Case Reports in Oncology

Case Rep Oncol 2023;16:55–61
DOI: 10.1159/000528899
Received: October 14, 2022
Accepted: December 21, 2022
Published online: February 7, 2023

Case Report

Copper Deficiency Mimicking Myelodysplastic Syndrome: Zinc Supplementation in the Setting of COVID-19

Maya Rosenberg[a] Sameep Thapa[b] Chetan Jeurkar[c] Margaret Kasner[c]

[a]Sidney Kimmel Medical College, Philadelphia, PA, USA; [b]Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, PA, USA; [c]Department of Medical Oncology, Thomas Jefferson University Hospital, Philadelphia, PA, USA

Keywords

Zinc supplementation · Copper deficiency · Myelodysplastic syndrome · Anemia · Cancer · Case report

Abstract

While copper deficiency is rare, it can have serious consequences, including pancytopenia and neuropathy. This treatable micronutrient deficiency can present very similarly to myelodysplastic syndrome (MDS), a group of myeloid neoplasms which can carry devastating prognoses. Copper deficiency is an essential differential diagnosis in suspected MDS, as it can present with similar laboratory findings, bone marrow biopsy, and clinical picture. While copper deficiency has multiple potential causes, it typically occurs in patients with a predisposing gastrointestinal pathology. One possible cause of copper deficiency is zinc overload. Interestingly, zinc over-supplementation has been prevalent during the COVID-19 pandemic, as some believe that zinc can help prevent COVID-19 infection. Multiple case reports have illustrated the similarities between copper deficiency and MDS. They have also highlighted zinc over-supplementation as a potential cause. The following case report is unique in that our patient lacked gastrointestinal pathology. He still presented with the clinical and laboratory findings of MDS in the setting of copper deficiency. These include anemia, leukopenia, fatigue, and neuropathy. Further, this deficiency was caused by zinc over-supplementation in efforts to prevent COVID-19. The deficiency and the accompanying symptoms were treated with copper supplementation and cessation of zinc intake.

Correspondence to:
Maya Rosenberg, maya.rosenberg@students.jefferson.edu

Case Rep Oncol 2023;16:55–61
DOI: 10.1159/000528899

Introduction

Copper deficiency is a rare clinical entity. Symptomatic copper deficiency has mostly been described in cases of patients with gastrointestinal pathology such as celiac disease, irritable bowel syndrome, status-post gastric bypass surgery, and those requiring total parenteral nutrition [1, 2]. Copper deficiency can have serious consequences, such as anemia, leukopenia, and irreversible neuropathy [3, 4]. The laboratory findings and symptoms of copper deficiency sometimes mimic those of myelodysplastic syndrome (MDS), a group of myeloid neoplasms characterized by abnormal differentiation and maturation of myeloid cells, bone marrow (BM) failure, and gene instability with high risk of transformation into acute myeloid leukemia [5].

In 2002, one case report described a patient with history of gastric resection who presented with chronic macrocytic anemia refractory to folate and B12 supplementation, leukopenia, progressive peripheral neuropathy, and optic neuritis. BM biopsy showed findings consistent with MDS. It was only once a nutrition consultation was obtained during evaluation for BM transplant that the copper level was found to be undetectable. With sufficient copper supplementation, the patient's laboratory values normalized, and BM biopsy showed reversal of previous abnormalities [6]. Another article strongly encouraged providers to consider copper deficiency in the differential diagnosis of MDS, reporting 5 patients who had presented with anemia and BM findings consistent with MDS and were later found to have copper deficiency [7]. Most of these patients had history of gastrointestinal disorder, presumably leading to copper malabsorption.

