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Case Report

Pancytopenia related to dental adhesive in a young patient

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Abstract: Copper deficiency resulting in hypocupremia is a rare cause of pancytopenia associated with a neurological syndrome. Hypocupremia may also occur as a consequence of excessive oral zinc consumption as described by Brewer et al and several other groups. Dental fixatives have been described as a potential source of hyperzincemia in patients. Despite the recently modified dental fixatives with safer zinc content, zinc poisoning results in hypocupremia secondary to inappropriate use of them can still happen and more likely be misdiagnosed. We describe a case of a patient with pancytopenia who was diagnosed with severe aplastic anemia and hypocellular myelodysplastic syndrome and was referred to us for consideration of bone marrow transplantation.

Keywords: Pancytopenia, dental, adhesive

Introduction

Copper deficiency resulting in hypocupremia is a rare cause of pancytopenia associated with a neurological syndrome and is reported in several case reports in the literature. Most cases of copper deficiency have been reported in patients with gastrointestinal disorders, malabsorption syndromes, gastric resection or bariatric surgery and patients receiving long term parenteral nutrition lacking in copper [1-4]. Hypocupremia may also occur as a consequence of excessive oral zinc consumption as described by Brewer et al and several others groups [5-9]. A high concentration of zinc in the small intestine induces enterocytic expression of metallothioneins which bind copper. Copper remains in the enterocytes and is lost through intestinal epithelial turn over into the stool [10]. As a result of copper deficiency, patients may develop a syndrome of myelopolyneuropathy with hematologic abnormalities. This syndrome, associated with hyperzincemia and hypocupremia, has been described by various groups [11-15]. Denture adhesives, as a possible source of hyperzincemia, was first reported by Spinazzi et al and Nations et al. Later Hedera et al. published a cohort of 11 patients with the syndrome and identified denture adhesive as a source of excessive zinc in 100% of their patients [3, 16, 17]. Large amounts of zinc-containing denture cream to provide a sufficient seal for poorly fitting dentures is the likely cause of hypocupremia, hyperzincemia, bone marrow suppression and neurological deficits in these patients.

Data on this subject is sparse, despite the case reports and cohorts in the literature, and, as a result, patients continue to be unrecognized or misdiagnosed [18]. We describe a case of a patient with pancytopenia who was diagnosed with severe aplastic anemia and hypocellular myelodysplastic syndrome and was referred to us for consideration of bone marrow transplantation.

Case report

A 34 year old Caucasian male with no significant past medical history was referred to our cancer center for evaluation and consideration for allogeneic bone marrow transplant. The patient was in his usual state of health about 4 months prior to presentation when he was

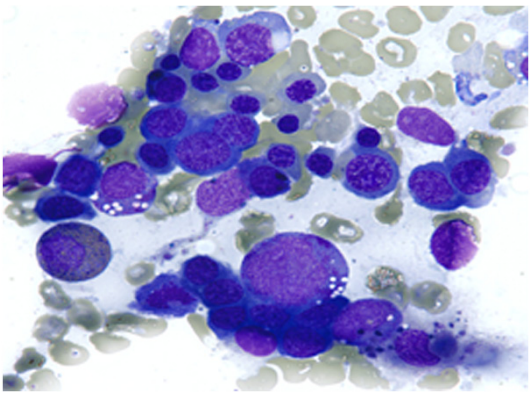

Figure 1. Pre-treatment bone marrow aspirate smear shows vacuolated promyelocytes in a background of erythroid precursors (Wright stain; 1000x).

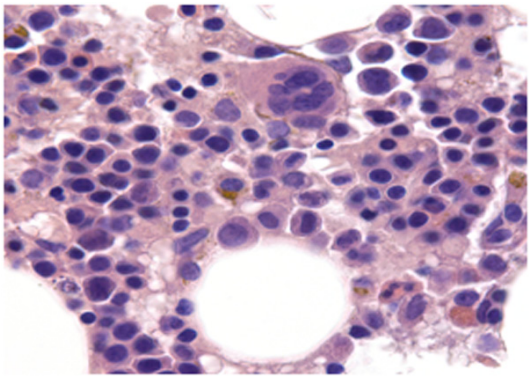

Figure 2. Pre-treatment bone marrow biopsy is hypocellular with moderate granulocytic hypoplasia and decreased myeloid: erythroid ratio (Hematoxylin and eosin stain; 1000x).

found to have pancytopenia. At that time, he was hospitalized for 6 days at a community hospital and was supported with transfusions and granulocyte colony stimulating factor (gcsf). Subsequently, he was seen as an outpatient by a community oncologist who performed a bone marrow biopsy that was suggestive of aplastic anemia. He was started on steroids, prednisone 40 mg/day, and was referred to a teaching hospital in Ohio for second opinion. A repeat bone marrow biopsy was performed and the patient was diagnosed with aplastic anemia with a concern for hypocellular myelodysplastic syndrome (MDS). He continued to be on steroids and suffered from two episodes of infectious events including pneumonia and cellulitis during this period of time.

