

# ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

---

## Copper Deficiency and Its Hematologic Manifestations

Robert L. Phyliky, MD  
Associate Professor of Medicine  
Mayo Clinic

### **H&O** Other than Wilson disease, what causes copper deficiency?

**RP** At the Mayo Clinic in Rochester, Minn we have found the most common cause of copper deficiency is surgery of the upper gastrointestinal tract. Recently, bariatric surgery has been noted as a cause of copper deficiency. Bariatric surgery bypasses the area of the body where copper is absorbed: the proximal small bowel and the stomach. Bariatric surgery probably will result in a number of patients developing copper deficiency up to 10 years after the procedure.

### **H&O** What are the most common hematologic manifestations of copper deficiency?

**RP** The major hematologic manifestations are refractory anemias and neutropenias. In addition to hematologic problems, copper deficiency may also produce serious neurologic abnormalities. Clinical presentation at times is similar to what would be expected in a patient with subacute combined degeneration, as would be seen vitamin B<sub>12</sub> deficiencies.

### **H&O** Are these hematologic and neurologic conditions generally reversible?

**RP** While the neurologic abnormalities may not be reversible, the hematologic ones often are. Some patients develop copper deficiency from ingesting high levels of zinc either therapeutically or accidentally. These patients may not have a satisfactory reversal of their hematologic problems unless large amounts of copper are given.

### **H&O** What is the connection between copper deficiency and the development of these hematologic problems?

**RP** There are important copper-containing enzymes in the body that are involved in heme synthesis. Ceruloplasmin is one of these. It converts ferrous iron into ferric iron so that it can be transported by transferrin. Hephaestin is another copper-containing enzyme that allows the egress of copper from enterocytes into transferrin. Cytochrome C oxidase is a copper-containing enzyme in mitochondria. All of these enzymes are important in the formation of hemoglobin. The impaired production from deficiencies in copper can result in anemia.

### **H&O** Does copper deficiency have an effect on platelets?

**RP** Although the reason is not known, there is a sparing of megakaryocytes and platelets with copper deficiency. As a result, most copper-deficient patients will have normal platelet counts.

### **H&O** What are the rates of occurrence of hematologic manifestations from surgery-associated copper deficiency?

**RP** The rates are currently not known, but our findings suggest surgery-associated copper deficiency is under diagnosed. At Mayo Clinic-Rochester, we found 46 patients who had symptomatic problems related to low copper. Twenty-five had hematologic manifestations, and 21 neurologic manifestations. Fifteen of the 25 had a history of gastrointestinal tract surgery. Clinicians are diagnosing the condition more often now than in the past, but it is difficult to assess how often it occurs. Once clinicians know to look for it, I suspect that copper deficiency will become a more commonly recognized abnormality.

### **H&O** Do all individuals with copper deficiency develop hematologic manifestations?

**RP** There are patients who have neurologic problems due to low copper and who are not anemic. Why some patients are anemic and some are not is not understood. For example, in an inherited disorder called Mencke disease, there is an impaired absorption of copper but not the hematologic abnormalities that one sees in a non–Mencke disease copper deficiency. There remains much to be learned about why some patients develop hematologic abnormalities and some do not. This is analogous to vitamin B<sub>12</sub> deficiency, which causes some patients to develop severe neurologic complications without hematologic abnormalities.

### **H&O** What preventive measures can be taken against copper deficiency or the resulting hematologic manifestations?

**RP** Copper deficiency has most commonly been associated with patients with short bowel syndromes, patients receiving total parenteral nutrition (TPN), and premature infants. Thus there is a recognition that in patients receiving chronic TPN, the preparation should contain copper. If a clinician is going to administer zinc, it is important to be alert to the possibility of copper deficiency. Clinicians monitoring patients who have had bariatric or gastrointestinal tract surgery should check for copper deficiency. It is also important to note that in some patients, copper deficiency will cause changes in the bone marrow that resemble myelodysplastic syndrome (MDS). At our institution, we have seen patients who were referred for a bone marrow transplant for the treatment of MDS who actually had copper deficiency. Serum copper and ceruloplasmin levels should be checked in patients with presumed MDS.

### **H&O** How do patients with copper deficiency manifesting in the bone marrow typically present?

**RP** Most patients present with a refractory anemia with or without neutropenia. Some have a pancytopenia. Typi-

cal deficiency-related bone marrow changes include excessive iron stores, ringed sideroblasts, iron incorporation in plasma cells, vacuolated erythroid and myeloid precursors, and varying degrees of cellularity. Some patients have hypercellular marrows while others may be normal or rarely hypocellular. Usually megakaryocytes appear normal. Better awareness of these findings by hematopathologists and clinicians would allow the diagnosis of copper deficiency to be made and hopefully some of its complications avoided.

### **H&O** What other precautions can physicians take to prevent copper deficiency?

**RP** It is important to think of the diagnosis in all patients with refractory anemias, MDS, and in patients with neurologic findings resembling subacute confirmed degeneration, and to be aware of potential problems associated with excess zinc, which are not often readily appreciated. Zinc is available over the counter and has been suggested as a possible cold remedy, and so the public is probably consuming larger amounts of zinc than clinicians realize. Clinicians need to be on the lookout for excess zinc as an unknown variable in patients presenting with findings found in copper deficiency.

### **Suggested Readings**

- Hoffman H, Phyliky R, Fleming C. Zinc-induced copper deficiency. *Gastroenterology*. 1988;94:508-512.
- Kumar N, Elliott M, Hoyer J, et al. "Myelodysplasia," myeloneuropathy, and copper deficiency. *Mayo Clinic Proc*. 2005;80:943-946.
- Monte W, Monaghan S, Miller M, et al. Zinc-induced copper deficiency. *Am J Clin Pathol*. 2005;123:125-131.
- Halfdanarson T, Hogan W, Phyliky R, et al. The increasing relevance of copper deficiency in hematological practice. *Blood*. 2005;106:479a-480a
- Halfdanarson T, Li C-Y, Phyliky R, et al. Hematopathological findings in patients with copper deficiency and hematologic manifestations. *Blood*. 2005;106:479a-480a.