Disseminated focal $^{18}$F-fluoro-deoxyglucose uptake upon granulocyte colony-stimulating factor therapy mimicking malignant bone infiltration: case report of a patient with very severe aplastic anemia

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**Abstract**

Combined $^{18}$F-fluoro-deoxyglucose ($^{18}$FDG) positron emission tomography and computed tomography ($^{18}$FDG-PET/CT) is increasingly used for the diagnostic and therapeutic management of hematologic and non-hematologic malignancies. Here, we describe a unique case of a patient presenting with very severe aplastic anemia and a mediastinal mass showing disseminated hypermetabolic lesions of the bones after receiving granulocyte colony-stimulating factor (G-CSF), highly suspicious for disseminated metastatic lesions. A 71-year-old patient presented with a 3-week history of dyspnea and fatigue. Blood tests showed severe pancytopenia and iliac crest bone marrow biopsy revealed an extensively hypoplastic bone marrow. Diagnostic work-up by histology, conventional cytogenetics and flow cytometry confirmed the diagnosis of very severe aplastic anemia. Besides blood transfusions, the patient was treated with G-CSF. Furthermore, computed tomography revealed a suspect mass in the anterior mediastinum, presenting with moderate glucose metabolism in the subsequent $^{18}$FDG-PET/CT scan. In addition, multiple disseminated and highly metabolic bone lesions of primarily the ribs were detected, suspicious of malignant bone infiltration. Since physiologic bone marrow activation by G-CSF-stimulation could not be ruled out, G-CSF therapy was interrupted to repeat the PET/CT scan 10 days later. On the second $^{18}$FDG-PET/CT the moderately hypermetabolic mediastinal mass persisted. However, the initially FDG-avid bone lesions almost completely resolved, rendering the diagnosis of G-CSF-induced bone marrow hypermetabolism very likely without the need for further invasive diagnostic procedures. The mediastinal mass was thereafter histologically verified as thymoma. Interpretation of $^{18}$FDG-PET/CT in patients with aplastic anemia may be complicated by the frequent therapeutic use of G-CSF. With G-CSF, islets of residual bone marrow activity can be visualized on $^{18}$FDG-PET/CT images that might be misinterpreted as malignant bone infiltration. Repeating PET/CT scan after G-CSF discontinuation can prevent unnecessary invasive diagnostic procedures in these patients.

**Keywords:** $^{18}$FDG-PET/CT, G-CSF, granulocyte colony-stimulating factors, skeletal metastasis, very severe aplastic anemia

**Background**

Combined $^{18}$F-fluoro-deoxyglucose ($^{18}$FDG) positron emission tomography and computed tomography ($^{18}$FDG-PET/CT) is increasingly used for staging, response evaluation and follow-up in hematologic and non-hematologic malignancies. Apart from nodal and extra-nodal lesions, the bone marrow (BM) compartment and its
Metabolic activity can be visualized and quantified using this imaging technique. The extent of hematopoietic FDG uptake within the BM compartment correlates with intrinsic (e.g. systemic inflammatory markers) as well as extrinsic [e.g. colony-stimulating factors (CSF)] factors.\(^1\) The influence of these factors should be carefully considered when interpreting [18F]FDG-PET images. We here describe a unique case of a patient with very severe aplastic anemia (VSAA) and thymoma, who showed disseminated focal BM hypermetabolism after granulocyte colony-stimulating factor (G-CSF) therapy, mimicking disseminated metastases.

