

CLINICAL VIGNETTE

An Unusual Cause of Imbalance, Anemia, Neutropenia

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Case Report

A 63-year-old practicing dentist presented to the ER with a 3 month history of increasing fatigue and a noticeable decrease in his exercise capacity. He had also noted a metallic taste in his mouth resulting in decreased appetite and a 25 lbs. weight loss over the same timeframe. The patient denied any history of bleeding or blood loss. His past medical history included hypertension, hypercholesterolemia, and a right hip replacement for osteoarthritis. His only medications were Lisinopril and Simvastatin. One year ago, he first began experiencing left hip pain attributed to osteoarthritis as well as low back pain due to spinal stenosis. Physical examination was remarkable for pallor. Part of the initial assessment included a CBC with an Hb of 5.2 g/dL and hematocrit of 15.5%, a MCV of 100 fL, a WBC of 3.1 with 26% neutrophils with no immature forms present, and a platelet count of 259.

He was admitted to the hospital and received a total of 5 units of packed red blood cells (PRBC) with an increment in his Hb to 9.8 g/dL and improved energy level. Other baseline laboratory studies included peripheral blood smear showed a normochromic normocytic anemia with neutropenia; erythropoietin 122 (4.3 – 18.0 mIU/mL); peripheral blood flow cytometry showed no blasts and no abnormal B- or T-cell populations; reticulocyte count 0.5%, direct Coombs test negative; CMP entirely normal, Ferritin 917 (10–210ng/mL), iron 98, iron saturation 48%, vitamin B12 1064, SPEP: Alpha 1 globulins 4.1% (1.6–3.4%), alpha 2 globulins 10.7%, beta globulins 8.7%, gamma globulins 7.0 % (8.6–16.3%), and albumin 3.8. There were no monoclonal bands. Work up for a GI source of blood loss was negative. Baseline imaging included a chest CT with contrast, which demonstrated a few tiny nonspecific subpleural nodules measuring up to 6-7 mm and minimal subsegmental atelectasis at the lung bases; CT abdomen and pelvis demonstrated a 1.2 cm hypodense lesion in the right lobe of the liver, the right hip prosthesis, and a large right inguinal hernia containing fat.

He was seen in consultation by a hematologist who obtained a bone marrow biopsy showing refractory anemia with multilineage dysplasia. Chromosomal analysis, flow cytometry, and MDS FISH were normal.

Two months later, he began treatment for red cell transfusion dependent MDS with Azacitadine 75 mg/m² subcutaneously day 1-7 q28 d, receiving a total of five cycles without significant hematologic improvement.

Three months after starting treatment, he began experiencing numbness in his distal right toes then subsequently on the left, which gradually ascended to just below his knees over a period of several months. He developed proprioceptive loss, making walking and climbing stairs more difficult. He had difficulty going up and down stairs or walking any significant distance. For the sensory loss in his legs, the orthopedic surgeon obtained an MRI of the lumbar spine demonstrating a 4 mm left > right annulus bulge at L4-5 with severe central canal stenosis. He began experiencing tingling in his hands and fingers three months after the onset of numbness in his toes. Due to his progressive imbalance and extremity numbness, neurologic evaluation was sought.

Neurologic examination revealed normal mental status and cranial nerves. Examination of his extremities revealed a 2-1/2 cm decreased circumference in the right biceps and 1 cm decrease in the right calf. Motor exam revealed 4-/5 strength in the iliopsoas, quadriceps, glutei maximus and medius, hamstrings, anterior tibialis, posterior tibialis, gastrocnemius, ankle dorsiflexors and extensors, and peronei hallucis longus muscles. Muscle stretch reflexes were diminished throughout. Both his stance and gait were quite unstable despite a cane. Cerebellar testing demonstrated a positive Romberg and abnormal heel-shin movement with decreased rapid alternating movements in the feet. Sensory examination revealed loss of vibratory and position sense throughout the lower extremities including the hips. Position sense was decreased in the upper extremities. Stereognosis and graphesthesia was abnormal in the lower extremities. There was decreased touch in the lower extremities to the knees and to 3" above the wrists in the upper extremities.

A clinical diagnosis of posterior column dysfunction with neuropathy was made and MRIs of the spine and brain were obtained. These demonstrated "diffuse, hypointense bone marrow, multilevel degenerative disc disease and facet hypertrophy, and diffuse high signal intensity within the posterior aspect of the cervical and thoracic cord involving the posterior columns, most likely representing pernicious anemia and a vitamin B12 deficiency". MRI of the brain demonstrated minimal small vessel ischemic disease. Nerve conduction studies revealed an axonal polyneuropathy of the lower extremities.

