Hematogone Hyperplasia in Copper Deficiency

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Key Words: Copper deficiency; Zinc excess; Hematogones; Cytoplasmic vacuoles; Iron-laden plasma cells

Abstract

Copper deficiency is likely an underrecognized cause of anemia and neutropenia and may masquerade as a myelodysplastic syndrome (MDS). We report 2 cases of copper deficiency in which the diagnosis was suggested based on the characteristic morphologic findings, such as cytoplasmic vacuolization of early granulocyte and erythroid precursors and iron-containing plasma cells. It is interesting that both patients had hematogone hyperplasia. This phenomenon, largely absent in MDS, may aid in distinguishing nonclonal causes of cytopenias, such as copper deficiency, from MDS. It is of crucial importance to identify treatable causes of cytopenias when MDS is suspected. We recommend copper level assessment in patients suspected of having low-grade MDS, especially patients with neuropathy and normal results of cytogenetic studies.

Case Reports

Case 1

The information in this case was reported previously by Willis et al2; however, flow cytometric results were not described. The clinical history is thus briefly summarized as follows. A 47-year-old man sought care in December 1999 because of progressive numbness and weakness of his lower extremities. Initial laboratory testing showed severe macrocytic anemia and leukopenia. The patient was also found to have a vitamin B12 deficiency, and appropriate treatment was started.
Despite vitamin B\textsubscript{12} replacement therapy, the patient continued to have worsening neuropathy, and he eventually became wheelchair-bound. In May 2002, the patient continued to have normocytic anemia and neutropenia. A bone marrow examination performed at that time showed morphologic findings consistent with copper deficiency. Flow cytometric analysis indicated hemaglophil hyperplasia and no increase in myeloblasts. The results of cytogenetic studies were normal. Serum copper and ceruloplasmin levels were markedly decreased, and the serum zinc level was elevated (Table 1). The results of all other metabolic and nutritional studies were negative, including vitamin B\textsubscript{12}, folate, and antigliaden and antiendomysial antibody testing.

Copper supplementation was started in August 2002. Approximately 2 months later, his hematologic values had returned to normal (WBC count, 7,100/µL [7.1 × 10\textsuperscript{9}/L]; absolute neutrophil count, 4,500/µL [4.5 × 10\textsuperscript{9}/L]; hemoglobin level, 14.1 g/dL [141 g/L]; platelet count, 322 × 10\textsuperscript{3}/µL [322 × 10\textsuperscript{9}/L]). The patient’s neuropathy, however, did not show signs of improvement. The patient’s copper deficiency appears to be a result of zinc excess. However, the cause of the zinc excess remains undetermined.

### Case 2

A 44-year-old man with a medical history of type 2 diabetes mellitus and lower extremity peripheral neuropathy of unknown etiology went to his primary care physician in October 2007, with symptoms of fatigue and was noted to have pancytopenia. A bone marrow biopsy was performed at that time at an outside institution and was reported to be unremarkable.

During the next few months, pancytopenia continued. In May 2008, the patient was admitted to our institution for further workup. A bone marrow biopsy was performed and showed minimally hypercellular marrow with mild dysmyelopoiesis,

