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CASE REPORT

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Zinc-induced hypocupremia and pancytopenia, from zinc supplementation to its toxicity, a case report

Ahsan Wahab [a], Kamran Mushtaq [b], Aqsa Khan [c], Muhammad Shahzeb Khan Khakwani [d], Adeel Masood [e], Jeremey Henderson [f] and Faizan Malik [g]

[a]Hospital Medicine/Internal Medicine, Baptist Medical Center South, Montgomery, AL, USA; [b]Hospital Medicine/Internal Medicine, Northeast Internal Medicine Associates, LaGrange, IN, USA; [c]Department of Medicine, Fatima Jinnah Medical University, Lahore, Pakistan; [d]Department of Medicine, Nishtar Medical University, Multan, Pakistan; [e]Hospital Medicine, TidalHealth Peninsula Regional, Salisbury, MD, USA; [f]Pathology Department, Delta Pathology, Shreveport, LA, USA; [g]Hematology Oncology Department, Northshore Oncology Associates, New Orleans, LA, USA

ABSTRACT

According to one estimate, zinc supplementation is widely used in the USA by almost 37% of the elderly population above age 71. Zinc has perceived benefits of immune system enhancement without realizing the harmful effects when used in excess. One of its under-recognized side effects is hypocupremia or copper deficiency due to excessive gastrointestinal losses as excessive zinc in the gut competes with copper for absorption. If severe, hypocupremia can cause hematologic changes (anemia, leukopenia/neutropenia, thrombocytopenia, and pancytopenia) with and without neurological deficits. Since zinc-induced hypocupremia is an overlooked entity, there is a lag of 12 months between the onset of symptoms and diagnosis. Most patients usually undergo a series of costly and sometimes invasive tests such as bone marrow biopsies during this lag time. Once diagnosed, the treatment is as simple as discontinuation of zinc and oral copper supplements. Here, we present a case report of zinc-induced hypocupremia and pancytopenia in an 81-year-old lady who was taking zinc supplements for macular degeneration. The patient presented with leukopenia with neutropenia, thrombocytopenia, and moderate anemia. This case report aims to educate clinicians since this is an easily missed entity and likely more prevalent than known due to widely used zinc supplementation.

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1. Introduction

Zinc is an essential trace micronutrient that regulates many vital functions in the human body, such as immunity, metabolism, repair, and regeneration [1]. About 50% of the adults in the USA (US) consume dietary supplements and about 33% of the population uses multivitamins and minerals (MVMs), including those containing zinc [2,3]. The use of MVMs in the US has reduced the nutritional inadequacies [2]. The consumption of zinc supplements seems to be the highest among those who are 71 years and above, approximately 37% of the US population. The highest prevalence of zinc supplementation among the US elderly population might be due to its antioxidant and anti-inflammatory properties favoring atheroprotection and prevention of neurodegeneration [4]. Zinc intake is also associated with the prevention of age-related macular degeneration in high-risk individuals. Though zinc intake has many beneficial properties, its excess is not without side effects [5]. The over-ingestion of zinc can cause hypocupremia, that is, copper deficiency in the serum. Both zinc and copper are divalent cations that compete with each other in the gastrointestinal tract and relative excess of zinc induces the defective absorption of copper. We report an elderly female who developed pancytopenia and neutropenia secondary to zinc-induced hypocupremia. She was taking an MVMs supplement containing 80 mg of zinc for macular degeneration. The discontinuation of zinc supplement and oral copper led to the improvement in blood counts.

2. Case report

An 81-year-old female with past medical history of anemia of chronic disease, ischemic stroke, chronic anticoagulation therapy, chronic renal insufficiency, liver disease (mild, chronic elevation of liver functions), and macular degeneration came to the hematology office as a referral from her primary care physician due to pancytopenia. She denied nausea, vomiting, headache, dizziness, myalgia, arthralgia, rash, bleeding, or clotting. The patient was a former smoker and did not drink alcohol. Her home medications included amlodipine, aspirin, cilostazol,

CONTACT Ahsan Wahab drahsan.wahab@gmail.com Baptist Medical Center South, Montgomery, AL 36116

