BOHR International Journal of Neurology and Neuroscience
2026, Vol. 4, No. 1, pp. 34–39
DOI: 10.54646/bijnn.2026.33
www.bohrpub.com

CASE REPORT

Tripping in the dark, pigmented in the light: a case of insidious myelopathy unmasked by an antifolate in a patient with rheumatoid arthritis

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Received: 14 May 2026; **Accepted:** 19 July 2026; **Published:** 03 August 2026

Introduction: We report an unusual case in which prominent cutaneous hyperpigmentation preceded a progressive myelopathy in a non-vegetarian patient with rheumatoid arthritis (RA) receiving long-term methotrexate (MTX) therapy—a combination that conspired to produce overt cobalamin deficiency through a shared disruption of one-carbon metabolism, despite concurrent folic acid supplementation.

Main symptoms and findings: A 64-year-old male presented with a one-year history of ascending paraesthesia and sensory ataxia, notably preceded by facial and acral hyperpigmentation. Examination revealed posterior column dysfunction and pyramidal signs, with bilateral mild hip flexor weakness. Macrocytic anemia and severely subnormal serum vitamin B12 (114 pg/mL) were confirmed. Serological screening (Venereal Disease Research Laboratory test [VDRL], HIV enzyme-linked immunosorbent assay [ELISA], hepatitis B surface antigen [HBsAg], and anti-hepatitis C virus [anti-HCV]) was negative. Spinal magnetic resonance imaging (MRI) demonstrated posterior column T2 hyperintensity from C6 to D7 with the characteristic inverted V sign on axial imaging.

Diagnosis, intervention, and outcome: Subacute combined degeneration (SCD) secondary to vitamin B12 deficiency was diagnosed. Parenteral hydroxocobalamin was commenced with significant neurological, hematological, and cutaneous improvement within 6 weeks.

Conclusion: Cutaneous hyperpigmentation is a clinically accessible early warning sign of cobalamin deficiency that predates neurological involvement and deserves active recognition. Folic acid supplementation does not prevent neurological injury from cobalamin deficiency. Routine B12 surveillance is essential in all patients on chronic MTX therapy.

Keywords: case report, megaloblastic anemia, methotrexate, rheumatoid arthritis, subacute combined degeneration, vitamin B12 deficiency

Introduction

Subacute combined degeneration (SCD) of the spinal cord is a demyelinating disorder arising from vitamin B12 (cobalamin) deficiency, characterized by bilateral degeneration of the posterior columns and lateral corticospinal tracts (1, 2). The term 'combined' captures the co-involvement of both pathways, producing the paradox of sensory ataxia superimposed on upper motor neuron signs. Classical causes include pernicious

anemia, strict vegetarianism, and post-gastrectomy malabsorption (3).

What distinguishes this case is the convergence of two underappreciated factors: age-related decline in intrinsic factor secretion and long-term antifolate therapy with methotrexate (MTX), a dihydrofolate reductase inhibitor that functionally depletes the folate substrate required for the B12-dependent methylation step (4, 5). Folic acid supplementation — correctly prescribed to offset hematological toxicity — does not restore cobalamin function and may mask the anemia, delaying diagnosis. Compounding the diagnostic interest, prominent cutaneous hyperpigmentation preceded the neurological presentation in this patient, providing an early and accessible clinical clue that is rarely foregrounded in neurology practice (6).

Case presentation

Patient information

A 64-year-old non-vegetarian male with a background of RA, managed with MTX 7.5 mg once weekly and folic acid on the remaining 6 days, presented with a two-stage illness. There was no history of alcohol use, gastrointestinal surgery, malabsorptive disease, diabetes mellitus, thyroid disease, chronic kidney disease, nitrous oxide exposure, or family history of hereditary neuropathy. This case was reported in accordance with the CARE case report guidelines (7).

His illness began insidiously several months before neurological symptoms, with progressive darkening of his facial skin, knuckles, and nails. Approximately 1 year before presentation, bilateral lower limb tingling began in the toes and ascended symmetrically to involve the legs and thighs. Gait unsteadiness developed concurrently, worsened in dim light, and had led to several near-falls. There was no limb weakness at onset, no hand clumsiness, and no bowel or bladder dysfunction.

Clinical findings

General examination revealed stable vital signs. No pallor, icterus, or lymphadenopathy was present. A systematic dermatological survey identified the following bilateral, symmetrical cutaneous findings:

- Diffuse facial hyperpigmentation with accentuation over the forehead and malar regions
- Bilateral periorbital pigmentation
- Hyperpigmentation over the dorsal aspects of the fingers and knuckles
- Diffuse nail bed pigmentation with longitudinal melanonychia-like streaking involving multiple digits (See **Figures 1** and **2**).

