Element of caution: a case of reversible cytopenias associated with excessive zinc supplementation

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Abstract

ZINC IS A COMMON SUPPLEMENT AND IS WIDELY AVAILABLE as a standard component of many over-the-counter products. A number of reports have identified an association between excessive zinc intake and severe cytopenia. We report a case of zinc-induced copper deficiency in a young adult to illustrate this under-recognized cause of anemia and neutropenia.

Severe anemia and neutropenia were identified during the investigation of mild edema in a 19-year-old woman with Hallervorden–Spatz syndrome. This rare, untreatable condition is characterized by progressive motor and cognitive impairment due to massive iron deposition in the basal ganglia. The patient's seizure-like episodes had been treated for many years with carbamazepine (Tegretol, 1900 mg daily); valproate (Epival, 500 mg daily) had been added 10 months before presentation. Her daily diet, via gastrojejunal feeding tube, consisted of 1000 mL of Jevity (Abbott Laboratories Ltd., Montreal, Que.) and 375 mL of Nutren 1.5 (Nestlé Clinical Nutrition Company, Deerfield, Ill.). As well, for the last 5 years she had been receiving supplemental vitamin E, vitamin C, *N*-acetylcysteine, selenium, riboflavin and zinc (50 mg twice daily).

Borderline anemia had been detected in a routine complete blood count 1 year before this presentation (Table 1). Now she was markedly anemic (hemoglobin level 49 g/L) and had severe neutropenia (neutrophil count < 0.1 × 10^9/L). The peripheral blood film (Fig. 1) revealed macrocytic anemia, with basophilic stippling of the erythrocytes and a low reticulocyte count, both features of ineffective erythropoiesis; the few neutrophils present showed nuclear hypolobation (acquired Pelger–Huët anomaly). These features had not been present in the blood film a year earlier.

Bone marrow biopsy showed extensive cytoplasmic vacuolation of erythrocyte (Fig. 2) and leukocyte (Fig. 3) precursors, with almost no evidence of normal leukocyte maturation. The increased numbers of dysplastic erythrocyte precursors with perinuclear iron ("ringed sideroblasts," not visible in the figures) confirmed the diagnosis of sideroblastic anemia.

The differential diagnosis of sideroblastic anemia includes lead intoxication, treatment with medications such as isoniazid, pyridoxine (vitamin B_6) deficiency, long-term alcohol ingestion and zinc toxicity. Further history-taking and laboratory tests, including measurement of the blood lead level and the activity of erythrocyte aspartate transaminase (normal activity indicates adequate pyridoxine status), excluded each of these possibilities except zinc toxicity. The blood levels of carbamazepine and valproate were within the therapeutic ranges.

The daily intake of zinc for the previous 5 years, calculated from the enteral feeds and supplementation, had been 121.25 mg, approximately 15 times the recommended dietary allowance (RDA)[1] (Table 2). In addition, the daily intake of copper, 2 mg, was approximately twice the RDA[1] (Table 2). Zinc toxicity was confirmed by the elevated

Table 1: Hematology profile of 19-year-old woman with zinc-induced copper deficiency at time of presentation as well as 1 year earlier and after cessation of zinc therapy

Blood parameter (reference range)	1 year before presentation	At time of presentation	After end of zinc therapy*
Leukocyte count (4.20–10.80 x 10^9/L)	8.34	1.3	5.7
Hemoglobin level (117–149 g/L)	116	49	133
Mean corpuscular volume (83.0–97.5 fL)	81.5	117	89
Platelet count (160–390 x 10^9/L)	412	473	370
Neutrophil count (1.9–7.4 x 10^9/L)	7.14	< 0.1	4.3
Lymphocyte count (1.0–3.3 x 10^9/L)	0.84	0.9	1.1
Reticulocyte count (20–110 x 10^9/L)	na	20	na
Serum zinc level (9.2–15.4 µmol/L)	na	34.7	16.8
Serum copper level (11.3–25.2 µmol/L)	na	0.3	15.3
Serum ceruloplasmin level (220–495 mg/L)	na	21	na

*Eight months after, except for serum zinc (3 weeks) and copper (5 months). N/A = not available.

serum zinc, low serum copper and low serum ceruloplasmin levels (Table 1).

