When Is Hilar Uptake of ^{67}Ga-Citrate Indicative of Residual Disease After CHOP Chemotherapy?

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The purpose of this study was to evaluate the prevalence and characterize the patterns of hilar uptake (HU) on ^{67}Ga-citrate imaging after cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy regimens for non-Hodgkin's lymphoma (NHL), to differentiate hilar lymphoma (HL) from HU of benign etiology. **Methods:** A total of 930 studies (698 planar, 232 thoracic SPECT) was reviewed retrospectively in 100 NHL patients (29 low-grade, 60 intermediate-grade, and 11 high-grade) treated with CHOP and followed up longitudinally with serial gallium studies (planar: median, 7; range, 3–16 studies in 100 patients; SPECT: median, 1; range, 0–11 studies in 72 patients) over a median duration of 36 mo (range, 6–112 mo) from diagnosis. Clinical outcome and size changes over time on correlative CT and/or radiographs were used to evaluate benign versus malignant changes within the hila. **Results:** HU after CHOP was present in 79% of patients (90% confidence interval [CI], 71%–85%), with 33% showing HU on SPECT alone. Once present, HU persisted for a median of 27 mo (range, 2–84 mo) from onset. The prevalence of HU and HL at various time points was as follows: baseline HU, 52% with HL 60%; mid-CHOP HU, 59% with HL 2%; post-CHOP HU, 52% with HL 6%; follow-up HU, 76% with HL 9%. HU of benign etiology was not significantly correlated with CHOP dosage. HU was symmetric in 90% of patients (90% CI, 82%–95%) and less intense than the original disease in 89% of patients (90% CI, 80%–95%), and these features were highly predictive of benign etiology (negative predictive value [NPV], 98.6% if symmetric; NPV, 96.5% if less than original disease; NPV, 100% if both present). Asymmetric HU equal in intensity to the original disease, however, was highly predictive of HL (positive predictive value [PPV], 87.5% if asymmetric; PPV, 85.7% if equal to original disease; PPV, 100% if both present). **Conclusion:** HU after CHOP is common (overall incidence, 79%), often seen only on SPECT, and most likely of benign etiology when symmetric and less intense than the original disease. Asymmetric HU that equals the intensity of the original disease, however, is a possible indicator for HL.

Key Words: hilar uptake; ^{67}Ga; non-Hodgkin's lymphoma; CHOP chemotherapy; radionuclide imaging

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In the evaluation of patients with Hodgkin's or non-Hodgkin's lymphoma (NHL), ^{67}Ga-citrate scintigraphy is of proven utility (*1–8*). It is important to obtain a baseline study before any therapy if this modality is to be used to evaluate therapeutic response or in the follow-up of these patients. The ability of ^{67}Ga-citrate scintigraphy to provide whole-body imaging as well as functional information regarding the tumor is complementary to the anatomic details provided by CT and MRI. Gallium is helpful in the differentiation of residual lymphoma from benign, post-therapeutic fibrosis when anatomical imaging modalities demonstrate a residual mass after treatment (*1–10*). Furthermore, gallium scintigraphy is also of value in predicting disease-free survival and overall survival when performed after therapy (*6,11–13*), as early as after 2–4 cycles of chemotherapy (*4,5*). The addition of SPECT examination to planar gallium imaging has further increased the sensitivity of this unique diagnostic tool (*3,10,14*).

Recent reports have raised the problem of false-positive gallium uptake in the pulmonary hila without corresponding clinical and/or CT/radiographic evidence of hilar lymphoma (HL) (*15–19*). This problem has become more apparent recently as the use of gallium thoracic SPECT examination has increased. In this study, we report the prevalence and patterns of hilar uptake (HU) on 930 gallium studies (698 planar, 232 thoracic SPECT) in 100 patients after cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy regimens for NHL. We also evaluate the relationship of HU to chemotherapy dose. Finally, we define in our study population those particular characteristics of HU on gallium scintigraphy that are highly predictive of HL lymphoma as opposed to benign etiology based on a median follow-up period of 36 mo (range, 6–112 mo) with serial clinical, CT/radiographic, and gallium examinations.

