Copper deficiency (hypocupremia) and pancytopenia late after gastric bypass surgery

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Hypocupremia, or copper deficiency, is a rare and underrecognized cause of bone marrow dysplasia. Most cases of copper deficiency in adults occurred historically in patients receiving total parenteral hyperalimentation or total parental nutrition. More recently, with the obesity epidemic and the prevalence of gastric bypass, cases of malabsorption-related copper deficiency have occurred. Copper deficiency can lead to significant cytopenias and possible neurologic sequelae, which can be misdiagnosed and mismanaged. Unfortunately, a delay in diagnosis and appropriate treatment may lead to permanent neurologic damage. We describe a woman with previous gastric bypass surgery who presented with pancytopenia and bone marrow biopsy findings consistent with a myelodysplastic syndrome with excess blasts. She was found to be significantly copper deficient. With replacement copper therapy, her cytopenias quickly resolved. We discuss the distinctive clinical and hematologic features of this rare cause of significant cytopenias and provide recommendations for monitoring and treatment of such patients. Moreover, this case is an important reminder that bariatric patients should have routine follow-ups after surgery and continue dietary supplements indefinitely.

Copper deficiency is exceedingly rare in the normal population. Historically, most cases of copper deficiency in adults occurred in patients receiving total parenteral hyperalimentation or total parental nutrition (TPN) (1). However, after bariatric surgery, copper supply is critical, as it appears to be required for the absorption and utilization of iron, already known to be malabsorbed in this setting. Copper is present in a number of metalloproteins, and it is required as a cofactor in many redox reactions. More than 90% of copper is bound to ceruloplasmin, an α_2 -globulin with ferroxidase activity. The copper-dependent ferroxidase hephaestin converts iron to the ferric (Fe^{3+}) state for its transport by transferrin (2). There is an increasing recognition of hypocupremia associated with anemia as a complication following TPN and bariatric surgery, specifically in the case of gastric resection or bariatric gastric reduction surgery (3). One characteristic associated with copper deficiency is an anemia that is unresponsive to iron supplementation but may present with pancytopenias and features of myelodysplastic syndrome (MDS). We report such a patient, discuss the distinctive clinical and hematologic features of this rarity, and provide recommendations for monitoring and treatment.

CASE PRESENTATION

A 51-year-old Caucasian woman presented to our outpatient clinic for evaluation of pancytopenia. In July 2012, a complete blood count was performed (*Table 1*). Her hematocrit was 33.2%, white blood cell count was 5.5 K/uL, and platelet count was 207 K/uL. In September 2012, reevaluation revealed worsening of the pancytopenia (*Table 1*). She received a transfusion of packed red blood cells and her hematocrit increased, but the effect was transient. At this point, the patient was referred to our office, where we performed a bone marrow biopsy. The aspirate revealed a hypercellular marrow with a mild increase in blasts (5%–6%) and trilineage dyspoiesis, morphologic findings consistent with refractory anemia with excess blasts (RAEB-1).

In taking the patient's history, we found that she had undergone a gastric bypass procedure 20 years earlier. On her first visit to our office, her weight was 200 pounds (body mass index 34.1 kg/m^2). She had diffuse musculoskeletal pain related to fibromyalgia. Since the bypass, she was taking oral iron for anemia. She was prescribed lithium for bipolar disorder and had been taking it for 6 years. She had no neurologic complaints, and she denied any excess tobacco or alcohol use. She took clonazepam, pregabalin, vitamin B_{12} , furosemide, promethazine, tramadol, an oral multivitamin, and vitamin D. At the time of her visit to our office in October 2012, her hematocrit was 30.2%; white blood cell count, 3.8 K/uL; and platelet count, 138 K/uL. Her lactate dehydrogenase was 134 IU/L, antinuclear antibody was nonreactive, ferritin was 354 ng/mL, and reticulocyte count was 3.1%.

The peripheral blood smear demonstrated pancytopenia with marked changes in red blood cells (*Figure 1*). There was a normochromic, normocytic anemia with marked anisopoikilocytosis that included occasional ovalocytes and dacryocytes. A distinct dimorphic red blood cell population was not evident. Among the leukocytes, there was neutropenia with relative eosinophilia and basophilia. White blood cells were morphologically normal.

