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Diagnosis of thyroid lymphoma and follow-up evaluation using Ga-67 scintigraphy

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A strong association between malignant lymphoma and Hashimoto's thyroiditis has frequently been reported. However, it is difficult to detect the lymphomatous transformation of Hashimoto's thyroiditis in the early stage. The purpose of the present study was to examine the usefulness of ^{67}Ga scintigraphy in the diagnosis and evaluation of the therapeutic effects during follow-up, in patients with a suspected diagnosis of primary thyroid lymphoma. Twenty-five patients who were suspected of having primary thyroid lymphoma and had undergone ^{67}Ga scintigraphy were studied. ^{67}Ga planar scintigraphy was performed 72 hours after injection of ^{67}Ga-citrate. The degree and pattern of ^{67}Ga accumulation were graded visually. Histopathology on biopsy examination revealed thyroid lymphoma in 17 and Hashimoto's thyroiditis in 8 patients. Abnormal accumulation of ^{67}Ga in the thyroid was seen in all of the 17 thyroid lymphoma cases with additional mediastinal and abdominal involvement in one. Fifteen of 17 thyroid lymphoma patients also underwent ^{67}Ga scintigraphy 2–4 weeks after chemotherapy and/or radiotherapy. All 15 patients showed diminishing ^{67}Ga accumulation and a good clinical course. In one patient with local recurrence, abnormal accumulation could be depicted by follow-up scintigraphy. However, diffuse or enlarged accumulation in the thyroid was seen in all of the 8 Hashimoto's thyroiditis cases. The degree of abnormal accumulation in the thyroid in clinically active phase thyroiditis was more intense than that in the chronic phase thyroiditis. ^{67}Ga scintigraphy was helpful to confirm the diagnosis of thyroid lymphoma and to evaluate the therapeutic effects during follow-up. However, ^{67}Ga scintigraphy may not always distinguish thyroid lymphoma from Hashimoto's thyroiditis, especially the active phase of the disease.

Key words: thyroid lymphoma, Hashimoto's thyroiditis, ^{67}Ga scintigraphy, therapeutic effects

INTRODUCTION

PRIMARY MALIGNANT LYMPHOMA of the thyroid gland is a rare disorder. It has been reported that this disease accounts for 1.8–8% of all thyroid malignancies.[1–3] A strong association of malignant lymphoma with Hashimoto's thyroiditis has frequently been reported.[4–7] Most patients with thyroid lymphoma are elderly women who have a rapidly enlarging thyroid mass and symptoms of obstruction.[3–11] Palpation of tumors is prevented in more than half of the patients with thyroid lymphoma due to coexistent Hashimoto's thyroiditis, which shows a diffuse thyroid goiter with a firm consistency.[12] Patients with thyroid lymphoma are treated with radiation therapy with or without chemotherapy, and extensive surgery is not the treatment of choice.[3,5] Since the prognosis and therapeutic schedule for the patients largely depend on the stage of the lymphoma, early diagnosis and accurate staging are vitally important.[3,5]

Gallium-67 (^{67}Ga) scintigraphy has become a standard procedure in the pre-treatment evaluation of malignant lymphoma. Besides lymphoma staging, ^{67}Ga scintigraphy plays a unique role in the evaluation of treatment of this disease.[13,14] Therefore, ^{67}Ga whole body scintigraphy is currently performed at diagnosis, in order to define

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^{67}Ga affinity to the tumor and to obtain a baseline study of the lymphoma in the individual patient, and after treatment, in order to evaluate the results of therapy[15,16] and the presence of residual disease.[17,18]

^{67}Ga scintigraphy has a well-documented role in nodal lymphoma, for both disease staging and assessing treatment response, but is yet to be established in extranodal lymphoma. There have been only a few reports of thyroid extranodal lymphoma involving the use of ^{67}Ga scintigraphy.[19–21] Furthermore, the role of ^{67}Ga scintigraphy in assessing the treatment response has not been firmly established in thyroid lymphoma.

The purpose of the present study was to evaluate the usefulness of ^{67}Ga scintigraphy in the diagnosis and evaluation of the therapeutic effects during follow-up, in patients suspected of primary thyroid lymphoma.

