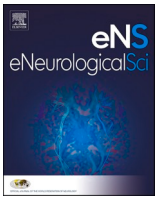
eNeurologicalSci 23 (2021) 100328

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: www.elsevier.com/locate/ensci



Letter to the Editor

D-penicillamine in Wilson's disease; recognizing the transition from benefit to harm

Dear Editor,

A 50-year-old Indian male was referred to us with severe atraumatic left calf pain of 8 months duration. This was associated with increasing lethargy, weight loss and progressive limb weakness. On clinical examination, there was generalized tenderness over bilateral calf and arm muscles and proximal weakness of his upper and lower limbs with hyperreflexia. He also had an erythematous, maculopapular rash over his chest and thighs.

He had a history of Wilson's disease, diagnosed at the age of 12 when he presented with deteriorating academic performance and involuntary movements of the left hand and tongue. On examination then, he was noted to have bilateral dysdiadochokinesia, generalized hypertonia and chorea. Kayser-Fleischer rings were present and he was found to have low serum caeruloplasmin with increased 24 h urinary copper levels. He had been on treatment with D-penicillamine since his diagnosis and was followed up with 24 h urinary copper levels, liver function tests and liver imaging. Neurological examination was subsequently normal, with no cerebellar signs or parkinsonism.

At the current presentation, his serum creatine kinase was normal but aldolase was mildly elevated at 9.9 U/L (normal range: 0–7.6 U/L). Inflammatory markers were also elevated. Autoimmune serology demonstrated raised double-stranded DNA antibodies (120 IU/mL, normal range: <100 IU/mL), elevated anti-ribonuclear protein and anti-Smith titres (2.2, positive: >2.0), as well as anti-PR3 positivity (83 U/mL, normal range: <20 U/mL). Antinuclear antibody and myositis panel were negative, but C3 was low at 78 mg/dL (normal range: 85–185 mg/dL). Proteinuria was present with total urine protein of 0.5 g/day. Caeruloplasmin and serum and urinary copper were within normal limits.

MRI of the left lower limb showed increased STIR-signal in all compartments. MRI of the whole spine also demonstrated enhancement in the paravertebral muscles. Electrodiagnostics revealed asymmetric sensory motor axonal peripheral neuropathy, suggestive of vasculitic neuropathy. There was also central nervous system involvement. MRI brain showed new cortical and subcortical T2/FLAIR hyperintense foci (Fig. 1A). CT angiography of the intracranial vessels demonstrated beading of medium-sized intracranial vessels. Cerebrospinal fluid analysis revealed elevated protein at 1.19 g/L (normal range: 0.1–0.4 g/L) without cellularity and negative microbiological studies.

A skin biopsy showed medium vessel vasculitis (Fig. 2). He was diagnosed with drug-induced systemic vasculitis likely secondary to D-pencillamine use, with cumulative manifestations of myositis, central nervous system involvement, proteinuria, vasculitic rash and constitutional features.

D-pencillamine was discontinued and the patient was continued on monotherapy with zinc. He was treated with high dose glucocorticoids and intravenous cyclophosphamide. There was improvement in symptoms, muscle strength, inflammatory markers and MRI lesions (Fig. 1B) one month after starting treatment.

D-penicillamine induced vasculitis can occur from a few months up till many years after treatment has been initiated, without preceding adverse events [1,2]. Patients commonly present with cutaneous, pulmonary and renal manifestations such as crescenteric glomerulonephritis [1–3]. We describe a patent who had the rare and delayed complication of both central and peripheral nervous system dysfunction from D-penicillamine induced vasculitis, along with systemic manifestations.

Our patient had myositis, a more common neurological adverse effect [4], and vasculitic neuropathy. He also had inflammatory CSF and multiple T2/FLAIR hyperintense lesions on magnetic resonance imaging of the brain. Other known D- penicillamine induced conditions include myasthenia gravis and optic neuropathy [5–7]. The exact mechanism of D-penicillamine induced vasculitis is still unclear but has been postulated to involve both cell-mediated and humoral immunity [1–3]. Potentially, this could be due to antigen/antibody interactions, impairment of the complement cascade in disposing of immune complexes, or cross-reactivity between drug metabolites and cytoplasmic antigens [1].

A potential differential diagnosis in this case is primary ANCA-associated vasculitis, which has similar clinical manifestations to drug-induced vasculitis. However, a multiplicity of positive antibodies, such as in this case, would be more consistent with a drug-induced aetiology of vasculitis [8]. Cessation of the offending drug is essential. Although the course of drug-induced vasculitis is usually milder than that of primary vasculitides, treatment may involve aggressive immunosuppression such as pulsed methylprednisolone and cyclophosphamide when severe organ involvement is present [8]. Improvement has been described within days to months of discontinuation of D-penicillamine [1]. Clinicians should remain vigilant in monitoring for adverse effects of D-penicillamine, regardless of dose or duration of treatment.

https://doi.org/10.1016/j.ensci.2021.100328
Received 30 November 2020; Received in revised form 12 January 2021; Accepted 2 February 2021
Available online 15 February 2021

