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ORIGINAL ARTICLE

Diffusely Increased Splenic Fluorodeoxyglucose Uptake in Lung Cancer Patients

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Abstract

OBJECTIVES: This study aimed to investigate the association of diffuse splenic F-18 fluorodeoxyglucose (FDG) uptake on positron emission tomography/computed tomography (PET/CT) with tumor maximum standardized uptake value (SUVmax), presence of distant metastases, and hematological and inflammatory parameters.

MATERIAL AND METHODS: Initial FDG PET/CT of 15 lung cancer patients with diffuse splenic FDG uptake were retrospectively analyzed (Group 1). Twelve patients who recently underwent FDG PET/CT for histopathologically proven lung cancer were enrolled as the control group (Group 2). All 27 patients had hematological data, including C-reactive protein (CRP) level, within 5 days before or after PET/CT. To determine SUVmax, the region of interests included the tumor, liver, spleen, and iliac crest. The possible associations between the spleen/liver (S/L) and bone marrow/liver (BM/L) ratios and tumor SUVmax, presence of metastasis, and hematological parameters were evaluated.

RESULTS: The S/L ratio and hemoglobin (Hb) levels were different between the two groups (p=0.000 and 0.05, respectively). The number of patients with anemia were significantly higher in Group 1 than in Group 2 (p=0.02). Although mean Hb levels were different between the two groups, there was no correlation between Hb levels and S/L ratios. There was no significant difference between the two groups with respect to the numbers of patients who had an accompanying infection site. Only CRP levels were correlated with S/L ratios in Group 1 among various other parameters (r=0.559, p=0.05).

CONCLUSION: Our results suggested that inflammation degree correlated with increased splenic FDG uptake in lung cancer patients and was enhanced by anemia. Systemic inflammation and anemia could be important causes of diffusely increased splenic FDG accumulation on PET/CT examinations of lung cancer patients.

KEYWORDS: Spleen, anemia, inflammation, lung cancer, fluorodeoxyglucose, positron emission tomography

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INTRODUCTION

In normal individuals, splenic F-18 fluorodeoxyglucose (FDG) uptakes are generally diffuse and less compared with hepatic FDG uptakes on positron emission tomography/computed tomography (PET/CT) and does not change with age or differ with sex [1]. Splenic uptake is always evaluated as a pathological finding, mainly representing a spleen neoplasm, splenic metastasis of other primary tumors, or an infection. Diffusely increased splenic FDG uptake on PET/CT is an incidental and rare finding, and its clinical implication remains unclear.

The spleen is the largest secondary lymphoid organ in our body and is responsible for initiating immune responses to antigens via deposited lymphocytes. Erythrocytes, granulocytes, and circulating mononuclear cells are also associated with the splenic cords. Extramedullary hematopoiesis is active in the red pulp during fetal life but can also be activated during chronic anemia [2]. The tumor weight stress was also suggested to be a cause of secondary (splenic) erythropoiesis, and we assumed cancer anemia to be a cause of increased splenic uptake. A few studies recently suggested that anemia, inflammations, and infections were associated with splenic FDG uptake in cancer patients on PET/CT [3-6]. Although anemia and infection are frequently observed in cancer patients, most patients do not show increased splenic FDG accumulation on PET/CT. This study aimed to investigate the association of diffuse splenic FDG uptake on PET/CT with tumor maximum standardized uptake value (SUVmax), presence of distant metastases, and hematological and inflammatory parameters to clarify the clinical significance of diffuse splenic uptake in lung cancer patients.

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MATERIAL AND METHODS

We retrospectively reviewed the FDG PET/CT examinations reported in our department between 2010 and 2015 and collected 145 reports that defined visually increased splenic uptake. After excluding most lymphoma patients and 11 patients with tumors other than lung cancer, 15 lung cancer patients (nine females and six males) with diffuse splenic FDG uptake on their initial scan, which also hematological data such as C-reactive protein (CRP) level in 5 days before or after PET/CT, were included as the patient group (Group 1; Figure 1). As the control group (Group 2), 12 randomly selected, histopathologically proven lung cancer patients (two females and 10 males), which also had hematological data such as CRP level in 5 days before or after PET/CT, were enrolled (Figure 2).

