



# Clinical Reasoning: Progressive visuospatial problems in a 71-year-old man

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## SECTION 1

A 71-year-old right-handed man presented with a 3-month history of progressive cognitive impairment. Six weeks before presentation, he became unable to use his mobile phone, with difficulties pressing the digits in the correct order. He had developed problems reading, describing a jumbled-up appearance of words on the page. He omitted single letters when writing, and had difficulty in using cutlery and accurately judging portion sizes. He had ceased driving due to navigational problems and because of repeatedly hitting the curb. In the last 4 weeks, he had developed difficulty dressing. Notably, he had good insight, being able to give a detailed description of symptoms.

Four years earlier, the patient had been diagnosed with rheumatoid arthritis (RA) and commenced immunomodulatory therapy with methotrexate (15 mg/wk plus folic acid 5 mg/wk) and hydroxychloroquine (200 mg/d). One year later, following an exacerbation of joint symptoms and the development of interstitial lung disease thought to be a systemic complication of RA, his methotrexate dose was increased to 25 mg/wk (subcutaneously) and leflunomide (10 mg/d) was added. At presentation, he remained on methotrexate and hydroxychloroquine at the same doses, but leflunomide had been discontinued and sulfasalazine (3 g daily) commenced. The only other history of note was an episode

of obstructive cholestasis. He was otherwise well, and the main carer for his wife.

Examination revealed marked visuospatial dysfunction and simultanagnosia. The patient was able to read when presented with one line of text, but unable to read a paragraph. Object recognition was preserved; however, he was unable to describe a picture of a scene. He could not recognize interrupted figures or letters. He had an ideomotor limb apraxia, with impaired gesture copying (e.g., extending the 1st and 2nd digits at right angles). He scored 16/30 on the Montreal Cognitive Examination (MoCA), with severe constructional apraxia, being unable to draw a cube or clock, performing poorly on the Trail-Making Test (figure, A), and additional impairments on vigilance testing and serial 7s, reduced verbal fluency, and impaired delayed recall. There was no dysgraphesthesia or neglect. Speech was intact, and he could understand and follow written commands. There were no parkinsonian features and the remainder of the neurologic examination was normal. Systemic examination revealed bibasal lung crepitations. His admission blood pressure was 128/75 mm Hg. There was no clinical evidence of active joint inflammation.

## Questions for consideration:

1. What is your localization at this point?
2. What is your differential diagnosis?
3. What further tests would you perform?