He was then referred to our cancer center for evaluation for allogeneic stem cell transplant.

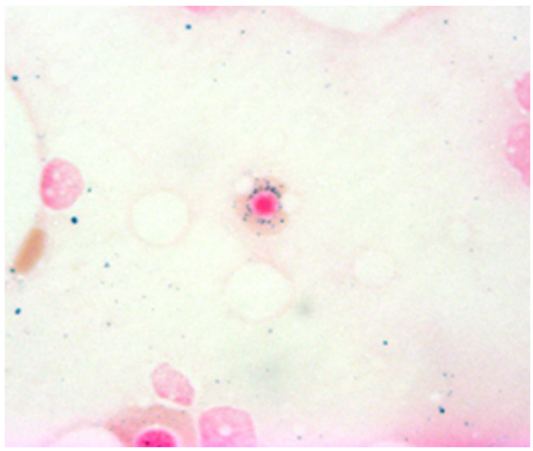

Figure 3. Abnormal erythroid iron incorporation results in many ring sideroblasts such as the one shown from the pre-treatment marrow evaluation (Iron stain; 1000x).

He was pale in appearance but was otherwise well with good performance status, ECOG PS 1, at the time he presented to our cancer center. He complained of generalized weakness, pain in his knees and ankles and numbness in both upper and lower extremities of about four months. He also complained of difficulty driving and walking, requiring a cane to walk due to loss of sensation in his extremities. The patient was working at an engine plant of an automobile manufacturer for the last couple of years and stopped working recently with the current diagnosis. He told us that there are chemical and heavy metal exposures at his work place. On examination, the patient demonstrated sensorineural loss and gait abnormality and additionally was noted to have poor dental hygiene. He reported tooth extraction in the past secondary to acid reflux and had a tooth implant and partial plate placed about 11 years ago. For this hardware, the patient used approximately 1 tube of Fixodent dental adhesive per week. On work up at our center, he had neutropenia with an ANC of 192/uL and normocytic anemia with hemoglobin and MCV of 9.4 g/dL and 95.3 fL, respectively. The platelet count was within normal limits. Based on his exposure history and unusual presentation, additional studies were performed to include checking for heavy metals, copper, zinc, Paroxysmal nocturnal hemoglobinuria (PNH) etc., and also repeated a bone marrow biopsy along with doing a pre-transplant evaluation. The bone marrow aspirate and biopsy showed hypocellu-

Table 1. Copper and zinc levels prior to and after starting treatment

	Pre treatment	On treatment (after count recovery)	Reference Range
Serum Copper	<0.10	0.77	0.75-1.45 mcg/ml
Serum Zinc	2.64	0.68	0.66-1.10 mcg/ml
Zinc protoporphyrin	123	53	<70 mcmol
24 hr Urine Copper Concentration	7	11	15-60 mcg/l
24 hr Urine Zinc Concentration	2533	2434	300-600 mcg/l

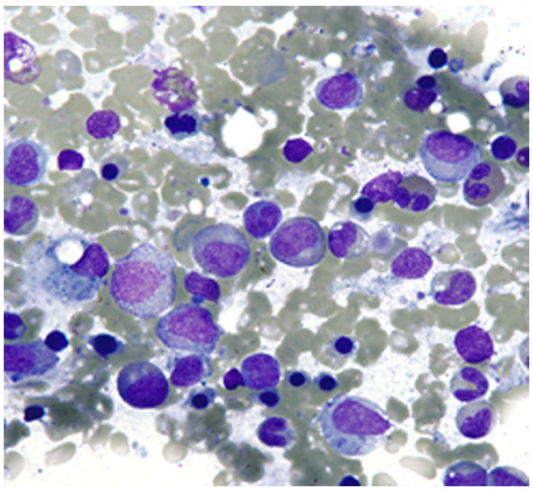

Figure 4. Post-treatment bone marrow aspirate smear shows no residual morphologic abnormalities (Wright stain; 1000x).

