

AMSER Case of the Month: September 2023

37-year-old female presenting with progressive numbness and weakness in bilateral upper and lower extremities

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Patient Presentation

37-year-old female presenting with progressive numbness and weakness in her bilateral upper and lower extremities

Past Medical History:

- Anxiety
- Gastric cancer s/p partial gastrectomy, chemotherapy and radiation (7 years earlier)
 - (complicated by chemotherapy induced neuropathy, since resolved)

Medications: Fluoxetine 60mg daily, Propranolol 10mg TID, Xanax 1mg TID, Adderall 20mg QID PRN

Allergies: No known drug allergies (NKDA)

Social History: Denies tobacco and alcohol use.

Endorses nitrous oxide use, (estimated use 3 times in the past 3 months, describes significant use- 50+ “whippets” each time)

Family History: Paternal uncle: Multiple Sclerosis, Father: Lupus

Maternal grandmother: Multiple Sclerosis, Mother: Neuropathy (unknown type)

Pertinent Labs

- CBC: WBC 7.7, Hgb 11.6, hct 36.4, plt 311, MCV 103.7
- Vitamin B12: 300 pg/mL (ref range 213-816)
- Folate: 32.5 ng/mL (ref range 5.0-20.0)
- Methylmalonic Acid: 1361 nmol/L (ref range 0-378)
- Homocysteine: 27.1 umol/L (ref range 0.0-15.0)

