Splenic Fluorodeoxyglucose Uptake Increased by Granulocyte Colony-Stimulating Factor Therapy: PET Imaging Results

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Using PET, we investigated the change in ^{18}F-fluorordeoxyglucose (FDG) uptake in the spleen after granulocyte colony-stimulating factor (G-CSF) treatment. **Methods:** Forty-two FDG PET scans in 12 patients with locally advanced breast cancer who received G-CSF treatment were studied (12 baseline, 10 during G-CSF, 20 after G-CSF treatment). The PET images obtained at 50–60 and 60–70 min after intravenous FDG (370 MBq) injection were assessed visually and were compared with those before G-CSF treatment. For a semiquantitative index of FDG uptake, we determined the standardized uptake value calculated on the basis of predicted lean body mass (SUL) on these images, and we calculated the SUL ratios normalized to their baseline SUL values. **Results:** During G-CSF treatment (n = 10), 9 scans (90%) showed increased splenic FDG uptake (3 slightly, 6 substantially). After G-CSF treatment (n = 20), 13 (65%) showed no change, 7 (35%) showed slightly increased uptake, but no case showed substantially increased FDG uptake in the spleen ($P = 0.0003$). Out of 30 PET scans obtained during and after G-CSF treatment, 16 (53%) showed increased FDG uptake in the spleen (10 slightly, 6 substantially), whereas 26 (87%) showed increased bone marrow FDG uptake (14 slightly, 12 substantially). The FDG uptake in other normal organs (liver, blood and lung) showed no change during or after G-CSF treatment. Similar to the change in the bone marrow, the SULs in the spleen significantly increased during G-CSF treatment (baseline, 1.50 ± 0.31, versus during G-CSF, 2.69 ± 0.84; $P = 0.0004$), then decreased after discontinuation of G-CSF (1.65 ± 0.23). There was a significant correlation between the SUL ratios in the spleen and those in the bone marrow ($r = 0.778$, $P < 0.0001$), whereas there were no correlations between those in other organs and those in the bone marrow. **Conclusion:** Substantially increased FDG uptake was observed in the spleen during and after G-CSF treatment, although this change was less frequent and not as marked as the change observed in the bone marrow. The recognition and understanding of this phenomenon will be increasingly important when interpreting FDG PET images in cancer patients to avoid confusing this normal phenomenon with pathological splenic (tumor) involvement.

Key Words: breast cancer; PET; fluorodeoxyglucose; spleen; granulocyte colony-stimulating factor

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Granulocyte colony-stimulating factor (G-CSF) is a glycoprotein hormone that primarily regulates proliferation and differentiation of granulocyte precursors (*1–3*). Human G-CSF, which is produced by recombinant deoxyribonucleic acid technology, has been used increasingly to improve chemotherapy-induced neutropenia in cancer patients and thus reduce days of hospitalization (*4*).

^{18}F-fluorodeoxyglucose (FDG) has been shown to accumulate in a diverse spectrum of malignant tumors because of their increased glucose metabolism (*5*). PET with FDG has been used extensively for differentiating malignant from benign tumors, for staging malignant tumors and for evaluating treatment efficacy in cancer patients (*6*).

With the increasing use of G-CSF as an adjunct to chemotherapy in cancer patients and of FDG PET studies in assessment of cancer patients, we have frequently observed increased FDG uptake in bone marrow. This phenomenon has been reported (*7–10*), and it is important that substantial increases in normal bone marrow FDG uptake should not be misinterpreted as bone or bone marrow metastases.

In some patients whose bone marrow FDG uptake increased after G-CSF treatment, we also observed diffusely increased FDG uptake in the spleen. Because diffuse metastasis to the spleen would be viewed as unlikely, we believed this phenomenon could be related to the G-CSF treatment. However, to the best of our knowledge, increased splenic FDG uptake has not been reported after G-CSF treatment. In this study, we retrospectively evaluated splenic FDG uptake before, during and after G-CSF treatment in patients with locally advanced breast cancer.

