

Combined spinal degeneration: a classic presentation that should not be overlooked.

Degeneração medular combinada: uma apresentação clássica que não deve ser esquecida.

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ABSTRACT

Subacute combined degeneration (SCD) of the spinal cord is a rare neurological condition associated with cobalamin deficiency. We report the case of a 48-year-old man presented with sensory ataxia, pyramidal signs, and ineffective erythropoiesis secondary to hypovitaminosis B12. Spinal MRI revealed extensive hyperintensity in the posterior and lateral funiculi. Anti-parietal cell antibodies were positive, and upper endoscopy showed severe atrophic pangastritis, consistent with autoimmune atrophic gastritis. The investigation of hypoproliferative anemia, combined with dorsolateral spinal cord syndrome, allows for the consideration of SCD and should include the measurement of not only vitamin B12 but also more sensitive biomarkers, such as: homocysteine and methylmalonic acid. SCD should be included in the differential diagnosis of subacute spinal cord syndromes, as it is a potentially reversible condition with high morbidity.

RESUMO

A degeneração medular combinada subaguda (DMCS) é uma condição neurológica rara associada à deficiência de cobalamina. Relatamos o caso de um homem de 48 anos com ataxia sensitiva, sinais de liberação piramidal e eritropoiese ineficaz secundários à hipovitaminose B12. RM de neuroeixo evidenciou extenso hipersinal nos funículos laterais e posterior. A pesquisa de anticorpos anticélulas parietais foi positiva e a endoscopia digestiva alta identificou pangastrite atrófica, compatível com gastrite atrófica autoimune. A investigação da anemia hipoproliferativa somada à síndrome de acometimento dorsolateral medular permite considerar DMCS e deve incluir a dosagem não apenas da vitamina B12, mas também de biomarcadores mais sensíveis, como a: homocisteína e ácido metilmalônico. A DMCS deve estar presente no diagnóstico diferencial das síndromes medulares subagudas, uma vez que se trata de condição potencialmente reversível e com alta morbidade.

Keywords: Vitamin B 12 Deficiency; Spinal Cord Diseases; Myelopathy; Subacute Combined Degeneration.

Palavras-chave: Deficiência de Vitamina B12; Doenças da Medula Espinal; Mielopatia; Degeneração combinada subaguda.

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INTRODUCTION

Subacute combined degeneration (SCD) of the spinal cord, characterized by dorsolateral spinal cord demyelination, is a rare neurological condition caused by cobalamin deficiency, copper deficiency, or zinc toxicity^{1,2}. However, it may also be induced by agents such as nitrous oxide and methotrexate, as well as autoimmune diseases and anatomical or functional changes in the gastrointestinal tract^{2,3}. Clinical manifestations include paresthesia in the limbs, sensory ataxia, gait instability, paraparesis, and pyramidal signs⁴. The diagnosis is supported by low serum vitamin B12 levels. Elevated homocysteine and methylmalonic acid levels are particularly useful in cases of borderline B12 deficiency and for therapeutic monitoring⁵. Magnetic resonance imaging (MRI) can help rule out differential diagnoses and may reveal signs suggestive of SCD, such as symmetrical hyperintensity in the dorsal spinal columns on T2-weighted images, including the "inverted V" or "inverted rabbit ears" sign in the cervical spine and the "binoculars" sign in the thoracic spine⁴. Early treatment reduces the risk of disease progression and irreversible damage of the central nervous system⁶.

CASE REPORT

A 48-year-old White man presented to the emergency department for evaluation of a 3-week history of exertional dyspnea (grade 3 on the modified Medical

