^{67}Ga Scintigraphy in B-Cell Non-Hodgkin's Lymphoma: Correlation of ^{67}Ga Uptake with Histology and Transferrin Receptor Expression

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^{67}Ga scintigraphy is routinely used in the management of non-Hodgkin's lymphomas (NHLs), but the heterogeneity of ^{67}Ga uptake in the different NHL histological subtypes has not been clearly explained. The transferrin receptors (TfR/CD71) play an important role in the mechanisms of ^{67}Ga uptake by tumor cells. However, the relationship between the ^{67}Ga uptake in NHL and the TfR/CD71 expression in lymphomatous cells remains to be defined. The aim of this study was to determine the intensity of ^{67}Ga uptake in different histological subtypes of B-cell NHL (B-NHL) and to compare this uptake with the expression of TfR/CD71 on lymphomatous cells. **Methods:** ^{67}Ga scintigraphy of 47 patients having histologically proven lymphomas was investigated. ^{67}Ga uptake was semiquantitatively evaluated in regions of interest and was reported as ^{67}Ga uptake index (GaUI). In all cases, biopsies were reviewed for classification of NHL. The expression of TfR/CD71 was determined on frozen sections and was semiquantitatively evaluated. The relationships between GaUI, histology and TfR/CD71 were investigated. **Results:** The values of GaUI were significantly related to the different histological subtypes analyzed ($P = 0.0007$) and to the presence of a large cells component, thus demonstrating that ^{67}Ga uptake rose with the grade of lymphoma. Moreover, the values of GaUI and TfR/CD71 were closely related in the tested cases ($P = 0.0059$). **Conclusion:** There were three factors influencing ^{67}Ga uptake in NHL: histology, TfR/CD71 expression and the presence of a large cells component. This justifies the usefulness of ^{67}Ga scintigraphy in staging the TfR/CD71-positive lymphomas.

Key Words: ^{67}Ga scintigraphy; non-Hodgkin's lymphoma; transferrin receptor CD71

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Edwards and Hayes (*1*) first reported high ^{67}Ga uptake in Hodgkin's disease and non-Hodgkin's lymphomas (NHL) suggesting that ^{67}Ga scintigraphy could be used in lymphoma management. This imaging technique is used for staging the extent of disease, detecting relapse or progression of disease and predicting response to therapy and outcome (*2–8*).

Because the results of ^{67}Ga scintigraphy in the NHL patient are heterogeneous (*9*), ranging from high rate of ^{67}Ga uptake in high-grade NHL to negative ^{67}Ga uptake mostly in low-grade NHL, the relationship between the histological data and the ^{67}Ga uptake in NHL needs to be defined. The mechanisms regulating the uptake of ^{67}Ga by neoplastic cells are partially dependent on the density of transferrin receptor CD71 (TfR/CD71) expression in these cells (*10,11*). In vitro studies of human lymphoid cell line models (*12,13*) confirmed that ^{67}Ga acts through a TfR/CD71-dependent mechanism. The correlation of TfR/CD71 expression with the morphologic grade in NHL was already known (*14,15*), but the relationship between the expression of TfR/CD71 and the ^{67}Ga uptake in patients with NHL was not yet established.

To this end, 47 B-cell NHL (B-NHL) patients were retrospectively evaluated (a) to determine the ^{67}Ga uptake in different histological subtypes and (b) to establish the relationship between TfR/CD71 expression and ^{67}Ga uptake. Our data confirm that histology and TfR/CD71 are two important factors regulating the uptake of ^{67}Ga in NHL patients.

MATERIALS AND METHODS

Patients

For the study, 47 patients were selected (20 males, 27 females; age range 16–83 y; mean age 53.1 y). They had been admitted between 1991 and 1996 to the Avicenne University Hospital (Bobigny, France) and were referred to its Nuclear Medicine Department with histologically proven B-NHL. The group included 31 patients who were evaluated at initial staging before treatment, 13 who underwent ^{67}Ga scintigraphy for disease recurrence and 3 who exhibited transformation of a chronic lymphoproliferative syndrome. Stage I patients with negative ^{67}Ga scintigraphy were excluded from the study.