MATERIALS AND METHODS

Patients

Twenty-five consecutive patients (3 males, 22 females; mean age, 66 ± 19 y; age range, 45–85 y) who were suspected of having primary thyroid lymphoma and had undergone ^{67}Ga scintigraphy at our hospital between July 1990 and March 2001 were examined retrospectively. All patients were suspected of having thyroid lymphoma based on the clinical manifestations and ultrasonography. None of the patients had received any treatment before the ^{67}Ga scintigraphy. Informed consent had been obtained from each patient at the time of scintigraphy.

Treatment

Treatment comprised chemotherapy, radiotherapy alone, or a combination of the two. Chemotherapy consisted of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), either as one unit or in various combinations of the four drugs, for three to eight cycles. Radiation treatment was performed according to institutional guidelines with a radiotherapy dose necessary for local tumor control (e.g., 40–60 Gy) depending on tumor histology and stage. Chemotherapy may suppress uptake of ^{67}Ga by an active lymphoma for a few days after administration. ^{67}Ga was, therefore, injected 2–4 weeks after the end of the cycle of chemotherapy. At this time, chemotherapy does not appear to affect ^{67}Ga uptake.[22] After treatment, disappearance of abnormal ^{67}Ga accumulation was considered a negative result.

^{67}Ga scintigraphy

^{67}Ga scintigraphy was performed using 148 MBq ^{67}Ga-citrate. Whole body and spot images were taken 72 hours after injection. Imaging was performed with a large field of view gamma camera (Prism 2000; Picker International, Cleveland, OH, GCA-90B; Toshiba, Tokyo, Japan, Ω500; Aloka, Tokyo, Japan) with medium-energy and general purpose collimator. Twenty-percent windows were placed symmetrically around each of the three main photopeaks of ^{67}Ga (93, 184 and 296 keV). SPECT images were not acquired. Whole body imaging was performed with both anterior and posterior view images at a speed of 15 cm/min. The spot images were obtained by collecting 300–500 k counts at the preset time of 5 min.

Table 1 The number of patients with thyroid lymphoma according to activity score and pattern of ^{67}Ga accumulation

Pattern	Activity score					
	0	1	2	3	4	5
Diffuse (normal size)	0	0	0	1	2	6
Focal	0	0	0	0	1	2
Enlarged	0	0	0	0	0	5

Activity score: 0 = equivalent to the background, 1 = equivocal, 2 = definite lesion less than the sternum activity, 3 = equal to the sternum activity, 4 = greater than the sternum activity, and 5 = greater than the liver activity

Table 2 The number of patients with Hashimoto's thyroiditis according to activity score and pattern of ^{67}Ga accumulation

Pattern	Activity score					
	0	1	2	3	4	5
Diffuse (normal size)	0	0	3	0	0	2*
Focal	0	0	0	0	0	0
Enlarged	0	0	1	1	1	0

*: Patients in clinically active phase
Activity score: 0 = equivalent to the background, 1 = equivocal, 2 = definite lesion less than the sternum activity, 3 = equal to the sternum activity, 4 = greater than the sternum activity, and 5 = greater than the liver activity

Table 3 Activity score and clinical evaluation on follow-up in 15 thyroid lymphoma patients

Follow-up evaluation stage	Activity score				
Before treatment	3	4	5	5	5
After treatment (2–4 weeks)	0	0	0	1	0
On follow-up (1–6 years)	0	0	0	0	5
Number of patients	1	2	9	2	1
Clinical evaluation	R	R	R	R	LR

R: Remission, LR: Local recurrence

Image analysis

The degree and pattern of ^{67}Ga accumulation were graded visually by the consensus of 2 observers who were unaware of the previous outcome. A 6-point scoring system was used to judge the degree of activity (0 = equivalent to the background, 1 = equivocal, 2 = definite lesion less than the sternum activity, 3 = equal to the sternum activity, 4 = greater than the sternum activity, and 5 = greater than the liver activity). The pattern of accumulation was scored on

a 3-point scale (Diffuse (normal size), Focal and Enlarged).