The laboratory data used for the evaluations included CRP level (mg/dL; normal range, 0-0.5 mg/dL) as the marker of active inflammation, white blood cell (WBC) ($x10^3$/uL; normal range, 4.0-11.0$x10^3$/uL), monocyte number (Mon) ($x10^3$/uL; normal range, 0.24-0.36$x10^3$/uL), neutrophil number (Neu) ($x10^3$/uL; normal range, 1.56-6.13$x10^3$/uL), lymphocyte number (Lym) ($x10^3$/uL; normal range, 1.18-3.74$x10^3$/uL), erythrocyte number (Erit) ($x10^6$/uL; normal range, 3.7-5.2$x10^6$/uL), hemoglobin (Hb) concentration (g/dL; normal range, 12.5-15.0 g/dL), and hematocrit (Htc) (%; normal range, 36.0%-46.0%).

FDG PET/CT Imaging Procedure

Positron emission tomography/computed tomography imaging was performed using a PET/CT equipment (G.E. Discovery STE) in our department. The patients were fasted for 4 h before PET/CT. Blood glucose levels of all patients were measured before the procedure using a glucometer (One Touch Select. China). Then, 296-555 MBq (8-15 mCi) FDG was injected via the antecubital vein of the patients when glucose levels were <180 mg/mL. Each patient was advised to remain idle for 60 min for accurate monitoring of the FDG bio-dispersion in the body. Following bladder drainage, the patients were supinely positioned on the PET/CT monitoring bed. Three-dimensional (3D) emission and transmission scanning with an average of 7-8 bed positions from the vertex to the thigh were completed in 30 min. Sequential cross-sections of 0.6-cm thickness were prepared, comprising the covered regions in axial, coronal, and sagittal planes.

SUV Measurement

For semi-quantitative evaluation, SUVmax normalized for body weight was calculated as follows: radioactivity in the region of interest (ROI; per ml)xlean body mass (kg)/injected radioactivity. ROIs were drawn including the majority of the organ of interest but within the borders (using the CT counterpart) at the same time. A spherical ROI: volume of interest (VOI) for 3D measurement was used for the liver, spleen, and bone marrow (BM). VOIs were manually placed on the tumor, liver, spleen, and iliac crest (for BM), to determine SUVmax. Liver SUVmax was calculated by allocating VOI with a volume of 20-50 cm^3 at the center of the right lobe. Spleen SUVmax was calculated by averaging the estimations of three 4-8 cm^3 elliptical VOIs, which were placed in different portions of the organ. BM SUVmax was determined by calculating the mean of the estimations of elliptical 2-5 cm^3 VOIs, which were allocated in both iliac crests. All ROI placements, so the measurements of SUVmax were performed by only one author, to avoid any possible effect of interobserver variability. Spleen/liver (S/L) and BM/liver (BM/L) ratios were calculated by dividing the spleen (S) and BM SUVmax by the liver SUVmax.