Histological Analysis

Conventional morphology was performed on paraffin sections using hematoxylin-eosin and Giemsa staining. All cases were

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reviewed with two experts in hematopathology and were classified according to the criteria of the Revised European-American classification of Lymphoid Neoplasms (REAL) classification (*16*).

Immunohistochemical Studies

Immunophenotypical Analysis. The immunoperoxidase technique was used on paraffin sections to detect the leukocyte common antigen CD45, the B-cell marker CD20 and the T-associated molecule CD3 using, respectively, the antiCD45 PD7/26 + 2B11 monoclonal antibody (mAb), the antiCD20 L26 mAb and the polyclonal antiserum against CD3 (Dako, Trappes, France). The slides were incubated with the primary mAb and then with the reagents of the commercially available labeled streptavidine-biotine (LSAB) kit, according to the manufacturer's recommendations (Dako, Trappes, France). Chromogen substrate (DAB-H_2O_2 solution) was then applied and was incubated for 10 min to yield a brown reaction product. Sections were counterstained with hematoxylin and were dehydrated and mounted using a synthetic medium.

Expression of TfR/CD71. This study was performed on frozen sections of tissue from 24 patients, using the B3/25 mAb to human TfR/CD71 from mouse-mouse hybrid cells (Boehringer Mannheim, Meylan, France). Sections 5-μm thick were cut, placed on slides and fixed in acetone for 10 min. Slides were transferred to Tris buffer and were incubated for 1 h with the B3/25 primary mAb diluted 1:1000. Expression of TfR/CD71 was detected using the LSAB kit. A control was run in all cases by omission of the primary antibody.

Immunohistochemical Grading. The semiquantitative expression of TfR/CD71 was evaluated without knowledge of the imaging data. This evaluation was based on the percentage of positive cells, as follows: negative, −: <10%; low, 1+: >10% and <30%; intermediate, 2+: >30% and <80% and high, 3+: >80%.

^{67}Ga Citrate Scintigraphy

Images were acquired using a single-head gamma camera on the three energy peaks of 93, 184 and 296 keV ^{67}Ga, 48 h after an intravenous injection of 111 MBq (3 mCi) ^{67}Ga citrate (mean dose injected for a patient of 70 kg). Anterior and posterior views of thorax, abdomen and pelvis as well as views of the head and neck were obtained and were analyzed on a dedicated Sun Sparc2 station (Bartec, Farnborough, United Kingdom) by two independent readers not blinded for the clinical data and CT scan results. The readers had no information concerning the histological or the immunohistochemical data. In each patient, ^{67}Ga uptake index (GaUI) was evaluated in all tumoral lesions (T) by drawing a region of interest (ROI); only the highest value was maintained. The background (BGD) was evaluated in a control area, which was a healthy adjacent tissue of the corresponding tumoral region. The GaUI was determined in each patient by [(T − BGD)/BGD].

Statistical Analysis

The GaUI in a group of patients was expressed as mean ± 1 SD. The nonparametric statistical analysis of the relation between the GaUI and the different histological subtypes or immunohistochemical grading of TfR/CD71 expression was performed by analysis of variance (ANOVA), followed by the Kruskal-Wallis test (GraphPad Prism 2.0; Software, Inc. Al., San Diego, CA). Significant P values were less than 0.05.

RESULTS

Clinical data including sex, age, site of biopsy, histology, staging and GaUI and TfR/CD71 expression are given in Table 1.

Histological Distribution

Ten histological subtypes of B-cell lymphoma were identified according to the REAL classification (Table 1). The 47 patients included 2 cases of small lymphocytic lymphoma (SLL), 1 case (patient 1) of a component consisting of paraimmunoblast cells, 1 case of lymphoplasmocytic lymphoma (LPL) and 1 case of mantle cell lymphoma (MCL). Eight cases were classified as follicular center lymphomas (FCL): 3 cases had predominantly small cells (FCL I), 1 case had mixed small and large cells (FCL II) and 4 cases had predominantly large cells (FCL III). Three cases were classified as Richter's syndrome and exhibited large-cell lymphoma associated with residual low-grade lymphoma. Twenty-eight cases were classified as diffuse large B-cell lymphoma (DLCL), 2 cases were classified as Burkitt's lymphoma (BL) and 2 cases were classified as lymphoblastic lymphoma (LBL).