MATERIALS AND METHODS

Patients

Forty-two FDG PET scans in 12 women (age range 33–64 y, mean age 51 y) with primary breast cancers were studied. FDG PET imaging studies were performed as part of ongoing studies assessing the utility of PET in early monitoring or prediction of the efficacy of various chemotherapeutic treatments. FDG PET scans were obtained at baseline before treatment and at varying times after chemotherapy. To be eligible, patients had to have histologically proven primary breast cancers, no evidence of metastases, no

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other significant systemic diseases and no known glucose intolerance. PET scans that did not include the spleen in the field of view were not included in this study. Written informed consent was obtained from all patients for the study, which was performed with institutional review board approval. All patients received sequential doses of multiagent chemotherapy, including cyclophosphamide, doxorubicin and fluorouracil, as previously reported (*9*). The subcutaneous administration of G-CSF (300 or 480 μg/d) was performed, if necessary, between days 16 and 28 in each chemotherapy cycle, as determined by the patient's granulocyte counts and the treating physician's judgment. Absolute neutrophil count (ANC) was generally monitored once a week (normal range of ANC was 1.4–7.5 × 10^3/μL in our institute). The duration of G-CSF treatment before the follow-up PET study and the interval from end of G-CSF treatment to the PET study are shown in Table 1.

PET Scanning

FDG was produced by a standard nucleophilic fluorination method, as previously described (*11*). FDG PET scans were performed with either a model 931 ECAT (15 scanning planes, 10-cm longitudinal field of view) or a model 921 EXACT (47 scanning planes, 15-cm longitudinal field of view) scanner (Siemens Medical Systems, Iselin, NJ). The reconstructed x-y resolution with a Hanning filter cutoff value of 0.3 was approximately 12 mm for both scanners. The average scanner efficiency rate was 179 (cts/pixel)/(KBq/mL) for the ECAT 931 scanner and 153 (cts/pixel)/(KBq/mL) for the EXACT 921 scanner. All patients fasted for at least 4 h before the FDG injection. Before tracer injection, at least one 10-min transmission scan was obtained using a ^{68}Ge ring or rod source for the purpose of attenuation correction of the emission images. Sequential dynamic scans over the middle thorax, lower thorax or both, including the primary breast cancer, were obtained immediately after tracer (370 MBq FDG) injection through to 60 min postinjection. Then, static scans were obtained at 60–70 min after injection at the upper level of the thorax to evaluate for lymph node involvement.

Image Analysis

The FDG PET images obtained at 50–60 and 60–70 min postinjection were visually assessed and were compared with those before G-CSF treatment. The changes of FDG uptake compared with the baseline images in bone marrow and those in spleen were visually classified into three scores (0 = no change, +1 = slightly increased, +2 = substantially increased) by one observer.

For a semiquantitative index of FDG uptake, regions of interest (ROIs) were placed on various organs on these images. Irregular ROIs were positioned over right upper lung, liver and spleen while avoiding the large vessels. The average sizes of ROIs for lung, liver and spleen were approximately 80, 300 and 100 pixels (14, 53 and 18 cm^2), respectively. The mean number of counts in each of these ROIs for lung, liver and spleen were approximately 350, 2050 and 1440 cts/pixel, respectively. A small square ROI (16 or 20 pixels) was positioned over the left atrium or ascending aorta to determine blood activity. Bone marrow uptake was measured by defining a circular ROI encompassing the marrow cavity of a lower thoracic vertebral body with the aid of the transmission image. To minimize the influence of the vertical axis position effects of marrow distribution, a small square ROI (16 or 20 pixels) with maximal FDG uptake was automatically positioned within the former larger ROI on one or two levels of lower thoracic vertebral body, as previously described (*9*). The mean number of counts in these small square ROIs for blood and bone marrow were approximately 1770 and 1490 cts/pixel, respectively. The standardized uptake value calculated on the basis of predicted lean body mass (SUL) was determined in these ROIs as follows: SUL = decay-corrected tissue concentration (Bq/mL) / injected dose per patient lean body mass (Bq/g) (*12*).

