

CASE REPORT



Copper deficiency, a new triad: anemia, leucopenia, and myeloneuropathy

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ABSTRACT

Clinical copper deficiency is now more frequently recognized. Hematologically, it can present as anemia (microcytic, normocytic, or macrocytic) and neutropenia. Thrombocytopenia is relatively rare. Neurologically, it can manifest as myelopathy and peripheral neuropathy simulating subacute combined degeneration. Bone marrow findings can mimic myelodysplasia resulting in occasional inappropriate referral for bone marrow transplantation. Other conditions with similar presentations include infections, drug toxicity, autoimmunity, B₁₂ deficiency, folate deficiency, myelodysplastic syndrome, aplastic anemia, and lymphoma with bone marrow involvement. Hematological, but not neurological, manifestations respond promptly to copper replacement, making early diagnosis essential for good outcome. Common risk factors for copper deficiency are foregut surgery, dietary deficiency, enteropathies with malabsorption, and prolonged intravenous nutrition (total parenteral nutrition). We present a unique case of copper deficiency, with no apparent known risk factors.

ARTICLE HISTORY

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KEYWORDS

Copper; anemia; leukopenia; myelopathy

1. Case report

A 72-year-old female with known phlebotomy-dependent hemochromatosis, pernicious anemia, hypertension, hypothyroidism, and bipolar disorder presented with progressive generalized weakness, lower extremity numbness, tingling, abnormal balance, and a 26-lb weight loss over several months. Her family history was significant for colon cancer in paternal grandfather, and pancreatic and breast cancer in her sisters. She lived alone, smoked cigarettes, but denied alcohol consumption. Her medications included acetaminophen, aspirin, carbamazepine, cyanocobalamin, darbepoetin alfa, fluticasone nasal spray, levothyroxine, lisinopril, magnesium hydroxide, meclizine, metoprolol tartrate, pantoprazole, fluoxetine, quetiapine, and multivitamins. Physical examination revealed pallor, lower extremity hypoflexia, and sensory ataxia.



Laboratory values checked at the time of presentation are displayed in [Table 1](#). Her complete metabolic panel was essentially unremarkable. Bone marrow biopsy showed myelodysplasia with no megaloblasts, with normal iron stains ([Figures 1](#) and [2](#)). Esophagogastroduodenoscopy and colonoscopy showed normal findings.

Her copper level was undetectable at <5 (reference range 70–125 µg/dL). She was given intravenous followed by oral copper supplementation. Within 4–6 weeks of copper replacement, her macrocytic anemia and leukopenia resolved but neurological

manifestation persisted. [Table 2](#) shows her laboratory values after copper supplementation. Her neurological symptoms started to alleviate in 5–6 months after copper supplementation but did not resolve completely. On subsequent outpatient visits over a year, her weight remained stable and she reported only mild generalized weakness.

2. Discussion

Copper, a trace element, is heavily involved in cell oxidation and signaling systems. Etiology of anemia in copper deficiency is complex and multifactorial. Ceruloplasmin, a major copper carrying protein in the blood, oxidizes ferrous iron to ferric form which allows iron to be transported in the circulation and bind to transferrin. Another important element in copper-iron interaction is Hephaestine, which is a copper-dependent ferroxidase. This is a transport protein involved in iron absorption from enterocytes [1], which can explain the development of microcytic hypochromic anemia in some patients. Macrocytosis, neutropenia, and neurological manifestations are related to the role of copper as an important cofactor in enzymatic processes involved in cell division and protein synthesis. Copper acts as a cofactor in several enzymes that have a critical role in the structure and function of the central nervous system. These enzymes include cytochrome-c-oxidase in the mitochondrial electron transport chain and oxidative phosphorylation, superoxide dismutase for oxidative

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Table 1. Laboratory values in parenthesis represent reference range.