RESULTS

Of the 25 patients, histopathology on biopsy examination revealed non-Hodgkin's primary thyroid lymphoma in 17 (open biopsy in 2 patients and fine needle aspiration biopsy in 15) and Hashimoto's thyroiditis in 8 patients. Abnormal accumulation in the thyroid was seen in all 25 patients. Of the 17 thyroid lymphoma patients, activity score 3 was shown in 1, score 4 in 3 and score 5 in 13 patients (Table 1). Nine of the 17 patients showed a Diffuse (normal size) pattern, 3 a Focal pattern and 5 an Enlarged pattern (Table 1). Of the 8 Hashimoto's thyroiditis patients, activity score 2 was shown in 4, score 3 in 1, score 4 in 1 and score 5 in 2 patients (Table 2). Five

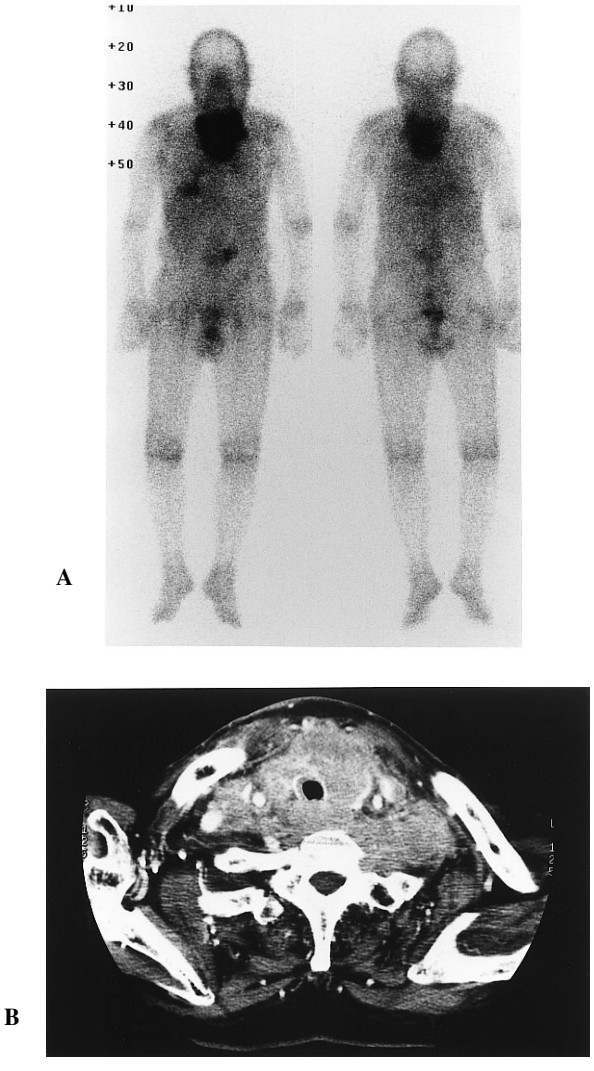


Fig. 1 Scintigraphic findings in an 83-year-old male with thyroid lymphoma. The whole body ^{67}Ga image before treatment demonstrates very intense and enlarged accumulation in thyroid with additional right hilum and abdominal involvement (A). The activity score was 5 and the accumulation pattern was Enlarged. CT shows an irregular giant thyroid mass encasing the trachea (B).

