Copper deficiency-induced pancytopenia after taking an excessive amount of zinc formulation during maintenance hemodialysis

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INTRODUCTION

Erythropoiesis-stimulating agent (ESA) has been recognized as an effective way in the treatment of anemia due to chronic kidney disease (CKD), but we sometimes see intractable hemodialysis (HD) patients. The causes of ESA-resistant anemia in HD patients include deficiency of trace elements. We report the case of an 89-year-old male who developed pancytopenia after taking an excessive amount of zinc formulation for ESA-resistant anemia during maintenance dialysis. He was prescribed zinc acetate hydrate formulation about 6 months before his presentation. We suspected a copper deficiency at the first visit and stopped zinc and added copper, and his condition subsequently improved without being handicapped. Zinc antagonizes copper, so we must take care to diagnose patients ingesting zinc supplements.

Key words: Copper deficiency, hemodialysis, pancytopenia, zinc

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The human body contains about 80 mg of copper, about 50% of which is distributed in the muscle or bone and about 10% in the liver. The amount of copper is maintained through a balance of absorption and excretion. Copper plays a vital role as a catalytic cofactor for a variety of metalloenzymes, including superoxide dismutase (for protection against free radicals), cytochrome c oxidase (mitochondrial electron transport chain), tyrosinase (pigmentation), peptidylglycine alpha-amidating mono-oxygenase (neuropeptide and peptide hormone processing), and lysyl oxidase (collagen maturation). Copper deficiency causes anemia, leukopenia, bone abnormalities, and neuropathy, among other issues. Copper is absorbed through either of two pathways: (1) through the absorption of Cu\(^{2+}\) by direct combination with divalent metal transporter 1 and competition with Fe\(^{2+}\) and Zn\(^{2+}\); and (2) through the reduction of Cu\(^{1+}\) in the duodenum and subsequent absorption through combining specifically with copper transporter 1, which is present in the brush border membrane of microvilli in small intestine epithelial cells. 

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We encountered a patient who developed pancytopenia after taking an excessive amount of zinc formulation for ESA-resistant anemia during maintenance dialysis. The pancytopenia improved rapidly by the administration of a copper supplement. We, herein, report this case with a discussion of the relevant literature.

**CASE REPORT**

An 89-year-old male had been receiving HD therapy for 5 years. He had ESA-resistant anemia and was prescribed zinc acetate hydrate formulation (NOBELZIN) 50 mg three times a day after meals about 6 months before his presentation. He was found to have pancytopenia 1 month before his presentation, at which point, he was introduced to our hospital [Figure 1].

He had a history of CKD, hypertension, diabetes, heart failure, arteriosclerosis obliterans, colon cancer, and abdominal aortic aneurysm with no allergies. On a physical examination, his conjunctiva was pale, but he did not have any neurologic symptoms. After consultation, we performed a blood test, and his results revealed severe pancytopenia: white blood cells 2000/μl (BAND 6.0%, SEG 46.5%, EOSINO 3.0%, Baso 2.0%, Mono 15.0%, and Lympho 27.5%), red blood cells 2.70 × 10^6/μl, hemoglobin (Hb) 9.6 g/dl, MCV 90.7 fl, platelets (Plt) 41 × 10^3/μl. There were no blast cells or atypical cells in a peripheral blood smear. Vitamin B12, folic acid, and antinuclear antibody levels were normal, and he requested not to undergo bone marrow aspiration. We suspected him of having a copper deficiency due to taking zinc acetate hydrate formulation, and indeed, his blood test revealed zinc excess and copper deficiency (Zn 264 μg/dl [normal range: 65–110 μg/dl], Cu <2 μg/dl [normal range: 68–128 μg/dl], ceruloplasmin 4 mg/dl [normal range: 21–37 mg/dl]) [Table 1]. Upper gastrointestinal endoscopy revealed no abnormalities.
We stopped the zinc acetate hydrate formulation and added copper orally. We also performed red blood cell transfusion and platelet transfusion to maintain his Hb level >8.0 mg/dl and Plt level >10–20 × 10^3/μl. His copper serum and ceruloplasmin levels recovered within 2 months, and his pancytopenia improved [Figure 2].

