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Copper Deficiency Myeloneuropathy: An Atypical Presentation of Guillain-Barré Syndrome

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Abstract

Copper (Cu) deficiency myeloneuropathy due to acquired Cu deficiency is both rare and debilitating. More women than men are affected, involving patients aged 32-80 years. Cu itself is a key component of the nervous system, involved in electron transport, oxidative phosphorylation, antioxidant defense, catecholamine synthesis, and iron homeostasis. Afflicted patients usually present with anemia and leukopenia, along with subacute gait disorder with prominent sensory ataxia/spasticity, impaired vibration/position sense, and a positive Romberg sign. Etiologies of Cu deficiency include gastric surgery, zinc overconsumption5, dietary deficiency, Celiac disease, Wilson's disease, cystic fibrosis, and IBS.

We present the case of a 63 y.o. woman with past medical history of limited stage small cell lung cancer in complete remission for 6 months, COPD, hypertension, supraventricular tachycardia status post ablation who presented with a 2-month history of shortness of breath and weakness, numbness and paresthesias of bilateral upper/lower extremities. Patient reported increasing difficulty grasping objects, increasing gait impairment, and 6-8 falls during this period. Initial workup at outside hospital (OSH) included normal findings on MRI Brain, C-spine, T-spine and L-spine. A normal cell count and protein lumbar puncture (LP) ruled out GBS. CSF cytology was negative for malignant cells. Paraneoplastic labs including acetylcholine receptor antibody and voltage-gated calcium channel antibody were negative. Given the unknown etiology of the patient's condition and her hypercoagulable state, Neurology at OSH deemed IVIG inappropriate. After transfer to our hospital, she displayed dysmetria and dysdiadochokinesia, diminished strength bilaterally, and fatigue. EMG showed diffuse primarily demyelinating > axonal polyradiculoneuropathy of the arms and legs concerning for peripheral demyelinating disease. Negative inspiratory force (NIF) was 60 and functional vital capacity (FVC) was 1350, thus mechanical ventilation was not indicated. She underwent plasmapheresis on 08/12/19 with concerns of GBS variant. IVIG was not considered with prior history of cancer. Repeat EMG on 08/23/19 showed worsening of the patient's neuropathy with greater axon loss and motor unit dropout in proximal lower extremity muscles, with demyelinating features largely unchanged. Neurology recommended vitamin deficiency labs, including vitamins B1, B3, B6, B12, and E, folate, zinc, Cu and heavy metals. Patient had a Cu level of 473, and Neurology recommended lifelong elemental Cu supplements, 6-month pyridoxine supplementation, and avoidance of zinc supplementation, citing 6 weeks' recovery time. Patient was discharged to a rehabilitation facility where her strength and sensation improved. She followed up with Neurology outpatient for care. We present an atypical case of GBS caused by Cu deficiency.

GBS was high on our differential in this case, and it is believed to be autoimmune in origin. Therefore, negative work up for autoimmune disease should prompt investigation into vitamin or mineral deficiencies in a chronically debilitated patient with neurologic dysfunction. While Cu deficiency is uncommon and requires years to manifest, it is important to consider in patients with ascending motor paralysis, gait issues, and sensory loss. Cu supplementation generally prevents further neurologic deterioration, but improvement of neurologic symptoms is variable and limited to sensory faculties. Most patients experience residual deficits, but hematologic parameters often respond completely.

Introduction

- Copper (Cu) deficiency myeloneuropathy (CDM) is rare and debilitating, with a predilection for middle-aged females
- Presentation: anemia and leukopenia, along with subacute gait disorder with prominent sensory ataxia/spasticity, impaired vibration/position sense and a positive Romberg sign[1]
- Etiologies: gastric surgery (50%), excess zinc (Zn) exposure, dietary deficiency, Celiac disease, Wilson's disease, cystic fibrosis, and IBS[2,3]
- Early recognition is difficult, especially when CDM from Guillain-Barré Syndrome (GBS) and vitamin B_{12} deficiency

Case Description

- 63 y.o. woman with PMH of limited stage small cell lung cancer in complete remission, COPD, hypertension
- Presented with a 2-month history of shortness of breath and weakness, numbness and paresthesias of bilateral upper/lower extremities
- ROS: Patient reported increasing difficulty grasping objects, increasing gait impairment, and 6-8 falls during this period