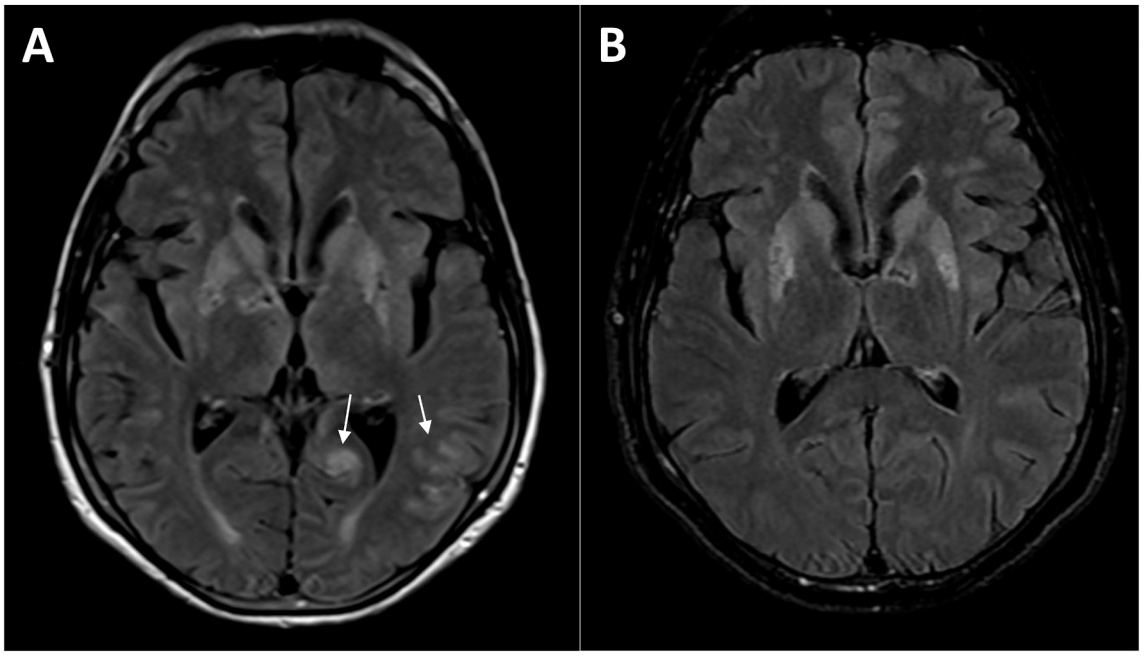


Fig. 1. Magnetic resonance imaging of the brain showing subcortical T2 hyperintense lesions (arrows) at presentation (1A) and improvement 1 month post treatment (1B). The T2 basal ganglia hyperintensities present are likely secondary to Wilson's disease.

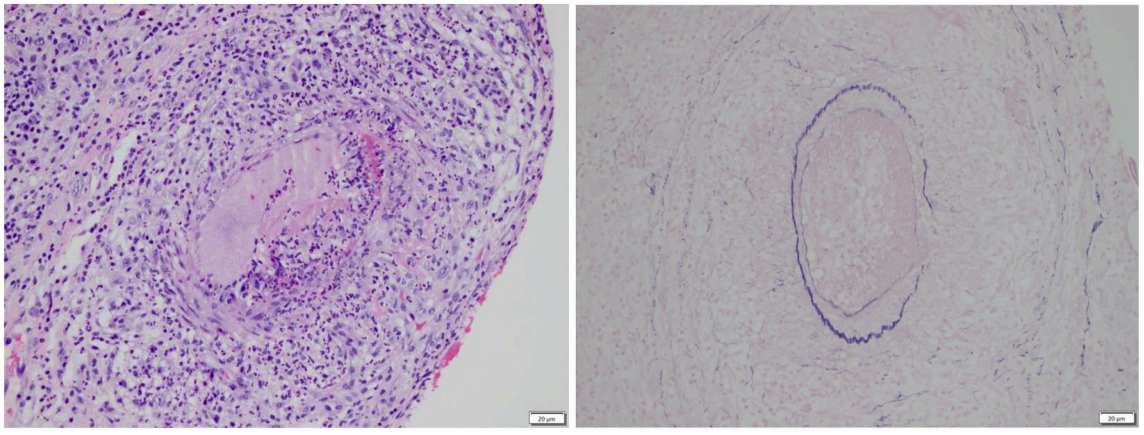


Fig. 2. Skin biopsy (haematoxylin and eosin stain, magnification x 100) (A) showing features of vasculitis involving a medium-sized artery within the deep dermis - extravasation of red blood cells, karyorrhexis, neutrophils extravasation, and fibrinoid necrosis of the blood vessel wall. Miller's elastic van Gieson stain (magnification x200) (B) highlights the internal elastic lamina within the arterial wall, which is partially disrupted by the inflammation and necrosis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Appendix A. Authors

Name	Location	Contribution
Yihui Goh, MRCP (UK)	Division of Neurology, Department of Medicine, National University Health System, Singapore	Conception, organization and execution of the research project; writing of the first draft and the review and critique of the manuscript
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Name	Location	Contribution
		Conception, organization and execution of the research project; review and critique of the manuscript
Justin SB Wong, FRCPath	Department of Pathology, National University Hospital	Conception, organization and execution of the research project; review and critique of the manuscript

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