^{67}Ga Uptake by the Different Histological Subtypes

For the 47 patients with B-NHL, the GaUI ranged from 0–6.13. Values differed according to the histological subtype (Fig. 1). In this study, we did not distinguish between LPL and SLL. There are in fact only small morphologic and clinical differences between them. We also did not differentiate between FCL I and FCL II, because there is little clinical difference between them, and among pathologists, the reproducibility of the distinction between them is poor. The results of GaUI in different histological subtypes are summarized in Table 2. In the SLL/LPL subtype, the GaUI was not measurable in two out of three cases. For the only patient in this group who had a GaUI of 2.00 (patient 1), the biopsy results revealed a paraimmunoblast cell component corresponding to large lymphoid cells. Three histological subtypes of low-grade lymphoma (SLL, MCL and FCL I and II) were analyzed in this study. When the GaUI of 2.00 was set as threshold, five out of eight low-grade lymphomas (63%) were below this threshold, whereas only 3 out of 8 (37%) patients (patients 1, 6 and 7) were slightly above it. All the cases of the high-grade lymphoma displayed an increase of GaUI exceeding the before mentioned threshold. The statistical analysis comparing the GaUI values in the different histological subtypes demonstrated that GaUI values were significantly related to the histological subtypes ($P = 0.0007$) and increased from low- to high-grade lymphoma subtypes.

Comparison Between GaUI and TfR/CD71

Expression of TfR/CD71 was tested in 24 patients; 20 out of 24 were positive (83%), but different immunostaining patterns were observed (Fig. 2). The TfR/CD71 expression of each histological subtype was summarized in Table 3. All the patients with the SLL/LPL and MCL histological

TABLE 1
Results of ^{67}Ga Scintigraphy and of Histological and Immunohistochemical Studies in 47 Non-Hodgkin's Lymphoma Patients

Patient no.	Age (y)	Sex	Histology			^{67}Ga scintigraphy	GaUI	Immunohistochemistry
			Histological subtype	Stage	Site of biopsy			TfR/CD71
1	78	M	SLL	IV	Lymph node	IS	2.00	—
2	51	M	SLL	C	Lymph node	IS	NM	—
3	50	M	LPL	IV	Lymph node	IS	NM	—
4	45	M	MCL	IV	Lymph node	IS	1.20	—
5	72	F	FCL I	IV	Lymph node	IS	1.70	+
6	79	F	FCL I	IV	Lymph node	IS	2.35	+++
7	52	F	FCL I	IV	Soft palate	IS	2.40	ND
8	83	F	FCL II	IV	Lymph node	IS	1.70	++
9	49	M	FCL III	II	Lymph node	IS	2.50	++
10	37	M	FCL III	II	Lymph node	IS	2.80	+
11	48	F	FCL III	II	Lymph node	R	3.00	+++
12	52	F	FCL III	IV	Spleen	R	3.20	++
13	70	F	Richter's syndrome	IV	Lymph node	R	2.60	ND
14	60	M	Richter's syndrome	IV	Stomach	R	3.50	ND
15	75	F	Richter's syndrome	IV	Lymph node	R	3.50	++
16	41	F	DLCL	IV	Chest	R	2.20	+++
17	79	F	DLCL	IV	Lymph node	IS	2.80	ND
18	69	F	DLCL	I Ab	Lymph node	R	2.80	+++
19	76	F	DLCL	IV	Stomach	R	2.91	ND
20	33	M	DLCL	IV B	Lymph node	R	3.02	+++
21	16	M	DLCL	III b	Lymph node	IS	3.08	+++
22	40	F	DLCL	IV	Lymph node	IS	3.12	ND
23	29	F	DLCL	II	Chest	R	3.28	ND
24	83	F	DLCL	I	Tonsils	IS	3.33	ND
25	19	F	DLCL	I	Mediastinum	R	3.35	ND
26	71	M	DLCL	I	Pleura	IS	3.40	ND
27	38	M	DLCL	IV	Liver	IS	3.45	ND
28	36	F	DLCL	I	Bone	IS	3.50	ND
29	37	F	DLCL	I	Peritoneum	IS	3.60	ND
30	76	F	DLCL	IV	Lymph node	R	3.70	+++
31	33	M	DLCL	I	Lymph node	IS	4.00	+++
32	69	F	DLCL	I Ab	Lymph node	R	4.00	+++
33	61	F	DLCL	III	Spleen	IS	4.00	ND
34	35	F	DLCL	II	Lymph node	IS	4.15	+++
35	66	M	DLCL	I	Mediastinum	R	4.30	ND
36	60	M	DLCL	II A	Lymph node	IS	4.37	+++
37	72	F	DLCL	I	Soft tissue	R	4.43	ND
38	73	M	DLCL	IV	Testicles	IS	4.76	ND
39	39	F	DLCL	II B	Mediastinum	IS	4.92	+++
40	43	M	DLCL	IV	Lymph node	IS	5.00	ND
41	68	F	DLCL	IV b	Bone	R	5.00	ND
42	58	M	DLCL	I	Lymph node	IS	5.20	ND
43	19	F	DLCL	I	Mediastinum	IS	5.54	+++
44	46	M	BL	IV	Cutaneous	IS	3.91	ND
45	36	M	BL	IV	Lymph node	IS	4.07	+++
46	35	F	LBL	IV	Bone marrow	IS	3.56	ND
47	41	M	LBL	IV	Chest	IS	6.13	ND

