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CASE REPORT

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Ischaemic stroke as the first presentation of antineutrophilic cytoplasmic autoantibody-associated vasculitis

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Abstract

The diagnosis of antineutrophil cytoplasmic autoantibody-associated vasculitis in first-episode strokes is particularly challenging, especially in patients lacking features of systemic vasculitis. We present the case of a 71-year-old woman with positive myeloperoxidase antineutrophil cytoplasmic antibodies and negative proteinase 3 autoantibodies. The patient presented with 1 week history of pyramidal weakness in both upper and lower limbs, hyperreflexia, and clonus. Magnetic resonance imaging of the brain demonstrated widespread bihemispheric cortical and deep white matter acute infarcts, which are consistent with features of stroke secondary to vasculitis. Myeloperoxidase antineutrophilic cytoplasmic autoantibody-positive vasculitis diseases are more commonly associated with renal, pulmonary, and cutaneous manifestations; however, in our patient, the central nervous system features predominated. This case highlights the challenges of diagnosing primary central nervous system vasculitis, in this case, an atypical myeloperoxidase antineutrophilic cytoplasmic autoantibody-positive disease without the classical disease course and clinical signs.

KEYWORDS

ANCA, myeloperoxidase antineutrophilic cytoplasmic autoantibody, proteinase 3 autoantibodies, stroke, vasculitis

1 | INTRODUCTION

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) is a rare pauci-immune small-vessel necrotizing vasculitis. This disorder encompasses three subsyndromes: eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA), and granulomatosis with polyangiitis (GPA).[1,2] The disease processes are multisystemic, and the presenting symptoms may include constitutional symptoms.[3] The ANCA serotypes myeloperoxidase antineutrophil cytoplasmic autoantibody (MPO-ANCA) and proteinase 3 antineutrophil cytoplasmic autoantibody (PR3-ANCA) play a crucial role in AAV.[3]

Central nervous system (CNS) involvement in AAV is uncommon, occurring in <15% of individuals with AAV.[3] There are only a few reported clinical studies on the association of stroke with AAV.[4] We therefore present a patient

with AAV and CNS involvement as the initial disease manifestation to aid recognition of this important clinical entity requiring time-critical management.

2 | CASE PRESENTATION/EXAMINATION

Ms B was an independent 71-year-old woman who presented with a four-day history of chest pain, lethargy, and upper and lower limb weakness. A subsequent brain computed tomography (CT) was deemed normal, and her chest pain was initially thought to be attributed to gastroesophageal reflux disease. However, 2 days later, her chest pain worsened, and there was progressive weakness in all four limbs. There were no headaches or visual changes, and she denied any muscle aches or any fevers. Her past medical history included hypertension, osteoarthritis, fibromyalgia, and diverticulitis. She was a lifelong nonsmoker and had no other cardiovascular risk factors other than a brother who had ischaemic heart disease in his 50s. Her regular medications included esomeprazole, pregabalin, cholecalciferol, and calcium tablets.

On examination, Ms B's Glasgow Coma Scale was 15, and she required a two-wheeled frame to ambulate. She was dysarthric with left-sided tongue weakness. There was severe weakness in all four limbs, hyperreflexia, and bilateral upgoing plantar reflexes. Cardiovascular, respiratory, and abdominal examinations were unremarkable.

3 | INVESTIGATION/TREATMENT

Renal and liver function tests were normal, but full blood examination revealed eosinophilia (1800 cells/μl [reference range:<600 cells/μl]). Magnetic resonance imaging of the brain (MRI) revealed widespread bilateral hemispheric cortical and deep white matter acute infarcts through a watershed territory with associated microhaemorrhage (Figure 1). There was no evidence of intracranial or extracranial vessel occlusion. Whole spine MRI was unremarkable.

Antiphospholipid antibody screen, extractable nuclear antigens (ENA), and viral serology (cytomegalovirus, Epstein–Barr virus, hepatitis B and C, and human immunodeficiency virus) were negative. She had negative strongyloides antibody and undetectable fecal ova, cysts, and parasites.