Research Council, mMRC, dyspnea scale), imbalance, fatigue, and hyporexia. Physical examination revealed severe malnutrition (body mass index 14.9 kg/m²), cognitive impairment, bradypsychism, pale skin and mucous membranes, mild jaundice, and impaired distal vibration sense in the lower limbs, with preserved conscious proprioception. Bilateral extensor plantar reflexes (Babinski sign) were present. There was no history of prior surgeries, alcoholism, vegan diet, or chronic gastrointestinal symptoms. Laboratory tests showed severe hypoproliferative normocytic anemia (hemoglobin nadir: 5.5 g/dL; absolute reticulocyte count: 17,500/mm³; mean corpuscular volume: 84.9 fL), with marked anisocytosis (red cell distribution width: 35.9%). Peripheral blood smear revealed schizocytes, elliptocytes, and dacrocytes. Additional findings included decreased haptoglobin (10 mg/dL; reference range [RR]: 30–200 mg/dL), mild indirect hyperbilirubinemia (1.7 mg/dL), and markedly elevated lactate dehydrogenase (LDH: 6,005 U/L; RR: 125–220 U/L). Direct Coombs test was negative. Serum vitamin B12 was undetectable (RR: 187–883 pg/mL), with elevated homocysteine (38.47 µmol/L; RR: 7.71–22.33 µmol/L). Methylmalonic acid testing was deemed unnecessary. Concurrent iron and folate deficiencies, as well as HIV, HCV, HBV, and syphilis infections, were ruled out. Spinal MRI demonstrated extensive T2/STIR hyperintensity in the lateral funiculi from C2 to T8 (Figures 1) and hyperintensity in the posterior funiculus at the cervical and lower thoracic levels (T12; Figure 2), without contrast enhancement.

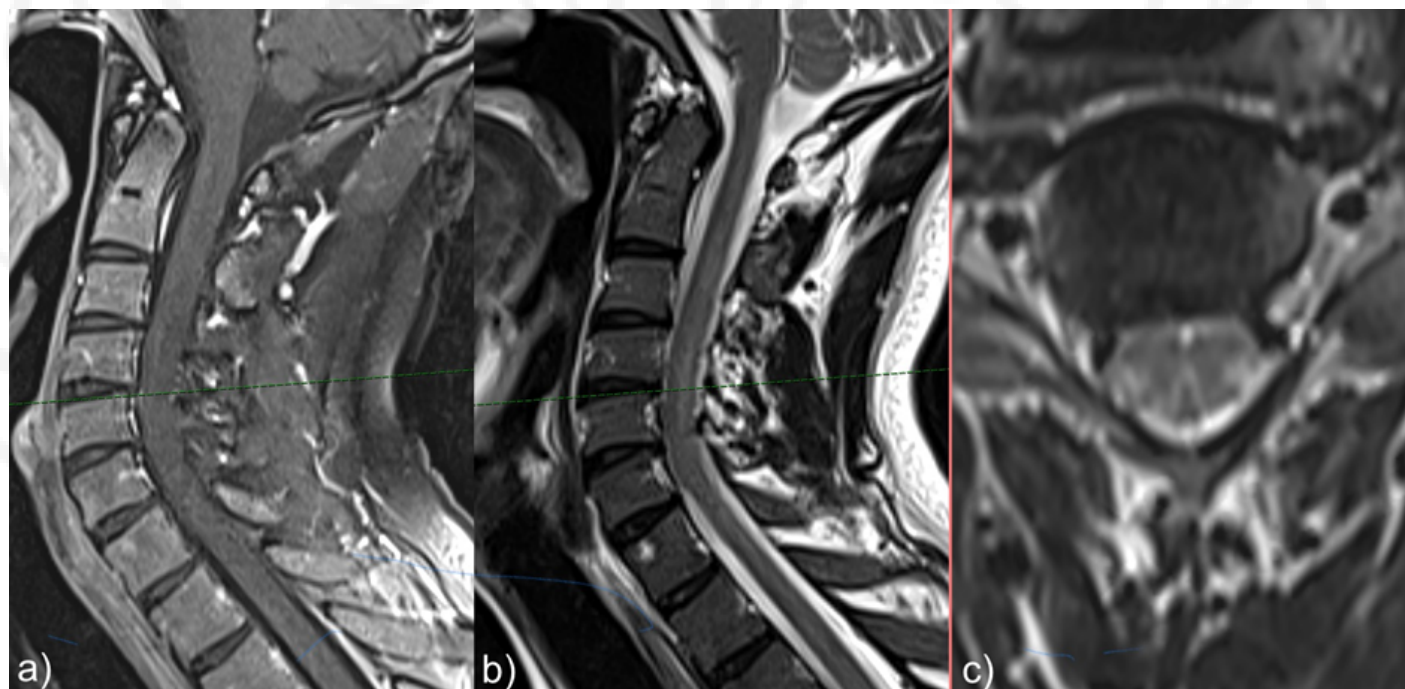


Figure 1. (a) Post-contrast sagittal T1-fat, (b) T2-weighted sagittal, and (c) T2-weighted axial magnetic resonance images showing a signal change in the spinal cord, without contrast enhancement, affecting the lateral and posterior fasciculi at the cervical level.

