Polyneuropathy and Pancytopenia Secondary to Copper Deficiency

Cesar V. Reyes, MD

Can you guess the cause of this patient's low serum copper level, leading to neurologic problems and pancytopenia?

A 39-year-old woman came to our clinic reporting lower back pain, which had become progressively worse during the past year. She also reported experiencing paresthesia in the distal lower extremities that moved proximally toward her waist over the preceding 6 months, as well as some tingling numbness in the hand and diminished clarity of vision during the past 2 months. The patient denied any changes in mental activity, motor deficits, and sensory ataxia. She experienced some urinary urgency at night but not during the day.

Physical examination and patient history revealed no risk or features of human T-lymphotropic virus, human immunodeficiency virus (HIV) infection, tabes dorsalis, overseas travel, unusual pets or hobbies, toxin exposure, previous myelographic studies, lupus erythematosus, cardiovascular disease, cancer, blood transfusion, or family history of neurologic disease. The patient regularly took self-prescribed over-the-counter (OTC) zinc in an attempt to prevent upper respiratory infection.

Vital signs and pertinent physical findings were normal, significant only for severe and impaired vibration and proprioception in both lower extremities, absent superficial abdominal reflexes, normal sensation for touch/pinprick/thermal stimuli, **brisk sym**pathetic deep tendon reflexes, absent pathologic reflexes, and with eyes closed, she could identify in which palm coins were placed.

Laboratory results revealed leukopenia (white blood cell count, 1,900 µ/L) (Figure 1). The white blood cell differential count showed lymphocytes 86%, granulocytes 8%, monocytes 4%, eosinophils 2%, and basophils 2%. The complete blood count revealed macrocytic normochromic anemia (red blood cell count, 2,290,000/µL; hemoglobin, 4.9 g/dL; mean corpuscular volume, 115 fL), thrombocytopenia (platelet count, 173,000/µL), and blood chemistry values within reference limits.

Results of special studies included rapid plasma reagin for syphilis nonreactive; Epstein-Barr virus (EBV) capsid nuclear antigen antibody positive, EBV capsid antigen immunoglobulin M (IgM) antibody negative, and EBV nuclear antigen antibody positive; hepatitis A IgM antibody negative, hepatitis B surface antigen negative, hepatitis B core antibody negative, and hepatitis C antibody negative; HIV-1 and HIV-2 antibody negative; parvovirus B19 immunoglobulin G (IgG) antibody and parvovirus B19 IgM antibody negative; rheumatoid factor titer and antinuclear antibody screen negative; and a normal urinalysis.

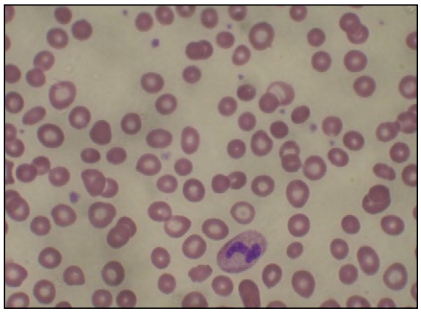

Figure 1. Peripheral smear showing pancytopenia: macrocytic to hypochromic anemia, leukopenia, and thrombocytopenia (May-Grünwald stain × 630).

Magnetic resonance imaging of the cervical, thoracic, and lumbar vertebrae demonstrated L5–S1 left paracentral disc protrusion and was negative for spinal cord disease. A right iliac crest bone marrow biopsy was markedly hypocellular and showed a few ringed sideroblasts (Figures 2 and 3). Vacuolated erythroid and myeloid precursors also were seen. These findings suggested possible myelodysplastic syndrome with rare monoclonal stem cells; flow cytometry analysis was negative for paroxysmal nocturnal hemoglobinuria phenotype. The cytogenetic analysis revealed a normal 46,XX female chromosome complement.

What's your diagnosis?

Dr. Reyes is a consultant in pathology laboratory medical services at the Hines VA Hospital in Hines, Illinois. In addition, he is an attending pathologist in the department of clinical laboratories at Morris Hospital in Morris, Illinois.