Baseline vitamin B12 predating the onset of his neurologic symptoms was normal; repeat Vitamin B12 was normal at 562 pg/mL. The differential for the combination of posterior column damage, anemia and neutropenia also includes copper deficiency. Serum copper was <10 mcg/dL (Normal range: 70–140), the ceruloplasmin <2, methylmalonic acid to 77, and repeat ferritin 2541. The cause of the copper deficiency was not initially apparent. Further inquiry revealed the patient, a dentist, had been filling his own cavities with DenTek Temparin Max, a zinc compound intended as a temporary filling repair. His serum zinc level was elevated at 248 mcg/dL (Normal range: 55-150). His temporary zinc fillings were replaced and he was started on supplemental copper. Within a month, his zinc level had fallen to 120 with his copper rising to 47. Three months later, his copper level had returned to the normal range (71 mcg/dL), and he was referred for physical therapy.

Repeat neurological examination revealed approximately a 60% improvement in his ambulation and steadiness. His lower extremity strength was normal. Stance was slightly wide-based but clearly more stable. He ambulated with a cane but did not rely on it. His Romberg testing was positive but only after standing with his eyes closed for 15 seconds. The lower extremity dysmetria had resolved. There was still decreased sensation below the knees with diminished vibratory sense but improved position sense in the proximal and distal lower extremities.

Discussion

Dietary copper deficiency is rare as it is widely distributed in readily available foods such as whole grains, nuts, cereals, and meat. Copper is an essential trace element, serving as a co-factor for many metalloenzymes and proteins important to hematopoiesis and central nervous system function.¹ The clinical circumstances by which copper deficiency can develop are becoming increasingly common and thus the clinical importance of this is increasing. Copper is predominantly absorbed from the duodenum and proximal jejunum and requires exposure to gastric acid to free copper from organic complexes and ligands. Interestingly, myelopathy and cytopenias were recognized in zinc-smelter workers in the late 19th century in both the German and English medical literature.²

Our observation of rapid and complete hematologic recovery with normalization of copper and zinc levels is consistent with what has previously been reported.

Copper deficiency myelopathy is often unrecognized and only recently reported.³ This nutritional myelopathy was first described in 2001 by Schleper and Stuerenburg.⁴ The most common causes appear to be malabsorption, gastric resection, and hyperzincemia.⁵ The second report of a similar condition due to copper deficiency was by Kumar in 2004 who published a group of 13 patients with sensory ataxia due to dorsal column dysfunction, gait difficulty, lower limb spasticity, and polyneuropathy.⁶ They had a very low serum

copper and ceruloplasmin with an elevated zinc level. The neurological symptoms improved with oral copper supplementation. Willis reported 3 additional cases associated with sideroblastic anemia and neutropenia along with the neurological abnormalities.⁷ Since that time, several other studies have revealed the association between low copper and posterior column myelopathy.⁸⁻¹⁴

In this case, the spine MRI abnormalities of increased signal on T2 weighted images involving the dorsal column were consistent with dorsal column dysfunction as a reason for his sensory ataxia. This is not always the case as Kumar reported that MRI studies were abnormal in only 44% of his 25 cases.⁶ The abnormalities of our patient's electrodiagnostic testing have been previously reported similarly as a primarily axonal polyneuropathy.

The biochemical cause of the spinal cord abnormalities remains uncertain. Theories include a dysfunction of the cytochrome- C oxidase, which is copper dependent, or an abnormality in the methylation cycle.¹⁵ It is clear that copper is an important micronutrient to the nervous system. Copper, when nutritionally deficient, can also cause visual loss due to optic neuropathy, peripheral neuropathy with large fiber and small fiber loss, or central nervous system demyelination. Prodan described a brain MRI showing white matter hyperintensities on T2 in the cerebellar peduncles, corpus callosum, and periventricular white matter.¹⁶ However all reported cases to date are consistent with the predominant manifestation being dorsal column dysfunction causing sensory ataxia. The sensory ataxia causes an individual to not be able to negotiate when walking, standing, or sitting due to the position sense loss to the limbs. Ultimately, a spastic ataxic paraplegia can occur if untreated.

Since copper deficiency can mimic the well-known vitamin B12 deficiency, copper levels should be considered in the same clinical circumstances as one would measure B12.

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