CT-PE (see **Fig. 1**)	Negative for PE/lobar consolidation
MRI Brain, C-Spine, T-Spine, L-spine	Normal findings
Lumbar Puncture	Normal cell count and protein level. CSF cytology negative for malignancy.
Paraneoplastic Labs: AChR-antibody and VGCC-antibody	Negative for AChR-antibody and VGCC-antibody

Table 1. Summary of lab findings at outside hospital (OSH)

- Given unknown etiology of patient's condition and her hypercoagulable state (h/o cancer), Neurology at OSH deemed IVIG inappropriate
- Of note, EMG and sural nerve biopsy were planned at OSH but were not performed due to technical difficulties
- After transfer to our facility, she displayed dysmetria and dysdiadochokinesia, diminished strength bilaterally, and fatigue
- No respiratory muscle weakness noted on physical exam, therefore no indication for mechanical ventilation

Hospital Course

Hospital Day 1	• **CXR**: Negative for PE or cancer (see **Fig. 2**) • **EMG**: diffuse primarily demyelinating > axonal polyradiculoneuropathy of the arms and legs concerning for peripheral demyelinating disease
Hospital Day 2	• **CBC:** WBC 5.7 K/µL, **Hgb 9.9 g/dL, Hct 28.8%**, Plts 312 K/µL • **Echocardiogram**: EF 67%, no heart failure
Hospital Day 4	• **Plasmapheresis** performed given concerns for **GBS variant** • **No IVIG** given the patient's history of cancer
Hospital Day 5	• **LP**: clear, colorless, Glucose 77 mg/dL, **protein 64.9 mg/dL**, RBC >5/cu mm, WBC < 3 cu/mm**, 11% neutrophils**, CSF culture **negative** • **Paraneoplastic labs:** comprehensive autoimmune workup **negative**
Hospital Day 15	• **Unresponsive to plasmapheresis; repeat EMG**: worsening neuropathy with greater axon loss and motor unit dropout in proximal lower extremity muscles; no ↑ demyelination • **Neurology: vitamin and metal labs** (B1, B3, B6, B12, E, folate, zinc, Cu…)
Hospital Day 19	• **Cu level**: **473** ug/L (reference range 810 - 1,990 ug/L) • Patient started on **Cu replacement, vitamin B6 supplementation, Zn avoidance** with 6 weeks expected recovery time
Hospital Day 29	• **Discharged: rehabilitation facility**, strength/sensation improved with a plan to follow up with Neurology for outpatient care

Case Images

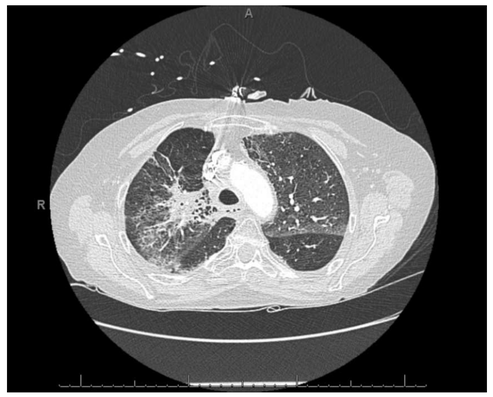

Figure 1. CT-PE from OSH was negative for PE. Lungs showed diffuse prominence of bronchovascular and interstitial markings, ground glass densities and atelectasis bilaterally, most significantly in the R upper lobe. No lobar consolidation or lymphadenopathy was present.

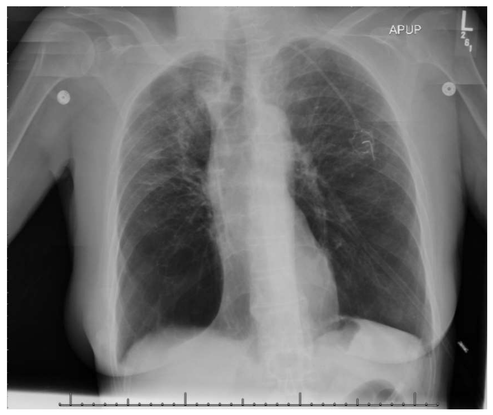

Figure 2. CXR on admission showed patchy opacities in the upper lobes bilaterally (R>L) unchanged from prior CT chest. Emphysema with bullous changes was noted in R lower lung.

