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Copper Deficiency: An Overlooked Cause of Anemia and Leucopenia

Avneek Singh Sandhu [α], James Kim [σ], Sivjot Binepal [ρ], Michael Gentry [ω] & Alejandro Calvo [¥]

I. Introduction

Copper deficiency (hypocupremia) is an acknowledged but often overlooked cause of anemia and leukopenia (1-4). It is recognized as a frequent cause of hypochromic microcytic anemia, leukopenia, and neuropathy. Copper deficiency anemia has been reported after gastric resection (e.g., Roux-en-Y) (1, 5, 6), excessive zinc consumption (1, 6-9), and in patients with short bowel syndrome receiving total parenteral or enteral nutrition lacking adequate copper supplementation (1, 2). We report a case of vitamin B12, and iron refractory severe anemia and leucopenia with history of Roux-en-Y surgery. Myelodysplastic syndrome was suspected. Bone marrow biopsy was consistent with copper deficiency and serum copper levels were undetectable. The patient experienced complete hematological recovery after copper replacement therapy.

II. Case Presentation

A 63-year old female was evaluated due to an 18-month history of anemia, alopecia, dyspnea, difficulty with ambulation, and intermittent dizziness leading to recurrent near syncope. Complete blood count showed a hemoglobin of 7.4 g/dl, mean corpuscular volume of 80 fL. White blood cell count was 2,800/mcl, platelets were 249,000/mcl. B12 was low at 138 pg/ml. She had borderline iron deficiency with a ferritin of 66 ng/ml, total iron binding capacity of 475 ug/dl, and iron saturation of 6%.

She had a history of Roux-en-Y bariatric surgery 11 years prior and had been taking zinc supplementation prescribed by her bariatric surgeon.

She received 2 units of packed red blood cell transfusion; she was started on parenteral B12 as well as intravenous iron. Despite these supplementations, her cytopenias persisted, raising the possibility of myelodysplastic syndrome. A bone marrow biopsy was performed. Bone marrow core biopsy was normocellular for age (20%) with a normal myeloid to erythroid ratio. There were mild dyserythropoietic changes with rare ring sideroblasts (3 ring sideroblasts/100 erythroid precursor cells), rare nuclear contour irregularities, and cytoplasmic vacuolization of scattered erythroid precursors. The myeloid lineage showed scattered precursors, including myelocytes with cytoplasmic vacuolization (Figure 1). Rare atypical megakaryocytes with widely spaced nuclear lobes or multinucleation were identified. The morphologic findings in the erythroid and myeloid lineages were highly suggestive of copper deficiency/zinc toxicity, although they overlap with primary myelodysplasia, other sideroblastic anemias such as chronic alcohol toxicity, chronic inflammation, and lead poisoning. Her copper level was undetectable at<5 mcg/dl (Reference range: 70-175 mcg/dl) and her zinc level was elevated at 161 mcg/dl (Reference range: 60-130 mcg/dl). The patient was instructed to discontinue zinc supplements and was started on oral copper replacement therapy. Within four weeks, her hematologic parameters recovered completely (Figure 2).