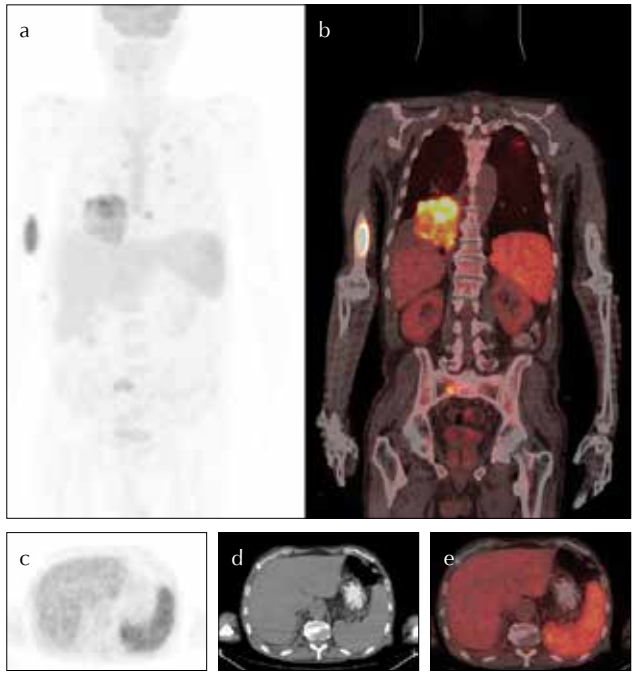

Figure 1. a-e. FDG PET/CT images of an 80-year-old patient with squamous cell carcinoma of the lung and accompanying pneumonia. The primary tumor in the lower lobe of the right lung and metastatic mediastinal lymph nodes, bone metastases were seen in the maximum intensity projection image (a). Coronal-fused FDG PET/CT (b), axial PET (c), CT (d), and axial-fused PET/CT (e) images show the diffuse splenic FDG uptake greater than the diffuse liver FDG uptake. The calculated SUVmax of the involving regions was as follows: TmSUVmax, 9.;, SSUVmax, 5; LSUVmax, 3; bmSUVmax: 2.8; S/L and BM/L ratios were 1.66 and 0.93, respectively. Laboratory findings were as follows: WBC, 5.5×10^3/uL; Neu, 4.3×10^3/uL; Hb, 9.5g/dL; Htc, 29%; Erit, 3.6×10^6/uL; and CRP, 12.9 mg/dL

Statistical Analysis

The differences between the two groups were analyzed to better understand the factors associated with the presence and absence of diffuse splenic uptake. Furthermore, the possible associations between S/L and BM/L ratios and tumor SUVmax, presence of metastasis, various hematological parameters were evaluated.

Mann-Whitney U test was used to compare continuous variables of the two groups, and T-test was used to evaluate the mean values of ages of two groups. The chi-square test was used to compare the two groups of categorical data. Spearman's rho correlation was used to determine the association between the parameters described above and diffuse splenic uptake, BM FDG uptake. A p value of ≤0.05 was defined to be statistically significant. Statistical evaluations were performed by Trakya University Medical Faculty Department of Biostatistics.

Exclusion Criteria

Patients with tumors other than lung cancer, those with a prediagnosis of lung cancer but without histopathological confirmation, lung cancer patients in follow-up who were previously treated, and those who did not have hematologi-

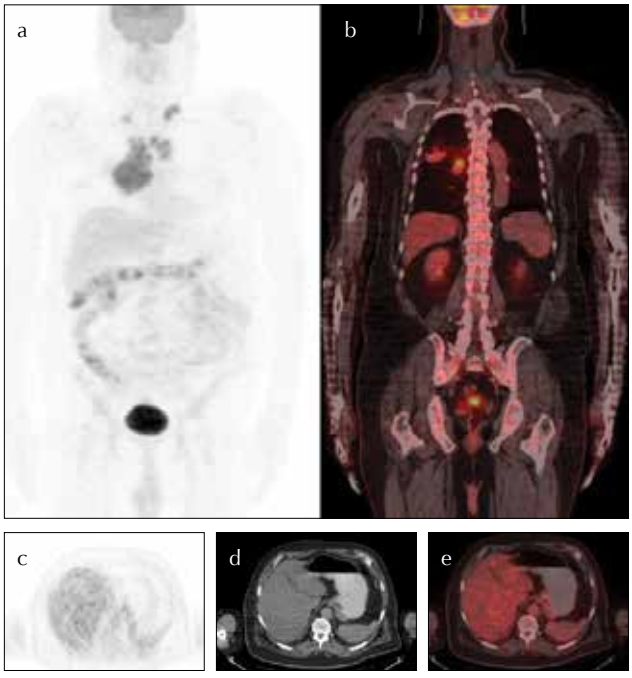

Figure 2. a-e. FDG PET/CT images of a 68-year-old patient with small cell lung cancer and accompanying pneumonia. The maximum intensity projection image (a) shows the primary 8-cm tumor in the hilum of the right lung and mediastinal, supraclavicular metastatic lymph nodes. The splenic FDG uptake was less than the hepatic FDG uptake, on coronal-fused FDG PET/CT (b), axial PET (c), CT (d), and axial fused PET/CT (e) images. The calculated SUVmax of the involving regions was as follows: TmSUVmax: 15.3, SSUVmax: 2.7, LSUVmax: 3.1, BMSUVmax: 3.5. S/L and BM/L were calculated as, 0.87, 1.1, respectively. Laboratory findings were as follows: WBC, 8.9×10^3/uL; Neu, 5.5×10^3/uL; Hb, 13.9g/dL; Htc, 41%; Erit, 4.6×10^6/uL; CRP, 3.03 mg/dL

