Copper Deficiency Masquerading as Myelodysplastic Syndrome

Xylina T. Gregg¹, Vishnu Reddy², Josef T. Prchal¹

¹Baylor College of Medicine, Houston Texas and ²Dpt. of Pathology University of
Alabama at Birmingham, Birmingham Alabama

Corresponding Author:

Josef T. Prchal, MD
Baylor College of Medicine
One Baylor Plaza, 802E
Houston, TX 77030
ABSTRACT
We describe a severely neutropenic, red cell transfusion dependent female, with previous Bilroth II surgery, whose marrow morphology was typical of myelodysplastic syndrome (MDS) with ringed sideroblasts. She had a transient reversal of her anemia and severe neutropenia following erythropoietin and granulocyte colony stimulating factor therapy. Because of relapse while on growth factors, she was referred for allogeneic bone marrow transplantation and a pre-transplant nutritional evaluation revealed severe copper deficiency; her hematological abnormalities fully resolved with copper therapy. This report underscores that copper deficiency should be an integral part of the differential diagnosis of sideroblastic MDS, even in patients not requiring parenteral nutrition.

CASE REPORT:
A 44 year old white female was referred for macrocytic anemia and leukopenia. Nine years previously, a gastric resection with Bilroth I anastamosis was performed for peptic ulcer disease. Four years after the original surgery, she developed recurrent gastric ulceration and gastric outlet obstruction and the Bilroth I anastamosis was converted to Bilroth II. She developed “dumping” symptoms with chronic diarrhea, but her weight remained stable.

The patient related a history of chronic anemia treated with oral and parenteral iron, B12, and folate without response. One year before referral her hematocrit was 23% and WBC was 2300/cmm. She required red cell transfusions approximately every two months. On presentation, WBC was 1500/cmm with 19% neutrophils, hemoglobin 6.4 g/dL, MCV 102 and platelet count 192,000/cmm; occasional oval macrocytes were observed on
her blood film. She was thin and chronically ill appearing, but physical exam was otherwise unremarkable. There was no splenomegaly. Serum B12, RBC folate, and ferritin levels were elevated. Albumin was 3.4 gm/dL (normal 3.9-4.8). A bone marrow showed dyserythropoiesis, dysmyelopoiesis, ringed sideroblasts, and prominent hemosiderin in plasma cells (see Figure 1 panels A & B and Table 1). Cytogenetic studies were normal.

Based on the bone marrow morphology, she was presumed to have a myelodysplastic syndrome (MDS), FAB subtype refractory anemia with ringed sideroblasts (RARS). There was no response to therapy with pyridoxine. She was started on granulocyte-colony stimulating factor (G-CSF) 75 µg/day and erythropoietin (EPO) 5000 units/day with normalization of peripheral blood counts (Table 1) three weeks after starting therapy and no further red cell transfusions were given.

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### Table 1

<table>
<thead>
<tr>
<th>Peripherals Blood</th>
<th>Bone Marrow</th>
</tr>
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<tbody>
<tr>
<td>Hb</td>
<td>MCV</td>
</tr>
<tr>
<td>Presentation</td>
<td>6.4</td>
</tr>
<tr>
<td>Initiation of EPO/GCSF</td>
<td>7.2</td>
</tr>
<tr>
<td>After 3 weeks of EPO/GCSF</td>
<td>12.4</td>
</tr>
<tr>
<td>After 3 months of EPO/GCSF</td>
<td>6.9</td>
</tr>
<tr>
<td>After copper therapy</td>
<td>13.2</td>
</tr>
</tbody>
</table>

*Transfused 2 units red blood cells

Hb - hemoglobin, MCV - mean corpuscular volume, WBC - white blood cell count, ANC - absolute neutrophil count, Pr - platelet expressed in mm$^3$

However, the hemoglobin response was not sustained, and 3 months after initiation of therapy, she again required frequent red cell transfusions. On the other hand, despite tapering the G-CSF dose to every other day, her WBC remained in the normal range (Table 1). A repeat bone marrow examination showed a hypercellular marrow with the same morphological abnormalities depicted in Figure 1 and Table 1.
Fig 1A – Initial bone marrow smear showing vacuoles in the erythroid precursors, dyspoietic changes and several ringed sideroblasts (inset). Iron granules in plasma cell cytoplasm (arrow head). Original magnification, x 890.
Fig 1B – Marrow aspirate smears (initial bone marrow aspirate) showed several plasma cells containing blue-black particulate material in the cytoplasm which stained positive with Prussian blue reaction (hemosiderin deposits). Original magnification, x 970.

During this interval, her diarrhea spontaneously resolved. An esophagastroduodenoscopy with small bowel biopsy was performed, which was normal. She was also found to have a severe progressive peripheral neuropathy and an optic neuritis.

