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Case Report

# Diffuse bone marrow uptake on $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography with copper-deficiency anemia ☆

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ABSTRACT

A 59-year-old man with pancytopenia underwent 18F-fluorodeoxyglucose positron emission tomography/computed tomography for suspected carcinomatosis. The scan revealed diffuse bone marrow uptake, prompting further investigation. Bone marrow analysis revealed no malignant cells; however, erythroblasts with cytoplasmic vacuolization were observed. Subsequent testing showed low serum copper and ceruloplasmin levels, indicating copper deficiency. Copper supplementation resulted in significant improvement in cytopenia. Notably, the bone marrow uptake on subsequent scans decreased significantly. This case highlights the importance of considering copper deficiency as a potential cause of diffuse bone marrow uptake of $^{18}$F-fluorodeoxyglucose on positron emission tomography/computed tomography.



## Introduction

$^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) is a widely employed tool in clinical practice for assessing malignancies. However, diffuse bone marrow uptake of $^{18}$F-FDG can be observed in both malignant and benign cases, raising questions about its specificity. This case report describes a patient with copper-deficiency anemia who exhibited diffuse bone marrow uptake on $^{18}$F-FDG PET/CT imaging, highlighting the need for further investigation into the association between copper deficiency and PET/CT findings.

☆ Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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**Table 1 – Laboratory data.**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| WBC | 2100 | /μL | TP | 7.3 | g/dL | Fe | 95 | μg/dL |
| Stab | 1 | % | Alb | 4.5 | g/dL | UIBC | 132 | μg/dL |
| Seg | 29 | % | T-bil | 0.6 | mg/dL | Ferritin | 751 | ng/mL |
| Lymph | 32.5 | % | AST | 37 | U/L | Folic acid | 5 | ng/mL |
| Mono | 31 | % | ALT | 20 | U/L | Vit.B12 | 126 | pg/mL |
| Eosino | 1 | % | γ-GTP | 93 | U/L | Zn | 74 | μg/dL |
| Baso | 5.5 | % | LDH | 128 | U/L | | | |
| Blast | 0 | % | BUN | 20.5 | mg/dL | Cu | 4 | μg/dL |
| RBC | $1.91 \times 10^6$ | /μL | Cre | 4.30 | mg/dL | Ceruloplasmin | 5 | mg/dL |
| Hb | 6.8 | g/dL | Na | 132 | mEq/L | | | |
| MCV | 105.8 | fL | K | 3.6 | mEq/L | | | |
| MCH | 35.6 | pg | Ca | 8.7 | mg/dL | | | |
| MCHC | 33.7 | % | | | | | | |
| Platelet | $10.4 \times 10^4$ | /μL | CRP | 1.05 | mg/dL | | | |
| Retic | 18 | % | | | | | | |

WBC; white blood cell, Stab; stab neutrophil, Seg; segmented neutrophil, Lymph; lymphocyte, Mono; monocyte, Eosino; eosinocyte, Baso; basophil, Blast; blastocyte, RBC; red blood cell, Hb; hemoglobin, MCV; mean corpuscular volume, MCH; mean corpuscular hemoglobin, MCHC; mean corpuscular hemoglobin concentration, Retic; reticulocyte, TP; total protein, Alb; albumin, T-bil; total bilirubin, AST; aspartate aminotransferase, ALT; alanine aminotransferase, γ-GTP; γ-glutamyl transpeptidase, LDH; lactate dehydrogenase, BUN; blood urea nitrogen, Cre; creatinine, CRP; C-reactive protein, UIBC; unsaturated iron binding capacity

## Case presentation

A 59-year-old man with pancytopenia undergoing hemodialysis for chronic renal failure was presented to the clinic. Despite increased erythropoietin doses, his anemia progressively worsened over 2 months. He was otherwise asymptomatic but had a past medical history of advanced gastric cancer (pT2N1M0, pStageIIB) treated with laparoscopic-assisted distal gastrectomy 1 year prior. Additionally, he had been taking zinc supplements for eczema for 1 year.

Upon examination, the patient was found to exhibit anemia, with no other abnormal physical findings. Laboratory results confirmed pancytopenia: white cell count of 2100/μL, hemoglobin level of 6.8 g/dL, and platelet count of 104,000/μL (Table 1). However, common causes of pancytopenia, including iron deficiency, folate deficiency, vitamin B12 deficiency, and zinc deficiency, were not found.