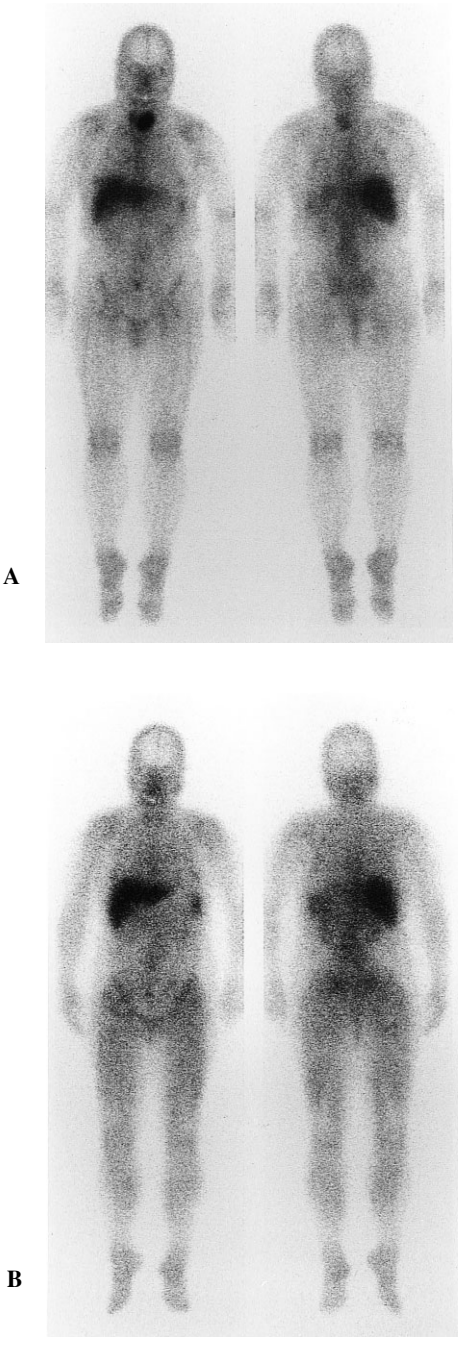
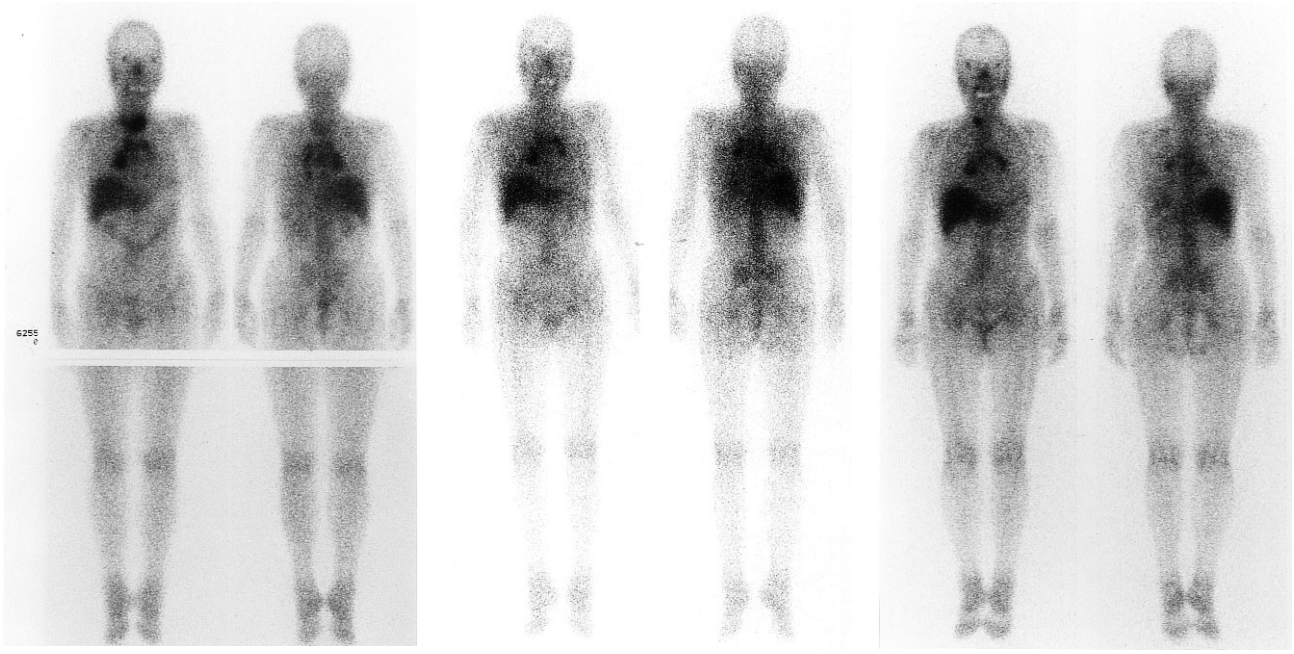


Fig. 2 Scintigraphic findings in a 59-year-old female with thyroid lymphoma. The whole body ^{67}Ga image before treatment demonstrates intense and focal accumulation in the left lobe of the thyroid (A). The activity score before treatment was 5 and the accumulation pattern was Focal. The whole body ^{67}Ga image 4 weeks after treatment demonstrates no abnormal accumulation (B). This patient showed a good clinical course.



