



Original Article

DIFFERENTIAL DIAGNOSIS OF DIFFUSE BONE MARROW UPTAKE ON ¹⁸F-FDG PET/ CT

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ABSTRACT

Background: Bone marrow is a frequent site of metastatic tumors, especially from breast, lung, and prostate cancers. Metastatic tumor in the bone marrow may influence the response to treatment, overall survival, and resulting decreased hematopoiesis. Diffusely and homogeneously bone marrow uptake in ¹⁸F-FDG PET/CT scan is frequently observed which can be caused by many conditions. **Material and methods:** We retrospectively analyzed the consecutive records of F-18 FDG PET scans performed from April 2011 to August 2013 at Mochtar Riady Comprehensive Cancer Center Siloam Hospital. A total of 2952 results were reviewed. 16 patients with diffusely and homogeneously bone marrow uptake in F-18 FDG PET/CT whole body scan between January 2012 and December 2013 were evaluated to find out the etiology. **Results:** From 2952 patients performed ¹⁸F-FDG-PET/CT there are 16 patients (5 men, 11 women) with diffusely and homogeneously increased FDG uptake in bone marrow, mean age: 52 years, range 5–82 years. It was found that 6 of 16 FDG PET/CT positive patients with solid tumors and 10 of 16 FDG PET/CT with nonsolid tumors. Malignancy was observed in 14 patients and benign in 2 patients. Diffusely and homogeneously uptake due to 1 patient with Idiopathic thrombocytopenic purpura (ITP), 6 patients with anaemia, 7 patients with chemotherapy, 1 patient with Granulocyte Colony-Stimulating Factor (G-CSF) and 1 patient with extra-nodal non-hodgkin lymphoma were observed. **Conclusion:** Diffusely and homogeneously increased bone marrow on ¹⁸F FDG PET/CT whole body scan uptake can be seen in malignant or benign disease and history of treatment. Spleen uptake is observed at the initial imaging than bone marrow involvement while spleen uptake more frequently reflects disease involvement.

KEYWORDS

FDG PET. Bone marrow involvement, solid tumor, nonsolid tumor.

INTRODUCTION

The International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization, released the latest data on cancer incidence, mortality, and prevalence worldwide including Indonesia. According to GLOBOCAN 2012, an estimated 14.1 million new cancer cases and 8.2 million cancer-related deaths occurred in 2012. The most commonly diagnosed cancers worldwide were those of the lung (1.8 million, 13.0% of the total), breast (1.7 million, 11.9%), and colorectum (1.4 million, 9.7%). The most common causes of cancer death were cancers of the lung (1.6 million, 19.4% of the total), liver (0.8 million, 9.1%), and stomach (0.7 million, 8.8%).^[1]

Bone marrow (BM) is one of the most common sites to be involved by tumors that metastasize via the bloodstream.^[2] Bone marrow is a frequent site of metastatic tumors, especially from breast, lung, and prostate cancers. Approximately 90% of metastases have been observed in concordance with the distribution of hematopoietic

marrow.^[3] Detection of metastatic tumors to the bone marrow is of great importance for the clinical staging of tumor spread because malignant infiltration of hematopoietic tissue can alter the clinical course of the disease. Metastatic tumor in the bone marrow may influence the response to treatment, overall survival, and resulting decreased hematopoiesis. The bone marrow provides erythrocytes, leukocytes, and platelets to the body, and usually accumulates small amount of F-18 fluoro-2-deoxyglucose (F-18 FDG) on positron emission tomography (PET) images. Bone marrow hypermetabolism might reflect characteristics of the neoplasm, although cytokines are produced not only by neoplasm but also as part of the inflammatory response.^[2,5] Though bone marrow involvement is most commonly seen with myeloid or lymphoid hematological malignancies, solid tumors may also spread to the bone marrow via the hematogenous route.^[2]

Many imaging modalities have been developed to detect and assess bone marrow metastases.^[2] Positron-emission

tomography (PET) using 2-fluorine 18-fluoro-2-deoxy-D-glucose (FDG) and other metabolic tracers has been shown to be a useful modality to stage malignant tumors and evaluate the efficacy of treatment. ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) or ¹⁸F-FDG PET/computed tomography (CT) is widely used for the diagnosis, staging, and response assessment of various types of malignancy.^[4]