MATERIALS AND METHODS

One hundred patients with biopsy-proven NHL of any grade or stage, who had received a CHOP chemotherapy regimen as initial treatment and who had been followed up over time with a minimum of 3 serial gallium studies, were identified (Table 1). Of these 100 patients, 29 had low-grade, 60 had intermediate-grade, and 11 had high-grade NHL by the Working Formulation histologic classification. The sex distribution was 59 men with a median age at diagnosis of 43.5 y (range, 20–80 y) and 41 women with a median age at diagnosis of 45 y (range, 20–81 y; overall median age at diagnosis, 44 y). These 100 patients underwent a total of 930 gallium studies (698 planar, 232 thoracic SPECT), which were retrospectively reviewed. Medical records were also reviewed to

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TABLE 1
Patient Characteristics*
(n = 100)

Sex	59 M, 41 F
Age	44 y (20–81 y)
Grade	29 low, 60 intermediate, 11 high
Planar studies	7 (3–16) in 100 patients
SPECT studies	1 (0–11) in 72 patients
Follow-up from diagnosis	36 mo (6–112 mo)
Follow-up from first HU	27 mo (2–84 mo)
No. chemotherapy regimens	1 (1–6)
No. CHOP cycles	6 (1–13)
CHOP dosage	31 patients MEGACHOP†, 69 patients CHOP

*Data expressed as median values with range in parentheses.
†High-dose CHOP as outlined in text.

obtain information regarding clinical outcome and the presence of abnormalities in the hilar and/or mediastinal regions on anatomical imaging modalities for evidence of HL.

To investigate the effect of dose intensity of chemotherapy on prevalence of HU, planar gallium studies were reviewed in 2 groups of patients. The first group received treatment with a conventional dose CHOP chemotherapy regimen. Of these 69 patients, 46 received CHOP alone (cyclophosphamide, 750 mg/m^2 intravenously, day 1; doxorubicin, 50 mg/m^2 intravenously, day 1; vincristine, 1.4 mg/m^2 up to 2.0 mg maximum intravenously, day 1; and prednisone, 100 mg/m^2, orally, days 1–5, repeated every 21 d), 11 received CHOP with methotrexate (200 mg/m^2 intravenously, days 8 and 15 or 12 g intrathecally on day 15), and 12 received CHOP with etoposide (100–160 mg/m^2 intravenously, days 1–3). A second group of 31 patients participated in either a dose-escalation study of high-dose CHOP (MEGACHOP) in 1 of 4 dosage levels as follows or in the follow-up trials for intermediate low-grade patients. Of these, 2 patients received dose level 1, 6 patients received dose level 2, 22 patients received dose level 3, and 1 patient received dose level 4. MEGACHOP is cyclophosphamide, 3000 mg/m^2 intravenously, divided over 2 doses, days 1 and 2; doxorubicin, 50 mg/m^2 intravenously, continuous infusion over 48 h, days 1 and 2; vincristine, 1.4 mg/m^2 (maximum dose 2 mg) intravenously, day 1; prednisone, 100 mg orally each day, days 1–5; granulocyte colony-stimulating factor, 10 μg/kg/d subcutaneously each day, starting on day 4–18; and mesna, 400 mg/m^2 intravenously 30 min, 3, 6, and 9 h after cyclophosphamide on day 1 and 30 min before and 3, 9, 12, 15, 18, and 21 h after cyclophosphamide on day 2. Cyclophosphamide and doxorubicin dosages in dose levels 1–4, respectively, are as follows: 3 g/m^2 and 50 mg/m^2, 3 g/m^2 and 70 mg/m^2, 4 g/m^2 and 70 mg/m^2, and 4 g/m^2 and 90 mg/m^2 (*5*).