A vasculitic screen revealed an elevated C-reactive protein (CRP) (69 mg/L), positive MPO-ANCA (44 IU/ml [reference range: <3 IU/ml]) but a negative PR3-ANCA. The remaining vasculitic screen including erythrocyte sedimentation rate (ESR) was unremarkable. Her urinalysis and urine chemistry showed only a few red cells and no glomerular red cells while her normal urinary protein-to-creatinine ratio negated the need for a renal biopsy.

She had an elevated Immunoglobulin E (IgE) level (180 kU/L [reference range: 7–16.5 kU/L]), which initially raised suspicion for hypereosinophilic syndrome. A subsequent gastroscopy showed no evidence of eosinophilic gastritis. Similarly, a bone marrow aspiration and trephine biopsy (BMAT) showed mild eosinophilia with no underlying lymphoproliferative, mastocytosis, or myeloproliferative disorders. Despite the raised IgE, she did not meet the criteria for hypereosinophilic syndrome (defined as an absolute eosinophil count >1500 cells/microgL on two blood tests done at least 1 month apart with or without tissue hypereosinophilia confirmation).[5]

Investigation of Ms B's chest pain included a normal electrocardiogram, an elevated troponin (429 ng/L [reference range:<14 ng/L]), and D-dimer (1.85 mg/L [reference range: <0.5 mg/L]). CT pulmonary angiogram did not demonstrate a pulmonary embolism, and she had patent coronary arteries on coronary angiogram. Her transthoracic echocardiogram was normal with good systolic function and no evidence of intracardiac shunts (negative

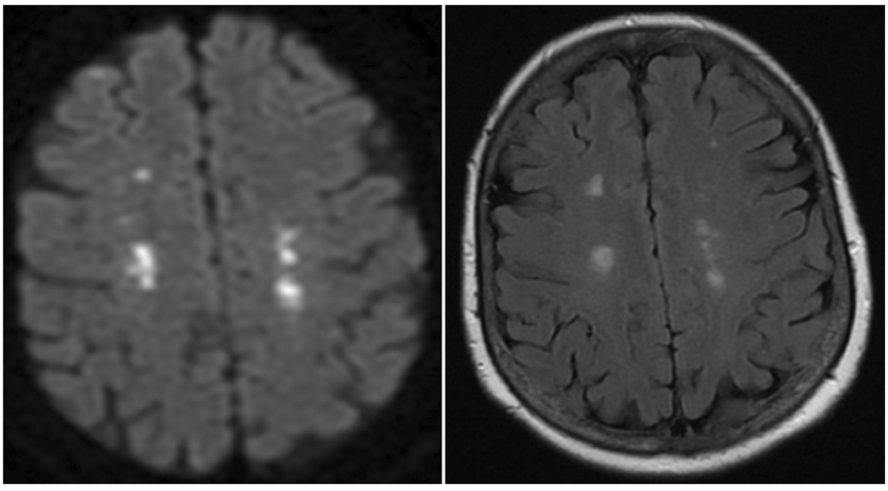

FIGURE 1 MRI brain (Left panel—DWI; Right panel—FLAIR): bihemispheric deep white matter infarcts. Cortical infarctions and microhaemorrhages (not shown) were also present. MRI, magnetic resonance imaging. DWI, diffusion-weighted imaging; FLAIR, fluid attenuated inversion recovery.

bubble study) thereby ruling out a potential cardioembolic source for her multifocal infarcts. Cardiac MRI was normal, as was the CT of the chest, abdomen, and pelvis. A 48-hour telemetry failed to demonstrate any arrhythmias such as atrial fibrillation, which would suggest an embolic cause for her stroke.

Our patient had multifocal brain infarctions associated with eosinophilia secondary to AAV. In addition, the chest pain and associated troponin rise suggest cardiac involvement despite normal cardiac MRI, angiogram, and echocardiogram. Although there was MPO-ANCA positivity, she had no other systemic features of ANCA vasculitis such as renal or pulmonary involvement at the time of admission or diagnosis.