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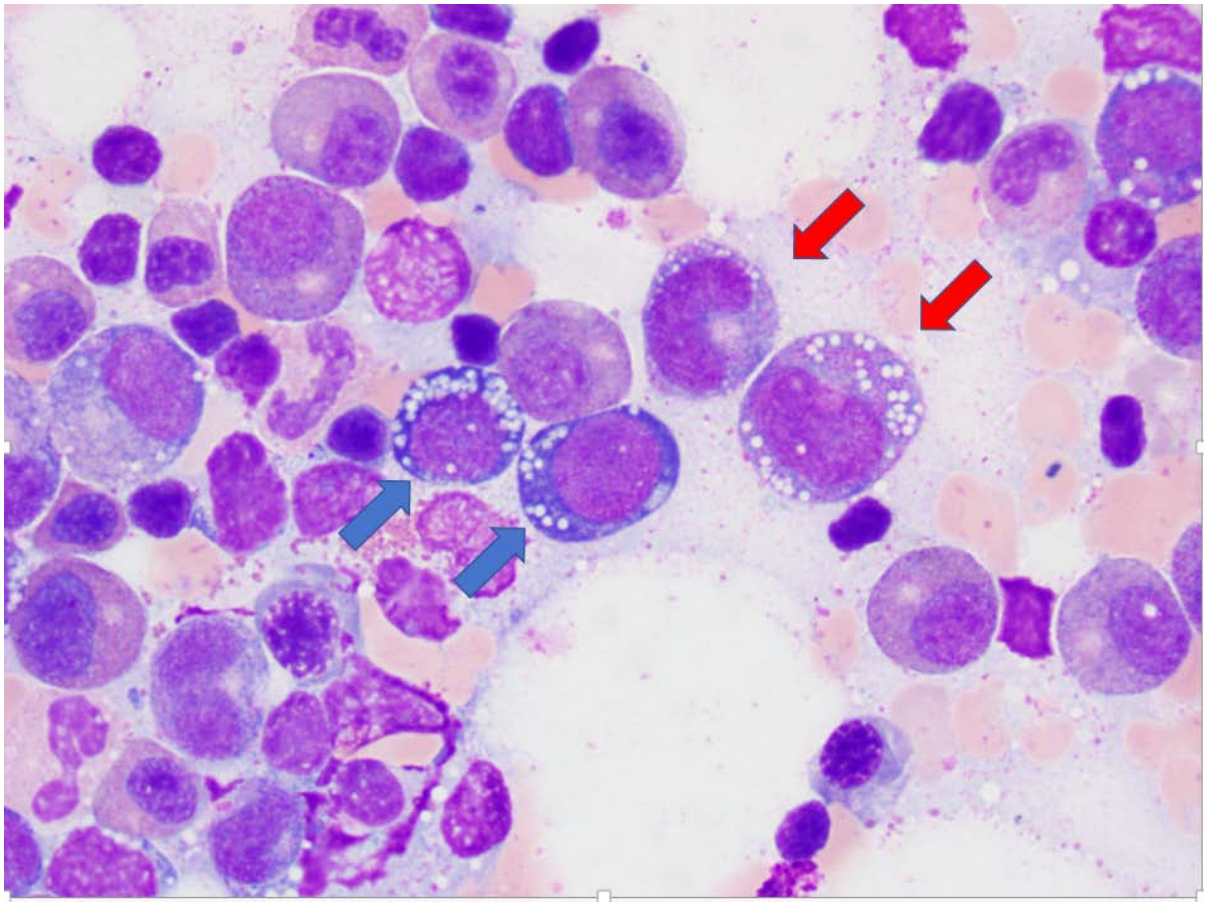


Fig. 1: Bone marrow aspirate showing cytoplasmic vacuolization of the erythroid (*blue arrows*) and myeloid lineages (*red arrows*), Original magnification 1000x