GaUI = ^{67}Ga uptake index; TfR/CD71 = transferrin receptor CD71; SLL = small lymphocytic lymphoma; LPL = lymphoplasmocytic lymphoma; MCL = mantle cell lymphoma; FCL I = follicular center lymphoma, predominantly small cells; FCL II = follicular center lymphoma, mixed small and large cells; FCL III = follicular center lymphomas of predominantly large cells; DLCL = diffuse large B-cell lymphoma; BL = Burkitt's lymphoma; LBL = lymphoblastic lymphoma; IS = initial staging; R = relapse; NM = not measurable; ND = not determined.

subtypes were CD71 negative, whereas the high-grade lymphomas were strongly positive (graded 2+ or 3+). Although the TfR/CD71 expression was heterogeneous in the FCL group, it was strongly expressed in predominantly large cells FCL. In addition, only large cells expressed TfR/CD71 in the Richter's syndrome tested case (Fig. 2). The mean GaUI was 0.80 ± 0.97 in patients with TfR/CD71 negative, 2.25 ± 0.77 in the patients with low TfR/CD71

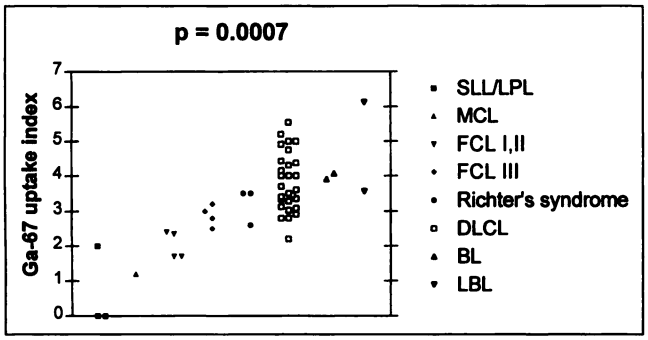

FIGURE 1. Comparison of GaUI and histological findings shows significant relationship between ^{67}Ga uptake and histological subtypes in non-Hodgkin's lymphoma ($P = 0.0007$). SLL = small lymphocytic lymphoma; MCL = mantle cell lymphoma; FCL I, II = follicular center lymphoma of predominantly small cells and mixed small and large cells; FCL III = follicular center lymphomas of predominantly large cells; DLCL = diffuse large B-cell lymphoma; BL = Burkitt's lymphoma; LBL = lymphoblastic lymphoma.