**Case presentation**

A 71-year-old patient presented with dyspnea and fatigue, aggravating over the course of 3 weeks. Laboratory tests revealed severe pancytopenia with a leucocyte count of 2.4 G/L, neutrophil count of 0.3 G/L, hemoglobin of 75 G/L, platelet count of 7 G/L and reticulocyte count of 13 G/L. Medical history was negative for previous intake of novel drugs or overt infectious episodes. Iliac crest bone marrow biopsy revealed an extensively hypoplastic BM with a cellularity of 5% and absence of clonal blasts. G-CSF (filgrastim 4 µg/kg/day; 30 I.E.) was initiated and the patient received erythrocyte and platelet transfusions. Further diagnostic work-up by histology, next-generation sequencing and flow cytometry was inconspicuous for myelodysplastic syndrome (MDS), paroxysmal nocturnal hemoglobinuria, or myeloproliferative disorders, thus prompting the diagnosis of VSAA according to established criteria.\(^2\) Computed tomography revealed a suspect mass in the anterior mediastinal region. For further assessment of this mediastinal mass [18F]FDG-PET/CT was performed. Interestingly, besides a moderately hypermetabolic mediastinal lesion, disseminated focal skeletal tracer uptake of high intensity was observed (Figure 1) on [18F]FDG-PET/CT, which was primarily interpreted as highly suspicious of skeletal metastases. However, this differential diagnosis seemed unlikely considering the clinical course of disease. At the time point of the PET/CT scan, the patient had received a 5-day treatment with G-CSF, which was subsequently discontinued to repeat [18F]FDG-PET/CT after 10 days. The following PET/CT scan revealed a subtotal metabolic regression of the disseminated skeletal lesions but metabolic persistence of the mediastinal mass, consistent with the diagnosis of G-CSF-induced BM hypermetabolism in residual hematopoietic islets, as it is usually seen in patients with aplastic anemia at the time point of diagnosis. Histopathological work-up of the mediastinal mass confirmed the diagnosis of type B1 thymoma. Due the suspicion of a paraneoplastic phenomenon causing VSAA, the patient underwent complete surgical resection of the thymoma. As VSAA did not resolve postoperatively, immunosuppressive treatment with cyclosporine and mycophenolic acid in combination with eltrombopag was initiated.

**Discussion**

This case presentation highlights the diagnostic pitfalls in patients undergoing [18F]FDG-PET/CT scans during G-CSF therapy, as this may induce significant hypermetabolic activity within the BM compartment. [18F]FDG physiologically accumulates within the BM showing low to moderate intensity in healthy individuals, with the BM and spleen appearing less intense than the liver. [18F]FDG uptake can be quantified by the maximum standardized uptake value (SUV\(_{\text{max}}\)).\(^3\)

From a pathophysiologic point of view, a homogeneously enhanced BM [18F]FDG uptake usually reflects a hyperplastic and activated BM and can evolve in response to hematopoietic cytokines such as G-CSF\(^1\) as well as systemic inflammatory processes. For example, a positive correlation between [18F]FDG activity and inflammatory parameters such as leucocyte and particularly neutrophil counts\(^9\) as well as C-reactive protein have been observed.\(^5-7\)

Clinically, diffuse [18F]FDG uptake of the BM can be observed in hematological neoplasms such as MDS,\(^8\) chronic myeloid leukemia\(^9\) and Hodgkin’s lymphoma,\(^10\) or solid malignancies due to paraneoplastic CSF production,\(^11,12\) after therapeutically used interleukin\(^11\) as well as in pyrexic states.\(^14\) As a critical differential diagnosis, disseminated marrow metastasis can present with diffuse [18F]FDG BM enhancement.\(^15\) A SUV cut-off as to differentiate normal BM from hyperplastic BM or neoplastic infiltration is lacking.

It is known that therapeutically used G-CSF (e.g. pegfilgrastim, filgrastim) can enhance BM [18F]FDG uptake, being mainly associated with a
Dose and duration of G-CSF therapy correlate with the extent of [18F]FDG uptake and an increased uptake can persist up to 4 weeks after completion of CSF therapy.\(^1\) Thus, the American Society of Clinical Oncology guidelines for [18F]FDG-PET/CT in lymphoma patients recommend a 10-day interval between G-CSF use and [18F]FDG-PET/CT scan.\(^16\)

In patients with aplastic anemia, a recent study described three different types of [18F]FDG-PET manifestations, including normal BM metabolism, generalized hypometabolism, and diffuse hypometabolism associated with focal hyperproliferation.\(^17\) As for the latter, the inhomogeneous BM metabolism and patchy distribution of [18F]FDG uptake (also described elsewhere in case reports\(^18\)–\(^20\)) most frequently occurs in the vertebral bodies, sternum and iliac bones.\(^17\) The spots probably indicate residual compensatory hyperplastic hematopoietic islands in an otherwise aplastic BM\(^17\),\(^20\) and are associated with an active phase of the disease. The patchy [18F]FDG distribution seems to persist even in patients in remission after immunosuppressive therapy.\(^21\) In contrast to other reports,\(^20\)\(^,\)\(^22\),\(^23\) in our patient the focal skeletal hypermetabolism and, thus, residual hematopoiesis was mainly restricted to the rib cage. The association of aplastic anemia and thymoma has been rarely reported in literature.\(^24\)