Few data are available regarding the diagnostic impact of ¹⁸F-FDG PET diffuse bone marrow uptake seen not rarely at initial staging of patients with hodgkin lymphoma in particularly for bone marrow involvement.^[5,6] However differentiating diffuse increase in bone marrow F-18 FDG uptake, attributable to the involvement of malignancy or hematopoietic disease from other causes, such as the administration of hematopoietic cytokines or the inflammatory response is important.^[5] The aim of this retrospective study was to describe the etiology of increased hypermetabolism diffusely dan homogeneous bone marrow FDG uptake. In the same way diffuse splenic uptake (SU) is frequently observed at initial staging too and its significance has not been clarified.

MATERIAL AND METHODS

Patients

We retrospectively analyzed the consecutive records of F-18 FDG PET scans performed from April 2011 to August 2013 at Mochtar Riady Comprehensive Cancer Center Siloam Hospital, A total of 2952 results were reviewed. We selected patients with FDG uptake in bone marrow. The criteria inclusion was homogenously and diffusely increased bone marrow FDG uptake with higher than liver background. The exclusion criteria were focals uptake in bone marrow. The analysis included 16 patients with diffusely and homogenously increased bone marrow FDG uptake on PET/CT whole body scan between January 2012 and December 2013 were evaluated to find out the etiology. The patient profile is summarized in Table 1.

Imaging

Patients were injected intravenously with 185–370 MBq (5–10 mCi) of ¹⁸F-FDG at least 6 hours after the fasting period for ¹⁸F-FDG PET-CT imaging. Approximately one hour after injection (40- 60 min), the patient rested in a reclining chair in a quiet room between the tracer injection and the start of PET/CT image acquisition. PET-CT scanning was performed from the head to the proximal thigh using a clinical PET-CT system.

Table 1. Clinical characteristic of the patients

Sex	N	%
Male	5	37
Female	11	63
Diagnosis		
Lymphoma	5	30
Cervic Ca	2	12
Thalasemia Mayor	1	6

Anaemia And Vena Porta Trombosis	1	6
Lymphoma Non Hodkin	3	18
Tongue Ca	1	6
Breast Ca	3	18

STATISTICAL ANALYSIS

Descriptive statistics used.

RESULTS

Patient characteristics

From 2952 patients performed ¹⁸F-FDG-PET/CT there are 16 patients (5 men, 11 women) with diffusely and homogenously increased FDG uptake in bone marrow, mean age: 52 years, range 5–82 years. It was found that 6 of 16 FDG PET/ CT positive patient with solid tumors and 10 of 16 FDG PET/CT with non solid tumors.

The solid tumours considered breast cancer in 3 patients, Carcinoma Cervic in 2 patients and tongue cancer in 1 patients. The non-solid tumours considered Hodgkin lymphoma in 5 patients, Thalasemia Mayor in 1 patient, Anaemia and Vena Porta Trombosis in 1 patients and Lymphoma Non Hodkin in 3 patients.

Diffuse uptake from solid tumours and non-solid tumours caused diagnosed by Idiopathic thrombocytopenic purpura (ITP), anaemia, post chemotherapy, extra nodule Non Hodgkin Lymphoma and Granulocyte Colony-Stimulating Factor (GCSF). There is one patient with non solid tumor cause by ITP, 2 patients with solid tumours and 4 patients with non solid tumour cause by anaemia, 4 patients with solid tumours and 3 patients from non solid tumours cause by post chemotherapy, 1 patients with non solid tumour cause by extranodule Lymphoma non Hodgkin and 1 patients with non solid tumours cause by after giving Granulocyte Colony-Stimulating Factor. 6/16 subjects come with solid tumour and 11/16 with non solid tumour.

Table 2. Cause of diffusely and homogeneous FDG uptake in the bone marrow.