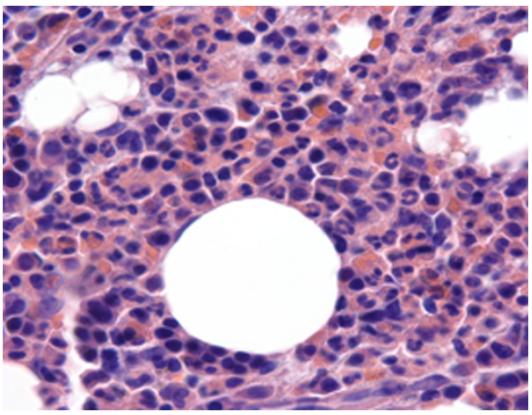

Figure 5. Post-treatment bone marrow biopsy is normocellular with reconstitution of granulocytic lineage and normalization of myeloid: erythroid ratio (Hematoxylin and eosin stain; 1000x).

larity with vacuolated erythroid and granulocytic precursors and numerous ring sideroblasts (**Figures 1**-**3**). Results of the testing showed a low serum copper and high serum zinc levels (**Table 1**). A diagnosis of hypocupremia due to hyperzincemia, possibly related to dental adhesive use, was made. The patient was started on oral copper replacement, 3 mg daily. He was counseled to discontinue zinc containing dental adhesives. He was seen two weeks after initiation of copper therapy and his peripheral blood counts recovered with ANC 12600/uL and Hemoglobin of 12.5 g/dL. We repeated a bone marrow biopsy after count recovery at about six weeks from initiation of copper replacement therapy that showed marrow recovery without morphologic abnormality or ring sideroblasts (**Figures 4**, **5**). Nerve conduction studies (NCS/EMG) showed chronic sensory and motor neuropathy suggestive of myelopolyneuropathy which is a hallmark of copper deficiency. After copper replacement for total of 6-month, he was able to completely normalize serium copper and zinc levels. His fine motor neurologic functions in his upper and lower extremities were significantly improved.

Discussion

Copper is an essential trace element involved in hematopoiesis, melanin formation, connective tissue synthesis, bone mineralization and immune function. It additionally functions as a cofactor in several biochemical pathways in human body. Hypocupremia causes bone marrow suppression resulting in pancytopenia and combined sensory and motor polyneuropathy. Cordano first described the association between copper deficiency and neutropenia in 1966 through his observations of Peruvian malnourished children [19]. Hyperzincemia resulting in hypocupremia results in similar manifestation as copper deficiency. The patient described in this case report had similar clinical manifestations of pancytopenia associated with neurological syndrome. Zinc containing dental adhesives have been found to be strongly associated with this phenomenon.

Zinc salts were introduced into copolymer mixtures of lower alkyl vinyl ether-maleic acid

blends that were invented by Shah et al. to stabilize denture adhesives [20]. The technology was licensed in 1990 when zinc was added to Fixodent denture adhesive by the manufacturer. Several other dental adhesive manufacturers followed suit but due to the increase in reported cases of hyperzincemia and hypocupremia associated with these dental creams, several manufacturers issued warnings and stopped or modified producing zinc-containing denture adhesives beginning in 2010. However, despite these events, zinc-containing denture adhesive products continued to be marketed and commonly used by denture users. Fixodent is one of the zinc-containing products being used by patients reported in this case report. The manufacturer of these zinc-containing denture creams claim that their products have low amounts of zinc and average users would absorb only about 2 mg of zinc per day, which is well below the recommended daily allowance of 8-11 mg. The fact that cases of hyperzincemia and hypocupremia associated with these products continue to be discovered, despite product warnings and changes in manufacturer guidelines, is likely related to the excessive use of these products due to ill-fitting dentures. Presumable reasons behind this could be lack of awareness among denture users and prescribing dentists, lack of counseling by prescribers, ill-fitting dentures and costs associated with getting dental hardware fixed or changed. Overcoming these limitations, in addition to addressing whether or not zinc-containing denture creams should continue to be available, are topics that will require further investigation. As a point of emphasis exemplified by this case report, it may be prudent to investigate the dental history, particularly with respect to the use of dental adhesives, when evaluating a patient with unexplained pancytopenia especially associated with myelopolyneuropathy. Determining zinc and copper levels in these situations would also be useful and may expedite diagnosis. Awareness of the etiologies of hyperzincemia and hypocupremia, in particular the association with zinc-containing denture creams, is an important step toward avoiding misdiagnosis, patient stress and morbidity, and unnecessary referrals for bone marrow transplants.

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