A B C

Fig. 3 Scintigraphic findings in a 72-year-old female with thyroid lymphoma. The whole body ^{67}Ga image before treatment demonstrates intense and focal accumulation in the left lobe of the thyroid (A). The activity score before treatment was 5 and the accumulation pattern was Focal. The whole body ^{67}Ga images 4 weeks after treatment demonstrates no abnormal accumulation in the thyroid (B). Six years after treatment, the whole body ^{67}Ga image demonstrates abnormal accumulation in the right lobe of the thyroid, corresponding to the recurrent lymphoma (C).

of these patients showed a Diffuse (normal size) pattern and 3 an Enlarged pattern (Table 2). Two patients who showed a Diffuse (normal size) pattern and activity score 5 were in the clinically active phase of thyroiditis.

Fifteen of 17 thyroid lymphoma patients also underwent ^{67}Ga scintigraphy 2–4 weeks after chemotherapy and/or radiotherapy for the evaluation of the therapeutic response and 1–6 years after treatment for the evaluation of follow-up. The activity scores after 2–4 weeks of treatment were diminished compared to those before treatment in all 15 patients, and they showed a good clinical course (Table 3). On the longer follow-up, 14 patients showed remission with no abnormal ^{67}Ga accumulation. One patient showed local recurrence with abnormal ^{67}Ga accumulation.

Case 1

An 83-year-old male with thyroid lymphoma. Whole body ^{67}Ga image before treatment demonstrates very intense and enlarged accumulation in thyroid with additional right hilum and abdominal involvement (Fig. 1A). The activity score was 5 and the accumulation pattern was Enlarged. CT shows an irregular giant thyroid mass encasing the trachea (Fig. 1B).

Case 2

A 59-year-old female with thyroid lymphoma. The whole

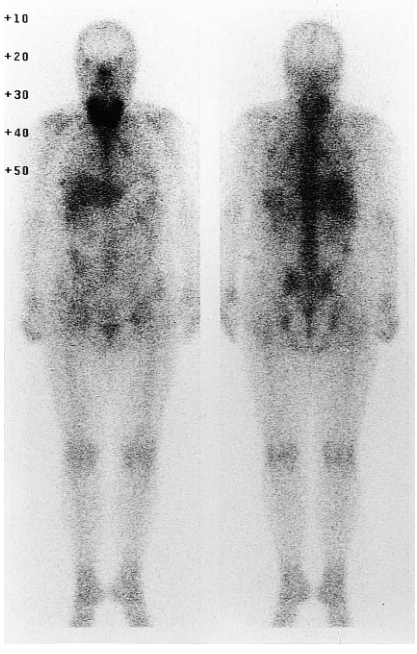


Fig. 4 Scintigraphic findings in a 60-year-old female with active phase of Hashimoto's thyroiditis. The ^{67}Ga image demonstrates very intense and enlarged accumulation in thyroid. The activity score was 5 and the accumulation pattern was Enlarged. In this case it was difficult to distinguish thyroid lymphoma from the active phase of Hashimoto's thyroiditis.

body ^{67}Ga image before treatment demonstrates intense and focal accumulation in the left lobe of the thyroid (Fig. 2A). The activity score before treatment was 5 and the accumulation pattern was Focal. The whole body ^{67}Ga image 4 weeks after treatment demonstrates no abnormal accumulation (Fig. 2B). This patient showed a good clinical course.