Kind of Tumour	Cause				
	IT P	Ana emia	Chemothe rapy	Extranodule LNH	GCSF
Solid		2	4		
Non Solid	1	4	3	1	1

PET/CT results

Criteria to assess positivity for bone marrow involvement on FDG PET/CT were either diffusely and homogeneous FDG uptake in the bone marrow higher than in the liver. PET/CT results were classified by cause diagnosed like ITP, Anaemia, Chemotherapy, Extranodule LNH, and GCSF. PET/CT was reported as diffuse uptake bone marrow in 16 patients. All of these patients also had negative uptake focal in bone. Maximum intensity projection (MIP) seen and SU (splenic uptake) was visually graded according to liver uptake:

1. Bone marrow FDG uptake can be caused by post chemotherapy seen diffusely and homogenously increase bone marrow on ¹⁸F FDG PET/ CT whole

body scan uptake. No uptake pathologies in other places.

2. Same as post-chemotherapy, bone marrow FDG uptake can be caused by anaemia seen diffusely and homogenously increase bone marrow on ¹⁸F FDG PET/ CT whole body scan uptake. Slowly increased FDG activity in the splenic uptake.
3. Bone marrow FDG uptake can be caused by Extranodal Lymphoma Hodgkin's seen diffusely and homogenously increase bone marrow on ¹⁸F FDG PET/ CT whole body scan uptake. Increased FDG activity in the splenic uptake.
4. Bone marrow FDG uptake can be caused by Granulocyte Colony-Stimulating Factor (G-CSF) seen diffusely and homogenously increase bone marrow on ¹⁸F FDG PET/ CT whole body scan uptake. Slowly increased FDG activity in the splenic uptake.

Post- Chemotherapy

Anaemia



Extranodal LH



SU higher than liver uptake



SU higher than liver uptake

G-CSF



Figure . FDG-PET/CT defined bone marrow involvement as diffusely and homogenously bone marrow uptake caused by many conditions

DISCUSSION

Positron emission tomography using ¹⁸F-fluorodeoxyglucose (FDG-PET) has come to be recognized as a useful modality for tumor imaging, which is based on the elevated glucose metabolism in tumor cells. Correlations have been reported between ¹⁸F-FDG uptake by the bone marrow and the peripheral blood neutrophil count.^[7] The bone marrow (BM) provides erythrocytes, leukocytes, and platelets to the body, and usually accumulates small amount of F-18 fluoro-2-deoxyglucose (F-18 FDG) on positron emission tomography (PET) images. Differentiating a diffuse increase in the BM F-18 FDG uptake, attributable to the involvement of malignancy or hematopoietic disease from other causes, such as the administration of hematopoietic cytokines or the inflammatory response, is important. Although the above-mentioned studies showed correlations between the bone marrow F-18 FDG uptake and age, hematological parameters or blood cytokine levels using groups of patients, the intensity of the bone marrow F-18 FDG uptake seems to have been determined subjectively as diffusely increased to make the diagnosis for individual patients.^[8]

During the past decade, a large body of evidence has confirmed the importance of positron emission tomography (PET) using 2-[¹⁸F]-fluoro-2-deoxy-D -glucose (FDG) as a diagnostic tool in the evaluation of malignant lesions, including lymphoma. Bone marrow is a frequent site of lymphoma involvement and of metastatic tumors from breast, lung, and prostate cancers.^[9] The diffuse increase in FDG uptake in the bone marrow not only may be caused by malignancy or hematopoietic disease, but also may be due to an inflammatory reaction, recent chemotherapy, or administration of hematopoietic growth factors. A diffuse increase in FDG uptake has also been reported in hyperplastic bone marrow with or without cytokine therapy.^[11] At a glance these findings are not compatible with the prior study that showed no change in the bone marrow uptake after a few cycles of chemotherapy.^[10] However, our findings are consistent with previously reported bone marrow reserve after chemotherapy.