Up to now, one case report has described that the application of G-CSF can highlight those BM areas spared from the hematologic disease in a patient with aplastic anemia.\(^22\) In this case, biopsy of a hypermetabolic lesion was conducted showing trilinear hematopoiesis and absence of malignancy. In our patient, the suspicion of thymoma-associated aplastic anemia made the occurrence of skeletal metastasis seem very unlikely, as thymoma do generally not metastasize, contrarily to thymic carcinoma. Therefore, follow-up [18F]FDG-PET/CT imaging could confirm our suspicion of G-CSF-induced skeletal hypermetabolism and prevented the need for further unnecessary invasive diagnostic procedures.

In conclusion, the presented case underlines the importance of careful clinical evaluation to not misinterpret G-CSF induced hypermetabolism

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**Figure 1.** [18F]FDG-PET/CT scan series of a patient with very severe aplastic anemia and mediastinal tumor. The patient was referred for evaluation of a mediastinal mass that showed a moderate [18F]FDG uptake (SUVmax: 5.1), suspicious for thymoma (b: fused axial PET/CT slice with red arrow pointing at the mass). In addition, multiple, highly metabolic bone lesions were detected, predominantly affecting the ribs, as demonstrated on MIP-maximum intensity projection (a) and fused axial slice (c, green arrows). After withdrawal of the ongoing G-CSF therapy a second [18F]FDG-PET/CT was performed 10 days after the first scan, showing an unaltered moderate tracer accumulation in the mediastinal mass with an SUVmax of 4.6 (e: red arrow). However, the initially highly FDG-avid bone lesions almost completely resolved, with only a faint uptake left in some residual lesions (d: maximum intensity projection and f: fused axial slice; green arrow pointing at residual focal uptake in the scapula with an SUVmax decreasing from 14.7 on the first scan to 2.6). The findings are highly suggestive of a G-CSF-induced [18F]FDG accumulation in the functionally active hematopoietic bone marrow.
with malignant bone infiltration on [18F]FDG-PET/CT.

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Authors’ contributions
LH and FK were major contributors in writing this case report. AS, DW, DN and CU corrected and reviewed the case report. CU analyzed imaging data and was responsible for figure design and description. All authors read and approved the final manuscript.

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Conflict of interest statement
The author(s) declare that there is no conflict of interest.

Compliance with ethical standards
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments. Ethical approval was waived, as the analysis was conducted retrospectively from data obtained for clinical purposes.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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References
1. Sugawara Y, Fisher SJ, Zasadny KR, et al. Preclinical and clinical studies of bone marrow uptake of fluorine-1-fluorodeoxyglucose with or without granulocyte colony-stimulating factor during chemotherapy. J Clin Oncol 1998; 16: 173–180.

2. Killick SB, Bown N, Cavenagh J, et al. Guidelines for the diagnosis and management of adult aplastic anaemia. Br J Haematol 2016; 172: 187–207.

3. Agool A, Glaudemans AW, Boersma HH, et al. Radionuclide imaging of bone marrow disorders. Eur J Nucl Med Mol Imaging 2011; 38: 166–178.

4. Murata Y, Kubota K, Yukihiro M, et al. Correlations between 18F-FDG uptake by bone marrow and hematological parameters: measurements by PET/CT. Nucl Med Biol 2006; 33: 999–1004.

5. Inoue K, Goto R, Okada K, et al. A bone marrow F-18 FDG uptake exceeding the liver uptake may indicate bone marrow hyperactivity. Ann Nucl Med 2009; 23: 643–649.

6. Lee JW, Na JO, Kang DY, et al. Prognostic significance of FDG uptake of bone marrow on PET/CT in patients with non-small-cell lung cancer after curative surgical resection. Clin Lung Cancer 2017; 18: 198–206.

