Case Report

Anemia and Neutropenia in Copper-Deficient Patients: A Report of Two Cases and Literature Review

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Copper deficiency is an uncommon, but treatable cause of hematologic abnormalities. We present and describe two interesting cases in this report. The first case was a 37-year-old man with history of short bowel syndrome and long-term total parenteral nutrition (TPN) presenting with pancytopenia and chronic symmetrical polyarthritis that resembled rheumatoid arthritis. The second case was a 64-year-old man with malabsorption from Cronkhite-Canada Syndrome (CCS) and history of subtotal gastrectomy presenting with macrocytic anemia and neutropenia. Bone marrow examination in both cases revealed cytoplasmic vacuolization of myeloid and erythroid precursors. After copper supplementation was initiated, hematological abnormalities and arthritis were significantly improved. We encourage clinicians to recognize early and identify copper deficiency in patients who have unexplained cytopenia, especially if there is history of upper gastrointestinal tract surgery, malabsorption, or long-term TPN.

Keywords: *Anemia, Copper deficiency, Malabsorption, Neutropenia, Pancytopenia, Total parenteral nutrition*

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Copper deficiency is not a common cause of cytopenia in adults. Patients with history of upper gastrointestinal (GI) tract surgery, malabsorption syndrome, and/or long-term total parenteral nutrition (TPN) are susceptible to developing copper deficiency. We report two cases of copper deficiency that presented with refractory cytopenia. Bone marrow examination revealed cytoplasmic vacuolization of erythroid and myeloid precursors. Low serum copper and plasma ceruloplasmin concentration confirmed the diagnosis. Hematological abnormalities resolved with copper supplementation in both cases.

Case Report

Case 1

The patient was a 37-year-old man with a 13-year history of short bowel syndrome, which was diagnosed after surgical correction of intussusception. He was given post-operative partial parenteral nutrition (PPN) six days per week and was able to maintain nutrition with oral intake of regular food.

In 2002, he was diagnosed with rheumatoid arthritis with morning joint stiffness and symmetrical polyarthritis at wrist, metacarpophalangeal, proximal interphalangeal, elbow, and knee joints. Radiograph of the hand showed juxta-articular osteoporosis and rheumatoid factor blood test was negative. Patient was then treated with chloroquine, methotrexate, and NSAIDs for two months. When complete blood count (CBC) revealed anemia and leukopenia, all medications were discontinued. Sulfasalazine was given for one month and then discontinued for the same reason. Megaloblastic anemia was one of the differential diagnoses, due to patient history of malabsorption syndrome. Accordingly, he was treated with folic acid and intramuscular cobalamin, but his hematologic parameters were not improved. Finally, he received cyclosporine (25 mg per day), which was continued for three years before admission due to fever.

Patient came to the hospital with high-grade fever for three days. Physical examination revealed normal skin and mucosa with no signs of joint inflammation, organomegaly, neurological abnormality, or any site of infection. CBC results revealed hemoglobin (Hb) 6.9 g/dL, hematocrit (Hct) 21.8%, mean corpuscular volume (MCV) 104 fL, white blood cell (WBC) count 850/mm^3 (N 18%, L 55%, ANC 153/mm^3), and platelet count 37,000/mm^3. Differential diagnoses for cause of pancytopenia included drug-induced, T-cell large granular lymphocytic leukemia, disseminated infection, myelodysplastic syndrome (MDS), and nutritional deficiency from short bowel

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syndrome. Consequently, a bone marrow study was performed.

Bone marrow examination revealed normocellular marrow, normal megakaryocytes, M:E ratio of 1-2:1, megaloblastic change and cytoplasmic vacuolization of erythroid precursors, left shift and cytoplasmic vacuolization of myeloid precursors, and no ring sideroblast. Vacuolization of erythroid and myeloid precursors fueled suspicions of copper deficiency.

Additional laboratory results revealed serum copper level of 0.03 µmol/L (normal range: 0.7-1.4) and plasma ceruloplasmin level 0.08 g/L (0.2-0.6). His serum cobalamin and serum folate levels were within normal limits. In the end, the patient was diagnosed with catheter-related blood stream infection and copper deficiency. He received intravenous antibiotics, removal of central venous catheter, and intravenous copper supplementation. Two months after initiation of treatment, his CBC count and arthritic symptoms were improved. He never had arthritis or significant cytopenia anymore.

Case 2

The patient was a 64-year-old man with a 3-year history of Cronkhite-Canada Syndrome (CCS), which was diagnosed in the presence of anorexia, significant weight loss, and chronic diarrhea. Computed tomography (CT) scans of the abdomen revealed circumferential mass with heterogeneous enhancement at stomach extending to duodenal bulb, multiple polyps at jejunum, ileum, and ascending colon, and ileocecal valve intussusception. Esophagogastroduodenoscopy revealed proliferative mass occupying nearly the entire stomach. Colonoscopy revealed intraluminal mass occupying almost the entire lumen at transverse colon and multiple polyps at descending colon. Subtotal gastrectomy and right half hemicolectomy was performed due to suspected malignancy. Histologic investigation for malignancy was negative. Gastrointestinal malabsorption resulted in malnutrition, although the patient was able to eat regular food. He was supplemented with cobalamin injection (1 mg, once a month), oral zinc sulfate, vitamin D, calcium carbonate, and ferrous sulfate.

