapy. It is known that thymic enlargement is occasionally observed after recovery from severe burns (*21*), corrective surgery for transposition of great vessels (*22*), cessation of adrenocorticoids (*19*) and during or after chemotherapy (*23*). Donahue reported a ^{67}Ga positive thymus which was histologically hyperplastic (*19*). It is possible that the seven grade 2 positive cases may have had thymic hyperplasia.

As discussed above, there are many interrelated variables which may affect the thymic ^{67}Ga uptake such as age, infections, drugs, and other stressful episodes. Recently, it was reported that T-lymphocytes stimulated by PHA show an increased affinity for ^{67}Ga (*24*). Therefore, the accumulation of ^{67}Ga in the thymus may suggest the presence of activated thymic lymphocytes and represent an immunologic response of the host to stimuli from probable tumor antigens. Although speculative at this moment, whether thymus positive patients with nonlymphoid tumors have a better prognosis in relation to such an immunologic response, is an interesting question to investigate in the future. In summary, we suggest that a grade 2 positive thymus in lymphoid tumors should be carefully differentiated from a malignant invasion, while that of nonlymphoid tumors need further studies to clarify if it represents an undetermined immunologic response.

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