Zinc therapy was stopped but valproate therapy continued. All hematologic and trace-metal parameters showed strong trends toward normal after 4 weeks and were normal after 8 months (Table 1).

Comments

Zinc supplementation is beneficial in the management of a number of conditions, including acute diarrhea,[2] the common cold,[3] acne[4] and progressive myoclonic epilepsy.[5] Its putative effect is the enhancement of immune function. Many over-the-counter (OTC) zinc-lozenge products are now available; in 1989, an estimated 16% of US citizens were taking zinc supplements orally.[6]

Copper-deficiency anemia secondary to zinc excess was first reported in 1977,[7] and 18 cases have subsequently been reported.[8–16] Most of these cases involved self-medication with OTC dietary supplements; the daily amount of zinc ranged from 29 mg for 7 months[12] to 2000 mg for 3 months.[16] The daily zinc intake of our patient was 100 to 120 mg for 5 years. Instructions on a bottle of OTC zinc lozenges recommend 5 to 20 mg every 2 hours during the onset of a cold, to a maximum of 50 mg daily.

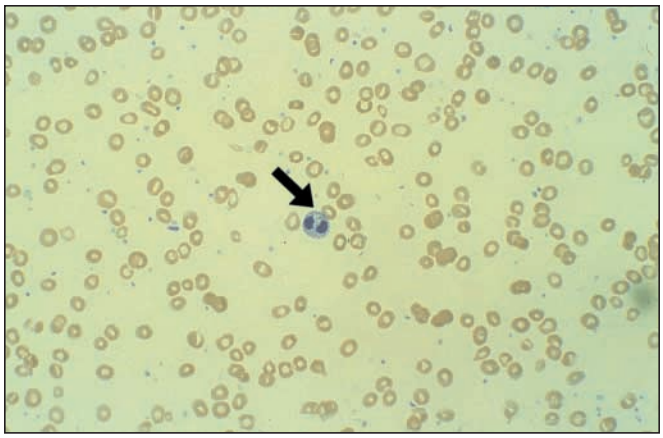

Fig. 1: Peripheral blood film at presentation, showing macrocytic anemia and neutropenia, with Pelger–Huët nuclear anomaly (note neutrophil with bilobed nucleus [solid arrow]) (Wright–Giemsa stain; ×200).

Copper deficiency secondary to zinc excess arises from an indirect interaction between the 2 metals in the intestine. When exposed to excess dietary zinc, the absorptive duodenal cells upregulate metallothionein, an intracellular metal-binding ligand.[17] Metallothionein binds both zinc and copper ions but has a much greater affinity for copper. Dietary copper that is bound to metallothionein becomes sequestered within the duodenal enterocytes, which are sloughed into the intestinal lumen.[18] Increased oral copper intake is ineffective in restoring the zinc–copper balance in the presence of excess dietary zinc, as the induced metallothionein continues to intercept the copper and reduce its absorption. This explains why our patient, despite taking twice the RDA of copper, became copper-deficient over time. Since ceruloplasmin, the main copper metalloprotein in the blood, is produced by the incorporation of cupric ions into a protein moiety, copper deficiency also results in reduced production and therefore a reduced serum concentration of ceruloplasmin.