cyanocobalamin, furosemide, metoprolol, pantoprazole, MVMs, potassium chloride tablets, and rosuvastatin. Her vitals were blood pressure: 144/63 mmHg, pulse: 89 beats/minute, respirations: 18/minute and temperature: 97.9°F. On examination, she appeared healthy without obvious signs of distress. Her oropharynx was unremarkable for stomatitis, mucositis, or ulcerations. There was no jaundice. Neck was without lymphadenopathy or thyromegaly. Lungs were clear to auscultate. Cardiovascular auscultation showed normal cardiac sounds without murmur, gallop, or rub. Abdomen was soft, non-tender without visceromegaly. Cranial nerves were intact, and there were no sensory or motor deficits. Skin had normal turgor and showed no petechiae, bruises or rash. Her labs showed white blood cell count of 1.35 × 10^9/l (reference range (RR): 4.5–11.0 × 10^9), hemoglobin 7.1 gm/dl (RR: 12.3–15.3), hematocrit 22.4% (RR: 35.9–44.6), mean corpuscular volume (MCV) 92 FL (RR: 80–96), mean corpuscular hemoglobin concentration (MCHC) 31.7 g/dl (RR: 33.4–35.5) and platelet count of 99 × 10^9/l (RR: 150–400 × 10^9). The patient was severely neutropenic with an absolute neutrophilic count of 0.1 × 10^9/l (RR: 1.8–7.8 × 10^9). Sodium level was 137 mmol/l (RR: 135–145), potassium 3.3 mmol/l (RR: 3.7–5.2), creatinine 1.46 mg/dl (RR: 0.6–1.3), BUN 27 mg/dl (RR: 6–20), bicarbonate 28 mmol/l (RR: 23–29) and chloride 104 mmol/l (RR: 96–106). Thyroid functions were within normal range. Aspartate aminotransferase (AST) was 106 U/l (RR: 8–33), Alanine transaminase (ALT) 102 U/l (RR: 4–36) and bilirubin 0.9 mg/dl (RR: 0.1–1.2). HIV, HBV, and HCV screens were negative. Vitamin B12 and folate levels were normal. Ultrasound abdomen was negative for hepatosplenomegaly. To rule out acute myeloid leukemia and myelodysplastic syndrome (MDS), bone marrow biopsy was performed which showed mild megaloblastoid changes, mild myeloid shift and nonspecific dyshematopoeitic changes. Erythroid and myeloid precursors with vacuolization and megalobastoid changes are shown in Figure 1. No ring sideroblasts were seen on bone marrow biopsy. Fluorescence in-situ hybridization (FISH) study for MDS Panel (5/5q, 7/7q, 8, MLL, 20q) was normal.

The patient had history of macular degeneration and was taking MVMs for many years. For possible zinc-induced hypocupremia, we ordered serum zinc and serum copper levels. Zinc level was 168 ug/dl (RR: 60–130) and the copper level was <10 ug/l (RR: 810–1990). MVMs containing 80 mg of zinc (this MVMs contained 2 mg of copper as well but apparently dose was not sufficient enough to compensate for zinc excess) was discontinued and the patient was started on oral copper 8 mg daily. With the two-week treatment of oral copper, the patient's white blood cell count improved from 1.35 to 7.13 × 10^9/l, hemoglobin from 7.1 to 9.8 g/dl and platelet from 99 to 216 × 10^9/l. Absolute neutrophil count improved to 5.1 × 10^9 from 0.1 × 10^9/l (Table 1). Serum zinc and copper levels normalized in 4 weeks period.

3. Discussion

About 5–8% of the US population that takes zinc supplements can exceed its daily tolerable upper limits (UL) [6]. For zinc, the daily tolerable UL is 40 mg, with recommended dietary allowance (RDA) of 8 mg and 11 mg/day for women and men, respectively [7]. The dose of elemental zinc in dietary supplements varies depending upon the formulation (zinc sulfate/oxide/acetate/gluconate) used which may also impact supplemental toxicity. Therefore, few compounds might offer more elemental zinc bioavailability compared to others and enhance toxic intake. Foods rich in zinc (seafood such as oysters/crabs/lobsters, beef chuck/patty, pork chop, baked beans, and pumpkin seeds) [8] in addition to daily supplements might perpetuate absorption. For copper, the RDA for both men and women is 900 mcg/day [7]. The excess intake of zinc interferes with the absorption of copper. Both these divalent cations are ligands of metallothionein proteins in enterocytes that regulate their absorption. When zinc exposure increases, it

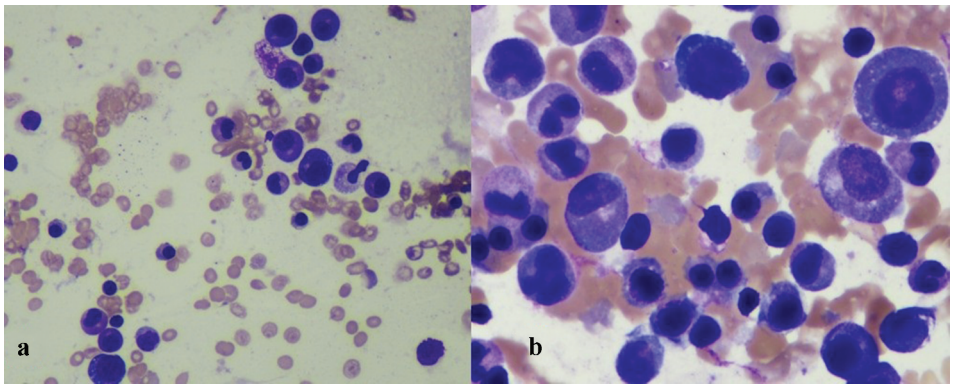

Figure 1. Bone marrow aspirate showing erythroid and myeloid precursors with vacuolization and megaloblastoid changes a: low power field, b: high power field.

Table 1. Showing laboratory trend of pancytopenia at baseline and at 2–4 week interval following zinc discontinuation and copper supplementation.