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Table 1. Complete blood cell counts and plasma copper levels in our patient over time

	7/2012	9/2012	10/2012 (following transfusions)	10/2012 (following copper supplements)	12/2012
Hematocrit (%)	33.2	20.7	31.0	30.2	39.3
White blood cells (K/uL)	5.5	1.9	2.3	3.8	8.6
Neutrophils (%)	64	33	27	29	78
Bands (%)	0	2	2	1	0
Lymphocytes (%)	17	37	32	40	12
Monocytes (%)	12	16	14	18	7
Eosinophils (%)	3	12	25	11	2
Basophils (%)	4	0	0	0	1
Platelets (K/uL)	207	121	137	138	152
Plasma copper (mcg/dL)			<20		101

Platelets were mildly decreased in number with occasional large platelets present. Bone marrow aspirate smears contained scattered small particles with cellular marrow (*Figure 2*). There was left-shifted granulocytic maturation with increased numbers of blasts (4%–6%) and promyelocytes. Morphologically, blasts were typical of myeloid blasts. Auer rods were not present. Features of dysgranulopoiesis included asynchronous maturation and occasional hyposegmentation of neutrophils. Many of the early granulocytic precursors (blasts and promyelocytes) contained multiple small cytoplasmic vacuoles. The erythroid lineage demonstrated left-shifted maturation with increased numbers of pronormoblasts and basophilic normoblasts, many of which contained multiple small cytoplasmic vacuoles. There were mild megaloblastoid changes and dyserythropoietic changes to include nuclear irregularities, nuclear lobulation, and nuclear fragmentation. The myeloid to erythroid ratio demon-

Figure 1. Peripheral blood smear with pancytopenia and anisopoikilocytosis of the red blood cells (Wright, $\times 400$).

strated a slight erythroid predominance at 1.7:1. Megakaryocytes were adequate in number with occasional dyspoietic forms. Prussian blue–stained aspirate smears showed mildly increased iron stores with storage iron and sideroblastic iron identified. Ringed sideroblasts were not observed.

The core biopsy specimen demonstrated a hypercellular marrow for the patient's age (70%–80%) with all lineages represented (*Figure 3*). The biopsy contained scattered immature cells. Megakaryocytes were adequate for cellularity, with focal clusters and occasional dyspoietic forms to include hypolobate and hyperlobate nuclei (*Figure 3*). A reticulin stain showed mildly to moderately increased reticulin fibrosis.

Flow cytometry studies performed on the bone marrow aspirate found increased eosinophils (19%) with no increase in myeloblasts (3%) or hematogones (2%). Cytogenetic analysis of the bone marrow aspirate was performed and an MDS fluorescence in situ hybridization (FISH) panel was found to be negative for deletions of chromosome loci 5q31, 7q31, and 20q, with no evidence of monosomy 7 or trisomy 8. FISH for a core binding factor subunit β rearrangement was negative. Chromosome analysis revealed a normal 46,XX female karyotype.

Given the bone marrow morphologic findings, MDS was strongly considered, although the patient was young for this diagnosis (median age 70) and had normal marrow cytogenetics. We also considered drug-induced cytopenias, with lithium or pregabalin considered the most likely inciting substances. However, lithium is generally associated with a leukocytosis, and pregabalin most commonly causes thrombocytopenia rather than pancytopenia. Nonetheless, these drugs were stopped. Given her history of bariatric surgery, which can have malabsorption-related complications, we checked her copper and zinc levels. The latter was within normal limits; however, the patient's copper level was extremely low (<20 mcg/dL; reference range 70–175 mcg/dL), so we initiated therapy with copper gluconate 4 mg orally three times a day. Two weeks later, her white count had improved, and approximately 6 weeks after initiation of copper replacement therapy, our patient's complete blood count had normalized (*Table 1*). Her copper level had risen from <20 to 101 mcg/dL. She resumed lithium and her blood counts remained normal.

DISCUSSION

MDS is characterized by ineffective hematopoiesis and functional abnormalities of hematopoietic lineages. In about one third of patients, this disease can transform into acute myeloid leukemia. The World Health Organization classification of MDS, updated in 2008, indicates that the features that define MDS include blood cytopenias, ineffective hematopoiesis,

Figure 2. Morphologic changes in marrow precursors in copper deficiency, some of which mimic a myelodysplastic syndrome. (a) Early myeloid and erythroid precursors with cytoplasmic vacuoles (Wright, $\times 1000$). (b) Myeloid blast and vacuolated early erythroid precursors (Wright, $\times 1000$). (c) Megaloblastoid change and dyspoiesis in late-stage erythroid precursors (Wright, $\times 1000$). (d) Dyspoietic ring neutrophil and vacuolated promyelocyte (Wright, $\times 1000$).

dyserythroidopoiesis, dysgranulopoiesis, dysmegakaryopoiesis, and increased myeloblasts (4). RAEB-1 is defined by cytopenias with unilineage or multilineage dysplasia and 5% to 9% blasts in bone marrow or 2% to 4% blasts in the peripheral blood. RAEB-1 is considered an intermediate-risk subtype of MDS. In the absence of specific cytogenetic abnormalities, MDS is a diagnosis of exclusion, and the diagnosis should only be made after careful review of clinical history and elimination of environmental or other nonclonal disorders that can result in myelodysplasia. Congenital diseases and other enzyme deficiencies are known to demonstrate myelodysplastic changes in a single lineage; however, trilineage dysplasia is unlikely in these entities. Substances with toxic effects such as chloramphenicol or arsenic can lead to dysplasia in all cell lines.