### Table 1

**Test Results in Two Cases of Copper Deficiency**

<table>
<thead>
<tr>
<th>Test</th>
<th>Case 1</th>
<th>First Biopsy, May 2008</th>
<th>Sixth Biopsy, October 2008</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute WBC count, µL (× 10\textsuperscript{9}/L)</td>
<td>2,100 (2.1)</td>
<td>500 (0.5)</td>
<td>1,000 (1.0)</td>
<td>4,100-11,100 (4.1-11.1)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>388 (0.4)</td>
<td>100 (0.1)</td>
<td>284 (0.3)</td>
<td>2,000-7,500 (2.0-7.5)</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1,213 (1.3)</td>
<td>292 (0.3)</td>
<td>452 (0.4)</td>
<td>900-4,700 (0.9-4.7)</td>
</tr>
<tr>
<td>Monocytes</td>
<td>252 (0.25)</td>
<td>99 (0.10)</td>
<td>160 (0.16)</td>
<td>100-900 (0.10-9.0)</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>42 (0.04)</td>
<td>15 (0.02)</td>
<td>71 (0.07)</td>
<td>0-500 (0.00-0.50)</td>
</tr>
<tr>
<td>Basophils</td>
<td>105 (0.11)</td>
<td>5 (0.01)</td>
<td>33 (0.03)</td>
<td>0-200 (0.00-0.20)</td>
</tr>
<tr>
<td>RBC count, × 10\textsuperscript{12}/L</td>
<td>3.22 (3.2)</td>
<td>2.17 (2.2)</td>
<td>2.46 (2.46)</td>
<td>4.27-5.99 (4.3-6.0)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>9.8 (98)</td>
<td>6.8 (68)</td>
<td>8.4 (84)</td>
<td>13.2-16.9 (132-169)</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>36.1 (0.36)</td>
<td>20.0 (0.20)</td>
<td>24.2 (0.24)</td>
<td>39.6-50.2 (39.6-50.2)</td>
</tr>
<tr>
<td>Mean corpuscular volume, µm\textsuperscript{3} (fL)</td>
<td>101 (101)</td>
<td>92 (92)</td>
<td>98.1 (98)</td>
<td>82-106 (82-106)</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin concentration, g/dL (g/L)</td>
<td>29.8 (298)</td>
<td>33.8 (338)</td>
<td>34.8 (348)</td>
<td>31.6-35.4 (316-354)</td>
</tr>
<tr>
<td>RBC distribution width (%)</td>
<td>21.7</td>
<td>17.3</td>
<td>ND</td>
<td>&lt;14.5*</td>
</tr>
<tr>
<td>Reticulocyte count, %</td>
<td>1.3 (0.013)</td>
<td>2.0 (0.02)</td>
<td>ND</td>
<td>0.5-2.8 (0.005-0.028)</td>
</tr>
<tr>
<td>Absolute reticulocyte count, × 10\textsuperscript{12}/L</td>
<td>41.9 (42)</td>
<td>46.8 (47)</td>
<td>ND</td>
<td>32-147 (32-147)</td>
</tr>
<tr>
<td>Platelet count, × 10\textsuperscript{9}/µL (× 10\textsuperscript{12}/L)</td>
<td>488 (488)</td>
<td>107 (107)</td>
<td>73 (73)</td>
<td>140-450 (140-450)</td>
</tr>
<tr>
<td>Zinc, µg/dL (µmol/L)</td>
<td>193 (29.5)</td>
<td>ND</td>
<td>1.64 µg/mL†</td>
<td>66-110 (10.1-16.8)'</td>
</tr>
<tr>
<td>Serum copper, µg/dL (µmol/L)</td>
<td>8 (1.3)</td>
<td>&lt;10 µg/mL†</td>
<td>51†</td>
<td>70-145 (11-23)†</td>
</tr>
<tr>
<td>Urate copper (U/24 h)</td>
<td>6</td>
<td>ND</td>
<td>ND</td>
<td>15-60</td>
</tr>
<tr>
<td>Ceruloplasmin, mg/dL (mg/L)</td>
<td>1.8 (18)</td>
<td>ND</td>
<td>13.8†</td>
<td>22.9-43.1 (229-431)*</td>
</tr>
<tr>
<td>Iron, µg/dL (µmol/L)</td>
<td>32 (5.7)</td>
<td>ND</td>
<td>ND</td>
<td>60-200 (10.7-35.8)</td>
</tr>
<tr>
<td>Total iron binding capacity, µg/dL (µmol/L)</td>
<td>261 (64.6)</td>
<td>ND</td>
<td>ND</td>
<td>262-474 (46.9-84.8)</td>
</tr>
<tr>
<td>Ferritin, ng/mL (µg/L)</td>
<td>9</td>
<td>ND</td>
<td>ND</td>
<td>20-50</td>
</tr>
<tr>
<td>Vitamin B\textsubscript{12}, pg/mL (µmol/L)</td>
<td>277 (204)</td>
<td>353 (260)</td>
<td>ND</td>
<td>211-911 (156-672)</td>
</tr>
<tr>
<td>Folate, serum, ng/mL (nmol/L)</td>
<td>5.8 (13)</td>
<td>ND</td>
<td>ND</td>
<td>2.8-18.0 (6-41)</td>
</tr>
<tr>
<td>Folate, RBC, ng/mL (nmol/L)</td>
<td>ND</td>
<td>622</td>
<td>ND</td>
<td>268-616</td>
</tr>
<tr>
<td>Homocysteine, mg/L (µmol/L)</td>
<td>0.65 (5)</td>
<td>ND</td>
<td>ND</td>
<td>0.68-2.03 (5-15)</td>
</tr>
<tr>
<td>Methylnalonic acid, µmol/L</td>
<td>&lt;0.16</td>
<td>0.13</td>
<td>ND</td>
<td>≤0.40</td>
</tr>
<tr>
<td>Hemochromatosis mutation test</td>
<td>ND</td>
<td>ND</td>
<td>+, heterozygous</td>
<td>—</td>
</tr>
</tbody>
</table>