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## SECTION 2

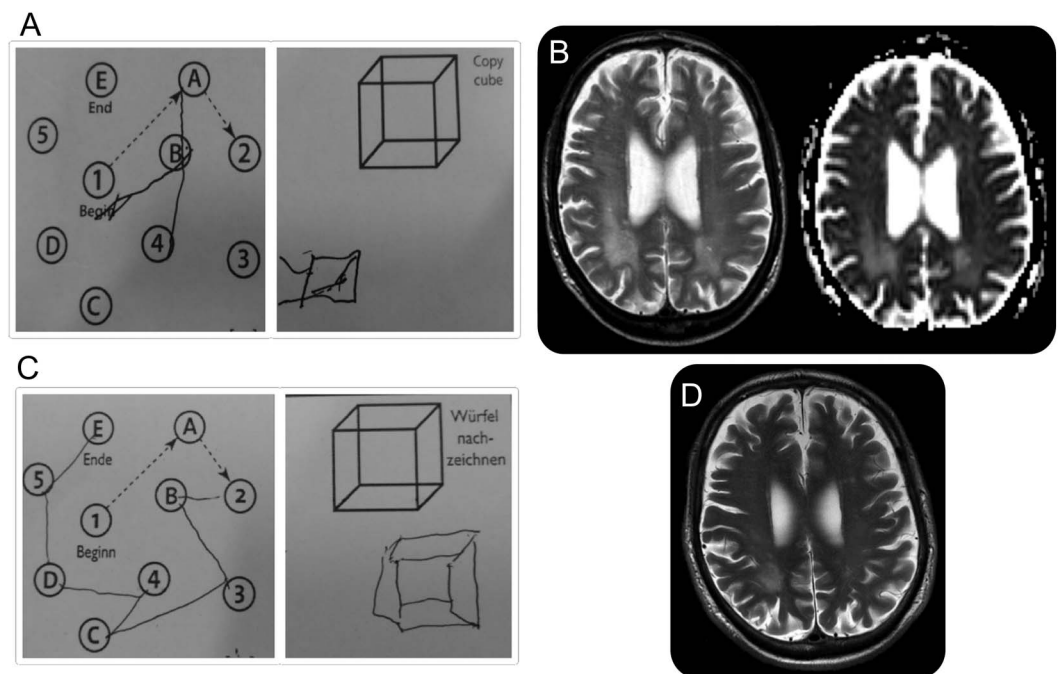
Our patient's marked visuoconstructive deficits but preservation of language suggests dysfunction of predominantly posterior brain regions. Problems with the Trail-Making Test indicate additional frontal-executive involvement. Difficulty in recognizing incomplete letters implies a degree of apperceptive visual agnosia, most typical of right hemispheric lesions, while ideomotor limb apraxia is usually seen in left hemispheric injury. The differential diagnosis after the clinical assessment thus comprised causes of progressive encephalopathy preferentially affecting bilateral occipital and parietal function. In order of likelihood, we considered a diffusely infiltrating space-occupying lesion prion disease (Heidenhain variant), given the rapid progression; a posterior reversible leukoencephalopathy syndrome (PRES), either associated with autoimmune disease or drug-induced; progressive multifocal leukoencephalopathy (PML), given the immunosuppression; or cerebral vasculitis related to RA. Demyelinating disease can also present as a diffuse encephalopathy or mimic space-occupying lesions. Nutritional deficiency could also produce

this picture; for example, B<sub>12</sub> deficiency can cause selective splenic demyelination. Extralimbic autoimmune encephalitis can cause progressive encephalopathy, although a posterior cortical syndrome would be unusual. Neurodegenerative disease seemed unlikely because of the rapid onset, although variants of corticobasal degeneration can present with rapidly progressive apraxia and visuospatial problems.

Blood tests revealed raised inflammatory markers (erythrocyte sedimentation rate 103 mm/h, C-reactive protein 89 mg/L), mild (hemoglobin 12.4 g/dL) normocytic anemia, and low iron (6.2 μmol/L) and transferrin saturation (13%). Serum electrophoresis revealed nonspecific polyclonal hypergammaglobulinemia. Electrolytes, liver, renal and thyroid function, and B<sub>12</sub> and folate levels were normal. Antineuronal antibodies (serum anti-Yo, Hu, Ri, NMDA, and voltage-gated potassium channel antibodies) were negative. A chest X-ray and CT showed pulmonary fibrosis and lower lobe consolidation but no malignancy.

CSF was acellular, with normal protein, glucose, and lactate. Oligoclonal bands, serum/CSF

**Figure** Initial cognitive examination and neuroimaging findings and improvement 4 months after presentation



(A) Impairment in visuospatial construction, with poor performance on the trail-making and cube-drawing components of the Montreal Cognitive Assessment (MoCA). (B) Left: T2-weighted MRI shows confluent symmetrical white matter signal abnormality in a periventricular and predominantly posterior distribution. The immediate deep periventricular white matter, subcortical U fibers, and corpus callosum are not involved. There was no associated mass effect or pathologic enhancement. Right: Apparent diffusion coefficient map: high signal in the posterior parietal lobe indicates facilitated diffusion. (C) T2-weighted MRI: regression of the radiologic changes 4 months after methotrexate cessation. (D) Improvement in visuospatial construction and trail-making components of the MoCA 4 months after treatment cessation.

JC virus screen, and syphilis serology were negative.

Brain MRI revealed bilateral, T2-hyperintense confluent changes, with facilitated diffusion, affecting predominantly the posterior subcortical white matter (figure, B).

