CLINICAL VIGNETTE

Neuropathy after Malnutrition: Is Copper Deficiency the Missed Diagnosis?

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Case Presentation

A 45-year-old male was transferred from an outside hospital with one and half years of chronic diarrhea and failure to thrive. The patient described the diarrhea as greasy and foul smelling stool occurring up to 8-10 times/day. He denied any abdominal pain but reported 60 pound weight loss of 60 pounds since the onset of symptoms. His diarrhea improved with fasting as well as with abstinence from alcohol. The patient had no improvement with lactose free diet trials or gluten free diet trials and was started on Total Parenteral Nutrition.

The patient also reported that on day of presentation he felt "out of it". He additionally noted that he was quite "dizzy", worse than the intermittent dizziness he had been experiencing for the past several weeks. The sensation was worse with standing.

He also complained of a tingling sensation of his extremities that started 8 months prior to admission. The sensation was initially isolated to his toes however had spread to affect his legs up to his upper thighs and subsequently affect his fingertips. He also reported that the sensation evolved to more of a burning sensation.

His past medical history was significant for latent tuberculosis with incomplete isoniazid treatment and a history of hepatic abscess which was treated. He had no family history of gastrointestinal or autoimmune conditions. The patient was originally from Mexico but had not travelled back in the several years preceding the admission. He had a history of cocaine use but none recently. He had a 26 pack year smoking history and a significant alcohol intake of 2-10 drinks daily, however was now sober.

The patient's prior evaluation was reviewed. He had a syncopal episode and was found to have orthostatic hypotension. After no response to intravenous fluid repletion and a negative work up for adrenal insufficiency, he had been started on midodrine and fludrocortisone. With respect to his potential neuropathy, he had a PET scan that was negative for malignancy, normal homocysteine and normal methylmalonic acid levels. He had multiple nutritional deficiencies including vitamin A, vitamin D, vitamin E, vitamin K, zinc and copper. His diarrhea was evaluated with three prior upper endoscopies and three colonoscopies. Biopsies showed increased intraepithelial lymphocytes of the duodenum. Further evaluation of the biopsy material is outlined below:

Further workup of intestinal biopsy

Whipple's Disease	Biopsy negative on PAS stain
Amyloidosis	Biopsy negative on PAS stain, congo red stain
Celiac Disease	Negative endomysial antibody, antigliadin antibody and tissue transglutaminase antibody
Microscopic Colitis	Not consistent with biopsy findings

A full infectious workup for his gastrointestinal complaints was negative. A paraneoplastic panel had been sent which was negative, as well as, a HIV antibody and a 5-hydroxyindoleacetic acid (5HIAA) level to evaluate for carcinoid syndrome. His PET scan was reportedly negative for malignancy. The patient had a low pancreatic elastase level and high fecal fat level.

On admission, physical exam was significant for a blood pressure supine of 133/92 and 81/51 with standing after receiving 1 liter of normal saline. The remainder of the vital signs were unremarkable. In general, the patient appeared emaciated and with temporal wasting but was in no acute distress. His heart and lung exam was within normal limits. His abdomen was scaphoid, nontender with hyperactive bowel sounds. Skin demonstrated some hyperpigmentation, particularly of his face but sparing his periorbital area. On sensory neurological exam he was found to have decreased pinprick in a stocking-glove distribution in his bilateral lower extremities to the level of his upper thighs and his bilateral upper extremities to the level of his elbow. He had a patchy sense of cold. He had diminished proprioceptive and vibratory sensation in his toes. A

clear sensation level change was noted at the level of T12 when his back sensation was evaluated. He was diffusely hyporeflexic. His gait exam was notable that for bilateral foot drop.

A CT of the patient's abdomen showed mild to moderate pancreatic atrophy. As patient had been placed on TPN for some time at prior hospital his micronutrient levels were re-assessed. He was deficient in vitamin A, copper and zinc. He was again ruled out for adrenal insufficiency. The completion of his peripheral sensory neuropathy work up was done by ruling out hepatitis C, multiple myeloma, diabetes and lupus. A thoracic spine MRI was also obtained which did not show any demyelinating lesions and a normal spinal cord. Additionally EMG/Nerve Conduction Studies were done which showed moderate sensorimotor axonal neuropathy.

The patient was ultimately diagnosed with pancreatic insufficiency from his pancreatic atrophy presumed secondary to chronic pancreatitis from alcoholism. As a result of his gastrointestinal symptoms, he was profoundly malnourished. His autonomic dysfunction and subacute ascending sensorimotor polyneuropathy were felt to be consistent with copper deficiency causing a clinical picture similar to subacute combined degeneration.

Discussion

Subacute combined degeneration of the spinal cord can be found in medical literature dating back to the year 1900 [1]. At its infancy, the condition was used to a clinical scenario in which a single insult can affect different tracts of the spinal cord with different functions. Even at the early stages it was noted that an anemia was frequently present. Hemmer et al[2] described nine patients with gait disturbances and impairment in position and sensation and found them all to have deficiencies in vitamin B12. All patients had some degree of improvement with treatment of the deficiency. It is now known that a deficiency in vitamin B12 can lead to a variety of neurological insults; with the hallmark bring subacute combined degeneration of the spinal cord. It is a disorder characterized by dysesthesia, disturbances in position sense, and either spastic paraparesis or tetraparesis. The axonal damage is preferential to the posterior columns of the spinal cord initially, and in some cases, hyperintense T2 lesions there can be seen there on MRI. The dorsal or posterior columns of the spinal cord carry the tracts which mediate position sense, vibratory sense and discriminative touch[3].

The neurological abnormalities associated with copper deficiency have now been identified as a mimicker of vitamin B12 deficiency[4]. The typical neurological symptoms of a patient with copper deficiency include abnormal gait which is attributed to a sensory ataxia from dorsal column dysfunction. There may or may not be lesion noted on neuroimaging. There may also be paraesthesia of the limbs and sensory impairment in a stocking and glove distribtion[5].

Copper is predominately absorbed in the duodenum and its absorption is relatively competitive with zinc. With the current obesity epidemic and bariatric surgery as a mainstay of therapy, clinicians are much more frequently presented with patients with multiple vitamin and mineral deficiencies as a result of a malabsorptive anatomy. It has been well established that copper deficiency is a relatively common finding in post op patients[6]. Copper deficiency is also potentially present in individuals with high intake of zinc, use of denture fixative containing zinc, inflammatory bowel disease and any malabsorption syndrome[7].

Copper deficiency presents with a spectrum of cytopenias as well as neurological symptoms. The deficiency is underdiagnosed as presentation leading to delays in starting therapy. A retrospective study looking at copper deficiency found a median time of 1.1 years from initial presentation with symptoms to a diagnosis of copper deficiency[7].

The treatment of copper deficiency includes replacing the deficient copper and treating the underlying etiology. There are no studies comparing doses used for repletion but a recommended regimen is oral copper 3- 8 mg/day until normal levels are achieved. In severe cases, intravenous copper at dose of 2-4 mg/day for six days can be used[8]. There is a variable response of the neurological symptoms to correction of the copper deficiency.

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