ND, not done.

* The reference ranges were different for case 2, as follows: RBC distribution width, 10.8%-13.8%; zinc, 0.66-1.10 µg/mL; serum copper, 75-145 µg/dL; ceruloplasmin, 14.0-21.9; ferritin, 10-320 ng/mL (10-320 µg/L). The units of measure for case 2 were sometimes different from those for case 1 and are shown in the table.

1 Performed 3 weeks after the sixth bone marrow examination.
cytoplasmic vacuoles, an increase in immature cells, and ringed sideroblasts. Flow cytometric analysis showed significant hematogone hyperplasia and a mild increase in myeloblasts. The results of cytogenetic studies were normal. The overall findings were thought to be compatible with nonclonal reactive conditions or MDS.

An extensive laboratory workup for a toxic, nutritional, or an infectious cause was performed, including red cell folate, vitamin B₁₂, hepatitis B and C viruses, Epstein-Barr virus, and cytomegalovirus; the results for all were negative (Table 1). The patient was assumed to have MDS. He required packed RBC transfusions every 3 to 4 weeks and was started in the clinical trial of vorinostat (histone deacetylase inhibitor). He received 5 cycles of vorinostat, and repeated 4-time bone marrow examination in monthly intervals during each cycle showed a poor response to the treatment; the bone marrow continued to demonstrate similar morphologic features. During this period, he had persistent pancytopenia (absolute neutrophil count in the range of 128-390/µL [0.1-0.4 × 10⁹/L], hemoglobin, 6.8-8.4 g/dL [68-84 g/L], and platelet count, 59.99 × 10⁹/µL [59.99 × 10⁹/L]), persistent hematogone hyperplasia, and repeated normal male karyotype. Fluorescence in situ hybridization studies for an MDS panel were negative.

In the examination of his last, sixth bone marrow biopsy specimen in October 2008, an alternative diagnosis of copper deficiency was made based on the overall morphologic and flow cytometry findings. The patient’s serum copper level was found to be undetectable (<0.10 µg/mL in September 2008). Oral copper supplementation was started in the first week of November and followed by intravenous cupric chloride (4 mg/d for 4 days) in the middle of November. Approximately 3 weeks after copper repletion, the patient’s serum copper levels had increased to 0.51 µg/mL, and the serum zinc level was mildly increased. Of note, the zinc level was not measured before the copper supplementation. The genetic test for hereditary hemochromatosis was positive for heterozygous mutation of HFE (C282Y mutation). His hematologic values had begun to normalize (WBC count, 6,700/µL [6.7 × 10⁹/L]; hemoglobin level, 10.9 g/dL [109 g/L]; and platelet count, 170 × 10⁹/µL [170 × 10⁹/L]). Approximately 4 weeks after copper repletion, his copper level (0.81 µg/mL) became low normal and the hemoglobin level continued to improve to 11.9 g/dL (119 g/L). The patient’s peripheral neuropathy has shown some signs of improvement. However, because the patient has had symptoms since 2003, the neuropathy may also be related to the diabetes mellitus, in addition to copper deficiency. The patient has an HFE heterozygous mutation and a history of exposure to cement factories, which may contribute to his zinc excess and copper deficiency.