Statistical Analysis

The SULs of various organs before, during (on) and after (off) G-CSF treatment were compared by analysis of variance before the Mann-Whitney test. The relationships between the SUL ratios normalized to the baseline (pretreatment) values in bone marrow and those in other organs were assessed with the Pearson coefficient (r) and were plotted with a linear regression equation. Differentiation of visual changes in the bone marrow and changes in the spleen during and after G-CSF treatment were evaluated by a chi-square test.

RESULTS

The baseline characteristics, the SUL changes, the scores of visual interpretation and the changes of ANC are shown in Table 1. Out of 30 FDG PET scans after chemotherapy, 10 were obtained during G-CSF treatment (on) and 20 were obtained after the discontinuation of G-CSF treatment (off). A substantial increase in ANC was observed during G-CSF treatment, and the ANC normalized promptly after the cessation of G-CSF treatment. The increased FDG uptake in bone marrow and spleen was generally observed in correlation with the increase of ANC, but in some cases there was a dissociation between the degree of changes in FDG uptake and that in ANC, presumably at least in part due to the difference between the PET scan date and the blood sampling date. As shown in Table 2, all 10 PET scans during G-CSF treatment (on) showed substantially increased bone marrow FDG uptake (+2); whereas after the discontinuation of G-CSF treatment (off, n = 20), 4 PET scans (20%) showed no change, 14 (70%) showed slightly increased (+1) and only 2 (10%) showed substantially increased (+2) FDG uptake in the bone marrow ($P < 0.0001$). Similarly, out of 10 PET scans obtained with the patients on G-CSF, 9 (90%) showed increased splenic FDG uptake (3 slightly, 6 substantially), whereas once off G-CSF, 13 (65%) showed no change, 7 (35%) showed slightly increased uptake and none showed substantially increased FDG uptake in the spleen ($P = 0.0003$). Out of 30 PET scans during and after G-CSF treatment, 26 (87%) showed increased bone marrow FDG uptake and 16 (53%) showed increased FDG uptake in the spleen relative to baseline.

When we compared the changes of FDG uptake in bone marrow to those in spleen (Table 3), we found that out of 14 scans in which bone marrow showed slightly increased FDG uptake, 9 (64%) showed no change and 5 (36%) showed slightly increased uptake in the spleen; whereas out of 12 scans in which bone marrow showed substantially increased FDG uptake, 1 (8%) showed no change, 5 (42%) showed slightly increased uptake and 6 (50%) showed substantially increased uptake in spleen ($P = 0.0014$). In all 4 cases in