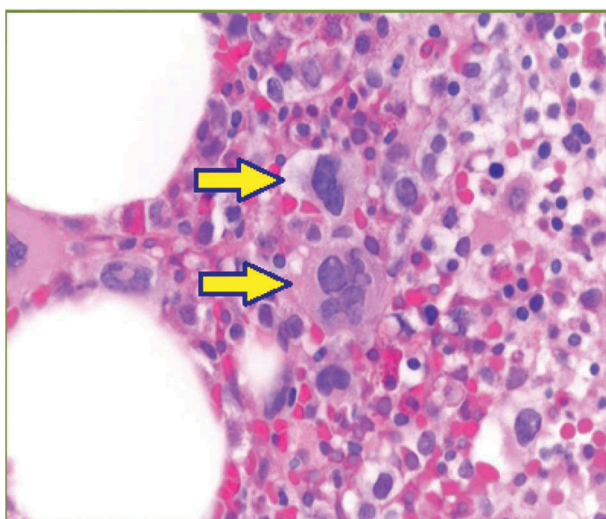
Hemoglobin (11.6–14.6 g/dl)	12.1 g/dl	7.7 g/dl
Hematocrit (38–50%)	35.6	22.9
Mean corpuscular volume (80–95)	95.9	106.2
Platelets (150–450/mcl)	266	237
Leukocyte count (3500–10,500/mcl)	5.8	2.3
Ferritin (8–252 ng/mL)	53 ng/mL	228 ng/mL
Zinc (60–130 mcg/dL)		109 mcg/dL
Copper (70–125 µg/dL)		<5 µg/dL
Carbamazepine (8–12 ug/mL)	7.7 ug/mL	9.8 ug/mL
TSH (0.34–4.8 uIU/mL)	0.45 uIU/mL	0.06 uIU/mL
RBC Folate		817 (ref.range >280)
Vitamin B12		869 (ref.range 200–1100)

Table 2. Laboratory values after copper supplementation.

Lab	At diagnosis	Four weeks post copper supplementation	One year post copper supplementation
Hemoglobin (11.6–14.6 g/dl)	7.7 g/dl	11.8 g/dl	13.0 g/dl
Hematocrit (38–50%)	22.9	36.6	38.7
MCV (80–95)	106.2	106.3	100.1
Leukocyte count (3500–10,500/mcl)	2.3	8.0	8.2
Copper (70–125 µg/dL)	<5 µg/dL	99 µg/dL	109 µg/dL

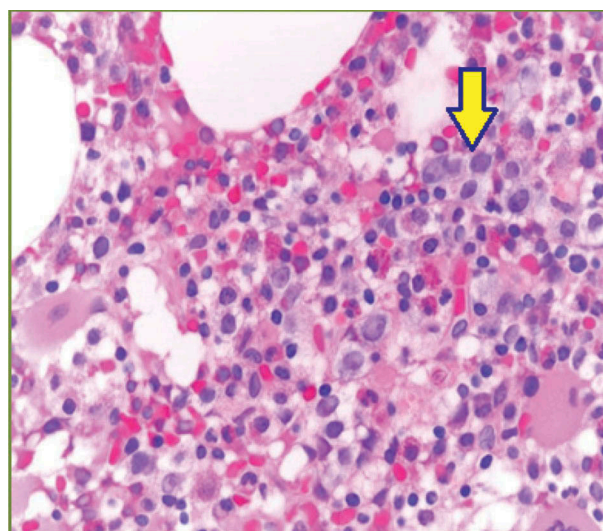
Table 3. Common causes of copper deficiency.

Malabsorption of copper
Gastric surgery, including gastric bypass or gastrectomy
Enteropathies such as inflammatory bowel disease, cystic fibrosis, and celiac disease
Excessive use of copper chelators
Zinc supplement overuse, parenteral overdosing, denture cream ingestion
Chronic total parenteral nutrition, prolonged jejunal enteral feeding
Diet low in copper
Cause unknown

**Figure 1.** Dysmegakaryopoiesis: hyper- and hypo-lobulated nuclei (solid arrows).

protection, crosslinking of collagen and elastin by lysyl oxidase, dopamine beta-hydroxylase for catecholamine biosynthesis, and peptidylglycine alpha-amidating monooxygenase for peptide neurotransmitters and hormones processing [2].

Neurologically, copper deficiency can manifest as myelopathy and peripheral neuropathy simulating

**Figure 2.** Dyspoietic changes in myeloid cells (center and top right): hypogranularity and megaloblastoid changes (solid arrow).

subacute combined degeneration [3,4]. Unlike Wilson disease, in which excessive copper deposition in tissues leads to cardiac dysfunction, liver cirrhosis, and pancreatic dysfunction, copper deficiency has not been reported to affect these organs.