The patient developed fatigue and exertional dyspnea for one week. Physical examination revealed moderate pallor, no jaundice, no organomegaly, and normal neurological examination. CBC results revealed Hb7.9 g/dL, Hct 24.8%, MCV 114 fL, WBC count 2,100/mm^3 (N 26.3%, L 56.5%, ANC 550/mm^3), and platelet count 306,000/mm^3. He was suspected of having megaloblastic anemia due to history of subtotal gastrectomy and malabsorption from small intestinal lesions, though his serum cobalamin and folate levels were within normal limits. Cobalamin was replaced intramuscularly (1 mg per day for one week, then 1 mg per week for two months), but his symptoms were not improved. CBC results revealed Hb 6.5 g/dL, Hct 18.9%, MCV 104 fL, WBC count 1,300/mm^3 (N 40.6%, L 37.5%, ANC 527/ mm^3), and platelet count 306,000/mm^3. Bone marrow study was then performed to investigate the cause of bicytopenia.

Bone marrow aspiration revealed mild hypocellularity, normal megakaryocytes, M:E ratio of 4:1, and cytoplasmic vacuolization of some erythroid and myeloid precursors. Patient did not have history of alcohol, drug, or chemotherapy exposure, any or all of which can cause cytoplasmic vacuolization of hematopoietic precursors. Patient serum copper level was 0.002 µmol/L (0.7-1.4) and plasma ceruloplasmin level was 0.09 g/L (0.2-0.6). Accordingly, copper deficiency was suspected as the cause of the patient's anemia and neutropenia.

Two weeks after intravenous copper was initiated, patient CBC results revealed Hb 8.3 g/dL, Hct 25.4%, MCV 108.1 fL, WBC count 10,240/mm^3 (N 76.2%, L 10.5%, ANC 7,782/mm^3), and platelet count 328,000/mm^3. As a result of the patient's problem with food nutrient absorption, home TPN was started and included intravenous copper. Oral zinc sulfate was discontinued due to its interference with copper absorption. Patient Hb and MCV levels returned to normal level in eight and 10 months, respectively.

Discussion

Copper is abundant in many foods, particularly in grains, nuts, legumes, seeds, organ meat, and shellfish[1]. As a result, acquired copper deficiency occurs infrequently. The Recommended Dietary Allowance (RDA) of copper is 0.9 mg/day in adults older than 19 years of age[1]. Median intake of copper in adults is 1 to 1.6 mg/day[1]. The primary locations of copper absorption are the duodenum, and to a lesser extent, the stomach[2]. Major causes of copper deficiency are classified into three categories, 1) intestinal malabsorption, such as celiac disease, cystic fibrosis, short bowel syndrome[3], and gastric or small bowel resection[4], 2) inadequate copper supplementation, such as individuals receiving long-term TPN, and 3) excessive oral zinc intake[5]. Excessive intake of zinc causes intestinal cells to

upregulate intracellular metallothionein, which has a higher affinity for copper than zinc, resulting in copper becoming trapped in intestinal cells. Continuous sloughing of intestinal cells ultimately causes copper deficiency[6-8]. In many cases, the etiology of copper deficiency was uncertain[9].

Copper is an essential trace element for normal function of multiple enzymes in humans. Lysyl oxidase is involved in the processing of elastin and collagen; therefore, enzymatic defect of lysyl oxidase results in bone and cartilage instability[10]. Absence of enzymes involved in neurologic function can cause symptoms resembling subacute combined degeneration due to cobalamin deficiency[9].

The mechanisms of copper-induced cytopenias remain unclear. Speculation regarding etiology of anemia includes absence of the copper-containing enzymes, ceruloplasmin[11], and hephaestin[12], which are necessary for the transport of iron from non-intestinal cells and intestinal cells, respectively. Copper-deficient rats were shown to have decreased red cell survival, possibly secondary to alterations in red cell membrane fluidity and increased oxidative damage[13].

The etiology of neutropenia is less well understood than the etiology of anemia. Mechanisms include destruction and maturation arrest of myeloid precursors in bone marrow, impaired egress of neutrophils from bone marrow, and increased clearance of neutrophils from circulation[14].

Halfdanarson et al reviewed hematological manifestations of copper deficiency in 40 patients[15]. Patients had anemia and leukopenia, isolated anemia, pancytopenia, anemia and thrombocytopenia, and isolated neutropenia in 52.5%, 30%, 10%, 5%, and 2.5% of cases, respectively. Values of hematologic parameters at diagnosis were Hb of 10.6 g/dL (range: 7.9-13.6), MCV varying with a wide range of microcytic, normocytic, and macrocytic indices (70.3-114.1 fL), WBC count 3,250/mm^3 (1,000-10,900), ANC 1,410/mm^3 (180-8,690), and platelet count 219,000/mm^3 (24,000-554,000).

