

A rare case of pancytopenia in a child with cystic fibrosis: Can copper cure it all?

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Abstract

Nutritional deficiencies such as iron, vitamin B12 and folate are recognized as etiologies for several cytopenias; although copper's role in multiple metabolic enzymes is well-established, copper deficiency is often overlooked as a contributing entity. Frequently diagnosis is delayed, patients may undergo bone marrow investigations with findings overlapping a myelodysplastic process, which can lead to further testing and treatment considerations including hematopoietic stem cell transplant referral. We present a case of a young boy with cystic fibrosis with biliary dysplasia corrected with hepato-portoenterostomy and distal intestinal obstruction syndrome resulting in jejunal resection, with severe anemia and thrombocytopenia requiring transfusion support. Initial evaluation had been unremarkable, ongoing pancytopenia prompted bone marrow studies, which revealed vacuolated granulocytic and erythroid precursors and ring sideroblasts, suggestive of copper deficiency. Serum copper and ceruloplasmin were consistent with severe deficiency, attributed to insufficient absorption intestinal resection, chronic parenteral nutrition and prior zinc supplementation. Following enteral copper supplementation, anemia, leukopenia and thrombocytopenia significantly improved, however upon cessation, counts again worsened and has since been maintained on daily copper supplementation without further transfusion needs. Our experience exemplifies the importance of early consideration for copper deficiency in children with cytopenias, especially within context of intestinal malabsorption or inadequate nutritional intake which often occurs in children with cystic fibrosis.

Title Page

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Running title: Pancytopenia and copper deficiency in a child with CF

To the Editor

We present a nine-year-old boy with cystic fibrosis, biliary dysplasia corrected with hepato-portoenterostomy, and distal intestinal obstruction syndrome resulting in jejunal resection with intermittent cytopenias since two years of age. Namely, a macrocytic anemia with mean corpuscular volume (MCV) 87–109 fL, leukopenia below 3 thou/uL, neutropenia 0.035–0.705 thou/uL and mild to moderate thrombocytopenia of 48–147 thou/uL. He had frequent episodes of culture-negative sepsis syndrome requiring intensive care stays ever 2-3 months, during which he required frequent transfusions with packed red cells, often once hemoglobin reached below 7 g/dL, as well as intermittent platelet transfusions.

Our patient presented to general hematology with pancytopenia at 3 years. Initial evaluation included negative Coombs and anti-neutrophil antibody with normal folate, vitamin B12, methylmalonic acid (MMA), vitamin E, iron studies and soluble transferrin receptor. Peripheral smear revealed no morphologic abnormalities. His physical exam was notable for pallor, lower extremity weakness and mild hepatosplenomegaly. Initially, anemia and thrombocytopenia were attributed to hypersplenism; however, with persistent pancytopenia, bone marrow evaluation was performed. Marrow studies showed progressive myelopoiesis without evidence of dysplasia or malignancy, but the presence of vacuolated granulocytic and erythroid precursors and ring sideroblasts prompted evaluation of a potential copper deficiency. A serum copper level of <5 (reference range 117-181 mcg/dL) and serum ceruloplasmin level of <3 (reference range for male 7-9 is 25-52 mg/dL) confirmed his severe copper deficiency.

Our patient's copper deficiency was attributed to poor absorption secondary to his cystic fibrosis and gut resection. In addition, prior zinc supplementation, used to promote growth in CF, was thought to compound deficiency due to zinc's interference with copper metabolism.¹ After two months of enteral supplementation with copper gluconate at 2 mg daily, serum copper and ceruloplasmin levels normalized (**Figure 1**). There was significant improvement in hematological parameters: normalization of hemoglobin, MCV, WBCs and neutrophils, and as stabilization of his platelet count (**Figure 1**). Given his response, supplementation was suspended for some time; however, later resumed upon recurrence of pancytopenia.