cal data in 5 days with FDG PET/CT dates were excluded. Patients with liver cirrhosis, autoimmune disease, sarcoidosis, or hematopoietic diseases were also excluded.

Ethics

This retrospective study was approved by the Scientific Ethics Committee of Trakya University Medical Faculty.

RESULTS

Table 1 summarizes the characteristics of the patients in the two groups. Although the mean BM SUVmax and BM/L ratios of Group 1 were higher than those of Group 2; this difference was not statically significant. Liver SUVmax and tumor SUVmax were not different between the two groups. CRP levels of all patients in Groups 1 and 2 were higher than the normal range. Moreover, CRP levels of the two groups were not significantly different. Only SSUVmax, S/L ratios, and Hb levels of the two groups were significantly different (p=0.000 and 0.05, respectively).

Although all 27 patients had increased CRP levels, some did not have a proven site of infection in their records (Table 2). The number of patients who had an accompanying infection was not significantly different between the two groups. Presence of distant metastases did not significantly differ between the two groups. The number of patients with anemia were significantly higher in Group 1 than in Group 2 (p=0.02; Table 3).

Table 1. Patient characteristics and differences in parameters between the groups

	Group		
	1 (Patients; n=15)	**2 (Controls; n=12)**	**p***
Age (year)	66.07±12.139	70.58±9.298	0.29**
Hb (g/dL)	10.040±1.6326	11.467±2.0015	0.05*
Htc (%)	30.407±5.0089	34.567±6.3784	0.09
Erit ($\times10^6$/uL)	3.6420±.62923	3.9775±.61834	0.29
WBC ($\times10^3$/uL)	14.8400±21.16185	11.2100±7.46666	0.96
Lym ($\times10^3$/uL)	1.4813±1.53968	1.4958±.87843	0.42
Mon ($\times10^3$/uL	0.4973±.32756	0.6900±.31720	0.08
Neu ($\times10^3$/uL)	13.0173±21.22921	8.7683±7.07956	0.92
CRP (mg/dL)	9.6200±6.61490	7.2608±5.40268	0.30
Ssuv	3.553±.8895	2.358±.3450	0.000*
Lsuv	2.553±.7367	2.542±.5368	0.96
BMsuv	2.613±.7160	2.258±.8361	0.19
S/L	1.4233±.25559	0.9292±.10291	0.000*
BM/L	1.0580±.31992	.8733±.24077	0.11
tmsuv	11.533±8.6472	11.311±6.9452	0.54

Hb: hemoglobin; Htc: hematocrit; Erit: erythrocyte number; WBC: white blood cell; Lym: lymphocyte number; Mon: monocyte number; Neu: neutrophil number; CRP: C-reactive protein; Ssuv: spleen SUVmax; Lsuv: liver SUVmax; BMsuv: bone marrow SUVmax; S/L: spleen/liver ratio; BM/L: bone marrow/liver ratio; tmsuv: tumor SUVmax. * Mann-Whitney U test, ** T-test

Table 2. Diagnosis for accompanying infection/ inflammation

	Group 1 (n=15)	**Group 2 (n=12)**	**Diagnostic criteria**
No evidence of İnfection or Inflammation	6	6	No radiological and clinical evidence
Pneumonia	7	4	Fever, CT,±sputum culture
Mastoiditis		1	Cranial MR
Meningitis	1		Cerebrospinal liquid culture
Osteomyelitis	1		Microbiologic culture
Lymphadenitis		1	Microbiologic culture