Studies have also shown that copper deficiency can be caused by zinc overload [8, 9]. It is thought that increased zinc content in the gastrointestinal tract stimulates the upregulation of metallothionein in enterocytes. This protein is responsible for binding and excreting both zinc and copper. Copper has a higher binding affinity to metallothionein than zinc, meaning that increased zinc ingestion has the potential to cause increased copper excretion and decreased copper absorption [10]. With the unprecedented surge of COVID-19 in the USA in March 2020, many people were willing to go to great lengths to avoid getting infected. Zinc made news headlines as various articles were written with the implication that zinc, which is accessible over the counter, could help in preventing and improving the prognosis and treatment of COVID-19 [11]. However, many argue that this impact had not been sufficiently studied [12]. A 2020 report discussed a patient with history of irritable bowel syndrome who presented with anemia and neutropenia, with a subsequent normal BM biopsy. Copper level was found to be undetectable, at which point it was discovered that the patient had been taking zinc supplementation in hopes of strengthening her immune system to prevent COVID-19 infection. The patient had been taking eight times the recommended daily amount of zinc for women, which is 8 mg/d. Following filgrastrim and blood transfusion, the patient was instructed to stop zinc supplementation and was started on copper supplementation. Her neutropenia quickly resolved [13]. This case is one example of the implications of zinc ingestion during the COVID-19 pandemic. In the following case, we discuss a patient with no significant past medical history who attempted to use zinc supplementation to prevent COVID-19 infection, resulting in life-threatening complications of copper deficiency which mimicked MDS.

Case Presentation

A 48-year-old male with no significant medical history presented to his local emergency room (ER) at an outside hospital at the recommendation of his primary care provider (PCP). He had sought care for persistent fatigue, for which general laboratory tests were ordered and

Case Rep Oncol 2023;16:55–61
DOI: 10.1159/000528899

revealed anemia and leukopenia. On arrival, the patient was hemodynamically stable. Review of symptoms was positive for paresthesia in both hands, which had previously been attributed to cervical spondylosis seen on X-ray. The patient also reported reduced exercise tolerance, noting that he was previously able to ride his bike for eight miles per day. More recently, the patient had struggled to carry groceries or complete his yardwork.

Initial laboratory results revealed macrocytic anemia with hemoglobin (Hgb) of 6.7 g/dL and a mean corpuscular volume (MCV) of 107 fL, leukopenia with a white blood cell (WBC) count of 1.4×10^3/μL and an absolute neutrophil count (ANC) of 490/μL, along with platelets of 459×10^9/L. Additional history revealed COVID-19 infection 6 months prior to the presentation. He otherwise denied any recent infections, family history of malignancy or autoimmune diseases, or new medications. He did endorse taking multiple supplements at home, the contents of which were unknown. Further workup showed low iron of 22 μg/dL, normal iron-binding capacity of 318 μg/dL, elevated ferritin of 1,160 ng/mL as well as normal folate and vitamin B12 levels. Viral serologies including hepatitis B and C, cytomegalovirus, Epstein-Barr virus, and human immunodeficiency virus were all negative. Peripheral smear review was significant for macrocytosis, target cells, dacrocytes (tear drop cells), along with atypical immature white blood cells concerning for blasts. Given these findings, the patient was transferred to a tertiary center for further care.

Upon arrival at our hospital, physical exam was unremarkable. Further workup for suspected MDS was ordered, including a hematologic gene malignancy panel, fluorescence in situ hybridization, flow cytometry, serum and urine electrophoresis, and reticulocyte count. BM biopsy revealed hypercellular marrow (80–90%) with dysplastic features in the erythroid lineage. There were cytoplasmic vacuoles in erythroid and myeloid precursors with rare erythroid cells also showing nuclear budding, as seen in Figure 1a and b, respectively. These findings were consistent with the possible diagnosis of MDS. Additionally, ring sideroblasts were increased by 14%, as seen in Figure 2. There was no increase in blasts.

Given the fact that ring sideroblasts can be seen in a diagnosis of copper deficiency, the patient's copper level was drawn. The testing revealed that the patient's copper level was <5 μg/dL. When asked specifically about his supplement intake, the patient stated that he had previously been taking large amounts of zinc supplementation as he believed it would be helpful in the prevention of COVID-19 infection. He was unsure of the daily dose he had taken but stated he took the supplements for about 6 months and had stopped 2 months before presenting to the hospital. A zinc level was then drawn which was elevated at 133 μg/dL (60–130 μg/dL). At a follow-up visit, the patient was asked to bring the zinc supplements he had previously consumed. He provided a 100-count package of 50 mg zinc tablets, which was about 95% empty.

These findings pointed toward a potential role of zinc overdose in inducing severe copper deficiency. This deficiency is likely what resulted in the patient's anemia, leukopenia, and paresthesia. The patient was started on copper supplementation of 8 mg daily with instruction to decrease the dose by 2 mg every week and was advised to stop taking zinc. His Hgb and WBC counts subsequently improved, as illustrated in Table 1.