Patients were followed up longitudinally with serial gallium studies (planar: median, 7; range, 3–16 studies in 100/100 patients; SPECT: median, 1; range, 0–11 studies in 72/100 patients) over a median duration of 36 mo (range, 6–112 mo) from diagnosis. At our institution, the protocol for gallium scintigraphy is to image 72 h after intravenous injection of 370 MBq (10 mCi) ^{67}Ga-citrate at baseline (pretherapy), after 2–3 cycles of CHOP (midtherapy), and after 4–6 cycles of CHOP (post-therapy). When possible, a minimum 3-wk interval between the last cycle of treatment and ^{67}Ga scintigraphy was observed, as chemotherapy may prevent ^{67}Ga uptake in viable tumor if imaging is performed earlier (*20,21*). Once complete remission had been achieved, follow-up scans were obtained at 6 and 12 mo thereafter, then annually for detection of recurrent disease (or earlier at the clinician's discretion). Imaging was performed with a rotating γ camera equipped with a medium-energy parallel-hole collimator with the patient in the supine position, arms extended over the head. Energy photopeaks were set at 15%–20% windows centered at 93, 185, and 300 keV. Spot views were obtained to allow for optimal counting statistics as follows: anterior/posterior (ant/post) chest with arms above the head (2 million counts), ant/post abdomen (1.5 million counts), ant/post pelvis (1.5 million counts), ant/post femora (to time of the pelvis), and right and left lateral skulls (600,000 counts/time). SPECT imaging was acquired on a dual-head system (MultiSpect-2; Siemens, Hoffman Estates, IL), matrix size 64 × 64, with 64 images in 360° rotation at 50–70 s per stop. SPECT data were processed with Siemens software and reconstructed into coronal, sagittal, and transaxial planes. Earlier SPECT studies were obtained on a single-head system (Picker SX-300; Picker, Cleveland, OH) in a similar fashion.

The study used 2 reviewers who were unaware of clinical stage, grade, and point in therapy, with rare discrepancies resolved by consensus. HU was rated as to its presence or absence. If present, HU was qualitatively rated as to the intensity of uptake on planar and/or SPECT examination relative to the intensity of the original disease on the baseline scan, whether it was symmetrical or asymmetrical, and when it first appeared in relation to CHOP chemotherapy and the length of time that it persisted after CHOP chemotherapy.

To evaluate for residual or recurrent HL, all 100 patients were observed clinically, radiographically (CT and/or radiographs), and with serial gallium scans over a median follow-up period of 36 mo (range, 6–112 mo). Progressive hilar adenopathy with subsequent response to additional therapy or subsequent clinical deterioration was evidence for recurrent disease, whereas the absence of interval size change in the hila, absence of new or progressive adenopathy elsewhere, and favorable clinical outcome were evidence for disease-free status.

Comparisons of HU across CHOP dosage were assessed using the Fisher exact test (*22*). Ninety percent confidence intervals (CIs) were calculated by exact methods (*22*). Positive predictive values (PPVs) and negative predictive values (NPVs) for HL were calculated for various patterns of HU (*23*).

TABLE 2
Prevalence (%) of HU and HL During CHOP Chemotherapy

Stage	HU* (%)	HL† (%)
Baseline	47/90 (52)	28/47 (60)
Mid-CHOP	41/69 (59)	1/41 (2)
Post-CHOP	47/91 (52)	3/47 (6)
Follow-up	69/91 (76)	6/69 (9)

*As defined by its presence or absence.
†As defined by clinical outcome and/or size changes on correlative CT and/or radiographs.