TABLE 1
Patient Data

Patient no.	Age (y)	G-CSF* (d)	FDG PET Scan date†	SUL Lung	SUL Blood	SUL Liver	SUL BM	SUL Spleen	Visual change BM	Visual change Spleen	ANC Sampling date‡	ANC Count ($\times 10^3/\mu L$)
1	57	0	Baseline	0.24	1.66	1.77	1.15	0.90			Baseline	2.5
		10	On d9	0.26	1.82	2.03	6.50	2.20	+2	+2	On d7	20.3
		10	Off d9	0.36	2.21	2.51	1.90	1.67	+1	+1	Off d8	1.6
		10	Off d14	0.26	1.58	1.79	1.44	1.20	+1	0	Off d15	1.7
2	59	0	Baseline	0.35	1.41	2.05	1.26	1.60			Baseline	4.6
		10	On d9	0.34	1.53	2.02	3.63	2.22	+2	+1	On d7	15.3
		10	On d6	0.34	1.58	1.78	2.96	1.64	+2	0	On d7	12.4
		10	Off d14	0.46	1.81	2.16	1.83	1.64	+1	0	Off d8	3.7
3	64	0	Baseline	0.33	1.99	2.19	1.35	1.25			Baseline	3.4
		10	Off d15	0.36	1.88	2.21	1.86	1.44	0	0	Off d15	1.1
		5	Off d15	0.36	2.19	2.39	2.27	1.54	+1	0	Off d15	2.0
4	51	0	Baseline	0.53	2.08	2.35	1.59	1.75			Baseline	3.0
		7	Off d8	0.36	1.73	2.09	1.95	1.67	+1	0	Off d9	1.6
		10	Off d15	0.43	1.86	2.12	1.61	1.74	0	0	Off d15	1.5
		4	Off d23	0.32	1.79	2.37	1.94	1.69	0	0	Off d23	1.2
5	54	0	Baseline	0.33	2.44	2.71	1.88	1.96			Baseline	4.6
		10	Off d3	0.35	2.67	2.77	2.91	2.24	+1	+1	Off d7	3.6
		10	On d10	0.32	1.96	2.52	4.12	3.16	+2	+2	On d7	8.5
		10	On d10	0.35	2.19	2.46	4.32	2.67	+2	+2	On d10	13.0
6	58	0	Baseline	0.35	1.86	1.89	1.71	1.30			Baseline	6.2
		10	Off d1	0.40	1.67	1.77	2.41	1.56	+2	+1	Off d4	6.0
		7	Off d4	0.38	1.70	1.53	1.30	1.17	0	0	Off d7	2.6
7	52	0	Baseline	0.35	1.64	1.99	1.55	1.38			Baseline	3.5
		9	Off d2	0.29	1.69	1.97	2.49	1.99	+2	+1	On d9	51.6
		9	Off d3	0.34	1.91	2.27	1.89	1.70	+1	0	Off d7	3.1
8	44	0	Baseline	0.34	1.53	1.70	1.55	1.39			Baseline	3.8
		10	Off d7	0.35	1.89	2.17	1.85	1.71	+1	0	Off d8	2
		11	Off d5	0.33	2.03	2.16	2.18	1.65	+1	0	Off d7	2.2
		11	Off d4	0.31	1.55	1.88	1.93	1.55	+1	0	Off d7	1.6
9	60	0	Baseline	0.42	2.05	2.18	1.69	1.33			Baseline	5.3
		10	On d5	0.38	1.31	1.34	3.50	1.82	+2	+2	NA	NA
		10	Off d4	0.44	2.16	2.37	2.20	1.68	+1	0	Off d4	7.2
		14	On d7	0.30	1.84	2.31	3.77	2.17	+2	+1	NA	NA
10	41	0	Baseline	0.48	1.83	2.01	1.82	1.52			Baseline	5.9
		10	Off d4	0.40	1.66	2.11	2.29	1.67	+1	+1	Off d4	4.6
		10	Off d4	0.41	1.74	2.22	2.16	1.70	+1	+1	Off d4	4.6
		10	Off d3	0.46	1.96	2.38	2.53	1.82	+1	+1	Off d4	4.6
11	41	0	Baseline	0.35	2.07	2.87	1.90	1.66			Baseline	4.2
		7	On d7	0.33	1.79	2.29	5.34	3.90	+2	+2	Off d1	45.3
		9	On d6	0.32	1.78	2.26	7.02	4.08	+2	+2	NA	NA
12	45	0	Baseline	0.30	1.91	2.37	1.24	1.98			Baseline	3.4
		7	On d7	0.27	1.59	2.04	5.03	3.00	+2	+2	Off d1	14.1

*Duration of G-CSF administration.
†Date of PET scan (interval from the G-CSF treatment); "on" means during G-CSF, "off" means after G-CSF treatment.
‡Sampling date closest to PET scan date.
FDG = fluorodeoxyglucose; G-CSF = granulocyte colony-stimulating factor; SUL = standardized uptake value calculated on the basis of predicted lean body mass; ANC = absolute neutrophil count; BM = bone marrow; d = day; NA = not available.

which bone marrow showed no change, there was also no change of FDG uptake in spleen.