FIGURE 1 | Clinical photograph demonstrating diffuse facial and periorbital hyperpigmentation with malar accentuation.

FIGURE 2 | Bilateral dorsal hand hyperpigmentation, knuckle accentuation, and longitudinal melanonychia-like nailbed pigmentation.

No postural hypotension was detected. Serum cortisol was 18.6 μg/dL (reference 6.2–19.4 μg/dL), and electrolytes were normal, effectively excluding adrenocortical insufficiency as the cause of pigmentation.

Neurological examination revealed normal higher cognitive functions and intact cranial nerves, including

fundoscopy (no optic atrophy or papilledema). Motor examination demonstrated normal bulk in all four limbs. Upper limb tone and power were normal (Medical Research Council [MRC] grade 5/5). In the lower limbs, mild bilateral spasticity was present with bilateral hip flexor weakness (MRC grade 4/5); remaining lower limb muscle groups were MRC 5/5. Deep tendon reflexes were symmetrically brisk at the knees and ankles; plantar responses were extensor bilaterally, indicating pyramidal tract involvement.

Sensory examination disclosed a dissociated pattern. Vibration sense was absent in the bilateral lower limbs to the hip level and impaired in the fingers of both hands, indicating extensive posterior column involvement. Joint position sense was impaired in the lower limbs. Pain and temperature sensation were relatively preserved, consistent with intact spinothalamic function. Romberg's test was markedly positive. The "wash basin sign" (8) was positive. Gait was broad-based and sensory ataxic; tandem walking, significantly impaired. Heel-knee-shin testing showed mild proprioceptive impairment; finger-nose testing was normal. Neurological localization indicated bilateral posterior column and corticospinal tract involvement at the cervical cord level—the hallmark of SCD.

Timeline

For further details, please see **Table 1**.

Diagnostic assessment

Hematological evaluation revealed macrocytic anemia: hemoglobin 10.7 g/dL, MCV 111.5 fL, red blood cell (RBC) 2.8 × 106/μL, packed cell volume (PCV) 32%. Peripheral blood smear demonstrated macrocytes, oval macrocytes, hypersegmented neutrophils (>5% with ≥5 lobes), and anisocytosis, consistent with megaloblastic hematopoiesis. Serum vitamin B12 was markedly subnormal at 114 pg/mL (reference 200–900 pg/mL). Serum folate (12.4 ng/mL), serum copper (14.1 μmol/L), and serum cortisol (18.6 μg/dL) were all within normal limits. Full results are summarized in **Table 2**.

Serological screening was also performed: Venereal Disease Research Laboratory test (VDRL), HIV enzyme-linked immunosorbent assay (ELISA) (4th generation), hepatitis B surface antigen (HBsAg), and anti-hepatitis C virus (anti-HCV) antibody were all negative.

Magnetic resonance imaging (MRI) of the cervical and thoracic spine (**Figures 3** and **4**) demonstrated a long segment of T2 hyperintensity within the dorsal columns, beginning at C6 and extending to the D7 vertebral level on sagittal imaging. Axial T2-weighted images showed symmetric high signal confined to the dorsal columns, producing the characteristic inverted V sign—a radiological hallmark of SCD (9). There was no cord compression,

TABLE 1 | Clinical timeline.

Timeline	Clinical event
~15–16 months prior to presentation	Insidious onset of progressive cutaneous hyperpigmentation - face, knuckles, nail beds - several months before onset of neurological symptoms.
~1 year prior to presentation	Onset of bilateral lower limb paraesthesia (toes, ascending to thighs); progressive gait unsteadiness with near-falls.
Presentation (Day 0)	Admitted with sensory ataxia, posterior column and pyramidal signs, macrocytic anemia, and serum B12 of 114 pg/mL.
Day 1	Magnetic resonance imaging (MRI) spine: posterior column T2 hyperintensity C6–D7; inverted V sign on axial imaging. Parenteral B12 commenced.
Week 6	Paraesthesiae reduced; gait improved; Romberg sign attenuated; Hb 12.8 g/dL, MCV 95 fL; hip flexors approaching 4+/5.
Months 2–3	Cutaneous hyperpigmentation showing progressive lightening; maintenance B12 continued.

TABLE 2 | Key investigations. Abnormal values shown in bold.