She was referred for evaluation for bone marrow transplant for MDS. As part of the pre-transplant evaluation, a nutrition consult was obtained. Her copper level was undetectable at < 10 mcg/dL (normal 70-155). She was treated with intravenous copper chloride 2.5 mg QD for 14 doses (total dose 35 mg) and the EPO and G-CSF were discontinued.
Her hemoglobin concentration normalized within 6 weeks. She was placed on oral copper supplementation with copper sulfate 3 mg TID. Three months after initiation of copper therapy, her copper level was normal at 92 mcg/dL, ceruloplasmin was normal, and her CBC was normal with a normal MCV. Bone marrow aspiration and biopsy showed reversal of previous abnormalities (Table 1). Hemosiderin was only seen in macrophages and plasma cells did not contain histologically identifiable iron. Her general well-being improved, but the peripheral and optic neuropathies persisted and her weight remained stable.

DISCUSSION:

Deficiency of copper is reported to result in anemia, neutropenia (1) and less commonly thrombocytopenia (2). Bone marrow morphology varies, but vacuolated erythroid precursors are often found. Other abnormalities include megaloblastic changes and ringed sideroblasts. Although textbooks describe anemia of copper deficiency as microcytic (3), review of the literature reveals that macrocytic, microcytic, and normocytic anemia occur (1,4-6). Our patient had macrocytic anemia, with occasional oval macrocytes, a finding further supporting the diagnostic suspicion of MDS. The significance of the plasma cell iron in this patient is unclear; however, it was likely secondary to copper deficiency since it resolved following copper therapy.

Most cases of copper deficiency in adults occur in patients on total parenteral hyperalimentation (3), although there have been cases resulting from non-copper containing enteral feeding (7). To our knowledge, there have been only two previous reports (4,5) of copper deficiency from intestinal malabsorption following partial
gastrectomy in patients, who, like ours, were not on parenteral or enteral nutrition. One of these patients (5) also had neurological abnormalities.

The mechanism by which copper deficiency induces anemia and other cytopenias is unknown. Copper is an essential cofactor for various redox enzymes and decreased activity of copper dependent enzymes, such as ceruloplasmin ferroxidase and cytochrome oxidase, has been hypothesized as potential causes. Mitochondria isolated from copper-deficient animals were deficient in cytochrome oxidase activity and failed to synthesize heme from ferric iron and protoporphyrin at the normal rate, perhaps leading to mitochondrial iron accumulation, i.e. ringed sideroblasts (8). The association of copper and iron metabolism is of increasing interest. The molecular basis of the sex-linked anemia (sla) mouse due to a defect in intestinal iron transport has been recently identified as a multicopper ferroxidase – hephaestin (9). The Wilson's disease protein product was localized to mitochondria (10), the copper containing mitochondrial transporter frataxin was identified in yeast (11) and its human analogue subsequently identified (12).

Interestingly, acquired somatic mutations of mitochondrial cytochrome c oxidase (a copper containing enzyme) was reported in two subjects with acquired sideroblastic anemia (MDS); one of these had macrocytic anemia, the other microcytic anemia (6). An acquired somatic mutation is not a satisfactory explanation for our patient since the hematological abnormalities rapidly reversed with copper repletion. The molecular defect of the sideroblastic anemia of copper deficiency remains to be elucidated.

The etiology of the neutropenia seen in copper deficiency remains obscure, but is seen consistently (8). Similarly, it is speculative whether the severe peripheral and optic neuropathies, which did not respond to copper replacement, were related to copper
deficiency. However, copper deficiency associated with myelopathy in a patient who also had microcytic anemia and neutropenia (no mention of ringed sideroblasts) was reported (5), and myelopathy is also reported in copper deficient sheep (13).

Our patient responded to hematopoietic growth factors with normalization of hemoglobin and neutrophil count, although the hemoglobin response was transient. To our knowledge, this response has not previously been reported. However, this observation underscores that therapeutic responses to these cytokines may occur regardless of the causative event.

Copper deficiency is not often considered as a cause of cytopenias in adults. Most current hematology textbooks do not list copper deficiency in the differential diagnosis of RARS, demonstrating limited awareness of this correctable cause of sideroblastic anemia that as shown here can be at times particularly severe. The diagnosis may not be suspected in patients not on nutritional support, as one recent hematology text discusses hematological complications of copper deficiency and states that copper deficiency occurs "only in malnourished premature infants or patients receiving long-term parenteral nutrition" (14).

This report underlines the non-specificity of morphological abnormalities and demonstrates that copper deficiency should be considered as a potential cause of RARS even in patients who are not on parenteral nutrition. It also demonstrates that this entity can transiently respond favorably to cytokine therapy.

REFERENCES:


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