During his most recent visit, the patient noted that his neuropathy was still present, although improved. He denied significant fatigue, shortness of breath, fevers, or chills.

Discussion

This case emphasizes the importance of including copper deficiency as a differential diagnosis for MDS, even in patients without typical predisposing risk factors. It also illustrates

Case Rep Oncol 2023;16:55–61
DOI: 10.1159/000528899

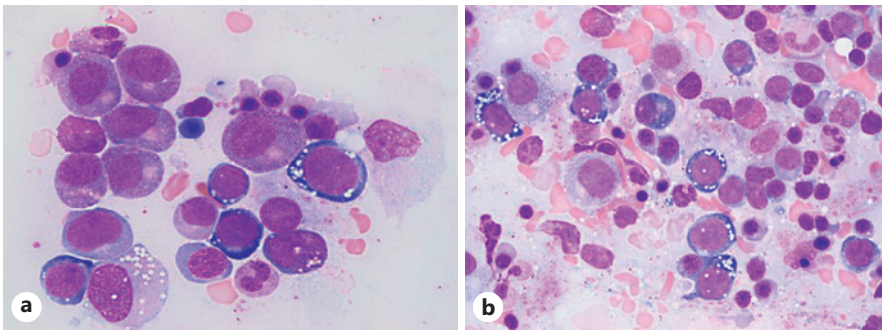

Fig. 1. a BM aspirate, Wright-Giemsa stain. Cytoplasmic vacuoles in erythroid and myeloid precursors. BM biopsy revealed hypercellular marrow (80–90%) with dysplastic features in the erythroid lineage. These changes included cytoplasmic vacuoles in erythroid and myeloid precursors. These findings pointed toward a diagnosis of MDS. **b** BM aspirate, Wright-Giemsa stain: Rare erythroid cells with nuclear budding BM biopsy additionally revealed rare erythroid cells also showing nuclear budding, which contributed to the possible diagnosis of MDS.

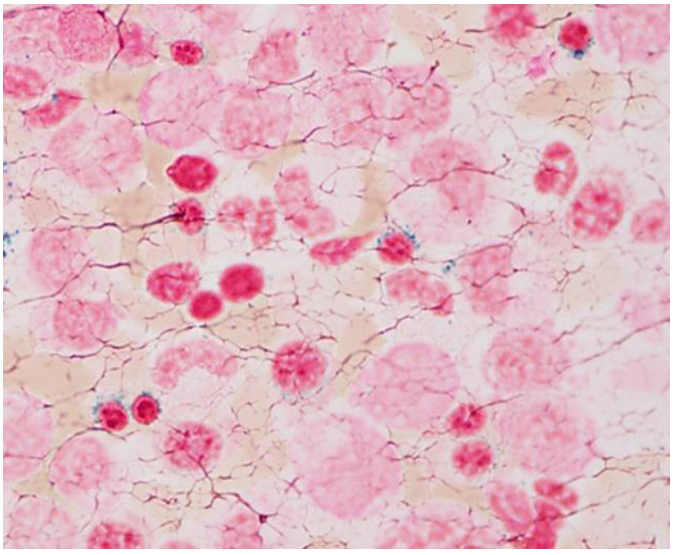

Fig. 2. BM aspirate, iron stain. Ring sideroblasts. BM aspirate also revealed ring sideroblasts, which are not consistent with the diagnosis of MDS. This finding prompted the team to draw a copper level, as this finding can be seen in copper deficiency.

Table 1. Hemoglobin and WBC prior to and following copper supplementation

Date	Hemoglobin, g/dL	WBC, $\times 10^3/\mu L$
5/16: admission to hospital	6.7	1.4
5/18: discharged from hospital	7.7	2.0
5/25	7.7	2.5
5/26: begins copper supplementation		
6/6	9.7	3.8
6/20	10.5	7.2

the impact of zinc supplementation in causing copper deficiency, specifically when taken in attempted prevention of COVID-19 infection.