Materials and Methods

Case Identification

Copper deficiency is a rare disease. There were only 4 cases diagnosed at our institution during the last 20-year period, 2 of which had flow cytometric analysis and were described in this study; the other 2 cases were described previously.²

Morphologic Examination

Bone marrow trephine biopsy specimens were fixed in B-5 or Zenker solution, washed, decalcified, and processed. Paraffin-embedded sections of the core biopsy specimens were stained with H&E. Peripheral blood smear, bone marrow direct smear, particle crush, buffy coat, and touch preparations were prepared and stained with Wright-Giemsa and Prussian blue stains as previously described.¹²,¹³

Flow Cytometric Studies

Four-color flow cytometry was used for immunophenotyping by FACSCalibur flow cytometric instruments with CellQuest software (BD Biosciences, San Jose, CA). Bone marrow processing and antibody staining were performed as previously described.¹⁴ The panel of antibodies was used as previously described.¹¹,¹⁴ Cluster analysis was performed using BD Paint-A-Gate software (BD Biosciences). The entire population of hematogones was identified as CD10+/CD22+ and the population of stage I hematogones as CD10⁺bright/CD45⁻/dim/CD20⁻/CD22⁺/CD34⁺.

Results

Peripheral Blood Smears

The peripheral blood smear in case 1 showed dimorphic RBCs with a minor population of microcytic, hypochromic RBCs and scattered teardrop cells, target cells, and elliptocytes. The peripheral blood smear in case 2 showed moderate nonspecific anisopoikilocytosis with occasional elliptocytes and teardrop cells. The WBC and platelet morphologic findings were unremarkable for both patients despite persistent thrombocytopenia in case 2. Repeated examinations in case 2 showed similar morphologic changes.

Bone Marrow Aspirate

The bone marrow aspirates in both cases, including multiple bone marrow examinations in case 2, demonstrated similar morphologic features. There was vacuolization of early granulocytes (mostly promyelocytes and myelocytes) in a small subset of granulocytes, constituting 18%
of granulocytic cells in case 1 and 10% to 25% in case 2. Image 2A and Image 2B. Left-shifted granulopoiesis was consistently noted, which was more pronounced in case 1 and in the third biopsy in case 2, in which there was little maturation beyond the myelocyte stage Image 2C. Myeloblasts were not increased in case 1 but were mildly increased in case 2, in the range of 2.6% to 6.5%. In addition, subtle morphologic abnormalities were present in the maturing granulocytes, consisting mainly of megaloblastoid changes.

In the erythroid lineage, there was left-shifted maturation with vacuolization of a minority of early erythroblasts, predominantly pronormoblasts and basophilic normoblasts, constituting 11% of the erythroblasts in case 1 and 15% to 25% in case 2 (Images 2A and 2B). In addition, subtle morphologic abnormalities were noted, mainly consisting of mild megaloblastoid changes and mild terminal dyserythropoiesis. The myeloid/erythroid ratios were 1.1 in case 1 and in the range of 0.8 to 1.9 in case 2. Megakaryocytes were normal in number and morphologic features in both cases.
Hematogones were occasionally noted in case 1 but were readily recognizable in case 2. They were mainly medium-sized lymphoid cells with round or oval nuclei, condensed but homogeneous chromatin, inconspicuous nucleoli, and scant or no discernible cytoplasm. Scattered plasma cells showing dark green-black inclusions in the cytoplasm were present only in case 2, constituting approximately 30% of plasma cells. Iron stains of the aspirate smear with Prussian blue identified inclusions as hemosiderin. In addition, iron stains revealed the presence of storage iron, sideroblastic iron, and scattered ringed sideroblasts (5% of erythroids in case 1 and in the range of 2%-5% in case 2).

**Trephine Biopsy**

The trephine biopsy specimen from case 1 was mildly hypocellular for age (~35%-40% cellularity; age, 47 years) but otherwise morphologically unremarkable with the exception of multiple small lipogranulomas. Multiple trephine biopsy specimens from case 2 were normocellular to mildly hypercellular for age (in the range of 40%-70%; age, 44 years) and otherwise morphologically unremarkable.

**Flow Cytometric Findings**

Flow cytometric analyses in both cases demonstrated hematogone hyperplasia, which was more pronounced in case 2, notable for persistency and high numbers.