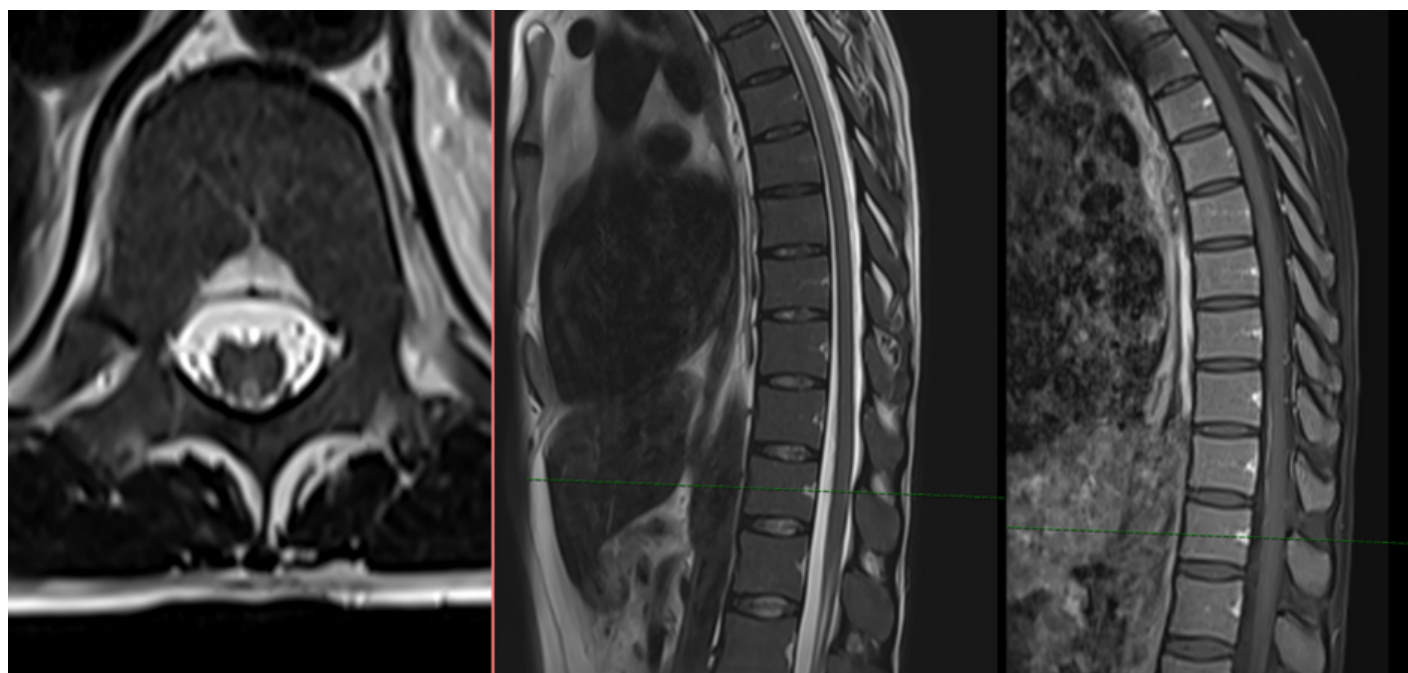


Figure 2. At the level of the thoracic spinal cord, a focal change in the posterior fasciculi is noted.

Anti-parietal cell antibodies were positive, and upper endoscopy revealed severe atrophic pangastritis in the corpus and fundus, confirmed by histopathology, which showed moderate glandular atrophy and complete intestinal metaplasia, with no *Helicobacter pylori* infection. Neurocognitive changes, sensory ataxia, pyramidal signs, and intramedullary hemolysis due to ineffective erythropoiesis were therefore attributable to severe vitamin B12 deficiency. Parenteral replacement was initiated with intramuscular cyanocobalamin (5,000 mcg/day for 5 days), followed by a spaced-dosing regimen per institutional protocol. During the 8-day hospitalization, the patient received 2 units of packed red blood cells due to symptomatic severe anemia and postural hypotension. At a 2-month follow-up visit, improvements in fatigue, vibration sense, and gait ataxia were noted. Ongoing gastroenterology care was arranged for autoimmune atrophic gastritis management.