CT: computed tomography; MR: magnetic resonance

Table 3. Number of patients with anemia, infection, and distant metastases in each group

	Group 1 (n=15)	**Group 2 (n=12)**	**p***
Anemia (n)	13	5	0.037*
Infection (n)	9	6	0.61
Distant metastases (n)	7	5	1.000

* chi-square test

Table 4. Comparison between four literature reviews

	S/L		BM/L	
Spearman's	**r**	**p**	**r**	**p**
tmsuv	–0.292	0.29	0.459	0.08
CRP	0.508	0.05*	0.140	0.61
Hb	0.072	0.80	–0.108	0.70
Htc	–0.020	0.94	–0.208	0.45
Erit	–0.143	0.61	–0.290	0.29
Mon	0.241	0.38	0.559	0.03*
Neu	0.011	0.97	0.581	0.02*
Lym	0.138	0.62	0.201	0.47
WBC	0.018	0.95	0.559	0.03*
Age	0.136	0.62	–0.124	0.66

tmsuv: tumor SUVmax; CRP: C-reactive protein; Hb: hemoglobin; Htc: hematocrit; Erit: erythrocyte number; WBC: white blood cell; Lym: lymphocyte number; Mon: monocyte number; Neu: neutrophil number; S/L: spleen/liver ratio; BM/L: bone marrow/liver ratio

The mean Hb levels were different between the two groups, but there was no correlation between the Hb levels and S/L ratios. CRP levels had a significant positive correlation with S/L ratios in only Group 1 among various parameters (r=0.508; p=0.05). BM/L ratios were positively correlated with WBC, Neu, and Mon in all 27 patients (r=0.559, p=0.03; r=0.581, p=0.02; and r=0.559, p=0.03, respectively). Table 4 shows the correlation coefficients and significances between S/L ratios of Group 1 and multiple parameters and correlation coefficients and significances between BM/L ratios of all 27 patients and multiple parameters. There were no significant correlations between S/L ratios of Group 2 and any of the parameters (data not shown; p>0.05).

DISCUSSION

The spleen, the largest secondary lymphoid organ, is associated with immune responses, as well as secondary hematopoiesis when needed. Extramedullary hematopoiesis is active, especially in the fetal life, but can also be activated during chronic anemic processes [2]. The impaired erythropoietin production in cancer patients who have anemia may be partly because of the production of inflammatory cytokines in response to the tumor [7,8]. Such cytokines also could distort the ability of BM to respond the circulating erythropoietin. Few studies have recently suggested that anemia, inflammatory cytokines, and refractory acute infections were associated with splenic FDG uptake on PET/CT in cancer patients [3-6]. Moreover, anemia and infection are frequently observed in cancer patients, and most patients do not show increased splenic FDG uptake on PET/CT. Because tumors were suggested to be the cause of stress, high cytokine levels, inflammation, and anemia, we investigated whether tumor SUVmax and tumor spread had an association with increased splenic uptake. Some tumor types have been reported to have a tendency to show increased splenic FDG uptake [4]. To avoid this kind of association and to homogenize patient population, we particularly investigated lung cancer patients. We also enrolled a control group, consisting of patients who underwent FDG PET/CT for staging of histopathologically proven lung cancer and who also had hematological data, within 5 days before or after PET/CT. Tumor SUVmax, presence of distant metastases, and hematological and inflammatory parameters were evaluated to clarify the difference between the two groups and clinical significance of diffuse splenic uptake in lung cancer patients. All the patients in both the groups had elevated CRP levels; the mean tumor SUVmax and tumor spread were not different between the two groups. Furthermore, there was no significant difference between the number of patients with known infection site in both the groups. In contrast to previous studies, we did not determine a direct significant correlation between Hb levels and S/L ratios [3]. Nevertheless, patients with anemia were higher in Group 1 than in Group 2 and had increased splenic uptake and decreased Hb levels. We may assume that patients with anemia have a tendency to show increased splenic uptake. This assumption is consistent with the spleen being a hematopoietic organ. However, only anemia itself did not appear to be the direct cause of increased splenic FDG uptake. The patients in both groups had high CRP levels but we determined that only CRP levels correlated with S/L ratios among various parameters in Group 1. This finding was in-line with that reported in previous studies of Nam et al.[3] and Pak et al.[4]. Activation and proliferation of macrophages is observed after the injection of granulocyte colony-stimulating factor (G-CSF) and this could be the reason of diffusely increased splenic uptake [9]. The tumor itself may secrete G-CSF and cause impaired erythropoietin production, anemia, and activation and proliferation of macrophages. Thus, the association between tumorigenesis, anemia, and inflammation is unique in an individual and is complicated.