Parameter	Result	Reference range
Hemoglobin	**10.7 g/dL**	13.0–17.0 g/dL
Red blood cell (RBC) Count	**2.8 × 106/μL**	4.5–5.5 × 106/μL
Packed cell volume (PCV)	**32%**	40–52%
MCV	**111.5 fL**	80–100 fL
Peripheral smear	**Macrocytes, oval macrocytes, hypersegmented neutrophils (≥5 lobes), anisocytosis**	—
Total leucocyte count	Within normal limits	—
Platelet count	Within normal limits	—
Serum vitamin B12	**114 pg/mL**	200–900 pg/mL
Serum folate	12.4 ng/mL	3.1–17.5 ng/mL
Serum copper	14.1 μmol/L	11–22 μmol/L
Serum cortisol	18.6 μg/dL	6.2–19.4 μg/dL
VDRL	Negative	—
HIV ELISA 4th generation	Negative	—
Hepatitis B surface antigen (HBsAg)	Negative	—
Anti-hepatitis C virus (anti-HCV) antibody	Negative	—
MRI spine	**Posterior column T2 hyperintensity; no compressive myelopathy**	—

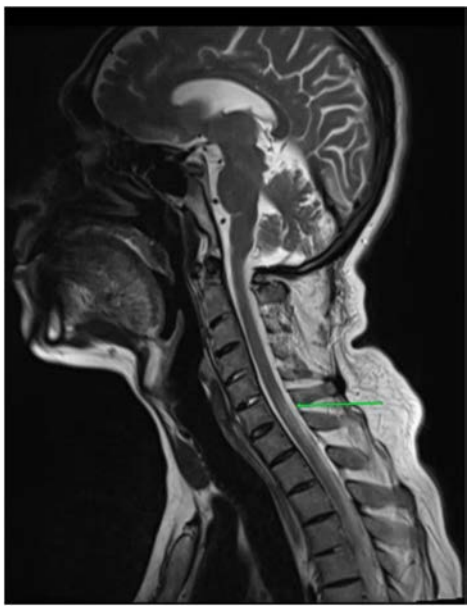

FIGURE 3 | Sagittal T2-weighted MRI spine demonstrating long-segment posterior column T2 hyperintensity (green arrow) beginning at C6 and extending to D7.

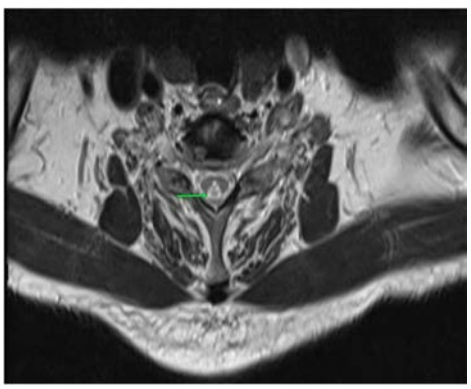

FIGURE 4 | Axial T2-weighted MRI at the level of the cervical cord demonstrating bilateral symmetric dorsal column hyperintensity producing the inverted V sign (green arrow).

intrinsic tumor, or demyelinating plaque to suggest an alternative etiology.

The following differential diagnoses were systematically evaluated. Copper deficiency myelopathy was excluded by normal serum copper (14.1 μmol/L). Compressive cervical myelopathy was excluded by MRI (important given rheumatoid arthritis (RA) predisposition to atlantoaxial instability). Multiple sclerosis was excluded by the longitudinal contiguous posterior column lesion pattern and absence of relapsing course. Nitrous oxide toxicity was excluded by history. Neuromyelitis optica spectrum disorder (NMOSD) was considered unlikely because the selective dorsal column T2 signal with inverted V sign is atypical for NMOSD; there was no optic neuritis, area postrema syndrome, or relapsing course. AQP4-IgG was not tested (limitation). MOG-antibody-associated disease (MOGAD) was considered unlikely as the imaging phenotype and monophasic course are atypical; MOG-IgG was not tested (limitation). Neurosyphilis (tabes dorsalis) was considered unlikely in this clinical context; serum VDRL was negative. HIV-associated vacuolar myelopathy was excluded because the HIV ELISA (4th generation) was negative; HBsAg and anti-HCV antibody were also negative. HTLV-1-associated myelopathy (HAM/TSP) was considered less likely given the complete metabolic explanation and clear treatment response favoring SCD; HTLV-1 serology was not performed, which is a limitation. Paraneoplastic myelopathy was considered unlikely because there were no constitutional features or known malignancy; paraneoplastic antibody panel was not performed (limitation). Vitamin E deficiency was considered unlikely because there was no fat malabsorption; serum vitamin E not measured (limitation). Serum methylmalonic acid (MMA) and homocysteine were not measured (limitation). The diagnosis was confirmed by the complete clinical, biochemical, radiological, and therapeutic response.