Laboratory	Baseline	At 2–4 weeks	Reference values
White blood cells	1.35 x 10^9/l	7.13 x 10^9/l	4.5–11.0 x 10^9/l
Absolute neutrophils	0.1 x 10^9/l	5.1 x 10^9/l	1.8–7.8 x 10^9/l
Hemoglobin	7.1 g/dl	9.8 g/dl	12.3–15.3 g/dl
Platelets	99 x 10^9/l	216 x 10^9/l	150–400 x 10^9/l
Serum zinc	168 ug/dl (High)	Normal	60–130 ug/dl
Serum copper	<10 ug/l (Low)	Normal	810–1990 ug/l

potentiates the production of more and more metallothionein proteins so that zinc can bind with those proteins and prevent its excessive absorption. But as metallothionein production amplifies in enterocytes, it preferentially binds with copper rather than zinc given a higher affinity for copper hampering its absorption into the systemic circulation [9]. Hypocupremia, copper deficiency, can present with hematologic (micro/macro/normocytic anemia, leukopenia, and neutropenia) and neurological complaints (myelopathy, neuropathy, optic neuropathy) [10]. In a national study from Scotland, among 16 patients identified with copper deficiency, 15 patients had hematologic presentation as an initial feature followed by neurological complications [11]. The neurological deficits can range from mild sensory loss to severe symptoms of ambulatory dysfunction that can be debilitating for patients. Hematologically, pancytopenia or isolated thrombocytopenia are rare features of hypocupremia when compared with anemia or leukopenia [10]. Our patient presented with pancytopenia which itself due to hypocupremia is rare. Bone marrow findings in copper deficiency are nonspecific and may commonly contain vacuolization of myeloid and erythroid precursors and dysplastic changes and uncommonly ring sideroblasts [11]. Virtually, any formulation of zinc (zinc creams, Pica, topical ointments, MVMs) should be able to cause zinc toxicity. Apart from oral or enteral route, topical forms are reported to cause zinc-induced hypocupremia. With oral supplements of MVMs, only a couple of cases have been reported thus far [12]. Previously oral denture creams have been reported causing zinc-induced hypocupremia, this can also be considered as form of oral supplement, though the intent of use might be different. Oral dental fixatives are relatively a common cause of hypocupremia when compared to oral MVMs [11,12]. Our patient was using zinc supplement for macular degeneration and developed pancytopenia. Zinc toxicity and copper deficiency were able to explain the cause of pancytopenia in the presence of supplemental history. There is an average delay of 12 months before the diagnosis of symptomatic hypocupremia [11] and primary care physicians, however, can effectively diagnose and manage such conditions with simple testing and management strategies, i.e., blood testing for zinc and copper levels and discontinuation of zinc supplements. When pancytopenia presents in primary care setting in an apparently healthy individual without obvious concerns for malignancy/chemotherapy toxicity, sepsis or disseminated intravascular coagulation, basic workup may include complete metabolic panel, vitamin B12, folate, zinc, copper, Hepatitis B and C, HIV, EBV, ANA and peripheral blood smear.

The discontinuation of zinc supplements with or without copper supplements might avoid more cumbersome or invasive investigations, such as bone marrow biopsy. Diets rich in copper (beef liver, seafood (oysters, crabs, and salmon), chocolates, vegetables (mushrooms, potatoes, and chickpeas) and grains (cashew nuts, sunflower seeds, and millets) may be advised ensuring that they do not interfere with or exacerbate patient's existing health problems [13].

Increment in copper levels could be expected in 3–4 weeks following withdrawal of zinc and/or supplementation of copper [14]. Copper supplements when used can be given for a period of 1 to 6 months depending upon choice of empiric regimen (examples, regimen 1: Starting from 8 mg of oral copper daily for 1st week followed by 6 mg daily for a week followed by 4 mg daily for a week and then 2 mg daily afterward; regimen 2: Oral copper 2 mg 3 times a day; regimen 3: IV copper chloride 1–1.75 mg daily for 4–5 days followed by same dose once-weekly or every other week) and serial copper and zinc levels [12,15,16]. Zinc supplements could be restarted in future, preferably after correction of copper deficiency and when there is evidence of zinc deficiency. Serial copper and zinc levels should be performed to tailor therapy, i.e., stopping copper versus continuing it, holding zinc vs resuming zinc.

Cytopenias usually respond promptly to the copper supplement as shown in our patient but when patients have profound neurological complaints at late stages [10], they might be irreversible leaving patients as wheelchair bound.

4. Conclusion

Zinc supplements in the elderly may cause hypocupremia which in return may lead to pancytopenia. In other words, zinc supplementation may lead to toxicity and copper deficiency. Simple serum copper and zinc levels can reveal the etiology of pancytopenia. Discontinuation of supplements and oral copper can revert pancytopenia. Early diagnosis and treatment can prevent significant neurological morbidity.

Disclosure statement

No potential conflict of interest was reported by the author(s).

ORCID

Ahsan Wahab http://orcid.org/0000-0003-3597-1838

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