Núñez et al.[10] reported that hematological parameters such as Hb, WBC, and platelet counts were correlated with the degree of splenic and BM FDG uptakes. We could not identify any association between BM FDG uptake and Hb levels or anemia. We determined that BM uptake reflects the number of circulating leucocytes in general. BM/L ratios were positively correlated with WBC and Neu in all 27 patients (r=0.559; p=0.03 and r=0.581; p=0.02, respectively). This finding was consistent with the previous reports that rendered diffuse BM uptake could be more likely because of the BM inflammatory changes; therefore the degree of BM FDG uptake correlates only with WBC, and the strongest correlation was determined with Neu [3,5]. This can be explained by the fact that BM FDG accumulation mainly reflects the total uptake by hematopoietic and vascular tissue. Because the neutrophil cell series is predominant in healthy BM hematopoietic cells [11].

Altogether, we determined a positive correlation between CRP levels and increased splenic uptake. The mean Hb levels were low in patients with increased splenic uptake. Although the mean CRP levels were not different between the two groups, we could not determine any association between CRP levels and splenic uptake of Group 2. Nevertheless, the degree of inflammation and anemia appear to be among the important causes of increased splenic FDG uptake on PET/CT in some lung cancer patients. Previous studies suggested that anemia, refractory infection site during PET/CT examinations, and possible systemic inflammations were the cause of diffusely increased splenic FDG uptake. However, in these

studies, either the direct results of the patient group were given or normal biochemical parameters and/or biochemical parameters of patients without cancer were used as reference. This study demonstrated that compared with a control group comprising lung cancer patients, it would be difficult to narrow the cause of diffusely increased splenic FDG uptake down to anemia and/or infection. This may be explained by the different immune responses of cancer patients among other things because we did not study different types of cytokines and the possible differences between predominating cytokine types and quantitative cytokine levels of the patients in the two groups. The difference between the duration and severity of anemia in the two groups may be another reason. As secondary information, we determined that BM FDG uptake could more likely reflect the inflammatory changes of BM. The degree of BM FDG uptake correlated only with WBC. The strongest correlation was determined between BM FDG uptake and the neutrophil cell series. We suggest that biochemical (hematological and inflammatory) test results of the patients should also be considered during PET/CT evaluations of cancer patients for correctly interpreting BM and splenic uptake.

Our study has some limitations because of its retrospective design. The patient population was small because the event was rare. Histopathological confirmations could not be obtained. Moreover, no follow-up data were available to make a prognostic assumption. Further well controlled prospective studies are needed to clearly determine the pathophysiological pathways and implications of diffusely increased splenic uptake and possible effect of it on prognosis during lung cancer surveillance.

Our results suggest that the degree of inflammation is correlated with an increased splenic FDG uptake in lung cancer patients, and it is enhanced by anemia rather than by an accompanying infection site. Systemic inflammation and anemia could be important causes of diffusely increased splenic FDG accumulation on PET/CT in lung cancer patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Trakya University School of Medicine.

Informed Consent: This study was a retrospective review of medical records, and requirement for informed consent was waived by our institutional review board.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - G.E.A., A.S.; Design - G.E.A., A.S.; Data Collection and/or Processing - G.E.A., S.S.D.; Analysis and/or Interpretation - G.E.A., A.S.; Literature Search - G.E.A., A.S., S.S.D.; Writing Manuscript - G.E.A.; Critical Review - A.S., G.E.A.; Other - T.Ç., İ.S.K., Y.B.Ü.

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