**Questions for consideration:**

1. How do these findings narrow your differential diagnosis?
2. How would you manage this patient?
3. What is the prognosis?

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### SECTION 3

This patient's imaging showed symmetrical, predominantly posterior white matter changes. These were too extensive for leukoaraiosis, especially as our patient was not hypertensive. Sparing of subcortical U-fibers would be highly unusual for PML. The lack of any definite diffusion restriction made active vasculitis unlikely. Features were also atypical for prion disease, which characteristically shows restricted diffusion in the striatum and cortex. The imaging appearance and clinical presentation in a patient on methotrexate were believed to be most likely due to methotrexate neurotoxicity.

High-dose intrathecal or IV methotrexate, commonly used in hematologic malignancies with CNS involvement, can cause neurotoxicity and demyelination, with a rapid or insidious onset. However, after low-dose methotrexate treatment, as here, this complication is very rare.

Although in some cases steroids have been used, clinical and radiologic features of methotrexate toxicity can fully resolve simply following drug withdrawal. In our patient, we discontinued methotrexate (continuing sulfasalazine and hydroxychloroquine) and followed him closely. Over 4 months, he improved considerably, and on repeat cognitive testing scored 28/30 on the MoCA (figure, C), losing points for delayed recall. He had no residual cognitive symptoms, normal reading and writing abilities, and no figure construction or visual perception problems. On repeat MRI, the white matter changes had regressed significantly (figure, D).

**DISCUSSION** We present a patient with a subacute posterior leukoencephalopathy, which almost fully resolved after stopping methotrexate treatment. Whereas methotrexate encephalopathy is well-recognized, it usually occurs after high-dose therapy. An association with low-dose therapy has rarely been reported.

Methotrexate can cause several CNS complications, including aseptic meningitis, myelopathy, acute and subacute encephalopathy, and posterior leukoencephalopathy. The latter was present in our patient, but is much more common with high-dose intrathecal or systemic methotrexate, particularly in conjunction with cranial radiotherapy. Clinical features vary, but frequently arise from the posterior brain. Outcome is variable, ranging from recovery after treatment cessation to progression and death. In addition to our patient, we know of only 10 reported cases where posterior leukoencephalopathy occurred after low-dose methotrexate (table e-1 on the *Neurology*<sup>®</sup> Web site at [Neurology.org](http://Neurology.org)). Generally, patients presented with visuospatial problems, although 2 patients had cerebellar syndromes. Outcomes varied: 7 patients improved after treatment cessation, but 3 progressed despite this.

Interestingly, patients with poor outcomes had CSF pleocytosis and raised CSF protein, whereas these were normal in patients with good outcomes.

On imaging, methotrexate toxicity is often associated with confluent, mainly posterior white matter changes. These T2-hyperintense lesions can be reversible. In some cases, contrast enhancement<sup>1</sup> and restricted diffusion<sup>2</sup> have been described. It is uncertain if methotrexate-related neurotoxicity is due to direct glial and neuronal toxicity, which would be associated with cytotoxic edema and diffusion restriction,<sup>3</sup> or due to microvascular endothelial damage, associated with vasogenic edema and facilitated diffusion,<sup>4</sup> as found in our patient. It is possible that both processes occur concurrently. Given our imaging findings of vasogenic edema, and reversible clinical deficits, this could also be described as methotrexate-induced PRES, although symptom onset was over a significantly longer period than usually expected in this condition. Normal imaging has also been described,<sup>5</sup> suggesting that the severity of clinical and imaging abnormalities is not always related.

Methotrexate inhibits dihydrofolate reductase and homocysteine metabolism, with diverse effects on myelin, vascular endothelium, and neuronal excitability.<sup>3</sup> Genetic polymorphisms in the methionine-homocysteine pathway could therefore influence an individual's sensitivity to side effects. Furthermore, external factors also contributing to this pathway could increase the risk of methotrexate toxicity. These include low B<sub>12</sub> levels,<sup>5</sup> concurrent or previous cyclosporine treatment, other immunosuppressants, cytotoxic medication,<sup>6,7</sup> drug interactions (e.g., omeprazole, which can increase methotrexate levels<sup>8</sup>), and genetic polymorphisms altering methotrexate metabolism and transport.<sup>9</sup> Despite a reasonable assumption that the risk of toxicity should increase with total cumulative dose or duration of methotrexate treatment, these were highly variable in the reported cases, suggesting no clear association between clinical risk, duration, and dose of treatment.