Hodgkin's Lymphoma is highly FDG avid. Diffusely and homogeneous bone marrow uptake over the axial skeleton and proximal appendicular skeleton is not a pattern of BMI in Hodgkin's disease and is due to inflammation and effect on bone marrow driven by cytokine release.⁽⁹⁾ Since Hodgkin and aggressive non-Hodgkin lymphomas show an intense glucose metabolism and therefore a high FDG uptake. FDG PET/CT can be helpful in both nodal and extra-nodal staging of lymphoma, including the bone marrow assessment. Criteria to assess positivity for bone marrow involvement on FDG PET/CT in patients with Hodgkin lymphoma may vary from one study to another: bone marrow FDG uptake higher than the liver, focal, multi-focal or abnormally increased FDG uptake, or bone marrow FDG uptake higher than the mediastinal blood pool as reference.^[12] Diffuse SU (without focus) could reflect lymphoma infiltration but could reflect activation and proliferation of macrophages as observed after granulocyte colony-stimulating factor (G-CSF).^[6]

Despite excellent performance in bone marrow staging in both Hodgkin and non-Hodgkin lymphomas, FDG PET/CT false-positive findings may occur, especially when diffuse bone marrow and splenic uptake are observed at the initial imaging. As demonstrated by **Salaun et al.**^[13] diffuse bone marrow uptake is more likely to be due to inflammatory changes than bone marrow involvement, while splenic uptake more frequently reflects disease involvement.^[12] But this pattern was differentiated from diffuse homogeneously increased uptake in the skeleton, which is often seen in HL patients at staging and in most cases is due to paraneoplastic bone marrow activation and not to diffuse BMI by HL.^[14] The presence of extranodal involvement is very important for staging NHL and HL. In general, extranodal involvement is more common in NHL than in HL, while it is frequently observed in recurrent disease and immune deficiency-related lymphomas. Primary and secondary extranodal diseases have different prognostic implications. Lymphomas that initially appear to have the bulk of the disease at extranodal sites are described in primary extranodal lymphoma and categorized as stage I or II. ^[15] The pattern of the FDG uptake in the bone marrow sites is directly dependent on the pattern of infiltration of the marrow by the disease. Lymphomas may often manifest one or a mixture of the focal (involving one or more areas), diffuse (replacing the adipose tissue and hematopoietic elements), or dispersed (in the form of single or a limited number of neoplastic cells distributed in between the hematopoietic elements) patterns irrespective of the topographical location.^[16]

In this study, FDG uptake was significantly increased in patients treated with G-CSF. Granulocyte colony-stimulating factor (G-CSF) is hematopoietic cytokines that regulate proliferation and differentiation of hematopoietic progenitor cells in the bone marrow. Human G-CSF has been produced by recombinant DNA technology, and exogenous administration of these factors has been shown to increase circulating neutrophil levels dramatically. G-CSF has been used increasingly to prevent chemotherapy-induced infections. With the increasing use of cytokine therapy and of FDG PET for the assessment of the efficacy of chemotherapy, increased FDG uptake in normal bone marrow during and after cytokine therapy. This increased uptake in normal bone marrow during and after G-CSF may mimic progressive bone or bone marrow metastases, and metastatic lesions may be obscured by the elevated FDG accumulation in the bone marrow. Hematopoietic CSFs have been used to treat the myelo suppressive effects of chemotherapy since the 1990s G-CSF has been used to stimulate differentiation and production of progenitor cells. In clinical studies, G-CSF has been shown to significantly reduce the duration of neutropenia. G-CSF has also been identified as a cause of increased bone FDG uptake.^[10] Because normal bone marrow usually shows only a minor amount of FDG uptake, increased FDG uptake may resemble bone marrow metastases or make true metastatic lesions difficult to see. It was shown that a substantial increase in bone marrow FDG uptake is rapidly induced by colony stimulating factor treatments and should

not be misinterpreted as diffuse bone metastases or bone marrow disease.^[11]

CONCLUSION

The pattern of bone marrow uptake in oncological cases could be diffuse, focal, or mix. Diffusely and homogeneously increase bone marrow uptake on ¹⁸F FDG PET/ CT whole body scan can be seen in malignant or benign disease and history of treatment. Spleen uptake observed at the initial imaging than bone marrow involvement while spleen uptake more frequently reflects disease involvement.

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