TABLE 3
Predictive Value of HU Patterns

	Predictive value
Pattern for benign uptake	
Symmetric HU	NPV 98.6% (70/71)
Intensity less than original disease	NPV 96.5% (55/57)
Above features both present	NPV 100% (54/54)
Pattern for HL	
Asymmetric HU	PPV 87.5% (7/8)
Intensity equal to original disease	PPV 85.7% (6/7)
Above features both present	PPV 100% (5/5)

RESULTS

HU of ^{67}Ga-citrate after CHOP chemotherapy regimens was present in 79 of 100 patients (overall incidence, 79% [90% CI, 71%–85%]), with 26 of 79 (33%) present on SPECT alone. HU was seen as early as after the first cycle of CHOP and persisted a median of 27 mo (range, 2–84 mo) from onset. The prevalence of HU and HL, respectively (as defined by clinical outcome and size changes over time on correlative CT and/or radiographs), at various time points is outlined in Table 2. HU of benign etiology was not significantly correlated with CHOP dosage (37/69 CHOP versus 13/31 MEGACHOP, P = NS) on planar gallium scintigraphy. When present, HU after CHOP chemotherapy was symmetric in 71 of 79 (90%) and asymmetric in 8 of 79 (10%) patients. In 64 evaluable patients with baseline gallium scans, the intensity was less than the original disease in 57 of 64 (89%) or equally intense in 7 of 64 (11%).

Baseline CT and/or radiographs demonstrated abnormalities consistent with active mediastinal and/or HL in 28 of 100 patients (28%). Of these, abnormal HU on baseline gallium scintigraphy was present in 28 of 28 patients (100%), with 14 of 28 (50%) demonstrating mediastinal and bihilar uptake, 10 of 28 (36%) mediastinal and right HU, and 4 of 28 (14%) mediastinal and left HU. Specifically, in the mediastinal and bihilar uptake group, 14 of 14 had CT/radiographic evidence of large anterior mediastinal masses and/or bihilar lymphadenopathy. In the right HU group, 6 patients had mediastinal and right HL, 2 patients had mediastinal and right infrahilar masses, 1 patient had mediastinal and right paratracheal adenopathy, and 1 patient had right internal mammary adenopathy. In the left HU group, 3 patients had mediastinal and left HL and 1 patient had left superior mediastinal and left paratracheal lymphadenopathy.

Of the 79 patients with HU after CHOP chemotherapy, correlative CT and/or radiographs demonstrated abnormalities consistent with residual/recurrent mediastinal and/or HL in 8 patients (10%) for a total of 10 episodes of recurrent disease (1 patient's disease recurred 3 times within the mediastinum and left hilum). Of these, abnormal HU on gallium scintigraphy was present in all 8 patients, with 7 patients demonstrating asymmetric HU (5 right and 2 left HU) and 1 demonstrating symmetric bihilar uptake. CT/radiographic correlation in the right HU group revealed 3 patients with a right HL, 1 with a right paramediastinal mass, and 1 with right azygos region adenopathy. In the left HU group, 1 patient had increasing mediastinal soft-tissue opacity extending to the left and the other had left hilar adenopathy. The 1 patient with bihilar uptake demonstrated mild bilateral hilar enlargement. In 2 of 10 episodes of recurrent disease, gallium scintigraphy predicted recurrence 1 mo before abnormalities on CT/radiographs. In the remaining 8 of 10 episodes, gallium and CT/radiographs predicted recurrent disease simultaneously.

Symmetric HU less intense than the original disease was highly predictive of benign etiology, whereas asymmetric HU equal in intensity to the original disease was highly predictive of HL (Table 3). A typical case of symmetric benign HU is illustrated in Figures 1 and 2, and a case of asymmetric HU consistent with recurrent lymphoma is illustrated in Figures 3 and 4.