expression (1+), 2.72 ± 0.80 in the patients with intermediate TfR/CD71 expression (2+) and 3.70 ± 0.98 in the 13 patients with high TfR/CD71 expression (3+). Figure 3 shows the comparative results for the GaUI and semiquantitative evaluation of TfR/CD71 expression with an overlap between 2+ and 3+ patients. The statistical analysis showed that the GaUI rose significantly with the percentage of cells expressing TfR/CD71 ($P = 0.0059$).

DISCUSSION

The role of ^{67}Ga scintigraphy in the management of lymphoma compared to anatomical imaging is well established (*17–19*) and it has been useful in the detection of NHL, especially in intermediate- and high-grade lymphoma (*20*). Because NHL involves a heterogeneous group including different histological subtypes with different features, it is very important to determine the ^{67}Ga uptake values of each histological subtype. In our study, we documented this uptake in 47 patients with B-NHL, which included eight histological subtypes according to the new REAL classification, and we demonstrated that the GaUI is significantly related to these different histological subtypes. Ben-Haim et al. (*21*), using high-dose (296–370 MBq [8–10 mCi]) ^{67}Ga citrate and modern technology, improved the sensitivity of ^{67}Ga imaging in CFL (91%), but this sensitivity remains poor in patients with SLL and mucosa-associated lymphoid tissue lymphoma. In fact, the aim of our study was not to improve the sensitivity of ^{67}Ga scintigraphy in low-grade lymphoma but to report the intensity of ^{67}Ga uptake in different histological subtypes using our standard technology (111 MBq [3 mCi] ^{67}Ga citrate and single-head gamma camera) and to determine the factors explaining the heterogeneity of this uptake. Using our technique, all FCL patients were identified and a high rate of ^{67}Ga uptake (GaUI above our threshold) was found in six out of eight FCL histological subtypes (75%) and all high-grade NHL (Fig. 1), but no activity was measurable in two out of three SLL/PLL groups (75%). These findings confirm the reliability of our method. Moreover, in a recent study, Nakayama et al. (*22*) reported that the ^{67}Ga scans obtained in 46 NHL patients with only 74 MBq (2 mCi) ^{67}Ga citrate were similar to those reported by us using higher doses. In accordance with this study, we support that a dose of 111 MBq (3 mCi), routinely administered in our department, was sufficient for detecting high rate activity in NHL tumors.

TABLE 2
GaUI in Different Histological Subtypes

Histology	GaUI (mean ± SD)	GaUI <2	GaUI >2
SLL/LPL (n = 3)	0.66 ± 1.15	2 (66%)	1 (33%)
MCL (n = 1)	1.20	1 (100%)	0 (0%)
FCL I, II (n = 4)	1.56 ± 0.77	2 (50%)	2 (50%)
FCL III (n = 4)	2.87 ± 0.29	0 (0%)	4 (100%)
Richter's syndrome (n = 3)	3.20 ± 0.51	0 (0%)	3 (100%)
DLCL (n = 28)	3.96 ± 1.02	0 (0%)	28 (100%)
BL (n = 2)	3.99 ± 0.11	0 (0%)	2 (100%)
LBL (n = 2)	4.84 ± 1.82	0 (0%)	2 (100%)

GaUI = ^{67}Ga uptake index; SLL/LPL = small lymphocytic lymphoma and lymphoplasmocytic lymphoma; MCL = mantle cell lymphoma; FCL I, II = follicular center lymphoma of predominantly small cells and mixed small and large cells; FCL III = follicular center lymphomas of predominantly large cells; DLCL = diffuse large B-cell lymphoma; BL = Burkitt's lymphoma.