Case 3

A 72-year-old female with thyroid lymphoma. The whole body ^{67}Ga image before treatment demonstrates intense and focal accumulation in the left lobe of the thyroid (Fig. 3A). The activity score before treatment was 5 and the accumulation pattern was Focal. The whole body ^{67}Ga images 4 weeks after treatment demonstrates no abnormal accumulation in the thyroid (Fig. 3B). Six years after treatment, the whole body ^{67}Ga image demonstrates abnormal accumulation in the right lobe of the thyroid, corresponding to the recurrent lymphoma (Fig. 3C). Histopathology of the biopsied recurrent mass revealed the same histology as of the initial diagnosis.

Case 4

A 60-year-old female with Hashimoto's thyroiditis. The ^{67}Ga image demonstrates very intense and enlarged accumulation in thyroid (Fig. 4). The activity score was 5 and the accumulation pattern was Enlarged. In this case it was difficult to distinguish thyroid lymphoma from the active phase of Hashimoto's thyroiditis (CRP: 6 mg/d*l*).

DISCUSSION

Non-Hodgkin's lymphoma occurs at extranodal sites much more frequently than does Hodgkin's lymphoma. Thus, most primary thyroid lymphoma is non-Hodgkin's lymphoma.[23] In the present study, all thyroid lymphoma patients had non-Hodgkin's lymphoma histologically.

^{67}Ga imaging has proven useful for evaluating lymphoma patients. The overall ^{67}Ga scan positivity rate for non-Hodgkin's lymphoma arising in lymph nodes is 75% to 90%, slightly lower than that for Hodgkin's lymphoma (85% to 95%).[24] However, in the present study, abnormal accumulation of ^{67}Ga in the thyroid was seen in all thyroid lymphoma patients. This positivity rate is quite high because the lesion is located in a superficial location. These finding are similar to those obtained by Hussain et al. who reported that the positivity rate of thyroid lymphoma was 80% (4/5) with this rate similar to the incidence of ^{67}Ga scan positivity in nodal non-Hodgkin's lymphoma.[24] To our knowledge, there are no large series in which ^{67}Ga scintigraphic findings of thyroid lymphoma are described because of the rarity of this disease. There are sporadic case reports describing that ^{67}Ga accumulates in thyroid lymphoma.[19–21] However, whether or not ^{67}Ga scan is a reliable method for the diagnosis of thyroid lymphoma is not established. The population size in the present study is small, but results show that ^{67}Ga scintigraphy is useful for the diagnosis of thyroid lymphoma.

There is little literature specifically addressing the scintigraphic findings of mucosa-associated lymphoid tissue (MALT) lymphoma.[25,26] Because the most common histology among thyroid lymphomas is diffuse large cell lymphoma, which is classified as intermediate or high grade, previous descriptions of thyroid lymphomas may not truly represent the findings of low-grade lymphoma of the MALT type. It would be helpful for nuclear medicine physicians to elucidate scintigraphic findings in patients who were specifically diagnosed as having MALT lymphoma of the thyroid.

In patients with a rapidly enlarging thyroid mass, the differentiation between thyroid lymphoma and anaplastic thyroid carcinoma is necessary. The clinical features of anaplastic carcinoma are usually similar to those of thyroid lymphoma, but the treatment, prognosis and survival of patients with the latter are very different from those of patients with the former. Shiojima et al. reported that the differentiation of thyroid lymphoma and anaplastic carcinoma is easy on ^{67}Ga scintigraphy.[21] They found that ^{67}Ga accumulation disappeared in all thyroid lymphoma cases that received more than 20 Gy irradiation.[21] In the present study, ^{67}Ga accumulation disappeared after the treatment, and this result was similar to that of Shiojima et al.[21] Thus, therapeutic diagnosis using ^{67}Ga scintigraphy is useful for the differentiation between thyroid lymphoma and anaplastic carcinoma.

An etiologic association between Hashimoto's thyroiditis and the development of thyroid lymphoma has been postulated and confirmed by epidemiologic studies.[4–7] It is difficult to make a case that any imaging technique alone would be useful in the early detection of lymphomatous transformation of Hashimoto's thyroiditis. Needless to say, biopsy is useful in making a definitive diagnosis. However, this procedure is invasive and sampling error cannot be avoided. ^{67}Ga scintigraphy on the other hand is non-invasive and may have a complementary role in patients in whom biopsy site is difficult to identify due to indeterminate clinical or radiological findings and helps to determine the best location for biopsy. Furthermore, ^{67}Ga scintigraphy has the additional advantage of occasionally demonstrating distant involvement.[23] One of our cases (Fig. 1) showed hilar and abdominal involvement. Therefore, ^{67}Ga scintigraphy is useful for accurate staging of thyroid lymphoma.