DISCUSSION

The problem of HU of gallium in treated lymphoma patients in the absence of clinical and/or CT/radiographic evidence of hilar disease has previously been reported by multiple investigators. In 1991, Kaplan et al. (*15*) reported bihilar ^{67}Ga uptake in 23 of 27 (85%) patients, of whom only 4 (17%) had proven tumor. In 1992, Champion et al. (*16*) reported abnormal HU of gallium in 37 of 39 (47%) patients with intermediate-grade NHL, of whom only 5 of 23 evaluable patients (22%) had HL. In 1995, Even-Sapir et al. (*18*) reported ^{67}Ga uptake in the hilar and/or mediastinal regions in 59 of 107 (55%) gallium SPECT studies, in which

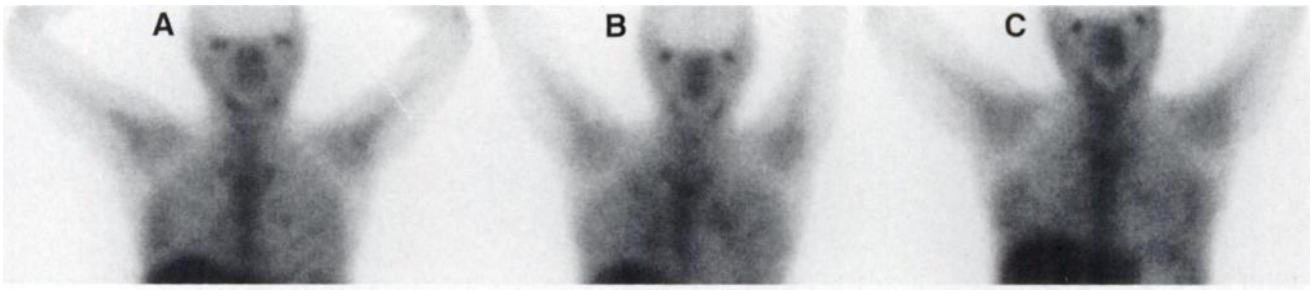

FIGURE 1. Anterior planar views of chest in patient with history of intermediate-grade lymphoma treated with MEGACHOP. Images were obtained at midtreatment (A), at the end of therapy (B), and 3 mo after end of therapy (C). Bilateral HU is seen in all 3 studies.

FIGURE 2. Axial SPECT studies in patient presented in Figure 1 obtained at same time points: midtreatment (A), end of therapy (B), and 3 mo after end of chemotherapy (C). Note symmetric HU in all 3 studies, most intense at end of therapy (B), but decreasing in intensity in symmetric fashion in follow-up study obtained 3 mo after end of therapy (C). Correlative chest radiographs obtained over that period of time showed no hilar abnormalities.

20 studies (34%) had corresponding CT/radiographic evidence of hilar and/or mediastinal lymphoma over more than 18 mo of follow-up. In addition, multiple reports have described benign mediastinal uptake of gallium (*24–26*). The etiology of such benign uptake, however, remains unknown.

The key issue in HU lies in the differentiation between HU that results from benign, post-therapeutic changes and that which results from residual or recurrent HL. In this regard, our review of 930 gallium examinations in 100 patients confirms the work of previous investigators that the vast majority of hilar uptake is benign. In this study, 90% (71/79 [90% CI, 82%–95%]) of instances of HU after CHOP chemotherapy were not associated with clinical and CT/radiographic evidence of residual or recurrent HL when observed longitudinally over a median follow-up period of 36 mo. Benign HU (Table 3) was almost always symmetric (NPV, 98.6%, 70/71) and less intense than the original disease (NPV, 96.5%, 55/57). When both of these features were present, HU was always benign in our series (NPV, 100%, 54/54).

In contrast, in the few cases in which HU was the result of HL after CHOP chemotherapy (8/79, 10%), the characteristics of HU resulting from HL were quite different. Specifically, HU resulting from HL (Table 3) was usually asymmetric (PPV, 87.5%, 7/8) and equal in intensity to the original disease (PPV, 85.7%, 6/7). When both of these features were present, HU was always the result of HL in our series (PPV, 100%, 5/5).