Despite low tumor marker levels (cancer embryonic antigen: 5.9 ng/mL and carbohydrate antigen 19-9: 28 U/mL), an $^{18}$F-FDG PET/CT scan was performed to assess for relapse or carcinomatosis from gastric cancer and showed diffuse bone marrow uptake (Fig. 1). Subsequent bone marrow aspiration revealed no malignant cells; however, 4% of the erythroblasts exhibited cytoplasmic vacuolization (Fig. 2), a characteristic finding in copper deficiency anemia. A CT-guided biopsy of the lumbar spine, which showed high uptake on the PET/CT scan, also revealed similar findings. Further investigations revealed low serum copper (4.0 μg/dL) and ceruloplasmin (5.0 mg/dL). Therefore, the patient's cytopenia was considered due to copper deficiency.

We administered pure cocoa powder orally (10 g/day), owing to its high copper content, and discontinued zinc administration as it could induce copper deficiency. The patient's clinical course is shown in Fig. 3. The cytopenia improved within a week following copper administration. Interestingly, despite the continued elevated erythropoietin dose, the previously observed uptake on $^{18}$F-FDG PET/CT scans disappeared 3 months after treatment initiation (Fig. 1).

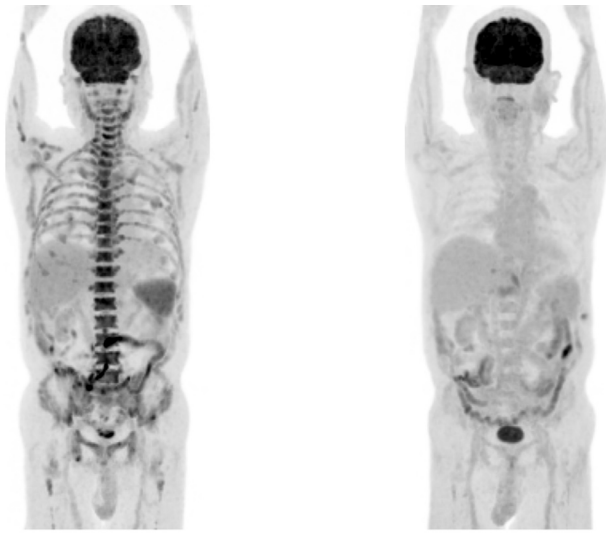


**Fig. 1 – $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography imaging with diffuse bone marrow uptake, resolved using copper replacement.**

After the patient recovered from cytopenia, an upper digestive endoscopy showed no findings suggesting any relapse of gastric cancer. Subsequent CT scans also revealed no tumors or enlargement around the remnant stomach or in the abdominal lymph nodes, and tumor marker levels remained low (cancer embryonic antigen: 5.0 ng/mL and carbohydrate antigen 19-9: 49 U/mL), further supporting the absence of cancer recurrence.

