

Image Diagnosis: Zinc-Induced Copper Deficiency Causing Pancytopenia Recognized on Bone Marrow Examination

Joyce Johnsrud, MD; Al-Ola Abdallah, MD; Steven A Schichman, MD, PhD; Zhifu Xiang, MD, PhD

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A 66-year-old man presented to the hospital with a 2-week history of generalized weakness, progressive fatigue, and shortness of breath. His medical history was significant for anemia of chronic disease, hypertension, hyperlipidemia, diabetes, gastroesophageal reflux, and Roux-en-Y gastric bypass surgery 30 years earlier. He denied having fever, chills, night sweats, weight change, cough, chest discomfort, hematochezia, melena, hematemesis, or bruising. On physical examination the patient was obese and pale. The rest of the examination was unremarkable. His complete blood count with differential showed white blood cell count of $2.4 \times 10^3/\mu\text{L}$, (38% neutrophils, 41% lymphocytes, 17% monocytes, 3.5% eosinophils, 0.5% basophils), absolute neutrophil count of $700/\mu\text{L}$, hemoglobin of 7.9 g/dL, mean corpuscular volume of 106.1 fL, and platelet count of $138 \times 10^3/\mu\text{L}$. The other blood tests revealed: reticulocyte count 1.2%, total bilirubin 1 mg/dL, vitamin B₁₂ 592 pg/mL, red blood cell (RBC) folate 1500 ng/mL, lactate dehydrogenase 170 U/L, haptoglobin 213 mg/dL, ferritin 183.4 ng/mL, total iron-binding capacity 297, and iron saturation 13%. Serum electrolytes and liver function tests were unremarkable. Peripheral smear (Figure 1) showed moderate anemia with anisocytosis and macrocytosis, as well as mild leukopenia and mild thrombocytopenia; the peripheral smear was negative for myelocytes or myeloblasts. The patient's baseline complete blood count 5 months before his admission showed white blood cell count of $5.8 \times 10^3/\mu\text{L}$, absolute neutrophil count of $4000/\mu\text{L}$, hemoglobin of 10.2 g/dL, mean corpuscular volume of 91 fL, and platelet count of $193 \times 10^3/\mu\text{L}$. Because of his age we proceeded with bone marrow biopsy examination to rule out myelodysplastic syndrome.

The bone marrow aspirate and biopsy showed 60% cellularity, with abnormal erythropoiesis including megaloblastic pronormoblasts with prominent nucleoli and multiple cytoplasmic vacuoles (Figure 2). Some nuclear/cytoplasmic dyssynchrony was noted, but no nuclear budding or bridging was seen in maturing erythroid cells. Myelopoiesis was shifted toward intermediate forms but was not obviously dysplastic. The myeloid:erythroid ratio was within normal limits. There were less than 3% myeloblasts. Megakaryocytes were increased in number without dysplastic features. Cytogenetic analysis showed the normal male karyotype (46, XY). Fluorescent in situ hybridization study of the most common myelodysplastic syndrome-related chromosomal abnormalities, which include +8, -5q, -7q, and -20q, was normal. The bone marrow biopsy results of megaloblastic pronormoblasts with cytoplasmic vacuolization

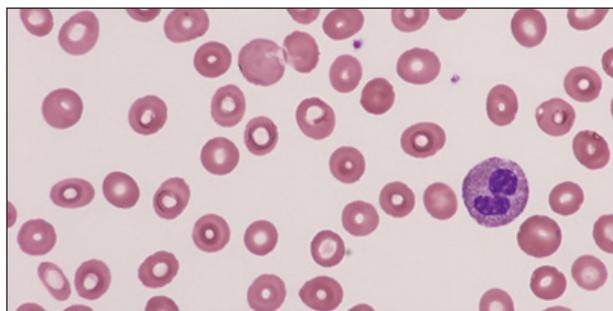


Figure 1. Peripheral smear of the patient's red blood cells, showing anisocytosis with macro-ovalocytes and occasional teardrop cells.

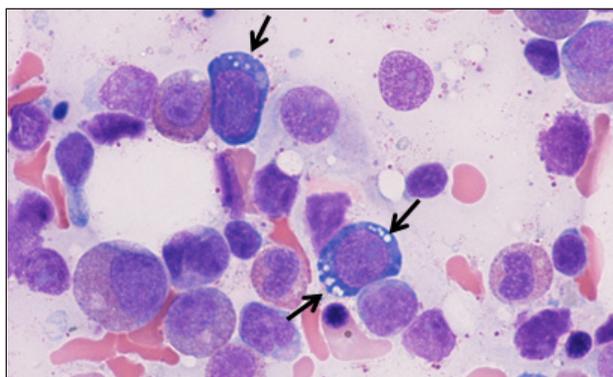


Figure 2. Bone marrow aspirate with the black arrows indicating megaloblastic pronormoblasts with prominent nucleoli and multiple cytoplasmic vacuoles.

suggested exposure to toxic substances or copper deficiency secondary to zinc toxicity. On further interview, the patient denied known toxin exposure but admitted taking daily zinc gluconate 200 mg in addition to other over-the-counter zinc supplements. Subsequent testing revealed an elevated plasma zinc level of 137 $\mu\text{g/dL}$ (normal range 56-134 $\mu\text{g/dL}$) and a markedly low plasma copper level of 7 $\mu\text{g/dL}$ (normal 72-166 $\mu\text{g/dL}$), and ceruloplasmin of 2.1 mg/dL (normal 20-60 mg/dL).