DISCUSSION

SCD of the spinal cord is a neurological complication that may occur in up to 15% of individuals with vitamin B12 deficiency⁷. This vitamin is essential for myelination, and its deficiency can lead to the accumulation of methylmalonic acid, a neurotoxic substance that damages myelin, resulting in demyelination of the dorsal columns and lateral spinothalamic tracts. The spinal cord is most commonly affected in the lower cervical and upper thoracic regions⁴. Severe anemia with signs of hemolysis—despite hypoproliferation—was interpreted as intramedullary hemolysis due to ineffective erythropoiesis,

alongside neurological changes characteristic of SCD, including sensory ataxia and pyramidal signs. It is worth noting that hypovitaminosis B12 can rarely trigger autoimmune hemolytic anemia, a condition ruled out in this patient⁸. Homocysteine and methylmalonic acid are confirmatory markers of vitamin B12 deficiency, often elevated even when serum B12 levels are borderline or in the "gray zone"^{9,10}. While neuroimaging findings support the diagnosis of SCD, MRI sensitivity is low, and in most cases, spinal cord imaging may not be mandatory⁷. The etiology of hypovitaminosis B12 in this case was attributed to autoimmune atrophic gastritis, a condition characterized by destruction of gastric parietal cells and subsequent reduction in intrinsic factor, which is essential for cobalamin absorption⁸. It should be emphasized that SCD is not only caused by B12 malabsorption but also by other factors, such as inadequate dietary intake (particularly in strict vegetarians and vegans), drug interference (e.g., nitrous oxide), problems with vitamin utilization, and congenital metabolic defects^{11,12,13}. The differential diagnosis of subacute combined myelopathies includes infectious causes such as vacuolar myelopathy from the human immunodeficiency virus (HIV) and myelopathy associated with human T-cell lymphotropic virus type 1 HTLV-1/tropical spastic paraparesis (HAM/TSP)¹⁴. The former appears in the advanced stages of HIV, when the CD4⁺ cell count is very low, and is clinically very similar to subacute combined degeneration, with progressive and painless spastic paraparesis, sensory ataxia, and bladder dysfunction⁴. On the other hand, HAM/TSP has a slower progression than HIV vacuolar myelopathy, marked by chronic spastic paraparesis, proximal lower limb weakness, early urinary

disturbances, and mild sensory disorders, and may present as a diagnostic clue anteroposterior atrophy of the spinal cord particularly at the thoracic level on magnetic resonance imaging¹⁵. And as already mentioned, nitrous oxide toxicity comprises the spectrum of hypotheses to be considered in the differential diagnosis of SCD. It is an inhalable gas, used as an anesthetic, capable of inactivating the B12 molecule and impairing the function of the methylcobalamin-dependent enzyme methionine synthase. In addition to the characteristic symptoms of longitudinal myelopathy, it is associated with psychiatric symptoms such as confusion, hallucinations, and memory changes^{4,13,14}. Also within the metabolic scope, copper deficiency, in most cases due to post-surgical intestinal malabsorption or high zinc intake, constitutes a differential diagnosis. The copper deficit leads to reduced activity of copper-dependent enzymes and clinically can present the symptoms of posterolateral spinal cord involvement associated with cytopenias¹⁴. Finally, it is important to highlight that the described conditions are characterized by a selective impairment of the long tracts of the spinal cord, particularly the posterior funiculi and the lateral funiculi, this focal pattern stands in contrast to the transverse involvement typical of other myelopathies¹⁴. In the management of these conditions, the therapeutic approach to myelopathy will vary according to its etiology. In clinical practice, intramuscular vitamin B12 administration is the established standard for most patients when the clinical presentation is associated with a deficiency of this vitamin².

CONCLUSION

SCD should be considered in the differential diagnosis of patients with subacute neurological dysfunction, characterized by paresthesias, gait disturbances, and signs of involvement of the corticospinal and posterior tracts of the spinal cord, Vitamin B12 deficiency should always be investigated in this scenario. This case, with its early diagnosis and a favorable clinical progression, highlights the importance of the prompt and accurate recognition and treatment of cobalamin deficiency-related neuropathy.

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