**DISCUSSION**

Copper-deficiency anemia is a relatively rare disease, but central venous nutrition, inflammatory bowel disease, gastrectomy, celiac disease, and excessive zinc ingestion sometimes cause copper-deficiency anemia according to several case reports.[9] Zinc is an essential trace element that plays important roles in taste, wound healing, and immunity. Previous reports have shown that zinc deficiency increases the risk of dengue fever.[10] We should take care to avoid excessive zinc ingestion.

Anemia and leukopenia often occur due to copper deficiency, but 10% of copper deficiency patients present with thrombocytopenia.[11] It is difficult to distinguish between copper-deficiency anemia and myelodysplastic anemia because copper-deficiency anemia is characterized by dysplasia, such as the presence of ring sideroblasts.[11] Its treatment is copper supplementation, and copper-deficiency anemia recovers within 4–12 weeks after the addition of copper.[12] One study showed that 93% of hematological abnormalities were completely improved with copper supplementation, but only 25% of neurological symptoms were improved.[9] The median time to the diagnosis of copper-deficiency anemia from the initial presentation with either neurology or hematology is 1.1 years, ranging from 10 weeks to 23 years in several reviews; this suggests that efforts to diagnose copper deficiency earlier should be made.[11]

The present patient had pancytopenia and was suspected of having a hematological disease, so he was introduced to our hospital. We suspected a copper deficiency at the first visit and started our treatment, and his condition subsequently improved without being handicapped. Zinc antagonizes copper, so we must take care to diagnose patients ingesting zinc supplements.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. Drüeke T. Hyporesponsiveness to recombinant human erythropoietin. Nephrol Dial Transplant 2001;16 Suppl 7:25–8.
2. Tsubakihara Y, Nishi S, Akiba T, Hirakata H, Iseki K, Kubota M, et al. 2008 Japanese society for dialysis therapy: Guidelines for renal anemia in chronic kidney disease. Ther Apher Dial 2010;14:240–75.
3. Kadoya H, Uchida A, Kashihara N. A case of copper deficiency-induced pancytopenia with maintenance hemodialysis outpatient treated with polaprezinc. Ther Apher Dial 2016;20:422–3.
4. Tonelli M, Wiebe N, Hemmelgarn B, Klarenbach S, Field C, Manns B, et al. Trace elements in hemodialysis patients: A systematic review and meta-analysis. BMC Med 2009;7:25.
5. Balamurugan K, Schaffner W. Copper homeostasis in eukaryotes: Teetering on a tightrope. Biochim Biophys Acta 2006;1763:737–46.
6. Fosmire GJ. Zinc toxicity. Am J Clin Nutr 1990;51:225–7.
7. Arredondo M, Muñoz P, Mura CV, Núñez MT. DMT1, a physiologically relevant apical Cu2+ transporter of intestinal cells. Am J Physiol Cell Physiol 2003;284:C1525–30.
8. Cobine PA, Pierrel F, Winge DR. Copper trafficking to the mitochondrion and assembly of copper metalloenzymes. Biochim Biophys Acta 2006;1763:759–72.
9. Williams DM. Copper deficiency in humans. Semin Hematol 1983;20:118–28.
10. Rerkxsupapphath S, Rerkxsupapphol L. A randomized controlled trial of zinc supplementation as adjuvant therapy for dengue viral infection in Thai children. Int J Prev Med 2018;9:88.
11. Halfdanarson TR, Kumar N, Li CY, Phylisky RL, Hogan WJ. Hematological manifestations of copper deficiency: A retrospective review. Eur J Haematol 2008;80:523–31.
12. Gabreyes AA, Abbasi HN, Forbes KP, McQuaker G, Duncan A, Morrison I. Hypocupremia associated cytopenia and myelopathy: A national retrospective review. Eur J Haematol 2013;90:1–9.