Therapeutic intervention

Parenteral vitamin B12 was commenced as hydroxocobalamin 1000 mcg intramuscularly daily for 7 days, followed by weekly injections for 1 month, then monthly maintenance (10). Folic acid supplementation was continued. The rheumatology team was consulted regarding the ongoing indication for MTX, balancing RA disease control against the documented neurological injury from cobalamin depletion.

Follow-up and outcomes

Progressive clinical improvement was evident within 6 weeks. Lower limb paraesthesiae reduced from constant bilateral distal tingling to occasional mild symptoms. Gait improved from a broad-based ataxic pattern requiring support to independent ambulation indoors; tandem walking partially recovered. Romberg's sign attenuated from markedly positive to mildly positive, and no further near-falls were reported. Hip flexor strength showed partial recovery (MRC grade 4/5 to approaching 4+/5). Hematological assessment at 6 weeks demonstrated improvement in hemoglobin to 12.8 g/dL (from 10.7 g/dL at presentation) and MCV normalizing to 95 fL (from 111.5 fL). Cutaneous hyperpigmentation showed progressive lightening over subsequent months, consistent with restoration of S-adenosylmethionine (SAM)-mediated tyrosinase promoter methylation. Formal neurological outcome scales were not administered, as this was a routine clinical encounter; this represents a recognized limitation.

No adverse events related to treatment were observed.

Discussion

This case illustrates how MTX, prescribed for RA, can unmask latent cobalamin deficiency through a biochemical mechanism distinct from simple dietary lack. MTX inhibits dihydrofolate reductase, depleting methyltetrahydrofolate—the folate substrate for methionine synthase, which requires methylcobalamin as a co-factor (4). When MTX compromises this pathway, cobalamin-dependent methylation is further impaired beyond any underlying subclinical deficiency. Folic acid supplementation, while appropriate for hematological protection, does not rescue methionine synthase activity and may reduce the overt hematological signal that would otherwise prompt B12 testing (3).

The neurological injury in B12 deficiency arises from reduced synthesis of SAM, which is essential for myelin basic protein methylation (1, 2). Concurrent aberrant incorporation of methylmalonyl-CoA into myelin lipids compounds vacuolar myelopathy. The predilection for long fibers of the posterior columns and lateral corticospinal tracts explains the classical syndrome, and the extension of vibration loss to the fingers in this patient indicates advanced upward spread. The presence of a bilateral inverted V pattern on axial MRI—dorsal column signal selective, symmetric, and non-compressive—is the imaging signature of SCD and was clearly demonstrated in this case (9). Emerging evidence further suggests that SAM depletion in cobalamin deficiency may additionally impair SIRT1 (Sirtuin 1) activity—a NAD^+-dependent deacetylase implicated in inflammatory regulation and cellular senescence—representing an area of potential mechanistic interest for future research.

The cutaneous phenotype — the true first symptom in this case — deserves particular emphasis. Facial, periorbital, knuckle, and nail bed hyperpigmentation resulting from B12 deficiency reflects reduced SAM-mediated methylation of the tyrosinase promoter, disinhibiting melanogenesis (6, 11). This pattern antedated neurological involvement by several months, making it the most accessible early clinical pointer and a potentially valuable screening trigger. The differential of Addison's disease was excluded by normal serum cortisol and copper deficiency myelopathy by normal serum copper (12).

Strengths of this case include multimodal evidence—biochemical, radiological (characteristic inverted V sign on MRI), and a definitive therapeutic response—combined with systematic exclusion of mimics. VDRL, HIV ELISA, HBsAg, and anti-HCV were performed and were negative. Limitations include the absence of anti-intrinsic factor and anti-parietal cell antibody testing; serum MMA and total homocysteine not being measured (13, 14); AQP4-IgG, MOG-IgG, HTLV-1 serology, paraneoplastic antibody panel, and serum vitamin E not being performed; and formal neurological outcome scales not being administered. These reflect the inherent constraints of retrospective clinical case reporting in a resource-limited setting. The primary takeaway is threefold: (1) chronic MTX therapy is an under-recognized precipitant of SCD (15); (2) cutaneous hyperpigmentation is an early and clinically accessible warning sign preceding neurological involvement; and (3) folic acid supplementation cannot substitute for vigilant B12 surveillance in patients on antifolate therapy.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images, including clinical photographs. The consent form is available upon request from the corresponding author.

Funding

No funding was received for this work.

Author contributions

KHM: clinical data collection, literature review, and manuscript drafting. MP: Neurological evaluation, MRI interpretation support, and manuscript critical revision. SR: clinical supervision and manuscript critical revision. All authors reviewed and approved the final manuscript.

Acknowledgments and AI disclosure

Artificial intelligence assistance was used only for language editing and formatting support. The authors reviewed, verified, and take full responsibility for all manuscript content.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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