In this regard, our results correspond with the observations of Even-Sapir et al. (*18*), who reported that the concentration of gallium in lymphoma is significantly higher

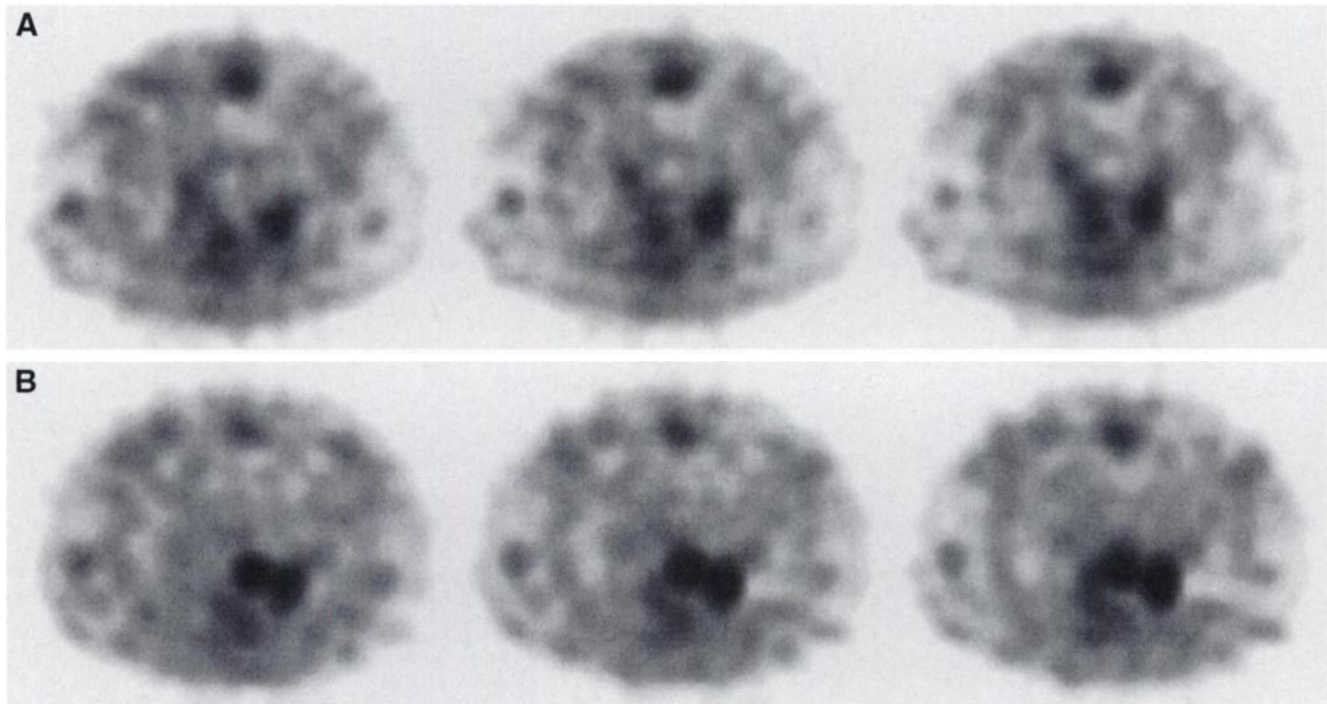

FIGURE 3. Three consecutive slices of axial SPECT studies in patient with transformed follicular lymphoma obtained at end of 6 cycles of CHOP (A) and 6 mo later (B). Note asymmetric HU with intense uptake in left hilum compared with right at end of chemotherapy (A). After 6 mo, focal uptake in left hilum has increased and new contiguous focus of abnormal uptake is seen (B).