What Imaging Should We Order?

Select the applicable ACR Appropriateness Criteria

Variant 1: Acute onset myelopathy. Initial imaging.

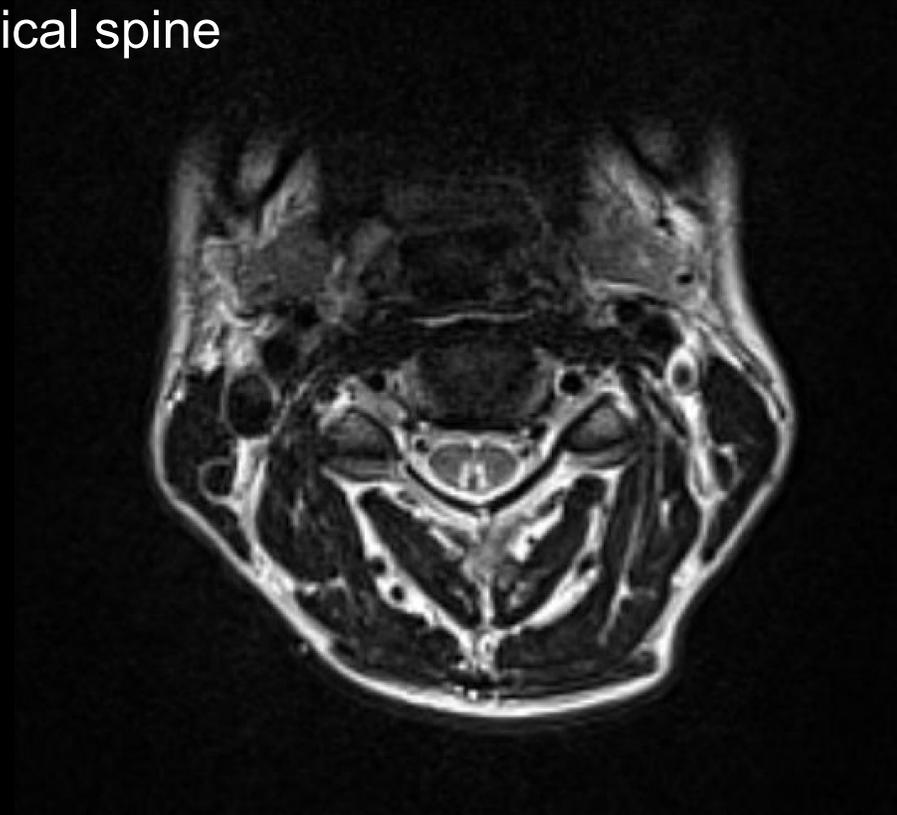
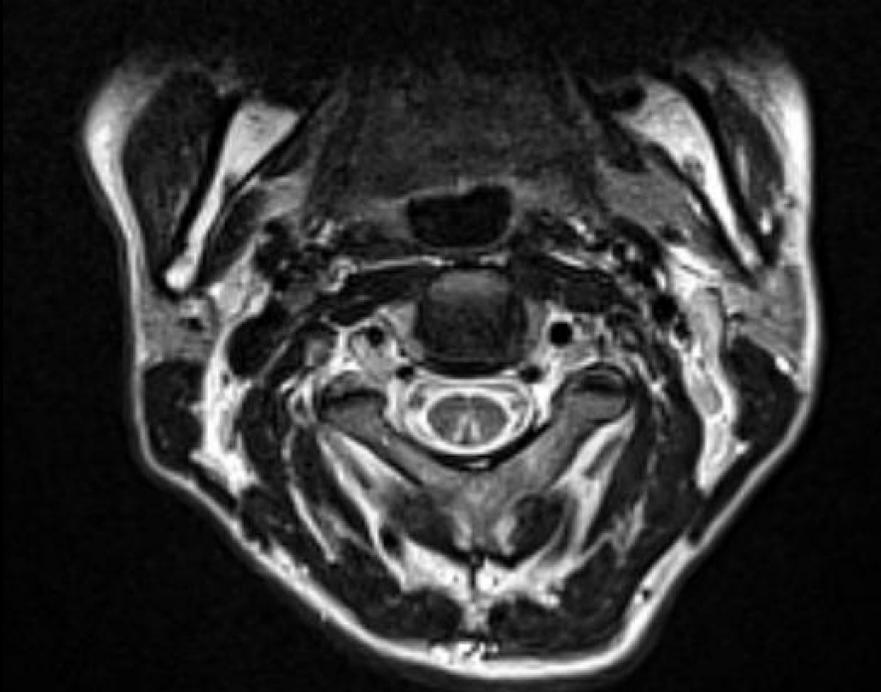
Procedure	Appropriateness Category	Relative Radiation Level
MRI spine area of interest without and with IV contrast	Usually Appropriate	0
MRI spine area of interest without IV contrast	Usually Appropriate	0
CT myelography spine area of interest	May Be Appropriate	Varies
CT spine area of interest with IV contrast	May Be Appropriate	Varies
CT spine area of interest without IV contrast	May Be Appropriate	Varies
Arteriography spine area of interest	Usually Not Appropriate	Varies
Radiography spine area of interest	Usually Not Appropriate	Varies
MRA spine area of interest with IV contrast	Usually Not Appropriate	0
MRA spine area of interest without and with IV contrast	Usually Not Appropriate	0
MRA spine area of interest without IV contrast	Usually Not Appropriate	0
MRI spine area of interest with IV contrast	Usually Not Appropriate	0
CT spine area of interest without and with IV contrast	Usually Not Appropriate	Varies
CTA spine area of interest with IV contrast	Usually Not Appropriate	Varies