The SUL changes at baseline, during (on) and after (off) G-CSF treatment are shown in Figure 1. The SULs in spleen significantly increased during G-CSF treatment (baseline, 1.50 ± 0.31, versus on G-CSF, 2.69 ± 0.84, $P = 0.0004$), then decreased after discontinuation of G-CSF (off G-CSF, 1.65 ± 0.23). As we reported previously (*9*), the SULs in bone marrow significantly increased during G-CSF treatment, then decreased after discontinuation of G-CSF, but they were still higher than their baseline values (baseline 1.56 ± 0.26; on G-CSF 4.62 ± 1.34, $P < 0.0001$; off G-CSF 2.05 ± 0.38, $P = 0.0004$). The SULs in other normal organs (liver, blood and lung) showed no change during or after

TABLE 2
Results of Visual Change in FDG Uptake

G-CSF	Bone marrow			Spleen		
	0	+1	+2	0	+1	+2
On (n = 10)	0 (0%)	0 (0%)	10 (100%)	1 (10%)	3 (30%)	6 (60%)
Off (n = 20)	4 (20%)	14 (70%)	2 (10%)	13 (65%)	7 (35%)	0 (0%)
Total (n = 30)	4 (13%)	14 (47%)	12 (40%)	14 (47%)	10 (33%)	6 (20%)
			$P < 0.0001$			$P = 0.0003$

FDG = fluorodeoxyglucose; G-CSF = granulocyte colony-stimulating factor.
Observed numbers for each group are presented. *P* values (differences between on G-CSF and off G-CSF) were obtained by chi-square test.

G-CSF treatment. There was a significant correlation ($r = 0.778$, $P < 0.001$) between the SUL ratios in spleen and those in bone marrow, whereas there were no correlations between those in other organs and those in bone marrow (Fig. 2).

Images from the patient who had the greatest G-CSF-induced changes in FDG uptake in bone marrow and spleen (patient 11) are shown in Figure 3. Substantially increased FDG uptake in the bone marrow and in the spleen were observed during G-CSF treatment compared with the baseline image, which showed very little if any normal FDG uptake in these tissues.

DISCUSSION

In this study, we observed increased splenic FDG uptake in many patients who received G-CSF treatment. We believe this phenomenon seen in spleen was caused by G-CSF treatment, akin to that seen in bone marrow, since no obvious change in FDG uptake had been observed in patients with chemotherapy alone, as previously reported (*13*). Although the increase in FDG uptake in the spleen was less frequent and not as great as the changes observed in bone marrow, this phenomenon should be considered when FDG PET images of cancer patients are evaluated, especially if only scans on G-CSF treatment are obtained.

As previously reported, hematopoietic cytokines substantially alter the glucose metabolism in normal bone marrow as shown by FDG PET (*7–10*). This increased glucose metabolism in bone marrow occurs promptly during G-CSF treatment, and it decreases after the cessation of G-CSF treatment. In this study, increased splenic FDG uptake was observed frequently during G-CSF treatment. Moreover, the splenic FDG uptake ratios normalized to their baseline values showed a strong relationship ($r = 0.778$) to those in bone marrow (Fig. 2). This suggests that the rapid "on" and relatively rapid "off" FDG uptake change due to G-CSF treatment appears to occur in the spleen, although it may not be as marked as in the bone marrow. Indeed, patients who receive G-CSF sometimes complain of bone and flank pain (left flank pain is rare, but bone pain is relatively common), which is usually relieved after the cessation of G-CSF treatment. These complaints are likely due to the metabolic or morphological changes that occur in the bone marrow and spleen during G-CSF treatment. FDG PET shows the metabolic changes that are rapidly induced after G-CSF administration.

TABLE 3
Comparison of Visual Change in FDG Uptake Between Bone Marrow and Spleen

Bone marrow	Spleen			Total
	0	+1	+2	
0	4 (100%)	0 (0%)	0 (0%)	4
+1	9 (64%)	5 (36%)	0 (0%)	14
+2	1 (8%)	5 (42%)	6 (50%)	12
Total	14	10	6	30
				$P = 0.0014$

FDG = fluorodeoxyglucose.
Observed numbers for each group are presented. *P* value was obtained by chi-square test.