Several cases in the literature have shown similar hematologic and neurologic findings in patients with copper deficiency, some of which are presumed to be due to zinc overload. These

Case Rep Oncol 2023;16:55–61
DOI: 10.1159/000528899

reports have mostly included patients with additional predispositions to copper deficiency, such as irritable bowel syndrome, celiac disease, or gastric bypass surgery. For example, one review article discussed 8 patients who had been referred for evaluation of unexplained anemia and neutropenia with myelodysplasia [14]. Like our patient, five of these patients also experienced peripheral neuropathy. Seven patients were treated with oral copper gluconate with subsequent hematologic and symptomatic recovery. In five of these patients, the cause of copper deficiency was felt to be gastrointestinal malabsorption. A 2006 case report similarly discussed a patient with history of gastrectomy with Roux-en-Y gastric bypass and partial small bowel resection who presented to the ER complaining of progressive numbness and tingling in the distal lower extremities. Laboratory results revealed hematocrit of 17%, MCV of 105.9 fL, WBC of 2×10^3/μL with 40% neutrophils, and normal B12 and folate levels. Peripheral smear showed nucleated red blood cells; however, a BM biopsy was refused by the patient. Eventually, further laboratory evaluation revealed a ceruloplasmin level of <10 mg/dL. The zinc level was normal at 96 μg/dL (60–130 μg/dL). The patient was started on 2 mg/d of intravenous copper sulfate with improvement of copper levels over 2 weeks [15]. Unfortunately, this patient's peripheral neuropathy was irreversible. In contrast, our patient's neuropathy resolved following copper supplementation. Additionally, the 2006 report describes a patient with a normal zinc level. This patient's copper deficiency was due to her abnormal gastrointestinal anatomy, leading to malabsorption. Although this is the most common reason for copper deficiency, it is important to note that copper deficiency can also occur in patients without history of gastrointestinal illness.

A 2002 case report described a 27-year-old male with history of acne who presented to his PCP with 1 month of fatigue, dyspnea on exertion, night sweats, and 4.5-kg (10 lb) weight loss. The patient was found to be profoundly anemic with Hgb of 5 g/dL and leukopenic with WBC of 1.2×10^9/L. Inquiry into medication history revealed that the patient had taken zinc gluconate, 850–1,000 mg/d for 1 year to help treat his acne. The patient's copper level was found to be 0.10 μg/mL, and his zinc level was 3.18 μg/mL (0.66–1.10 μg/mL). Unfortunately, the patient's hospital course was complicated by neutropenic fever due to acute sinusitis. His copper, zinc, WBC, and Hgb levels remained unchanged despite supplementation with intravenous (IV) copper sulfate at 2 mg/d. The patient required subcutaneous human granulocyte colony-stimulating factor for 5 days prior to count recovery and fever resolution. Upon discharge, an oral copper sulfate regimen was started at 10 mg/d for the first 10 days followed by 2 mg/d for 10 weeks. During the next 3 months, the patient's complete blood count and copper and zinc levels returned to normal [10]. Like our case, this case is an example of copper deficiency due to zinc overdose in a patient with no significant medical history. Additionally, this patient took zinc to treat another medical condition, which is like our patient, who took zinc in order to prevent COVID-19 infection. This patient experienced worse symptoms and laboratory findings than our patient, likely due to greater zinc intake over a longer period of time. This patient refused BM biopsy, and thus these findings cannot be compared.

One other case report has discussed copper deficiency caused by zinc overdose in a patient attempting to avoid COVID-19 infection. This case discussed a 66-year-old woman with history of irritable bowel syndrome with diarrhea, coronary artery disease, and macrocytic anemia on chronic B12 supplementation. This patient presented with worsening diarrhea. Laboratory results revealed macrocytic anemia with Hgb 8.8 g/dL, MCV of 130 fL, and neutropenia with ANC of 0.61/μL. The patient's copper level was undetectable, and zinc was elevated at 2.04 μg/mL (0.66–1.10 μg/mL). Additional laboratory studies, imaging, and BM biopsy were unrevealing. It was eventually noted that the patient had been taking at least 65 mg of zinc supplementation per day in hopes of strengthening her immune system during COVID-19, in place of vaccination. The patient received 3 days of filgrastrim and one blood transfusion and was discharged on copper supplementation with recommendation to discontinue zinc supplementation. Her ANC returned to normal over the course of 5 days, where

it remained for the subsequent 60 days of monitoring [13]. This patient is like our patient in that her copper deficiency was likely due to zinc overdose in an attempt to prevent COVID-19 infection. However, this patient's irritable bowel syndrome likely contributed to her nutritional deficiency, whereas our patient had no significant medical history. Lastly, this patient did not present with classic symptoms of copper deficiency, whereas our patient presented with fatigue and peripheral neuropathy.