Discussion

Copper is a trace element serving as a cofactor for enzymes involved in respiratory oxidation, iron transport and metabolism and neurotransmitter synthesis, also known as cuproenzymes.¹⁻² Copper homeostasis regulates absorption and distribution, with mechanisms to limit free radical production and copper overload.¹⁻² Dietary copper content drives intestinal absorption, which occurs primarily through the proximal small intestine, to a lesser degree the stomach.¹ The recommended dietary allowance for copper increases from infancy through adolescence and adulthood, up to 1000 µg/day in the United States and Canada.¹

Up to 70% of dietary copper is absorbed enterally; deficiency may occur secondary to states of malabsorption (e.g., celiac disease and small bowel Crohn's disease) as well as chronic inflammatory conditions. Acquired deficiency may be a complication following surgical resection, seen in short gut syndrome, gastrectomy and gastric bypass surgery.³ Additionally, prolonged parenteral nutrition without copper supplementation and excessive zinc intake lead to deficiency. Zinc and copper are described to have an antagonistic relationship, with excessive zinc intake interfering with copper absorption due to zinc-induced synthesis of a copper-binding ligand leading to sequestration within intestinal cells preventing entry into circulation.²

In a retrospective study of forty patients with copper deficiency and hematologic abnormalities, thirty-nine had isolated anemia or anemia with other cytopenias.⁴ Copper deficiency anemia can range from microcytic to macrocytic, with severity correlating to extent of deficiency.³ The pathophysiology of anemia is theorized to derive from copper's role in proteins involved in iron homeostasis and transport. Reduced transport of

iron across intestinal cells leads to impaired conversion of iron by ceruloplasmin and hephaestin (a copper-dependent ferroxidase), needed for loading onto transferrin and incorporation into protoporphyrin.³ With incomplete hemoglobin synthesis ring sideroblasts form and red cell membrane defects occur from decreased activity of copper superoxide dismutase against free radicals, leading to a shortened red cell lifespan.³

Leukopenia of copper deficiency primarily consists of neutropenia. Proposed hypotheses include impaired maturation and increased destruction of precursors within the marrow, in addition to limited neutrophil migration from marrow and increased clearance from circulation.^{3,5} Thrombocytopenia is a less frequent consequence and rarely copper deficiency presents as isolated thrombocytopenia. In the previously described cohort, thrombocytopenia was only noted in combination with anemia in two of forty patients.⁴ In copper deficiency, the bone marrow is typically hypercellular and with characteristic findings of cytoplasmic vacuolization of both erythroid and myeloid precursor cells.³ Iron stores are also increased with a prominence of ring sideroblasts.³ The constellation of all these findings is often misdiagnosed or mistaken for myelodysplastic syndrome (MDS) and with reports of copper deficiency identified upon referral for hematopoietic stem cell transplant.³ Timely diagnosis allows for appropriate intervention; of the previously described patients with available response to therapy follow up, 16 of 28 (57%) had complete normalization of cytopenias, nine with partial response and three with no response.⁴ This response underlies the importance of early consideration of copper deficiency in a differential for cytopenias.

Neurologic changes can frequently accompany hematologic findings and encompass a spectrum of disorders. This includes isolated peripheral neuropathy or polyneuropathy, motor neuron disease, myopathy, cerebral demyelination, cognitive dysfunction, optic neuropathy and myelopathy. In copper deficiency myelopathy, common presenting symptoms are gait difficulties secondary to sensory ataxia and dorsal column dysfunction with associated extremity paresthesias.⁵ In a review of 55 cases of patients with copper deficiency and neurologic symptoms, copper supplementation led to improvement in about half of patients with reported outcomes and stabilization of symptoms in the remainder.⁵

Conclusion

Our patient exemplifies the potential delay in identifying copper deficiency as an etiology for pancytopenia. Copper deficiency should be a consideration in the initial evaluation of children with restricted diets or concerns for malabsorption. Low levels of serum copper and ceruloplasmin are uniformly seen in all patients and essential to establish the diagnosis. Patient with copper deficiency could be misdiagnosed or mistaken for MDS and some patients identified only when referred for hematopoietic stem cell transplant. Enteral copper supplementation is feasible and effective in addressing these cytopenias, eliminating the need for transfusion support as well as improving patients' quality of life and neurological function.

Conflict of Interest: Author has no conflicts of interest to disclose.

Figure Legend:

Figure 1 : Trend in various hematologic indices following initiation of copper supplementation: (A) Total White Blood Cell Count, (B) Absolute Neutrophil Count, (C) Hemoglobin, and (D) Platelet Count. Changes in serum copper level (blue line) and time of initiation of copper supplementation (black arrow).

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