Imaging changes induced in the bone marrow by G-CSF treatment have been reported with various imaging modalities, including MRI (*14*) and radionuclide imaging such as ^{201}Tl-chloride (*15*), ^{99m}Tc-sulfur colloid (*16*) and ^{99m}Tc-methylene diphosphonate (*17*). This phenomenon has also been reported with FDG PET (*7–10*), and FDG PET appears to be sensitive to this phenomenon. Although changes in FDG uptake in other normal organs by G-CSF treatment were not appreciated initially, we recently observed increased splenic FDG uptake concurrently in patients whose bone marrow FDG uptake was increased by G-CSF treatment. Indeed, even though increased splenic FDG uptake concurrent with bone marrow-increased FDG uptake seems present in the figures of Hollinger et al. (*10*) on bone marrow tracer uptake, this splenic phenomenon has not been reported.

It has been reported that extramedullary hematopoiesis occurs in the spleen after high-dose G-CSF treatment (*18,19*), but Tsoi et al. (*20*) reported splenic hematopoiesis after only nine intermittent doses of G-CSF. Microscopically, the spleen showed an intact architecture with expanded red pulp, in which immature and mature granulo-

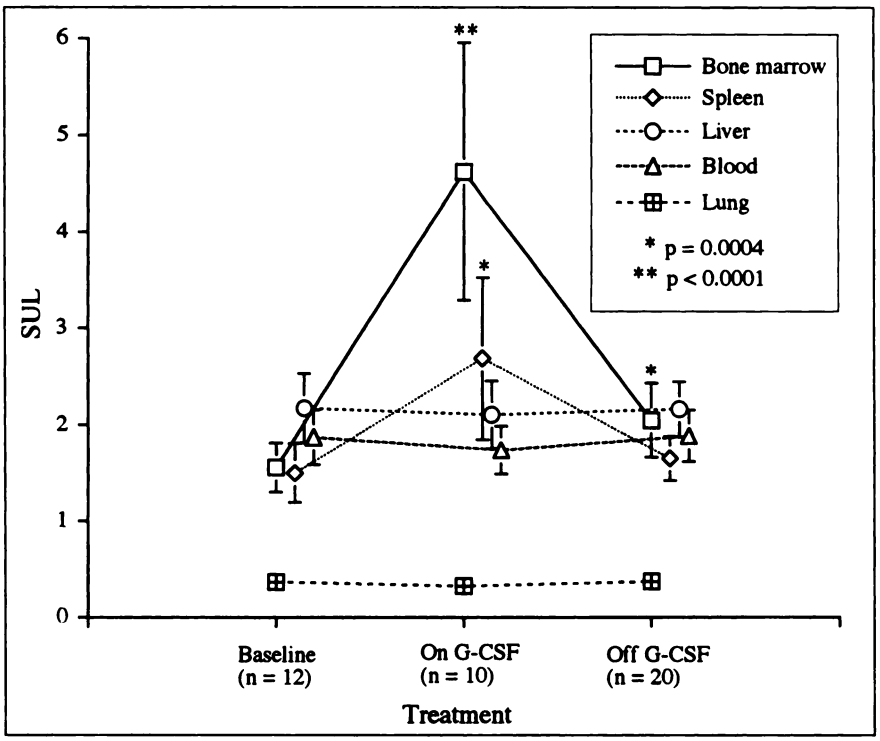

FIGURE 1. Comparisons of changes in standardized uptake values calculated on basis of predicted lean body mass (SULs) before (baseline), during (on) and after (off) granulocyte colony-stimulating factor (G-CSF) treatment in bone marrow, spleen, liver, blood and lung. Values are mean ± SD.

cytes were frequently observed. In this study, increased FDG uptake in the spleen was observed in patients who received relatively few doses of G-CSF. These observations suggest that extramedullary hematopoiesis (or at least the metabolic changes leading to it) may occur after just a few doses of G-CSF treatment, and increased FDG uptake may reflect an early glucose metabolism change and extramedullary hematopoiesis induced by G-CSF treatment. It is difficult to prove the cause, however, because histological confirmation was not obtained in this study.