The mechanisms of ^{67}Ga uptake were shown to be mediated by TfR/CD71 in U-715 and U-937 human lymphoid cell lines (*14,15*), however, only a few studies reported the relationship between the results of ^{67}Ga scintigraphy and TfR/CD71 expression (*23–25*). In literature, the expression of TfR/CD71 in NHL was already known: it was strong in high-grade and was heterogeneous in low-grade lymphomas (*12,13*); our data confirmed this statement. Feremans et al. (*24*) were the first to report that there was a direct link between TfR/CD71 expression and ^{67}Ga uptake in 14 NHL with only 2 cases of low-grade lymphoma. In a recent study, Gallamini et al. (*25*) explored the relationship between relative ^{67}Ga avidity and the TfR/CD71 expression in patients with low-grade NHL and clearly demonstrated that the TfR/CD71 expression correlated with the ^{67}Ga uptake in this category of lymphoma. In accordance with Gallamini's study, our data confirmed in both high-grade and low-grade NHL patients the significant relationship between ^{67}Ga uptake and TfR/CD71 whatever the histological subtypes. Because the TfR/CD71 expression was especially high in large cells, the presence of this cellular component might therefore explain why GaUI was higher in some low-grade lymphomas than was expected. Therefore, the increase in TfR/CD71 expression, as in patient 6, and the presence of large lymphoid cells, as in patient 1, may explain

