Sequential strokes in a hyperacute stroke unit

Jeban Ganesalingam1, Sandeep Buddha2, Anoma L Carlton-Jones3 and Richard Nicholas1

1Department of Neurology, Imperial College Healthcare Trust, London W6 8RF, UK
2Department of Stroke Medicine, Imperial College Healthcare Trust, London W6 8RF, UK
3Department of Radiology, Imperial College Healthcare Trust, London W6 8RF, UK

Corresponding author: Richard Nicholas. Email: richard.nicholas@imperial.nhs.uk

Lesson

Vasculitis is a rare, but treatable condition that can present to hyperacute stroke units. Thrombolysis does not treat the underlying pathology, and a rapidly evolving clinical picture drives clinical decision often before all the investigation results are available.

Keywords

stroke, vasculitis, antiphospholipid syndrome

Summary of case

A 63-year-old right-handed woman presented to the hyperacute stroke units (HASUs) 1½ h after developing a right-sided weakness. Twenty-four hours earlier, she had experienced a similar event lasting 30 min. She had a history of hypertension, hypercholesterolaemia, diabetes mellitus and ischaemic heart disease and was taking aspirin 75 mg. Her National Institute of Health Stroke Scale (NIHSS) score was 5. Blood pressure was 137/67 mmHg, glucose was 8.1 mmol/L and a plain computerised tomography (CT) was normal. In the absence of contraindications to thrombolysis, intravenous alteplase was given 2¼ h after symptom onset.

Twenty-four hours later, her NIHSS score was 2 and a post thrombolysis CT remained normal, but magnetic resonance imaging (MRI) of the brain demonstrated multiple acute infarcts in multiple territories. Given the differential diagnosis of cardioembolic/watershed infarcts, infective endocarditis or vasculitis, further investigations were completed. These showed an Erythrocyte Sedimentation Rate (ESR) of 36 and a positive Anti-nuclear antigen (ANA) (1:160; fine speckled pattern). Full blood count (FBC), C-reactive protein (CRP), cholesterol, Anti-nuclear cytoplasmic antibody (ANCA), double-stranded DNA (dsDNA), complement, rheumatoid factor, human immunodeficiency virus and hepatitis serology were unremarkable. Lumbar puncture revealed a Cerebrospinal fluid (CSF) protein of 0.53 g/L, CSF glucose was 6.8 mmol/L (serum glucose 13 mmol/L) and White cell count (WCC) 4. A trans-thoracic echocardiogram reviewed by a consultant cardiologist was normal, carotid Dopplers showed no significant stenosis, and subsequently a seven-day event recorder was normal. CT angiogram showed a modest stenosis in multiple territories (Figure 1). She was diagnosed with probable CNS vasculitis and was commenced on 1 g intravenous methylprednisolone daily for three days followed by oral prednisolone 60 mg daily and aspirin 300 mg daily.

One week later, the thrombophilia screen revealed a positive lupus anticoagulant, raised anticardiolipin antibodies and raised anti-beta2glycoprotein suggesting antiphospholipid syndrome (APL). Anticoagulation was started, and aspirin was discontinued once the INR was 2–3. A catheter angiogram demonstrated multiple areas of short segment vascular narrowing consistent with vasculitis (Figure 2).

During rehabilitation, the patient’s cognition deteriorated, and a repeat MRI demonstrated a new left cerebellar infarct. The target INR was increased to 3–4, and cyclophosphamide was given with the aim of inducing long-term remission, but after one dose and while on oral prednisolone 40 mg daily, she developed a left-sided weakness. She was not thrombolysed as INR > 2. MRI revealed acute right Middle cerebral artery (MCA) infarcts, and she received a further three doses of intravenous methylprednisolone 1 g daily followed by oral prednisolone 60 mg daily and also rituximab. Warfarin was replaced with unfractionated heparin due to risk of haemorrhagic transformation with planned reintroduction after two weeks. Mycophenolate mofetil (MMF) was initiated, and the patient remains stable on this regimen.

Discussion

Here, we present a case of probable cerebral vasculitis with coexisting APL. There are four case reports of biopsy-proven CNS vasculitis with coexisting APL2 though two had in addition systemic lupus erythematosus,3,4 and it has been proposed that the vasculitic damage induces exposure of phospholipids in the outer membrane of endothelium, leading to
production of antibodies. The developing clinical picture and subsequent clinical stabilisation prevented us getting biopsy confirmation of the diagnosis.