Also present in case 2 are megaloblastoid change of erythroids (red arrow), left-shifted granulopoiesis with little maturation beyond the myelocyte stage (C, from second biopsy; Wright-Giemsa, ×1,000), scattered hematogones (arrow) (D, from fourth biopsy; Wright-Giemsa, ×1,000), hemosiderin-laden plasma cells (arrow) by Wright-Giemsa stain (E, from fourth biopsy; ×1,000) and iron stain (F, Prussian blue, ×1,000), and ringed sideroblast (G, Prussian blue, ×1,000).
Hematogones exhibited a typical, consistent, complex spectrum of sequential antigen expression as described previously. Of total analyzed events, the percentage of hematogones was 2.4% in case 1 and in the range of 5.3% to 11% in case 2. Within the hematogone population, the percentage of stage 1 hematogones was 32% in case 1 and in the range of 22% to 32% in case 2. Myeloblasts were not increased in case 1 but were mildly increased in case 2, ranging from 2.6% to 4.6% with an unremarkable immunophenotype or mild immunophenotypic variations such as variable expression of CD38. Maturing granulocytic cells showed the features consistent with left-shifted granulopoiesis and otherwise were unremarkable. Maturing monocytic cells in both cases were unremarkable.

**Discussion**

It is customary to exclude vitamin B<sub>12</sub> and folate deficiency in cytopenic patients with a suspected MDS, but copper deficiency is often overlooked. We describe 2 patients with copper deficiency in whom the diagnosis was first suggested based on the characteristic morphologic findings in conjunction with hematogone hyperplasia.

Copper deficiency can cause various cytopenias and neurologic manifestations. Hematologic manifestations include microcytic, normocytic, and macrocytic anemia. Severe absolute neutropenia is characteristic, and thrombocytopenia occurs only in a small subset of patients. The 2 cases reported herein demonstrated bicytopenia in case 1 (normocytic anemia and severe neutropenia) and pancytopenia in case 2 (normocytic anemia, severe neutropenia, and moderate thrombocytopenia). Both patients had neurologic problems. The serum copper and ceruloplasmin levels were decreased, whereas the zinc levels were increased in both patients. Correction of the hypocupremia by copper supplementation resulted in prompt and essentially complete resolution of the hematologic manifestations. These findings imply that zinc-induced copper deficiency is the most likely cause of cytopenias.

The characteristic morphologic features of copper deficiency described previously, which include vacuolization of early granulocytic and erythroid precursors, ringed sideroblasts, and iron-laden plasma cells, were well illustrated in the 2 cases reported herein. Other morphologic changes described previously, including left-shifted granulopoiesis to maturation arrest, megaloblastoid changes in granulocytic and erythroid lineages, and mild terminal

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**Image 3** Hematogone hyperplasia in copper deficiency. Flow cytometric analyses reveal an increase in total hematogones, 2.5% of total analyzed events in case 1 (A) and 11% in case 2 (B, from fourth biopsy) and stage I hematogones (arrow: 0.8% of total analyzed events in case 1 and 2.4% in case 2). Hematogones are represented in violet and mature B cells in blue. APC, allophycocyanin; FITC, fluorescein isothiocyanate; PerCP, peridinin chlorophyll protein.
dyserythropoiesis in a variably cellular bone marrow with relative erythroid predominance, were consistently noted in the 2 cases described herein. In addition, the number of myeloblasts was mildly increased, with subtle immunophenotypic variations in case 2.

The novel finding in this study is hematogone hyperplasia in copper deficiency in both analyzed cases, which was evident by morphologic studies and by flow cytometry. Such a phenomenon has not yet been described in a comprehensive manner but was rather briefly described in a recent case report in which the percentage of hematogones was not given in a 2-color flow cytometric study, and the reported population appeared to represent only stage I hematogones by its immunophenotype of CD10+/CD19+/CD20−/CD22+/CD34+ and positive for terminal deoxynucleotidyl transferase.6 In this study, we systematically studied hematogones by 4-color flow cytometry. We found that hematogones exhibited a typical, consistent, complex spectrum of sequential antigen expression. Furthermore, stage I hematogones and the total number of hematogones were consistently increased in both analyzed cases of copper deficiency, compared with age-matched control patients.11,14