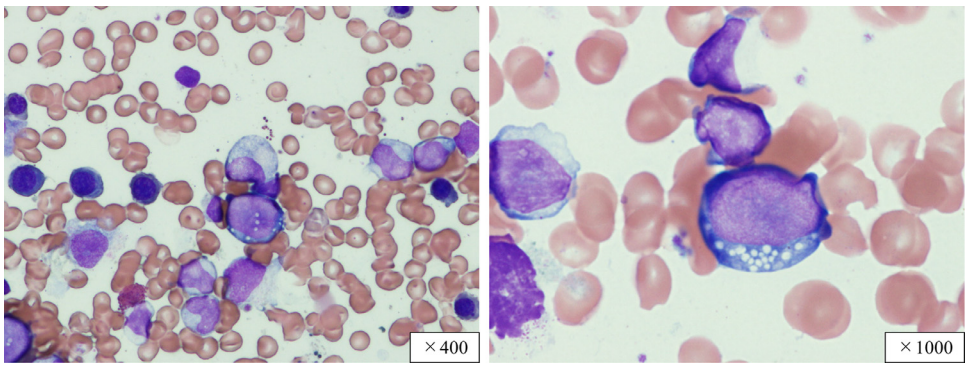


**Fig. 2 – Erythroblasts with cytoplasmic vacuolization observed in the bone marrow using May-Grünwald Giemsa stain.**

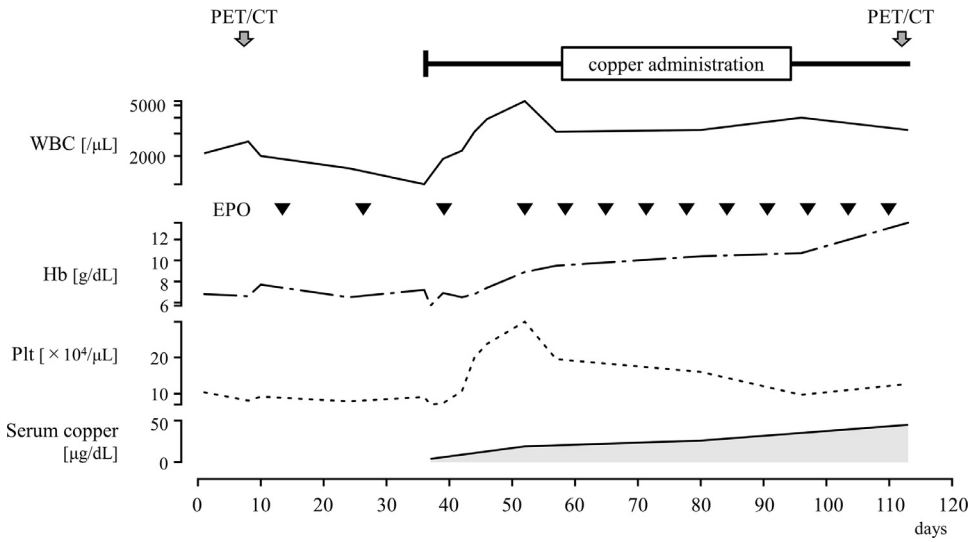


**Fig. 3 – Clinical course WBC, white blood cell, Hb, hemoglobin, Plt, platelet, EPO; erythropoietin (120 μg).**

## Discussion

This case report describes a patient with copper-deficiency anemia presenting with diffuse $^{18}$F-FDG uptake in the bone marrow. The association between this uptake and copper deficiency anemia has been rarely reported, highlighting the need for caution in interpreting such findings.

Diffuse $^{18}$F-FDG uptake in the bone marrow is commonly associated with malignancies, including hematological malignancies such as leukemia and malignant lymphoma, as well as bone marrow carcinomatosis secondary to solid tumors [1–3]; additionally, myelodysplastic syndrome can present with this finding [4]. However, the finding in this patient revealed a hypocellular bone marrow without abnormal cell proliferation, alongside no evidence of gastric cancer recurrence, suggesting the importance of investigating non-malignant causes.

Several benign conditions can also lead to diffuse $^{18}$F-FDG bone marrow uptake. Growth factors, such as granulocyte colony-stimulating factor and erythropoietin, have been documented to induce such a pattern [5,6]. Similarly, bone marrow recovery following chemotherapy-induced hypoplasia or systemic inflammation can enhance the uptake [7,8]. While this patient received erythropoietin for anemia associated with chronic renal failure, its administration did not appear to influence $^{18}$F-FDG uptake, as it resolved despite increasing erythropoietin doses.

Considering the unlikelihood of the aforementioned common causes in the patient and the remarkable decrease in $^{18}$F-FDG uptake observed following copper replacement therapy, it is thought that his copper-deficiency anemia induced the observed diffuse $^{18}$F-FDG bone marrow uptake.

While the precise mechanism underlying this association remains elusive, a potential explanation exists. One hypothesis suggests that copper deficiency triggers ineffective hematopoiesis, similar to that observed in myelodysplastic syndrome. Copper plays a crucial role in erythropoiesis through its involvement in iron transport, and its deficiency can impede this process [9]. This ineffective erythropoiesis is believed to trigger bone marrow activation, which may manifest as abnormal uptake in imaging studies.

However, the diffuse uptake may also be induced by leukocytopenia or thrombocytopenia arising from copper defi-

ciency. The exact mechanism by which copper deficiency leads to leukocytopenia and thrombocytopenia remains uncertain; however, the findings of this study suggest a potential link between ineffective hematopoiesis and these forms of cytopenia.

In conclusion, this report describes a case of copper deficiency anemia that resulted in diffuse bone marrow uptake on $^{18}$F-FDG PET/CT imaging. This case highlights the importance for clinicians to include copper deficiency anemia in the differential diagnosis of diffuse bone marrow uptake on $^{18}$F-FDG PET/CT scans, especially in the presence of cytopenia.

## Patient consent

Written informed consent was obtained for the publication of this report.

## Data statement

The data presented in this case report is available on request from the correspondent author.

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