Due to its rarity, there are no evidence-based guidelines on treating CNS vasculitis and no data in the context of coexisting APL, but immunosuppression is used in systemic vasculitis and a shared treatment approach. In vasculitis, initially oral prednisolone 1 mg/kg/day is used or in severe cases as here high-dose intravenous methylprednisolone followed by oral prednisolone. Despite this therapy, further infarcts developed either due to inadequate intensity of therapy or lack of time for it to take effect.

At this point, one could have waited, but aiming for longer term control, intravenous cyclophosphamide was commenced. There is no difference between modes of cyclophosphamide administration, oral or intravenous, in rates of remission or time to remission. Intravenous therapy delivers lower total dose with a lower likelihood of leucopenia; however, long-term follow-up indicates a potential higher relapse rate. Plasma exchange was an alternative approach but has many complications when used longer term, and its use was complicated here by the fact the patient was on warfarin.

Given the continued disease activity after a single infusion of cyclophosphamide, the dilemma was whether to give it time to act or to pursue an alternative. Rituximab has demonstrated non-inferiority compared to cyclophosphamide, furthermore, in relapsing disease, rituximab was superior to cyclophosphamide. This drove the decision to proceed to rituximab.

Oral immunosuppression was commenced as there is a lower risk of treatment-related toxicities with early transition to maintenance therapy, and azathioprine has superior efficacy to MMF and similar efficacy to methotrexate in maintaining remission. In this case,
MMF was chosen as it is quicker to titrate up to achieve a therapeutic level compared to azathioprine and methotrexate.

**Conclusion**

This challenging case highlights the real-time evolution of probable cerebral vasculitis and how the developing symptomatology drives clinical decision making in the absence of complete information.

Initial treatment with alteplase was correct with multiple vascular risk factors pointing to an embolic event, but the results of the emerging investigations suggested an underlying diagnosis. Once identified, this was treated with steroids, but disease evolution necessitated the use of cyclophosphamide, but again ongoing neurological injury led to revision of treatment plans before the potential benefits of cyclophosphamide could be realised. Changing treatment ultimately resulted in clinical stabilisation on rituximab, an emerging therapy for vasculitis and MMF.

The emergence of HASUs in the context of a changing National Health Service emergency referral structure has meant that a wide variety of pathologies are likely to present to them. This case highlights the importance of investigating for the underlying causes of a vascular event. This is especially important if such diagnoses are preventable with alternative therapies and even more so if the clinical situation is deteriorating as here.

**Declarations**

**Competing interests:** None declared

**Funding:** None declared

**Ethical approval:** Written informed consent for publications was obtained from the patient.

**Guarantor:** RN

**Contributorship:** All authors were involved in the conception, drafting, revision and final approval of the article.

**Acknowledgements:** None

**Provenance:** Not commissioned; peer-reviewed by Aron Chakera

**References**

1. Hajj-Ali RA and Calabrese LH. Diagnosis and classification of central nervous system vasculitis. *J Autoimmun* 2014; 48–49: 149–152.
2. Quintero M, Mirza N, Chang H and Perl A. Antiphospholipid antibody syndrome associated with primary angiitis of the central nervous system: report of two biopsy cases. *Ann Rheum Dis* 2006; 65: 408–409.
3. San Pedro EC and Mountz JM. CNS vasculitis in systemic lupus erythematosus complicated by antiphospholipid antibody syndrome: temporal evaluation of stroke by repeated Te-99m HMPAO SPECT. *Clin Nucl Med* 1998; 23: 709–710.
4. Stone JH. Antiphospholipid syndrome. In: Klippel JH, Stone JH, Crofford LJ, and White PH. *Primer on the Rheumatic Diseases*. Atlanta: Arthritis Foundation, 2001, pp. 423–426.
5. Espinosa G, Tassies D, Font J, Munoz-Rodriguez FJ, Cervera R, Ordinas A, et al. Antiphospholipid antibodies and thrombophilic factors in giant cell arteritis. *Semin Arthritis Rheum* 2001; 31: 12–20.
6. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum* 2005; 52: 2461–2469.
7. de Groot K, Harper L, Jayne DR, Flores Suarez LF, Gregorini G, Gross WL, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med* 2009; 150: 670–680.
8. Hiemstra TF, Walsh M, Mahr A, Savage CO, de Groot K, Harper L, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA* 2010; 304: 2381–2388.
9. Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med* 2008; 359: 2790–2803.