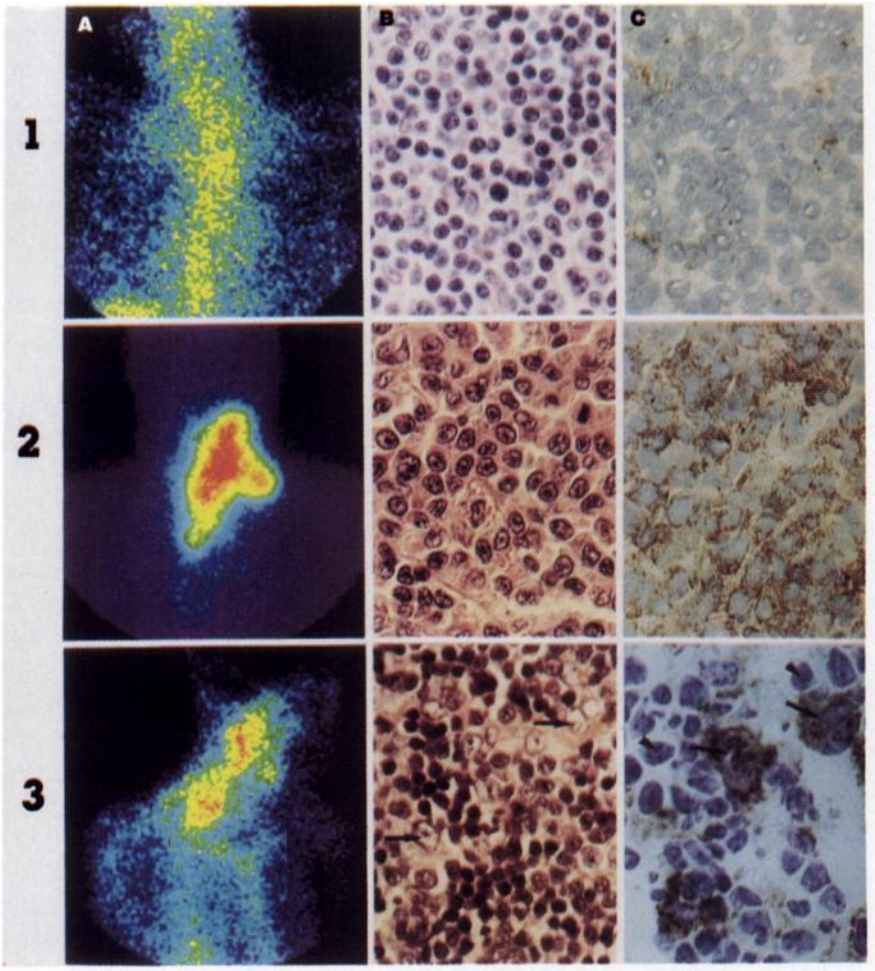

FIGURE 2. Three examples of comparison between ^{67}Ga uptake, histological findings and transferrin receptor CD71 (TfR/CD71) expression in B-NHL. (1A) Anterior thoracic view shows normal ^{67}Ga scintigraphy in 60-y-old man with proven low-grade lymphoma (patient 2). (1B) Histological analysis identified an SLL with lymphocytic infiltration in axillary lymph node. (1C). Immunohistochemistry analysis on frozen section shows negative expression of TfR/CD71. (2A) Abnormal ^{67}Ga scintigraphy in 60-y-old man (patient 35) with high-grade B-NHL. High GaUI (4.37) was evaluated in neck lesion. (2B) Biopsy identified DLCL. (2C) Immunohistochemistry on frozen section shows high expression of TfR/CD71 in all lymphomatous cells. (3A) Abnormal ^{67}Ga scintigraphy in 75-y-old woman (patient 15) with high GaUI (3.50) in neck lesion. (3B) Histological analysis identified Richter's syndrome with mixture of small lymphocytes and large cells (→) (3C) Immunohistochemical analysis on frozen section shows high expression of TfR/CD71 in large cells (→), whereas small cells (▶) were negative.

TABLE 3
Expression of TfR/CD71 and GaUI in B-Cell Non-Hodgkin's Lymphoma Patients

Histology	TfR/CD71 Expression			
	–	1+	2+	3+
SLL/LPL (n = 3)	3	0	0	0
MCL (n = 1)	1	0	0	0
FCL I, II (n = 3)	0	1	1	1
FCL III (n = 4)	0	1	2	1
Richter's syndrome (n = 1)	0	0	1	0
DLCL (n = 11)	0	0	0	11
BL (n = 1)	0	0	0	1
Total	4	2	4	14
GaUI (mean ± SD)	0.8 ± 0.97	2.25 ± 0.7	2.72 ± 0.8	3.65 ± 0.96

TfR/CD71 = transferrin receptor CD71; GaUI = ^{67}Ga uptake index; SLL/LPL = small lymphocytic lymphoma and lymphoplasmocytic lymphoma; MCL = mantle cell lymphoma; FCL I, II = follicular center lymphoma, predominantly small cells and mixed small and large cells; FCL III = follicular center lymphomas, predominantly large cells; DLCL = diffuse large B-cell lymphoma; BL = Burkitt's lymphoma.

the evidence of ^{67}Ga uptake in some low-grade lymphomas. This finding was clearly confirmed in the patients with Richter's syndrome, who exhibited some ^{67}Ga uptake in the region showing an infiltration of large cells (Fig. 2). Thus, this amount of large cells could be the explanation for the overlapping (Fig. 3) shown between 2+ and 3+ grading of TfR/CD71 expression.

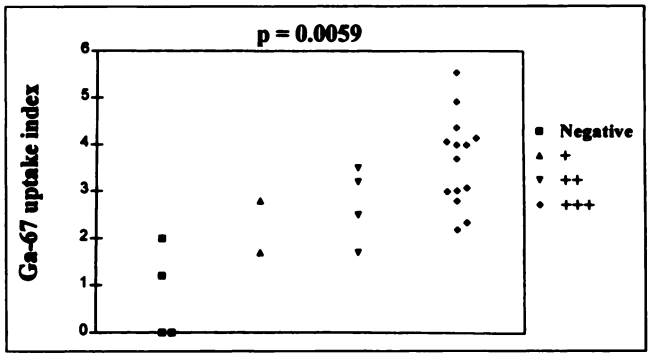

FIGURE 3. Comparison of GaUI and TfR/CD71 expression shows that ^{67}Ga uptake was related to expression of TfR/CD71 (P = 0.0059) in all histological subtypes.

CONCLUSION

Our study underlined three factors regulating ^{67}Ga uptake in NHL: histology, TfR/CD71 expression and presence of a large cells component. This finding confirmed the accuracy of ^{67}Ga scintigraphy in staging NHL patients, especially, the TfR/CD71-positive patients. This comparative study also emphasized the use of ^{67}Ga scintigraphy to detect a component of large cells in the evolution of low-grade lymphoma.

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