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LETTER TO THE EDITOR

An under-recognized cause of copper deficiency mimicking myelodysplastic syndrome

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Dear Editor,

Copper is a trace element that is a cofactor in many enzymatic reactions critical to bodily functions. The hematologic system is particularly impacted by copper deficiency and may mimic myelodysplastic syndrome (MDS) [1–3]. Common causes of copper deficiency include total parenteral nutrition, gastric bypass surgery, celiac disease, gastrectomy, and other malabsorptive syndromes [2, 3]. We present a case of copper deficiency secondary to zinc toxicity that was initially misdiagnosed as MDS.

A 47-year-old man initially presented to an outside institution in November 2016 with severe macrocytic anemia with hemoglobin 4 g/dL (range: 14.0–18.0) and neutropenia with absolute neutrophil count (ANC) 0.5×10^9/L (range: 2.4–8.1). Workup revealed folate deficiency at 2.1 ng/mL (range: 7.0–31.4) and presumed B12 deficiency at 311 pg/mL (range: 211–911). He received blood transfusion and was treated with parenteral B12 and oral folic acid. He was diagnosed with concomitant iron deficiency and treated with intravenous iron carboxymaltose. As initial nutritional supplementation did not improve his cytopenias, he underwent a bone marrow biopsy in March 2017 that revealed mild granulocyte atypia, and increased storage iron with occasional ring sideroblasts. Cytogenetics, fluorescence in situ hybridization (FISH) for MDS, and myeloid molecular panel were normal.

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He presented at our institution in April 2017. Laboratory results were significant for hemoglobin 9.1 g/dL and ANC 0.96×10^9/L. Despite supplementation, he remained folic acid and B12 deficient at 2.3 ng/mL and 206 pg/mL, respectively. A repeat bone marrow biopsy revealed dysplastic erythroid cells and ring sideroblasts in > 15% of red cell precursors, favoring a diagnosis of MDS. Additional workup revealed undetectable serum copper level at < 10 μg/dL (range: 72–166). He was started on oral copper gluconate 2 mg daily and increased to 8 mg daily six weeks later with no improvement. Assessment for malabsorption with esophagogastroduodenoscopy and colonoscopy was normal.

In August 2017, he developed peripheral neuropathy with diminished ankle reflexes, loss of proprioception in his toes, and unsteady gait. An elevated zinc level of 149 μg/dL (range: 60–120) that was ordered as part of his initial workup was noted. While prior providers had documented that he was not taking zinc supplements, further questioning revealed use of zinc-containing denture paste for > 10 years. He changed to a zinc-free denture paste and started intravenous copper infusion. He achieved excellent response with normalized laboratory findings eight weeks after starting copper infusions and stopping zinc denture paste (Fig. 1). It is unclear to what degree his neurologic symptoms will improve.

Copper is primarily absorbed in the duodenum, stomach, and ileum [2]. Excess zinc ingestion inhibits copper absorption via upregulation of metallothionein in enterocytes. Metallothionein has high affinity for copper, binding it within enterocytes. Dietary copper is lost as enterocytes slough off in the stool [3, 4]. As in our case, zinc toxicity is not typically overcome by oral copper supplementation until the zinc source is discontinued.

The potential toxicity of zinc-containing denture paste is under-recognized [5]. Although our patient saw numerous providers, his young age likely played a role as his providers did not realize he wore dentures. Early identification and

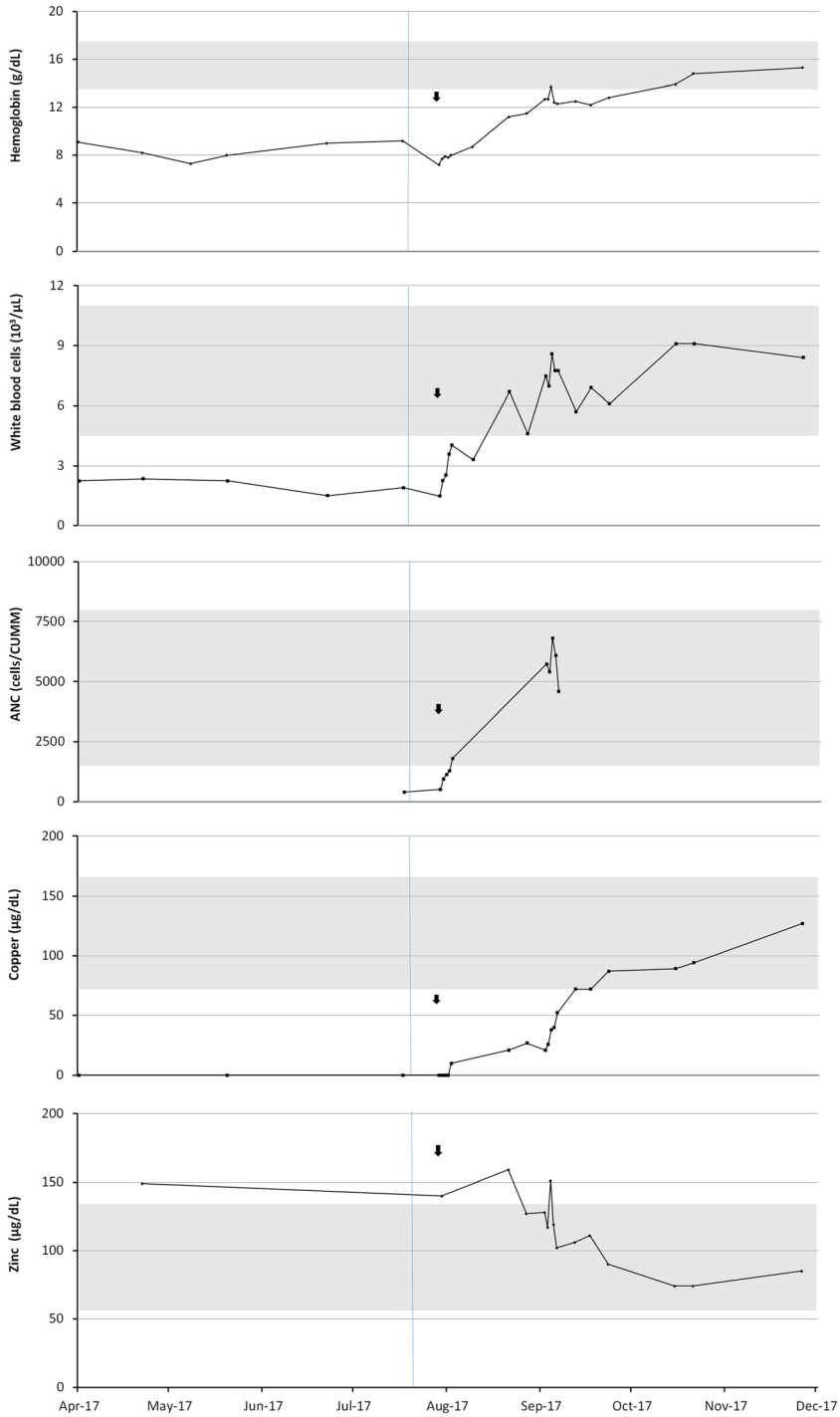

Fig. 1 *Solid blue line* represents date of stopping zinc denture paste. *Arrow* represents first of five daily doses of intravenous copper. *Shaded regions* designate normal range for lab values

treatment is critical to prevent development and progression of neurologic symptoms of copper deficiency and nearly universally results in correction of cytopenias [3].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the individual described in the study.

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