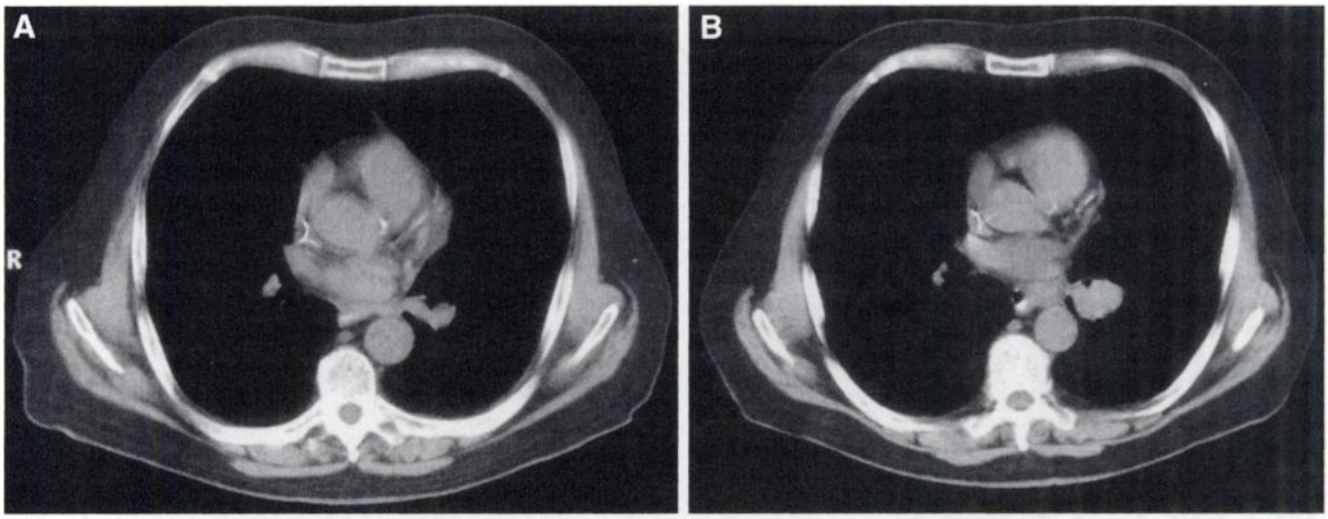

FIGURE 4. Axial CT images obtained in patient presented in Figure 3 at same time points. (A) At end of chemotherapy, no abnormality was seen in left hilum, which had remained anatomically stable compared with prior studies. (B) After 6 mo, definite mass is seen in left hilum and in parahilar region matching gallium findings. Gallium findings preceded anatomic changes in patient.

than in benign HU using quantitative SPECT analysis. Likewise, our findings indicate that the qualitative intensity of malignant HL is greater than that of benign HU and similar to the intensity of the original disease.

To our knowledge, the relationship between HU and chemotherapy dosage has not been evaluated. Our study compared the prevalence of HU on planar gallium scintigraphy in 69 patients treated with conventional-dose CHOP regimens and 31 patients treated with MEGACHOP. The data indicate that HU is independent of CHOP dosage, because the prevalence of HU in the CHOP and MEGA-CHOP groups was 54% and 42%, respectively (P = NS).

Although scintigraphy with ^{67}Ga-citrate remains the preferred imaging study for evaluation of lymphoma in many nuclear medicine departments, imaging with FDG will likely play an increasing role in light of the recent Health Care Financing Administration approval for this indication. Whereas FDG imaging has performed favorably compared with ^{67}Ga-citrate in early studies (*27–29*), FDG PET is technically more complex and more expensive than gallium scintigraphy, and the role of coincidence detection using γ cameras to image FDG remains to be fully evaluated. A well-controlled prospective study comparing ^{67}Ga-citrate scintigraphy and FDG PET in the same patient population would be helpful in this regard.

CONCLUSION

HU after CHOP chemotherapy is common (overall prevalence 79% [90% CI, 71%–85%]), often seen only on SPECT (33% [90% CI, 24%–43%]), and independent of CHOP dosage. When symmetric (90%) and less intense than the original disease (89%), it suggests a benign etiology (90% [90% CI, 82%–95%]) as shown in 100 patients followed longitudinally over a median 36-mo period of observation. Asymmetric HU equal in intensity to the original disease, however, is a possible indicator of HL.

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