This imaging modality was ordered by the consulting neurology physician in the ED

Findings (unlabeled)

T2 MRI axial cervical spine



Findings: (labeled)

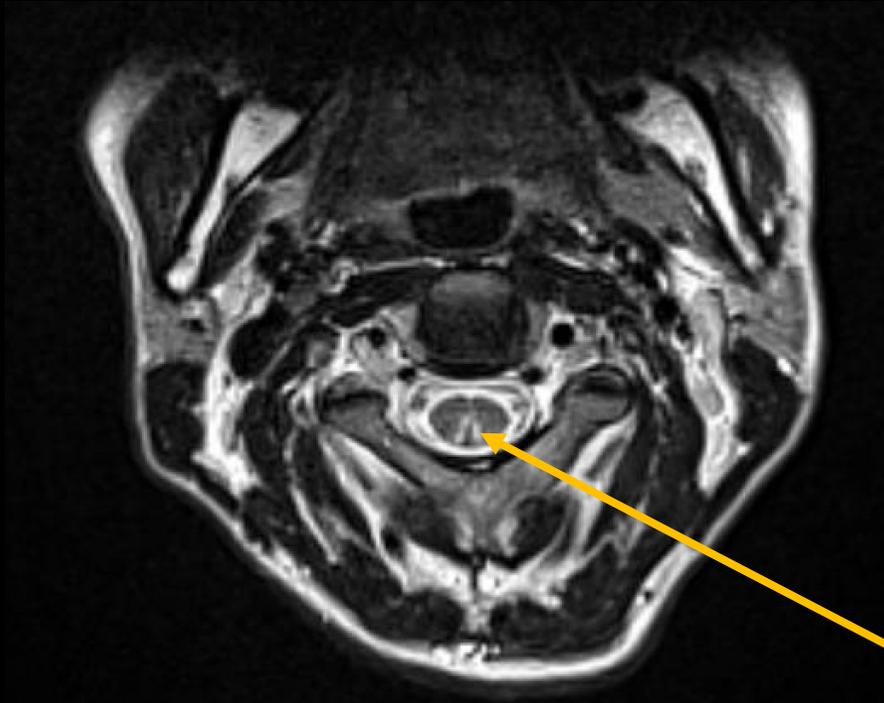
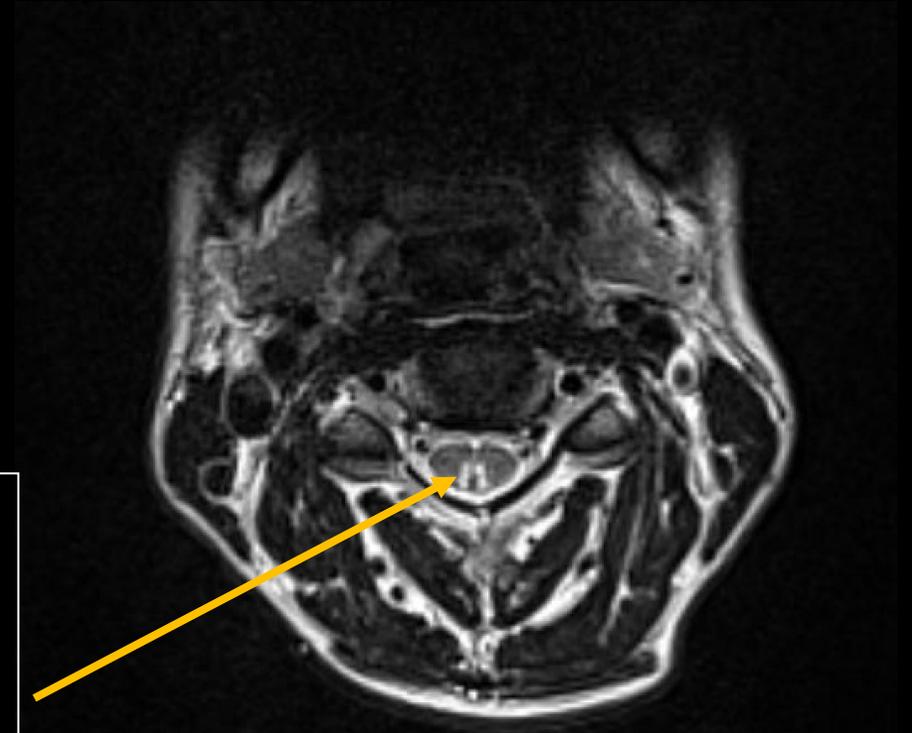


Fig 1. MRI of the cervical spine; T2 axial view

Abnormal T2 hyperintense signal within the dorsal columns, spans C1 to C5



Final Dx:

Subacute Combined Degeneration (SCD)
secondary to Vitamin B12 Deficiency

Differential Diagnosis

Nutritional or metabolic deficiencies/toxicities	Demyelination	Infectious myelopathy	Neoplasms	Other
Copper deficiency myeloneuropathy	Multiple Sclerosis	HIV+ vacuolar myelopathy	Astrocytoma	Inflammatory processes- Sarcoidosis
Vitamin E Deficiency	Transverse Myelitis	Tabes dorsalis	Ependymoma	Ischemia
Methotrexate-induced myelopathy				Hereditary syndromes- Friedreich ataxia, Leukoencephalopathy

Subacute Combined Degeneration (SCD)

- SCD is a **treatable and potentially reversible myelopathy caused by vitamin B12 (cobalamin) deficiency**, characterized by demyelination of the dorsal and lateral columns of the spinal cord.
- Patient presentation:
 - Patients with SCD commonly present with **symmetrical sensory deficits, paresthesia, weakness, ataxia, and gait disturbances**
- Neurological symptoms:
 - Dorsal column involvement: impaired tactile discrimination, proprioception, and vibration sense
 - Lateral corticospinal tract: muscle weakness, hyperreflexia, and spasticity
 - Spinocerebellar tract degeneration: gait abnormalities, (positive Romberg sign)
- The condition is **usually reversible with supplementation**, so prompt diagnosis is important to begin treatment