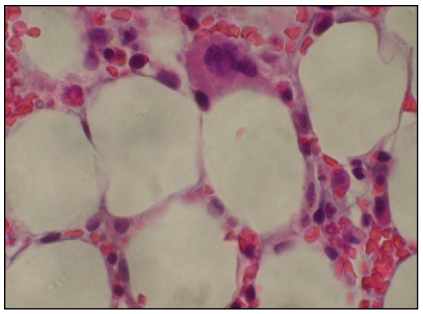

Figure 2. Markedly hypocellular bone marrow disclosing trilineage hematopoeisis (hematoxylin eosin stain × 630).

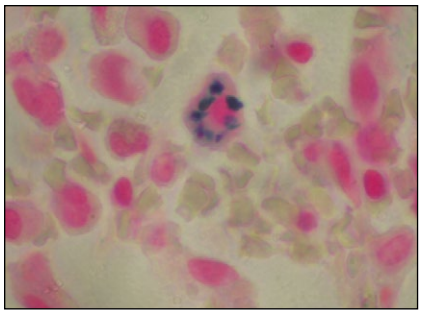

Figure 3. A few ringed sideroblasts on iron stain of the bone marrow section (× 1,000).

OUR DIAGNOSIS

The patient's serum copper level was < 0.1 µg/mL (normal, 0.75 µg/mL to 1.45 µg/mL) with normal ceruloplasmin. We, therefore, made a diagnosis of copper deficiency associated with myeloneuropathy and pancytopenia, noting that the deficiency probably was related to the patient's inordinate OTC zinc intake. Her serum zinc levels ranged from 150 µg/dL to 173 µg/dL (normal, 75 µg/dL to 120 µg/dL).

ABOUT THE CONDITION

While hematologic complications of copper deficiency are well recognized, neurologic effects are less known and only have been described recently. The first case of copper deficiency-associated myelopathy in humans was reported by Schleper and Sturenburg in 2001.[1,2] Published reports on this topic are still scarce and, therefore, the role of hypocupremia as a reversible cause of progressive myelopathy is not well understood.[3,4]

The anemia component of copper deficiency often is accompanied by neutropenia and, less commonly, thrombocytopenia. The anemia is almost always present and is as variable as the bone marrow findings, but copper deficiency frequently masquerades as myelodysplastic syndrome. The mechanism of anemia and pancytopenia is via impaired iron absorption, defective iron transfer from the reticuloendothelial cells to plasma, and decreased cytochrome oxidase activity in the mitochondria.[3–10]

The neurologic manifestations also can be variable but usually consist of myelopathy with or without neuropathy, sensory ataxia, central nervous system demyelination, peripheral neuropathy, and optic neuropathy.[3,4] Some of the abnormalities also seem to mimic multiple sclerosis. In fact, the first reported patient with copper deficiency-associated myelopathy also presented with concurrent severe optic and peripheral neuropathies.[1]

Copper deficiency also has been associated with malabsorption, gastric resection, and anticopper agents.[4] None of these factors was associated with our patient, except for inordinate OTC zinc intake, leading to a significantly elevated serum zinc concentration. Because the patient with copper deficiency may not have all the signs and symptoms of this condition, diagnosis usually is based on an awareness of the syndrome, a high level of suspicion, and demonstration of a low serum copper level.

Treatment

We administered a dose of intravenous copper chloride (2.0 mg of copper) and prescribed daily oral copper sulphate supplementation (2.0 mg/day). The patient's clinical status and laboratory results promptly improved. The serum copper level returned to normal and the hematologic abnormalities disappeared after 3 months, while the myeloneuropathy completely resolved and the serum zinc was within reference level after 6 months of replacement therapy.

IN SUMMARY

In half of reported cases of hypocupremia, the cause is not obvious. Unexplained pancytopenia concurrent with neurologic manifestations, therefore, should prompt serum copper evaluation because early recognition of easily reversible myeloneuropathy and myelodysplasia is essential to prevent progressive neurologic deterioration and possible leukemic transformation.[11]

Our patient received a dose of intravenous copper chloride, followed by oral copper sulfate supplements, which caused a dramatic improvement in the signs and symptoms of copper deficiency. Because the patient's serum copper level, leukocytic morphology, and mean corpuscular volume normalized after 3 months, while her myeloneuropathy completely resolved after 6 months of initiating therapy, it seems likely that her hypocupremia was related to inordinate zinc consumption. ●

Author disclosures

The author reports no actual or potential conflicts of interest with regard to this article.

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Government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.

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