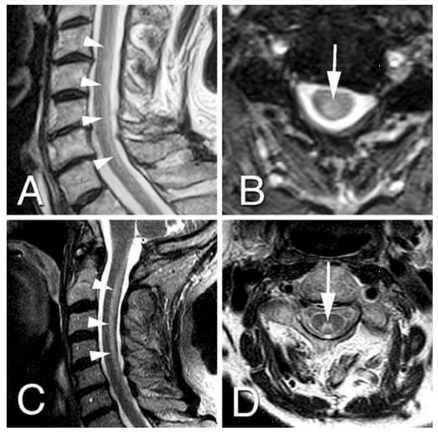

Figure 3. Sagittal and axial T2-weighted images of the cervical spine in two patients (**A,B** and **C,D**) showing increased T2 signal involving the midline dorsal cervical cord. T2 hyperintensity involved both the central and dorsal cord in **B**, while only the dorsal columns were involved in **D**. Our patient presented with normal MRI findings (*Reproduced from* PMID: 16261334).

Discussion

- Cu is key to proper CNS/PNS structure and functions[4,5] (see **Table 2)**
- Neurologic deficits in CDM mirror the symptoms subacute combined degeneration seen in vitamin B_{12} deficiency
- Nerve biopsies/autopsies from case series show axonal degeneration, particularly of the dorsolateral spinal columns[6,7]
- Sometimes visible as T2-enhancement on MRI, though absence of MRI findings does not preclude CDM (as with our patient) (see **Fig. 3**)
- Peripheral demyelination seen in both GBS and CDM; H&P is crucial
- Treatment involves aggressive Cu supplementation, avoidance of Zn overconsumption and replacement of other deficient vitamins (B_1, B_{12})

Cytochrome-c-oxidase	Electron transport and oxidative phosphorylation
Copper/Zinc superoxide dismutase	Antioxidant defense
Tyrosinase	Melanin synthesis
Dopamine ß-hydroxylase	Catecholamine biosynthesis
Monoamine oxidase	Serotonin synthesis
Ceruloplasmin	Brain Iron homeostasis

Table 2. Enzymes utilizing Cu for electron transfer

Conclusion

- Negative work up for autoimmune disease should prompt investigation into vitamin or mineral deficiencies in a chronically debilitated patient
- Consider CDM in patients with ascending motor paralysis, gait issues, and sensory loss, especially those with prior gastric surgery
- Cu supplementation generally prevents further neurologic deterioration
- Complete hematological recovery with residual neurological deficits[8]
- Obesity epidemic may lead to an increase in gastric surgeries, predisposing more patients to Cu deficiency in the future

References

1. Kumar N, Gross JB Jr, Ahlskog JE. Copper deficiency myelopathy produces a clinical picture like subacute combined degeneration. Neurology. 2004;63(1):33.
2. Kumar N, Ahlskog JE, Klein CJ, Port JD. Imaging features of copper deficiency myelopathy: a study of 25 cases. Neuroradiology. 2006;48(2):78. Epub 2005 Oct 28. PMID: 16261334.
3. Lanska DJ, Remler B. Myelopathy among zinc-smelter workers in Upper Silesia during the late 19th century. Neurology. 2014 Apr;82(13):1175-9.
4. Zatta P, Frank A. Copper deficiency and neurological disorders in man and animals. Brain Res Rev. 2007;54(1):19. Epub 2007 Jan 31.
5. Spinazzi M, Sghirlanzoni A, Salviati L, Angelini C. Impaired copper and iron metabolism in blood cells and muscles of patients affected by copper deficiency myeloneuropathy. Neuropathol Appl Neurobiol. 2014;40(7):888.
6. Weihl CC, Lopate G. Motor neuron disease associated with copper deficiency. Muscle Nerve. 2006;34(6):789.
7. Zara G, Grassivaro F, Brocadello F, Manara R, Pesenti FF. Case of sensory ataxic ganglionopathy-myelopathy in copper deficiency. J Neurol Sci. 2009;277(1-2):184. Epub 2008 Nov 20.
8. Kumar N. Copper deficiency myelopathy (human swayback). Mayo Clin Proc. 2006;81(10):1371.