This case makes clear that healthy individuals without significant medical history can also suffer the harmful consequences of copper deficiency, brought on by zinc supplementation, which might mimic other serious hematologic disorders such as MDS, and the workup should always include this consideration. Education of physicians and the public on this consequence of unsupervised zinc supplementation is extremely important. This case brings necessary attention to a rare but real consequence of zinc supplementation used to prevent COVID-19 infection. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000528899).

Statement of Ethics

This study protocol was approved and exempt by the Sidney Kimmel Cancer Center Protocol Review Committee, approval number 2022-128. Written informed consent was obtained from the subject in this study for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was required for this case report.

Author Contributions

Maya Rosenberg, Sameep Thapa, Chetan Jeurkar, and Margaret Kasner all contributed to writing and editing this report.

Data Availability Statement

All data generated or analyzed during this study are included in this article and the supporting files. Further inquiries can be directed to the corresponding author.

References

1 Kumar P, Hamza N, Madhok B, De Alwis N, Sharma M, Miras AD, et al. Copper deficiency after gastric bypass for morbid obesity: a systematic review. Obes Surg. 2016 Jun;26(6):1335–42.

Case Rep Oncol 2023;16:55–61
DOI: 10.1159/000528899

2 Halfdanarson TR, Kumar N, Hogan WJ, Murray JA. Copper deficiency in celiac disease. J Clin Gastroenterol. 2009 Feb 1;43(2):162–4.
3 Wazir SM, Ghobrial I. Copper deficiency, a new triad: anemia, leucopenia, and myeloneuropathy. J Community Hosp Intern Med Perspect. 2017 Oct 2;7(4):265–8.
4 Myint ZW, Oo TH, Thein KZ, Tun AM, Saeed H. Copper deficiency anemia: review article. Ann Hematol. 2018 Sep;97(9):1527–34.
5 Valent P, Horny HP, Bennett JM, Fonatsch C, Germing U, Greenberg P, et al. Definitions and standards in the diagnosis and treatment of the myelodysplastic syndromes: consensus statements and report from a working conference. Leuk Res. 2007 Jun 1;31(6):727–36.
6 Gregg XT, Reddy V, Prchal JT. Copper deficiency masquerading as myelodysplastic syndrome. Blood. 2002 Aug 15;100(4):1493–5.
7 Fong T, Vij R, Vijayan A, DiPersio J, Blinder M. Copper deficiency: an important consideration in the differential diagnosis of myelodysplastic syndrome. Haematologica. 2007 Oct 1;92(10):1429–30.
8 Hoffman HN, II, Phyliky RL, Fleming CR. Zinc-induced copper deficiency. Gastroenterology. 1988 Feb 1;94(2):508–12.
9 Duncan A, Yacoubian C, Watson N, Morrison I. The risk of copper deficiency in patients prescribed zinc supplements. J Clin Pathol. 2015 Sep 1;68(9):723–5.
10 Igic PG, Lee E, Harper W, Roach KW. Toxic effects associated with consumption of zinc. Mayo Clin Proc. 2002;77(7):713–6.
11 Souza AC, Vasconcelos AR, Prado PS, Pereira CP. Zinc, vitamin D and vitamin C: perspectives for COVID-19 with a focus on physical tissue barrier integrity. Front Nutr. 2020;7:606398.
12 Arentz S, Hunter J, Yang G, Goldenberg J, Beardsley J, Myers SP, et al. Zinc for the prevention and treatment of SARS-CoV-2 and other acute viral respiratory infections: a rapid review. Adv Integr Med. 2020 Dec 1;7(4):252–60.
13 Francis Z, Book G, Litvin C, Kalivas B. The COVID-19 pandemic and zinc-induced copper deficiency: an important link. Am J Med. 2022 Mar 31;135(8):e290–e291.
14 Huff JD, Keung YK, Thakuri M, Beaty MW, Hurd DD, Owen J, et al. Copper deficiency causes reversible myelodysplasia. Am J Hematol. 2007 Jul;82(7):625–30.
15 Wu J, Ricker M, Muench J. Copper deficiency as cause of unexplained hematologic and neurologic deficits in patient with prior gastrointestinal surgery. J Am Board Fam Med. 2006 Mar 1;19(2):191–4.