Flow cytometric analyses were not performed or the results not described in virtually all published series of copper deficiency, with the exception of the aforementioned case report.6 At our institution, 2 of 4 copper-deficient cases had flow cytometric analysis performed, and both revealed hematogone hyperplasia. Although the exact percentage of cases having this phenomenon is unknown, our results may suggest that hematogone hyperplasia is not uncommon in copper deficiency, and copper deficiency may add to the growing list of causes of hematogone hyperplasia.14 Further studies on a large cohort of patients are needed to validate our observation. More important, identification of hematogone hyperplasia may serve as an important clue to distinguish nonclonal reactive conditions, such as copper deficiency, from MDS in cytopenic patients because a low number to absence of hematogones is the common feature of MDS.8,10,11 Proposed mechanisms for this finding include an increase in myeloid-biased hematopoietic stem cells and apoptosis.

Diagnosis of copper deficiency may be difficult and is not uncommonly delayed, as seen in one of our cases, probably owing to rarity and lack of general awareness of morphologic features.1,4,7,19 Because of anemia, neutropenia, marrow erythroid hyperplasia with subtle dysplastic changes, ringed sideroblasts, and a mild increase in myeloblasts, a diagnosis of low-grade MDS or sideroblastic anemia may enter the differential diagnosis. Features that help with this distinction include cytoplasmic vacuolization of early erythroid and myeloid precursors, iron-containing plasma cells, lack of overt dysplasia, and hematogone hyperplasia in bicytopenic or pancytopenic patients with severe neutropenia and neurologic problems. Although not all of these features may be present in a given patient, a combination of certain features should prompt the performance of laboratory tests for copper and zinc levels. In MDS or sideroblastic anemia due to toxic effects of ethanol, erythroid but not granulocytic precursors can show vacuolization, helping to differentiate them from copper deficiency. Features that can be seen in MDS but that are usually not present in copper deficiency include abnormal nuclear lobation of erythroblasts and granulocytic cells, hypogranularity, and dysmegakaryopoiesis. It is of crucial importance to identify treatable causes of cytopenias when MDS is suspected. We recommend copper level assessment in patients suspected of having low-grade MDS, especially patients with neuropathy and normal results of cytogenetic studies.

It is interesting that iron-laden plasma cells were described in approximately 22% of copper-deficient patients in a recent large cohort of 40 patients.7 In our study, such iron-laden plasma cells were present in 1 of 2 patients who also had a heterozygous mutation for HFE, a gene implicated in homozygous-recessive hereditary hemochromatosis. It is interesting that this mutation was also detected in 1 recent case in which iron-laden plasma cells were also present.1 Hemochromatosis can cause raised hepatic zinc levels, possibly due to increased intestinal zinc absorption, and iron overload that may induce mild copper deficiency.20 Heterozygotes also accumulate excess iron, but not to the degree required to cause significant tissue damage. In our case (case 2), the serum ferritin level was markedly increased before RBC transfusion. It is possible that this complex trace element interaction may contribute to copper deficiency. The frequency of the heterozygous mutations of HFE (C282Y) in white populations of Northern European extraction is estimated to be about 11%.21 While the mechanism underlying iron deposition in plasma cells is unknown, given the similar prevalence of this morphologic finding (about 20% in copper deficiency), it is tempting to speculate that heterozygous mutation of HFE may contribute to this phenomenon at least in some copper-deficient patients. Therefore, the presence of iron-laden plasma cells may serve as an important clue to an HFE mutation and should prompt genetic testing for HFE mutations.