7. Lee JW, Seo KH, Kim E-S, et al. The role of 18F-fluorodeoxyglucose uptake of bone marrow on PET/CT in predicting clinical outcomes in non-small cell lung cancer patients treated with chemoradiotherapy. Eur Radiol 2017; 27: 1912–1921.

8. Inoue K, Okada K, Harigae H, et al. Diffuse bone marrow uptake on F-18 FDG PET in patients with myelodysplastic syndromes. Clin Nucl Med 2006; 31: 721–723.

9. Takalkar A, Yu JQ, Kumar R, et al. Diffuse bone marrow accumulation of FDG in a patient with chronic myeloid leukemia mimics hematopoietic cytokine-mediated FDG uptake on positron emission tomography. Clin Nucl Med 2004; 29: 637–639.

10. Chiang SB, Rebenstock A, Guan L, et al. Diffuse bone marrow involvement of Hodgkin lymphoma mimics hematopoietic cytokine-mediated FDG uptake on FDG PET imaging. Clin Nucl Med 2003; 28: 674–676.

11. Morooka M, Kubota K, Murata Y, et al. 18F-FDG-PET/CT findings of granulocyte colony stimulating factor (G-CSF)-producing lung tumors. Ann Nucl Med 2008; 22: 635–639.

12. Suzumura K, Imuro Y, Hirano T, et al. Granulocyte colony-stimulating factor-producing cholangiocellular carcinoma. Int Surg 2015; 100: 123–127.
13. Yi C, Shi X, Wang X, et al. The alteration of $^{18}$F-FDG uptake in bone marrow after treatment with interleukin 11. *Clin Nucl Med* 2014; 39: 934–935.

14. Zhou M, Chen Y, Liu J, et al. A predicting model of bone marrow malignant infiltration in $^{18}$F-FDG PET/CT images with increased diffuse bone marrow FDG uptake. *J Cancer* 2018; 9: 1737–1744.

15. Hollinger EF, Alibazoglu H, Ali A, et al. Hematopoietic cytokine-mediated FDG uptake simulates the appearance of diffuse metastatic disease on whole-body PET imaging. *Clin Nucl Med* 1998; 23: 93–98.

16. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *J Clin Oncol* 2007; 25: 571–578.

17. Chen M, Lu L, Li J, et al. Value of systemic PET/CT in the diagnosis and differential diagnosis of aplastic anemia. *Oncol Lett* 2018; 16: 3215–3222.

18. Okuyama C, Kubota T, Matsushima S, et al. FDG avid patchy bone marrow misinterpreted as melanoma metastases to bone in a case of aplastic anemia. *Clin Nucl Med* 2009; 34: 927–930.

19. Hirata H, Arai Y, Inano S, et al. [Serial FDG-PET evaluation of a patchy pattern of hematopoiesis at diagnosis in aplastic anemia]. *Rinsho Ketsueki* 2011; 52: 84–86.

20. Cicone F, Stalder M, Geiger D, et al. Visual and quantitative approach to bone marrow foci of increased glucose uptake on PET/CT in a case of aplastic anemia. *Nuklearmedizin* 2010; 49: N10–N12.

21. Hotta T, Murate T, Inoue C, et al. Patchy haemopoiesis in long-term remission of idiopathic aplastic anaemia. *Eur J Haematol* 1990; 45: 73–77.

22. Kouba M, Maaloufova J, Campr V, et al. G-CSF stimulated islands of haematopoiesis mimicking disseminated malignancy on PET-CT and MRI scans in a patient with hypoplastic marrow disorder. *Br J Haematol* 2005; 130: 807.

23. Piva R, Fiz F, Piana M, et al. $^{18}$F-fluorodeoxyglucose PET/CT in aplastic anemia: a literature review and the potential of a computational approach. *Clin Pract* 2014; 11: 613–621.

24. Gendron N, de Fontbrune FS, Guyard A, et al. Aplastic anemia related to thymoma: a survey on behalf of the French reference center of aplastic anemia and review of literature. *Haematologica* 2019; 105: e333–e336.