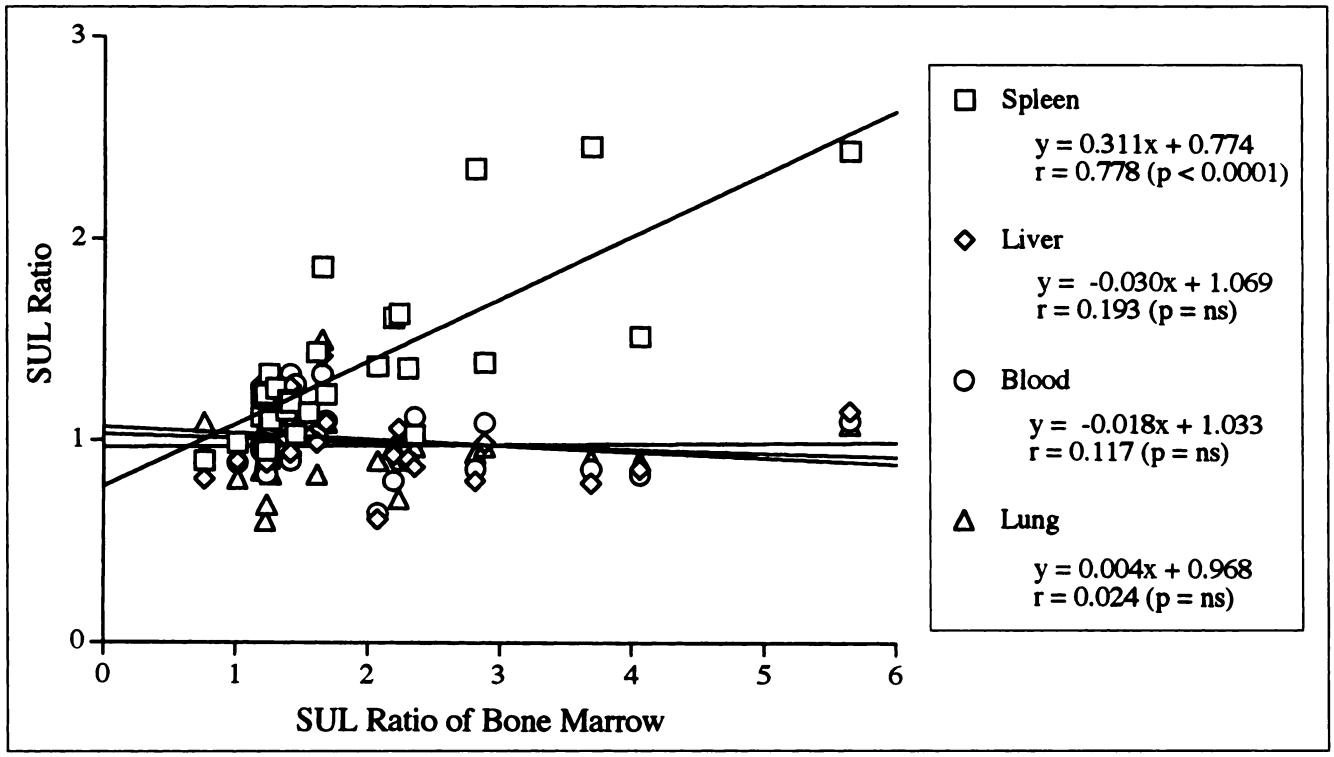

FIGURE 2. Relationships between ratios of standardized uptake value calculated on basis of predicted lean body mass (SUL) in normal organs (spleen, liver, blood and lung) and those in bone marrow.