The patient was diagnosed with pancytopenia secondary to hypocupremia from zinc toxicity, possibly exacerbated by his gastric bypass surgery 30 years before. He was started on copper gluconate 8 mg by mouth daily for 1 week, followed by 6 mg daily for 1 week, followed by 4 mg daily for 1 week, and then continued on 2 mg

Joyce Johnsrud, MD, is an Internist at the University of Arkansas for Medical Sciences in Little Rock. E-mail: jjohnsrud@uams.edu. Al-Ola Abdallah, MD, is a Physician in the Division of Hematology and Oncology for the Winthrop P Rockefeller Cancer Institute at the University of Arkansas for Medical Sciences in Little Rock. E-mail: abdallahalola@gmail.com. Steven A Schichman, MD, PhD, is a Pathologist at the University of Arkansas for Medical Sciences, and in the Pathology and Laboratory Medicine Service for the Central Arkansas Veterans Healthcare System in Little Rock. E-mail: schichmanstevena@uams.edu. Zhifu Xiang, MD, PhD, is a Physician in the Division of Hematology and Oncology for the Winthrop P Rockefeller Cancer Institute at the University of Arkansas for Medical Sciences, and in the Division of Hematology and Oncology for the Central Arkansas Veterans Healthcare System in Little Rock. E-mail: zxiang@uams.edu.

daily. He was scheduled for follow-up at our hospital but unfortunately died from unrelated issues before completion of therapy.

DISCUSSION

Acquired copper deficiency, or hypocupremia, is rare in healthy adults because of the wide distribution of copper in the average adult diet.¹ Conditions that lead to copper deficiency include parenteral hyperalimentation, protein-losing enteropathies, gastrectomy, gastric bypass surgery, hypoproteinemic states such as celiac disease, and complications of therapies such as high-dose zinc and penicillamine.¹ The hematologic findings that have been reported in copper deficiency include anemia with neutropenia² and pancytopenia.³⁻⁵ Anemia caused by copper deficiency is progressive in most cases and may have profound effects on bone marrow.⁶

This case of pancytopenia secondary to zinc-induced copper deficiency was initially recognized on bone marrow examination. The patient's zinc level was mildly elevated, and he had a markedly low level of plasma copper. This was possibly caused by malabsorption secondary to his gastric bypass surgery that might have bypassed the major copper absorption sites: the duodenum and the proximal jejunum.⁷ Our patient's bone marrow examination revealed abnormal erythropoiesis with prominent nucleoli and multiple cytoplasmic vacuoles. Similar findings were reported by Willis et al,⁸ who described 3 cases of zinc-induced copper deficiency where the vacuoles ranged from 1 μ m to 3 μ m in size and were present in granulocytes (mainly myelocytes) and the erythroid precursors. Although these vacuoles are not pathognomonic, they are often suggestive of copper deficiency and should prompt clinicians to consult with a hematologist for further evaluation.

Copper deficiency is a recognized cause of anemia and neutropenia.^{9,10} Excess zinc ingestion can occur in patients taking zinc therapeutically for decubitus ulcer healing, celiac disease, glucagonoma, hepatic encephalopathy, acne,^{11,12} and for reducing the duration of symptoms of the common cold.¹³⁻¹⁵ The mechanisms for how excess zinc interferes with copper absorption in enterocytes of the small intestine are not completely understood. Excess zinc levels induce the synthesis of the intracellular ligand metallothionein (MTO) in enterocytes. MTO has a high affinity for transition metals, and MTO-bound metals can be excreted in the feces through enterocyte shedding. Because of its higher affinity for MTO, copper may displace zinc and then be excreted in the feces, reducing the amount of copper delivered to the enterocytes.^{16,17}

Copper plays an essential role in several enzymatic reactions in RBCs, and copper deficiency interferes with iron transport and utilization and, therefore, with heme synthesis. Specifically, ceruloplasmin (which incorporates copper) is a ferroxidase that converts ferrous (+2) iron to ferric (+3) iron, allowing it to bind transferrin and be transported. The copper-dependent enzyme cytochrome-c oxidase also is required for the reduction of ferric iron to incorporate it into the heme molecule.^{1,18} In addition to interference with heme synthesis, there is an approximately 85% reduction of superoxide dismutase in the RBC membrane in copper deficiency, which decreases RBC survival time.¹⁹ The mechanism for neutropenia in copper deficiency is unknown; neutropenia has been demonstrated experimentally in copper-deficient mice and is associated with arrested erythroid maturation.²⁰

CONCLUSION

Acquired copper deficiency from zinc toxicity is rare and is recognizable from characteristic, though not pathognomonic, morphologic features on bone marrow examination. ❖

Disclosure Statement

The authors have no conflicts of interest to disclose.

How to Cite this Article

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