Causes of Vitamin B12 Deficiency

- **Nutritional deficiency:**
 - Vitamin B12 is a water-soluble vitamin, and is not produced by the human body (needs to be supplemented from dietary sources)
 - **Mainly present in foods derived from animals**- such as meat, fish, dairy, eggs
 - Vegetarians and vegans are often at higher risk of deficiency
- Reduced absorption due to altered gastrointestinal anatomy/function
 - **Gastric surgery or gastritis**- leads to **loss of parietal cells** of the stomach, lowers production of gastric acid and intrinsic factors needed for B12 absorption
 - High risk procedures include partial or total gastrectomy for gastric cancer, and bariatric surgeries such as sleeve gastrectomy and Roux-en-Y gastric bypass
 - Autoimmune gastritis, or pernicious anemia, is the most common cause of vitamin B12 deficiency
- **Small bowel disease**- can lead to **malabsorption** of vitamin B12
 - Includes inflammatory bowel disease, ileal resection, small intestinal bacterial overgrowth, and diverticulitis

Causes of Vitamin B12 Deficiency (continued)

- **Pancreatic disease-** Pancreatic enzymes are needed for cleaving of vitamin B12 from salivary proteins and transferring it to the intrinsic factor
 - Can be affected in patients with pancreatic insufficiency or chronic pancreatitis
- Drug-induced:
 - **Nitrous oxide:**
 - Can be from both recreational use or exposure to it as an anesthetic agent. Nitrous oxide inactivates vitamin B12 and inhibits methionine synthetase, disrupting methylation and DNA synthesis and leading to axonal injury
 - **Metformin:**
 - Interferes with calcium-dependent ileal absorption of the vitamin B12 & intrinsic factor complex. This can be reversed with calcium supplementation
 - **Gastric acid suppressants:**
 - Patients on high dose and long term histamine H2 receptor antagonists or proton pump inhibitors are at risk (due to gastric acid suppression, preventing vitamin B12 dissociation)

Patient Evaluation and Workup

- Bloodwork:
 - CBC and blood smear: expect **macrocytic anemia**- Low hemoglobin, elevated MCV
 - **Serum B12 levels**: there are several assays, so reference ranges vary. Also, serum levels are not a reliable marker for B12 physiological stores.
 - Generally, B12 levels > 300 pg/ml = normal, between 200-300 pg/ml are borderline, and <200 pg/ml are low.
 - Methylmalonic acid (MMA) and homocysteine- both are intermediates of B12 metabolism
 - Homocysteine can be elevated in both folate and B12 deficiency, but MMA is elevated only in B12 deficiency
 - **Elevation of both MMA and homocysteine** is used to confirm B12 deficiency
 - Folate levels- folate deficiency can have similar lab findings to B12 deficiency
- Thorough history- determining the cause of the B12 deficiency:
 - If no obvious cause is found, the patient should undergo testing for autoantibodies to detect pernicious anemia (anti-intrinsic factor antibody, anti-parietal antibodies)

Patient Evaluation and Workup

- Imaging:
 - **MRI of the spine** with and without contrast is recommended
 - In the early stages:
 - Demyelination is seen as bilateral paired regions of T2 hyperintensity in the dorsal columns of the cervical and upper thoracic spinal cord
 - Imaging finding is often called the “**inverted V**” sign, or the “**inverted rabbit ears**” sign
 - In the late stages:
 - T2 hyperintensity can also be seen in the lateral columns of the spinal cord

Treatment of SCD

- **Vitamin B12 supplementation is essential**
 - Options: IM, deep subcutaneous, oral, or sublingual
 - Common preparations: cyanocobalamin or hydroxocobalamin
- Decisions regarding dose, route, and duration of treatment should be made on an individualized basis for each patient
 - Patients with irreversible causes, such as gastric surgery or pernicious anemia will require supplementation for life
 - Patients with reversible causes such as drug-induced or dietary deficiencies are treated until the deficiency is corrected
- Response is assessed by monitoring hematological markers and improvement in symptoms

Case patient's diagnosis and treatment

- Patient's diagnosis is supported by:
 - Prior partial gastrectomy with poor adherence to diet/supplements
 - Recent nitrous oxide use
 - Lab findings of macrocytic anemia, elevated MMA and homocysteine, and serum vitamin B12 on the lower side of normal range
 - MRI findings of hyperintense T2 signal (degeneration) in the C1-5 posterior columns
- Patient was started on daily injections of B12 1000mcg IM for one week, and then transitioned to oral supplementation
- She was also started on gabapentin 600mg TID and Cymbalta 30mg daily for her neuropathic pain

References:

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