Bone marrow examination demonstrated normocellularity or hypocellularity, granulocytic hypoplasia, vacuolization of pronormoblasts and myeloid precursors, increased stainable iron within macrophages and plasma cells, and presence of ringed sideroblasts[15]. These findings are highly sensitive, but not specific to copper deficiency. In some cases, patients may be misdiagnosed as MDS or sideroblastic anemia.

Diagnostic tools for copper deficiency mostly rely on serum copper and plasma ceruloplasmin concentration due to widespread test availability. It should be noted, however, that low serum copper and low plasma ceruloplasmin concentration results indicate severe copper deficiency. Conditions that can result in falsely low serum copper level, such as corticosteroid or corticotropin exposure, should be excluded. Falsely high serum copper and plasma ceruloplasmin levels can be seen in pregnancy and inflammation. Copper-containing enzymes in blood cells, such as erythrocyte superoxide dismutase, may better reflect tissue copper stores, but the assays are not widely available[16].

In fact, no studies have explored the appropriate dose, duration, route, and form of copper supplementation. After initiating copper replacement, hematologic abnormalities were typically and significantly improved within one to two weeks[3,5,17,18]. In patients with zinc-induced copper deficiency, discontinuing the use of zinc may suffice.

Copper deficiency is not a common cause of cytopenia in adults; a clinical fact which often results in misdiagnosis or delayed diagnosis, as seen in the patients profiled in this report. Duration of symptoms before definitive diagnosis in case 1 and 2 was four years and 11 weeks, respectively. Both cases had hematological abnormalities, including macrocytic anemia, neutropenia, and vacuolization of myeloid and erythroid precursors. Copper supplementation significantly improved cytopenia in both cases and arthritic symptoms in case 1. We encourage physicians to early recognize and identify copper deficiency in patients with history of upper GI tract surgery, malabsorption syndrome, and/or who have had long-term TPN, and who have presented with cytopenia or neurological symptoms that mimic cobalamin deficiency.

What is already known on this topic?

Copper deficiency can cause multisystem abnormalities because copper is an essential trace element for normal function of multiple enzymes in humans. Copper deficiency is a rare cause of cytopenia, thus, the diagnosis is frequently missed or delayed. Bone marrow examination, serum copper and plasma ceruloplasmin concentration are available diagnostic tools. Copper replacement significantly improves hematologic abnormalities within one to two weeks.

What this study adds?

There are two points of interest. Firstly, this is the first report of the association of CCS and copper

deficiency. Secondly, copper deficiency should be one of differential diagnoses in patients with rheumatoid arthritis-like polyarthritis and cytopenia.

Potential conflicts of interest

None.

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ผู้ป่วยที่มีอาการซีดและเม็ดเลือดขาวต่ำจากการขาดธาตุทองแดง: รายงานผู้ป่วย 2 ราย และทบทวนวรรณกรรม

ฉัตรี หาญทวีพันธุ์, ยิ่งยง ชินธรรมมิตร์, นพดล ศิริธนารัตนกุล

ความผิดปกติของเม็ดเลือดที่เกิดจากการขาดธาตุทองแดงเป็นสาเหตุที่พบได้ไม่บ่อยในเวชปฏิบัติ แต่เป็นสาเหตุที่สามารถแก้ไขได้ง่าย ผู้ป่วยที่มีความเสี่ยงต่อภาวะดังกล่าวคือผู้ที่มีประวัติผ่าตัดทางเดินอาหารส่วนต้น เป็นโรคที่มีความผิดปกติของการดูดซึมสารอาหารหรือมีประวัติได้รับสารอาหารทางหลอดเลือดดำเป็นเวลานาน ดังตัวอย่างผู้ป่วย 2 ราย รายแรกเป็นผู้ป่วยชาย อายุ 37 ปี ได้รับการวินิจฉัยเป็น short bowel syndrome และได้รับสารอาหารทางหลอดเลือดดำมาเป็นเวลานาน มีอาการซีด เม็ดเลือดขาวต่ำ เกล็ดเลือดต่ำ ร่วมกับปวดข้อหลาย ๆ ข้อ คล้ายกับอาการของโรคข้ออักเสบรูมาตอยด์ รายที่สองเป็นผู้ป่วยชาย อายุ 64 ปี เป็นโรค Cronkhite-Canada syndrome ร่วมกับมีประวัติผ่าตัดกระเพาะอาหาร มาด้วยอาการซีด และเม็ดเลือดขาวต่ำ การตรวจไขกระดูกของผู้ป่วยทั้งสองรายพบ vacuoles จำนวนมากภายในเซลล์ต้นกำเนิดเม็ดเลือดแดงและเม็ดเลือดขาว หลังจากให้การรักษาผู้ป่วยด้วยธาตุทองแดงพบว่าความผิดปกติของเม็ดเลือดและอาการปวดข้อดีขึ้น