Methotrexate does not typically cross the blood-brain barrier in high concentration. However, it is possible that autoimmune disorders and a systemic inflammatory response, as was present here, lead to endothelial dysfunction and subsequent disruption of the blood-brain barrier, predisposing to increased CNS methotrexate concentrations and ensuing complications. Whereas several immunosuppressant medications have been associated with PRES, most commonly cyclosporine and tacrolimus, to our knowledge PRES has not been associated with leflunomide, hydroxychloroquine, or sulfasalazine. Conceivably, concurrent treatment with these agents could have increased the risk of methotrexate toxicity.

Chronic low-dose administration of methotrexate can cause hepatotoxicity, blood dyscrasias,

nephrotoxicity, and pulmonary toxicity (including fibrosis, interstitial pneumonia, hypersensitivity pneumonitis, organizing pneumonia, and pleuritis).<sup>10</sup> In our patient, it is unclear whether his lung disease was exclusively due to RA or whether there was a contribution from methotrexate therapy.

Our patient presented with a well-recognized complication of methotrexate therapy, unusually occurring after low-dose rather than high-dose intrathecal or IV therapy. The patient recovered well following methotrexate withdrawal. Our case highlights that methotrexate toxicity can occur in low-dose, chronic treatment. Clinicians should be mindful of drug-related encephalopathy in patients with subacute cognitive changes who are treated with methotrexate.

### AUTHOR CONTRIBUTIONS

Dr. Symmonds: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Dr. Kuker: analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Dr. G. Schulz: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, study supervision.

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### DISCLOSURE

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### REFERENCES

1. Hart C, Kinney MO, McCarron MO. Posterior reversible encephalopathy syndrome and oral methotrexate. *Clin Neurol Neurosurg* 2012;114:725–727.
2. Marcon G, Giovagnoli AR, Mangiapane P, Erbetta A, Tagliavini F, Girotti F. Regression of chronic posterior leukoencephalopathy after stop of methotrexate treatment. *Neurol Sci* 2009;30:375–378.
3. Vezmar S, Becker A, Bode U, Jaehde U. Biochemical and clinical aspects of methotrexate neurotoxicity. *Chemotherapy* 2003;49:92–104.
4. Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. *Am J Neuroradiol* 2008;29:1036–1042.
5. Sommer WH, Ganiere V, Gachoud D, et al. Neurological and pulmonary adverse effects of subcutaneous methotrexate therapy. *Scand J Rheumatol* 2008;37:306–309.
6. Raghavendra S, Nair MD, Chemmanam T, Krishnamoorthy T, Radhakrishnan VV, Kuruvilla A. Disseminated necrotizing leukoencephalopathy following low-dose oral methotrexate: disseminated necrotizing leukoencephalopathy. *Eur J Neurol* 2007;14:309–314.
7. Shah-Khan FM, Pinedo D, Shah P. Reversible posterior leukoencephalopathy syndrome and anti-neoplastic agents: a review. *Oncol Rev* 2008;1:152–161.
8. Renard D, Westhovens R, Vandenbussche E, Vandenbergh R. Reversible posterior leukoencephalopathy during oral treatment with methotrexate. *J Neurol* 2004;251:226–228.
9. González-Suárez I, Aguilar-Amat MJ, Trigueros M, Borobia AM, Cruz A, Arpa J. Leukoencephalopathy due to oral methotrexate. *Cerebellum* 2014;13:178–183.
10. Lallana EC, Fadul CE. Toxicities of immunosuppressive treatment of autoimmune neurologic diseases. *Curr Neuroparmacol* 2011;9:468.

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