Copper deficiency has been reported to result in an MDS-like picture. Patients often present with anemia, neutropenia, and, less commonly, thrombocytopenia (1, 5). Copper is present in a number of metalloproteins that are vital for normal homeostasis and include such enzymes as cytochrome-c oxidase, dopamine β -hydroxylase, and superoxide dismutase. It is unclear how copper deficiency causes anemia and other cytopenias. A decrease in the copper-dependent enzymes (ceruloplasmin and cytochrome-c) that aid in iron metabolism and transportation has been proposed as a potential factor for anemia (6). Mitochondria from copper-deficient animals are deficient in cytochrome oxidase activity and fail to synthesize heme from ferric iron and protoporphyrin at the normal rate, leading to mitochondrial iron accumulation (7, 8). The mechanism underlying neutropenia in hypocupremia remains unknown. Suggested etiologies have included destruction of myeloid progenitor cells in

the bone marrow, inhibition of differentiation and self-renewal of CD34⁺ hematopoietic progenitor cells, impaired egress of neutrophils from the bone marrow, and increased clearance of neutrophils from the circulation (9, 10).

The anemia of copper deficiency often is associated with the presence of ringed sideroblasts and occurs in a number of clinical settings, including a microcytic, macrocytic, or normocytic anemia. Marked vacuolization of both erythroid and myeloid precursors has been consistently reported in bone marrow (1–7, 11). Megaloblastic changes, ringed sideroblasts, and multilineage dyspoiesis characteristic of MDS have been described (3, 10–13). In comparison, our patient's bone marrow had numerous myeloid and erythroid precursors with cytoplasmic vacuolization, but lacked ringed sideroblasts. Of note, our patient's bone marrow demonstrated increased numbers of myeloblasts (4%–6%) with trilineage dysplasia, suggesting RAEB-1. A case report described a 19-year-old man with intestinal amyloid and secondary copper deficiency that presented with trilineage dysplasia and increased numbers of immature cells, up to 19% (13). Though originally interpreted as blasts morphologically consistent with lymphoblasts, the immature cells in question turned out to be hematogones, or B lymphocyte precursors. Hematogone hyperplasia has been described in association with copper deficiency secondary to zinc excess, with bone marrow findings that overlap with MDS (13, 14). Sixteen patients were reported with copper deficiency over a 5-year period, 94% of which had hematologic features as their initial manifestation. Of the seven patients who had a bone marrow biopsy done, only one had an appearance consistent with RAEB-1 (15).

Figure 3. Hypercellular marrow for age with occasional dyspoietic megakaryocytes. **(a)** Hypercellular marrow particle with all lineages represented (hematoxylin and eosin, ×200). **(b, c)** Dyspoietic changes in megakaryocytes (hematoxylin and eosin, ×600).

Gastric surgery seems to be an increasingly common cause of acquired copper deficiency that can go unrecognized for years (16). Acquired copper deficiency can cause a myelopathy in humans (17) and is usually accompanied by the more typical anemia and leukopenia. Spinal and peripheral nerve injury can occur; patients can present with subacute gait disorders and prominent sensory ataxia and/or spasticity. Magnetic resonance imaging shows subcortical white matter changes, atrophy of the cerebellum, as well as signal changes in dorsal columns (15)—neurologic deficits similar to those of vitamin B₁₂ deficiency. Though copper supplementation generally prevents further neurologic deterioration, improvement in neurologic symptoms with treatment is variable (18, 19). It is unclear if our patient's history of fibromyalgia or diffuse musculoskeletal pain was related to her copper deficiency. She had no focal neurologic deficits at the time of initial examination, and musculoskeletal symptoms persisted after copper repletion.

Copper is an essential trace element absorbed in the stomach and proximal duodenum, both of which can be altered in bariatric surgery. Unfortunately, there have been no studies

addressing the appropriate dose, duration, or form of copper supplementation, nor are there specific guidelines for replacing low serum copper. Commonly used salts include copper gluconate, copper sulfate, and copper chloride. Because of the need for long-term therapy, parenteral therapy is not recommended, although intravenous copper can be used for several days as a bridge to the oral form. A 60-year-old man with early onset copper deficiency after Roux-en-Y surgery was supplemented daily with 4 to 10 mg of oral copper (20). Monitoring the patient's blood copper levels every few months for the first year to confirm normal serum levels is important to establish the appropriate dose. Our case is an important reminder that bariatric patients should have routine follow-ups after surgery and continue dietary supplements indefinitely. Abnormalities on routine laboratory tests should prompt a search for vitamin and trace mineral deficiencies, as early detection can prevent debilitating symptoms.

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