Copper’s ubiquitous distribution and low daily requirement make acquired deficiency in humans rare.22 It is absorbed through the intestinal mucosa across the basement membrane into the bloodstream via energy-dependent mechanisms. There are a number of causes leading to copper deficiency, including prolonged parenteral nutrition, partial gastrectomy, excess zinc ingestion, malabsorption such as celiac disease, and amyloidosis.3,4,6,7,19,23,24 In our studies, case 2 had an HFE heterozygous mutation and a history of exposure to cement factories, which may have contributed to the zinc excess and copper deficiency,25,26 whereas case 1 has no identifiable cause of hypocupremia and hyperzincemia.
Of significant interest is the physiologic relationship between copper and zinc. Hyperzincemia in copper-deficient patients who are not ingesting excessive amounts of zinc has been reported, as seen in our cases. In patients with excessive zinc intake, high zinc levels result in increased metallothionein production in enterocytes. The high affinity of copper for metallothionein displaces zinc and, thus, leads to the accumulation of copper in the enterocytes. The enterocytes are ultimately shed into the gastrointestinal tract, leading to copper elimination.

The pathogenesis of anemia in copper deficiency is complex and seemingly multifactorial, which may be related to the role of copper-dependent enzymes, such as hephaestin, ceruloplasmin, and cytochrome-c oxidase, in iron metabolism and transportation. Hephaestin, a copper-containing ferroxidase expressed in the duodenum, is implicated in iron export from the duodenal mucosa. Ceruloplasmin has serum ferroxidase activity and is essential for the mobilization of iron from the monocyte-macrophage system to plasma. It is necessary for the export of iron from nonintestinal cells, and its absence can lead to iron accumulation in macrophages, anemia, and neurodegeneration.

Copper deficiency may result in reduction in cytochrome-c oxidase, leading to a slower rate of electron flow and adenosine triphosphate production and, ultimately, diminished hemoglobin synthesis. Superoxidase dismutase, another copper-containing enzyme, is decreased in copper deficiency, so the erythrocyte lifespan may be shortened by disturbed elimination of superoxide, leading to cell membrane injury. Diminished levels of superoxidase dismutase and cytochrome-c oxidase may also cause iron accumulation in the mitochondria, leading to the formation of ring sideroblasts.

The cause of the neutropenia observed in copper deficiency is even less well understood than that of the anemia. Speculations on the cause of neutropenia include destruction of myeloid progenitor cells in the bone marrow, impaired maturation of myeloid precursors, impaired egress of neutrophils from the bone marrow, and increased clearance of neutrophils from the circulation. The latter may be associated with the formation of antineutrophil antibodies.

Idiopathic hyperzincemia and hypocupremia associated with extensive central nervous system demyelination, similar to that seen in case 1, and with progressive peripheral neuropathy, similar to that seen in case 2, were reported. While repletion of copper is effective in rapidly correcting hematologic manifestations in nearly all reported cases, reversal of neurologic abnormalities is limited. In our cases, only case 2 showed some signs of improvement. Of note, his neuropathy may also have been contributed to by diabetes mellitus. This general lack of improvement in neuropathy emphasizes the importance of prompt diagnosis because the consequence of a missed diagnosis can be serious.

A diagnosis of copper deficiency is usually established by measuring serum copper or ceruloplasmin levels. Measurement of serum copper levels may have limitations because it is subject to fluctuations and may be relatively insensitive in detecting milder forms of copper deficiency. The ceruloplasmin level is an excellent surrogate marker of copper status, and the various factors that can elevate ceruloplasmin levels, such as inflammatory disease and hormone therapy, do not interfere with this use. Measurement of the ceruloplasmin level, rather than the serum copper level, is the better way to detect copper deficiency. Other potentially more sensitive new methods, but not available in routine clinical practice, include erythrocyte and extracellular superoxide dismutases, leukocyte copper, platelet cytochrome-c oxidase, and serum lysyl oxidase.

We reported 2 cases of copper deficiency resulting in anemia, severe neutropenia, and neuropathy. While the morphologic manifestations of copper deficiency are not pathognomonic, the combination of cytoplasmic vacuolization of erythrocyte and myeloid precursors and iron-containing plasma cells should lead to a suspicion of copper deficiency. It is of crucial importance to identify treatable causes of cytocontrols. We recommend copper level assessment in patients suspected of having low-grade MDS, especially patients with neuropathy and normal results of cytogenetic studies. The presence of hematogone hyperplasia in copper deficiency would be helpful in distinguishing nonclonal causes of cytocontrols from MDS. In addition, the presence of iron-laden plasma cells may serve as an important clue to HFE mutation and should prompt genetic testing for HFE mutations.

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References