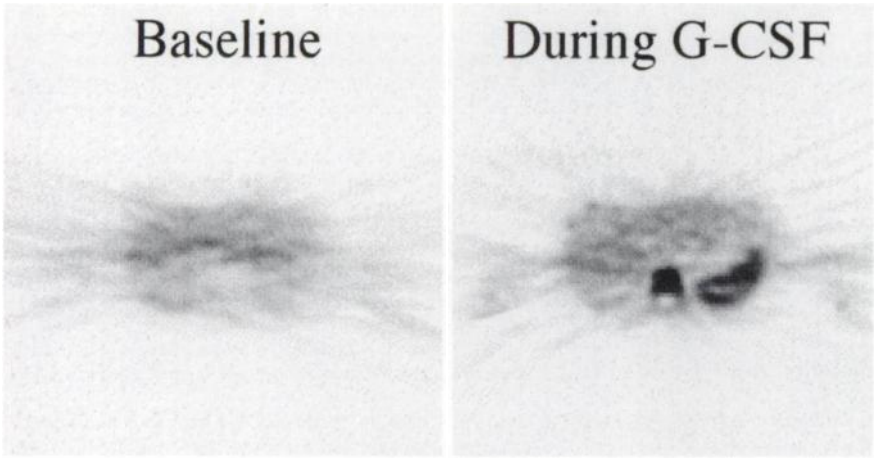

FIGURE 3. Transverse FDG PET images in patient 11. During granulocyte colony-stimulating factor (G-CSF) treatment, substantially increased FDG uptake is observed in bone marrow and in spleen.

Similar to the change in ANC, the change in FDG uptake in the bone marrow and spleen occurred promptly after G-CSF treatment. It has been reported that FDG PET is useful in monitoring treatment response to anticancer drugs and that FDG PET can predict treatment efficacy earlier than morphological changes that are imaged by other modalities (*13*). In a preclinical study, Wahl et al. (*21*) reported that uterine FDG uptake increased in response to estrogen stimulation. Thus, we suggest that FDG PET has the potential to monitor noninvasively the pharmacodynamics of many drugs, including anticancer agents and biotechnology agents, if the effects of the drug result in changes in glucose metabolism.

In this study, we evaluated FDG uptake in other organs (lung, blood and liver) in addition to bone marrow and spleen, and there were no significant changes in FDG uptake in these normal organs during or after G-CSF treatment. G-CSF usually stimulates granulocyte colonies selectively, but at high doses, it can stimulate monocyte-macrophage cell lines as well, similar to other cytokines such as granulocyte-macrophage colony-stimulating factor or macrophage colony-stimulating factor (*1*). Kondoh et al. (*22*) reported that enhanced ^{67}Ga-citrate uptake was observed in the bone marrow, liver and spleen during G-CSF treatment. Berlangieri et al. (*16*) reported that ^{99m}Tc-sulfur colloid activity increased significantly not only in bone marrow but also in lung during high-dose G-CSF treatment. In this study, however, no increased FDG uptake was seen in the liver or lung after G-CSF treatment. Several mechanisms may contribute to our findings and further studies will be needed to ascertain the cause. However, it is clear from this study that increased splenic FDG uptake commonly occurs after G-CSF therapy and that this normal uptake should not be confused with pathological uptake.

CONCLUSION

We observed increased FDG uptake in the spleen concurrently with increased bone marrow FDG uptake during G-CSF treatment in breast cancer patients. With the increasing use of G-CSF treatment and FDG PET in cancer patients, we expect to observe this phenomenon more frequently. We suggest that this increased FDG uptake in the spleen may reflect early changes of extramedullary hematopoiesis and that it should not be mistaken for splenic tumor involvement. The spleen is not a common site of metastases in breast cancer, but for tumors like lymphoma, which occur in the spleen, the G-CSF-induced changes may be of considerable diagnostic importance. The recognition and understanding of this phenomenon will be increasingly important and helpful in appropriately interpreting FDG PET images in cancer patients.

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