An overview of copper metabolism in humans is highlighted in Figure 3. The highest content of copper is found in the liver. The total amount of copper in an adult human body is approximately 50–120 mg. The liver is the fundamental organ involved in copper hemostasis. The recommended dietary allowance (RDA) for copper is 900 mcg/day in adults. Copper is predominantly absorbed in the stomach and duodenum. P-type ATPase (ATP7A) is an intestinal copper transporting protein which is deficient in Menkes disease. The latter is an x-linked genetic disorder caused by an inactivating

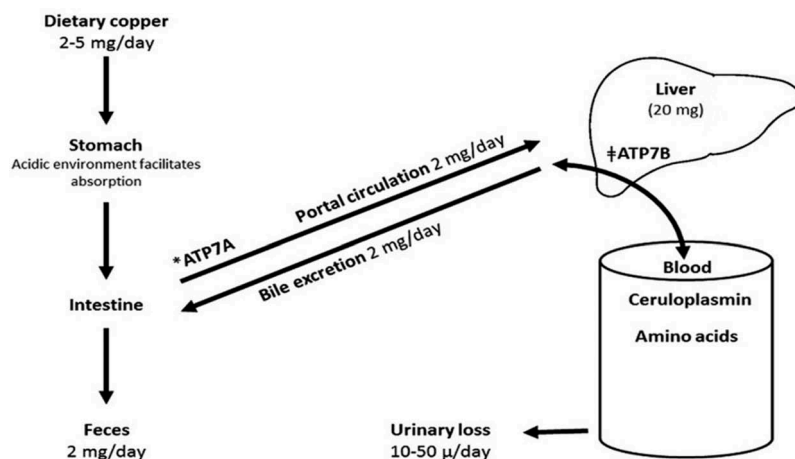


Figure 3. Metabolism of copper [5]. The numbers represent average amount in healthy adults. Copper is largely absorbed in stomach and proximal small intestine. It is transported via portal vein to liver for ceruloplasmin biosynthesis, which carries copper to peripheral tissues. Roughly 50% copper is excreted in bile.

*Menkes P-type ATPase: a transmembrane protein, which regulates copper absorption from intestine into the blood.

#Wilson P-type ATPase: copper transporting protein, involved in copper excretion into bile and plasma.

mutation of the ATP7A gene. It is characterized by severe copper deficiency, progressive neurological decline, and early childhood death.

Causes of copper deficiency are listed in Table 3. The most common cause of acquired copper deficiency is malabsorption due to bariatric surgery [6–8]. Copper is largely absorbed in the stomach and proximal small intestine [9]. Myelopathy due to copper deficiency can mimic vitamin B₁₂ deficiency [10]. Symptoms can take up to a decade to appear after the initial surgery [11]. Both zinc and copper are absorbed in the stomach and proximal duodenum. Excess zinc increases the production of metallothionein, a heavy metal binding protein, by enterocytes. Copper binds with high affinity to metallothionein within the enterocytes leading to its excretion through the intestinal tract [12]. Myeloneuropathy due to copper deficiency has been reported following treatment of Wilson disease with chelation and zinc [13–15].

Other causes of copper deficiency include enteropathies associated with malabsorption such as celiac disease and inflammatory bowel disease [16]. Copper deficiency can occur in prolonged total parenteral nutrition with inadequate copper supplementation, with hematological abnormalities responding promptly to copper replacement [17–20]. Estimated copper requirement in patients receiving total parenteral nutrition is approximately 0.3 mg/day in the adult [17].

Dietary deficiency is rare but it is possible. In our patient, rapid increase in serum copper level (Table 2) after oral supplementation suggest dietary deficiency the most likely cause. Weight loss over several months also points towards poor eating habits. Copper deficiency has not been reported in hemochromatosis, which is an autosomal recessive disease characterized by increased intestinal iron absorption. Excessive dietary iron ingestion caused severe copper deficiency in mice [21].

3. Conclusion/learning points

Gastrectomy and gastric bypass surgery are common causes of acquired copper deficiency. Due to the high prevalence of obesity in the USA, the number of bariatric procedures is increasing. It can take several years before the body copper stores are depleted [10]. Therefore, for patients with hematological abnormalities (anemia, neutropenia, myelodysplasia) and especially neurological deficits resembling vitamin B₁₂ deficiency after gastric surgery, deficiency of copper should be considered in the differential diagnosis [22].

Copper deficiency may be mistaken for vitamin B₁₂ deficiency or myelodysplasia. Hematological manifestations almost universally respond to copper supplementation, whereas neurological improvement is often reported as slow, incomplete, or even absent [23], making prompt diagnosis and treatment essential for successful outcomes.

A written consent was obtained from the patient.

Disclosure statement

No potential conflict of interest was reported by the authors.

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