In the present study, all patients were suspected of having thyroid lymphoma based on the clinical manifestations and ultrasonography. On ^{67}Ga activity scoring, all thyroid lymphoma patients (17/17) showed an activity score of more than 3. On the other hand, half of Hashimoto's thyroiditis patients (4/8) showed an activity score of less than 2. Therefore, if thyroid ^{67}Ga activity is stronger than that of sternum, thyroid lymphoma is strongly suspected. However, in the present study, half of Hashimoto's

thyroiditis patients (4/8) also showed an activity score of more than 3. Two patients with Hashimoto's thyroiditis showed an activity score of 5, and these had Hashimoto's thyroiditis in its active phase (Fig. 4). Thus, ^{67}Ga scintigraphy may not always distinguish thyroid lymphoma from Hashimoto's thyroiditis, especially in the latter's active phase. In other words, ^{67}Ga scintigraphy appears to reflect the activity of Hashimoto's thyroiditis.

In the present study, ^{67}Ga accumulation pattern was reevaluated retrospectively. The most prevalent pattern was Diffuse (normal size) in lymphoma with this pattern observed in 52.9% (9/17) of the cases and in 62.5% (5/8) of Hashimoto's thyroiditis. By contrast, Focal pattern was seen in only 17.6% (3/17) of lymphoma cases and in none of Hashimoto's thyroiditis. Thus, high accuracy in identifying patients with thyroid lymphoma was obtained when the ^{67}Ga accumulation pattern was Focal. ^{67}Ga focal abnormality and very avid accumulation in the thyroid are strong indications of thyroid lymphoma. However, 2 patients in whom stronger ^{67}Ga accumulation in thyroid than in liver was observed showed diffuse thyroid accumulation. Thus, ^{67}Ga scintigraphy did not differentiate thyroid lymphoma from Hashimoto's thyroiditis absolutely in the interpretation of diffuse or enlarged ^{67}Ga accumulation.

^{67}Ga scintigraphy is known to be useful for not only the diagnosis, but also for monitoring the treatment response in thyroid lymphoma patients.[21] The present study had 15 patients in whom the ^{67}Ga scintigraphy was performed to assess the therapeutic response. In all 15 patients the degree of abnormal ^{67}Ga accumulation diminished in comparison with the pre-treatment ^{67}Ga study, and these patients were considered to be in remission clinically. Thus, ^{67}Ga scintigraphy is useful in the evaluation of the therapeutic response. Furthermore, in these 15 patients ^{67}Ga scintigraphy was also performed for the longer follow-up evaluation. Fourteen of the 15 cases showed no abnormal accumulation in the follow-up study and these patients had no recurrence, clinically. However, one of the 15 patients showed abnormal ^{67}Ga accumulation 6 years after treatment, and this patient had local recurrence (Fig. 3). These findings suggest that ^{67}Ga scintigraphy is useful not only for evaluating the therapeutic response, but also for the follow-up study. This scintigraphic workup should facilitate early detection of tumor recurrence and appropriate therapeutic schedule for patients with thyroid lymphoma. Further well-designed studies including the use of biological tumor markers such as interleukin 2 receptor are required to determine the appropriate role for ^{67}Ga scintigraphy in the proper management of patients with thyroid lymphoma.

CONCLUSION

^{67}Ga scintigraphy was helpful to confirm the diagnosis and systemic extent of thyroid lymphoma. However, ^{67}Ga scintigraphy may not always distinguish thyroid lymphoma from Hashimoto's thyroiditis, especially in the latter's active phase. Furthermore, ^{67}Ga scintigraphy may be more useful for the assessment of treatment response and follow-up evaluation of thyroid lymphoma.

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