In all the case reports, copper deficiency was associated with anemia. Bone marrow aspirates revealed vacuolation of erythroid and myeloid precursors, as well as ringed sideroblasts. Neutropenia with arrested granulocyte maturation has also been described.[11,14] After zinc therapy was stopped, the hematologic indices reverted to normal in weeks to months.[14]

Possible contributing factors, such as prescription medications and underlying medical conditions, are important to consider in the differential diagnosis of sideroblastic anemia. In our patient, valproate therapy may

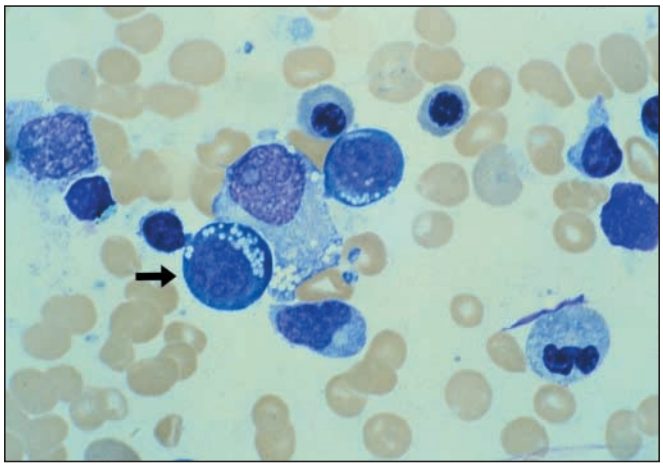

Fig. 2: Bone marrow aspirate, demonstrating extensive vacuolation of erythroid precursor (solid arrow) (May–Grünwald–Giemsa stain; ×1000).

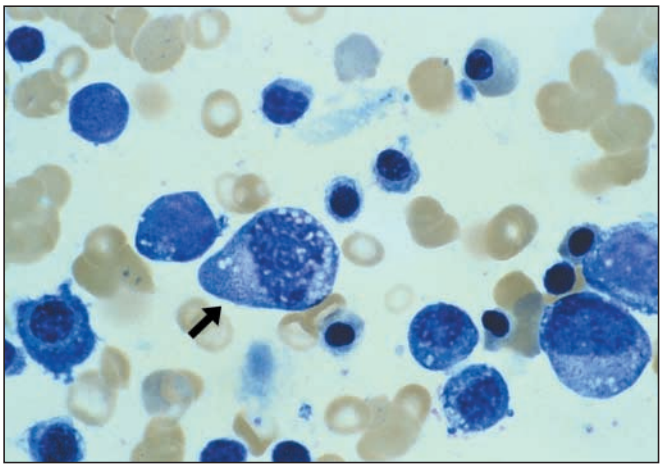

Fig. 3: Bone marrow aspirate, demonstrating extensive vacuolation of myeloid precursor (solid arrow) (May–Grünwald–Giemsa stain; ×1000).

Table 2: Daily recommended dietary allowance and adequate intake* of zinc and copper[1]

Age	Zinc (mg)	Copper (μg)
0–6 mo*	2	200
7–12 mo*	3	220
1–3 yr	3	340
4–8 yr	5	440
9–13 yr	8	700
14–18 yr	11 (M), 9 mg (F)	890
≥ 19 yr	11 (M), 8 mg (F)	900

Note: M = for men, F = for women.

have accounted for the severity of the abnormalities. In some studies, valproate has been associated with lower copper levels in serum or hair.[19] Patients with Hallervorden–Spatz syndrome are thought to have altered iron metabolism only within the central nervous system. In our patient, the serum valproate levels were within the therapeutic range. Furthermore, the hematologic indices reverted to normal when the zinc therapy was stopped and the valproate and carbamazepine therapy continued at the previous dosages.

Excess zinc intake must be included in the differential diagnosis of sideroblastic anemia. Patients and caregivers may be unaware of zinc's potential toxicity when doses intended for short-term use are maintained long term. This lack of awareness is a particular concern with OTC remedies, which may be continued without input from a caregiver. In a patient with a history of excess zinc ingestion, the diagnosis of zinc-induced copper deficiency can be established from the decreased serum copper and ceruloplasmin levels along with the increased serum zinc level. All the hematologic effects are potentially reversible after the oral zinc therapy is stopped, although some patients require intravenous copper repletion.

As zinc supplementation is common, clinicians and pathologists should be alert to the serious hematologic effects of zinc-induced copper deficiency and recognize this condition as an avoidable and readily managed cause of anemia and neutropenia.

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