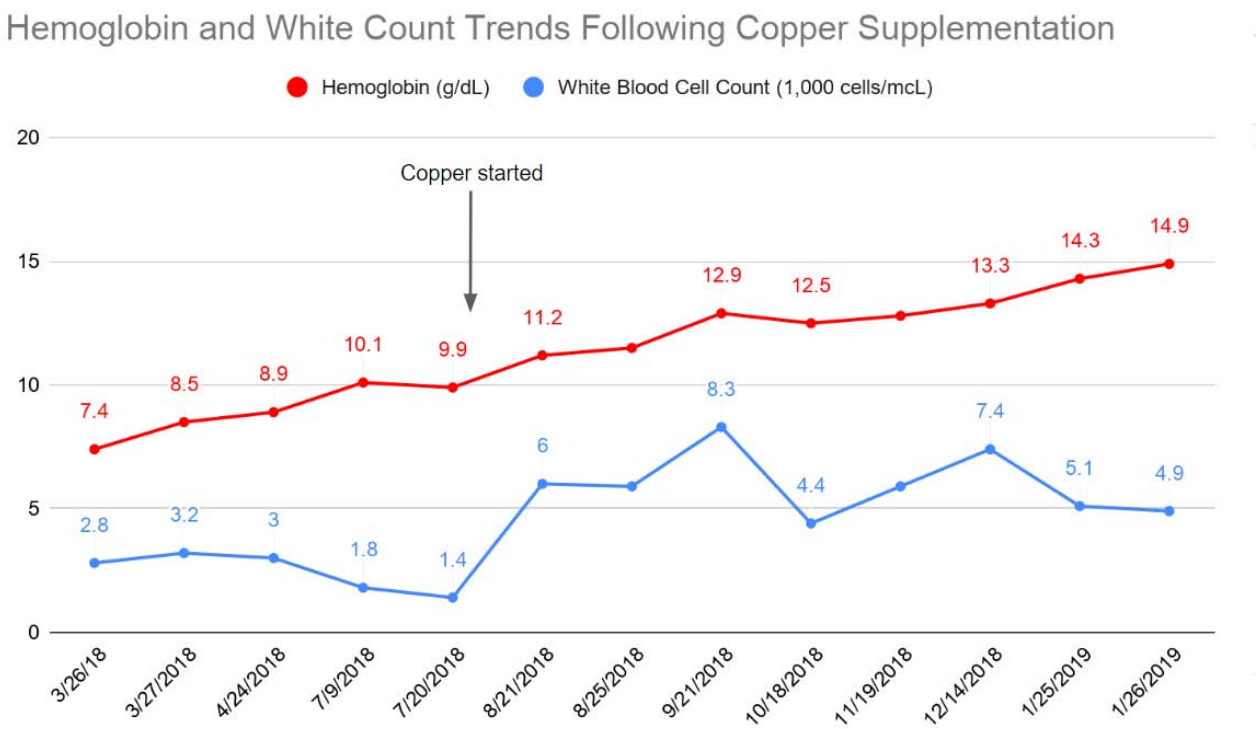


Fig. 2

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III. Discussion

Due to the high prevalence of obesity in developed countries, bariatric surgery has become increasingly popular. It is not well-known that gastric bypass procedures can cause acquired copper deficiency.

Hypocupremia is a commonly missed diagnosis in patients presenting with bi lineage cytopenias. Anemia and leukopenia can be seen. Anemia is usually microcytic, but cases of normocytic and even macrocytic anemia can be seen. Thrombocytopenia, however, is rare in copper deficiency (10). Physiologically, copper is absorbed in the gastric mucosa and proximal duodenum. The most common causes of hypocupremia are upper GI tract surgeries, especially bariatric procedures. Other causes include zinc toxicity, malabsorptive states, total parenteral nutrition, enteropathies associated with inflammatory bowel disease, and celiac disease. Hypocupremia due to a dietary deficiency is rare (11, 12).

A retrospective report of 40 patients with hypocupremia associated with hematologic abnormalities was reported by the Mayo Clinic (13). Ten patients were status post weight-reduction surgery, and 14 were status post other GI surgeries. Anemia and leukopenia were the most common hematologic abnormalities. Bone marrow studies revealed erythroid hyperplasia, vacuolization of pro-normoblasts, and myelocytes. Other reports also observed hepatic steatosis and myelopathy, resembling subacute combined degeneration secondary to vitamin B12 deficiency. Myelopathy is most likely caused by cytochrome-c oxidase dysfunction which is copper-dependent (11). Copper deficiency should be suspected in bariatric surgery patients who present with hematological disorders associated with neurological deficits (12).

Excessive zinc supplementation has to be significant, usually 50 mg/day or more, and prolonged to cause anemia. Previous studies have concluded that zinc and copper metabolism antagonize each other at the level of intestinal absorption through a family of proteins called metallothioneins (MTs). MTs are cystine-rich heavy metal-binding proteins that attach to certain metals and prevent their absorption by trapping them in intestinal cells. Zinc increases the synthesis of MTs in the enterocytes. Copper has a stronger affinity to bind with MTs. Because of this higher affinity and the MTs upregulation, copper absorption is decreased, and excretion is increased in the GI tract leading to hypocupremia (12, 14, 15).

Copper deficiency causes anemia due to defective iron mobilization. Metabolically, copper is involved in an intricate pathway, notably for erythropoietic activity. In enterocytes, hephaestin, a copper-dependent transmembrane protein, helps export iron from the gut into the circulation via transferrin. In hepatocytes, ceruloplasmin, which also binds with copper, facilitates iron transport from the liver to blood also via transferrin. In copper deficiency, hephaestin decreases, causing decreased enterocyte iron efflux. Iron transport from the liver to the blood would also fail. Ultimately, defects in these pathways would blunt iron's ability to reach the bone marrow for heme synthesis.

Copper deficiency may also lead to a low white cell count and increased susceptibility to infection. The mechanism of copper deficiency-induced leukopenia is not well understood. Proposed postulates include decreased survival of neutrophils or inhibited differentiation of CD34+ progenitor cells (16).

Our case report brings awareness about copper deficiency as one of the potential causes of hypochromic microcytic anemia and leukopenia. Knowledge about this nutritional deficiency is important in the setting of the growing population undergoing bariatric surgery. Copper deficiency can also cause peripheral neuropathy and myelopathy, leading to significant disability, which, if recognized late, can be irreversible. Therefore, prompt recognition and early treatment are key for successful treatment of neurological complications.

The current recommendation for oral copper supplementation is a loading dose of 8 mg of elemental copper each day for a week, 6 mg for the second week, 4 mg for the third week, and 2 mg daily afterward. And if an intravenous form is required, it is recommended to use 2 mg daily (administered over 2 hours) for five days and then intermittently as needed. If there is evidence of elevated zinc levels and excessive zinc ingestion, recommendations are to discontinue zinc supplements without changing copper dosing (17).

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