4 | OUTCOME/FOLLOW-UP

Ms B was commenced on intravenous methylprednisolone (1 g daily) for 3 days, followed by oral prednisolone (50 mg daily) and oral cyclophosphamide (50 mg daily) with prophylactic antibiotic coverage. Prednisolone was gradually tapered (5 mg daily), and cyclophosphamide was reduced and eventually switched to azathioprine due to ongoing cytopenia. She was initially given 50 mg of azathioprine and then uptitrated to 100 mg daily. Aspirin and atorvastatin were prescribed for stroke prevention. The patient continued to improve, and she was able to ambulate independently after 2 weeks in rehabilitation. A repeat MRI brain 4 months after discharge from rehabilitation showed significant improvement in appearances of the corona radiata when compared to the previous study with no evidence of any new infarction or focal lesions. She is being regularly monitored in the outpatient neurology and rheumatology clinics to ensure adequate response to treatment and to address any adverse effects of the medication regimen. For the past 12 months, Ms B had no constitutional symptoms and is tolerating the medication regimen; a bone density scan is being considered. Renal function tests and routine chest imaging are regularly monitored for extra-CNS manifestations; all of which have been negative to date.

5 | DISCUSSION/CONCLUSION

Vasculitis is a rare cause of stroke and therefore is easily missed. Untreated, the risk of recurrent stroke is extremely high[6,7]; thus, early diagnosis and treatment are mandatory to minimize[8] disability and death. Clinical suspicion of CNS vasculitis should be triggered by the presence of multi-territory infarctions, often accompanied by microhemorrhages, in individuals lacking conventional vascular risk factors, or in those with an unidentified cause for their stroke. Distal penetrating vessels are affected predominantly in AAV infarcts typically presenting as isolated or multiple lesions in the white matter as observed with our patient.[3]

Central nervous system vasculitis patients also have an increased risk of haemorrhagic transformation after reperfusion therapy.[3] A case study by Fattahi et al.[8] reported a presentation of intracranial hemorrhage following thrombolysis in a patient with known EGPA. The authors stated that although EGPA has never been considered an absolute contraindication to thrombolysis, it should be used with caution in the absence of other risk factors for stroke.[8]

It has been proposed that AAV affects the CNS by one of the following mechanisms: inflammation or obstruction of small- to medium-sized cerebral vessels granuloma formation within the CNS and compression due to granulomatous infiltration of adjacent structures[3] such as the pituitary gland and meninges. The pathophysiology of intracranial hemorrhage in AAV remains poorly understood. Following a cohort of patients with primary CNS vasculitis presenting with intracranial hemorrhage, Salvarani et al. hypothesized that intracranial hemorrhage may be a result of necrotizing vasculitis resulting in the weakening of the blood vessel wall. This in turn increases the risk of blood vessel rupture and aneurysmal dilatation.[9]

Despite the usual multi-system involvement seen in AAV, our patient manifested with ischaemic stroke and possible cardiovascular involvement. Neurological manifestations more commonly include peripheral neuropathy (e.g., mononeuritis multiplex) and headaches, and less commonly, ischemic infarction, intracranial haemorrhagic, ischemic strokes, encephalopathy, and seizures.[3,10]

Uppal et al.[11] described a similar case where a patient without any risk factors was diagnosed with AAV following a first-episode ischaemic stroke and developed haemorrhagic transformation after reperfusion therapy. Similar to our case, the patient did not have any other organ involvement; however, the stroke was preceded by a one-month history of fevers,[12] which was not seen in our patient. Bares et al.[13] meanwhile presented a case of a patient who was diagnosed with GPA following a first-episode ischemic stroke and similar to our case, the patient did not have any organ involvement on admission. This patient, however, developed acute kidney failure and constitutional symptoms 1 month after being diagnosed with GPA,[13] which is more expected with the trajectory of this disease process. By contrast, Taraschenko et al.[14] described a patient with a lateral medullary ischemic stroke secondary to GPA who at the time of presentation was also found to have diffuse necrotizing crescentic glomerulonephritis. Their case demonstrated a more typical

presentation of AAV with multi-organ involvement as opposed to our subject who did not have widespread organ involvement.

The diagnosis of vasculitis is based on multiple features: pattern of organ injury, histopathology, size of vessels involved, and characteristic findings on imaging.[15] A thorough history and physical examination are warranted for all patients suspected of vasculitis. In addition to routine blood tests (including elevated CRP and ESR), specific laboratory investigations aid in the identification of AAV. ANCA directed against either PR3 or MPO is highly specific (>95%) to AAV.[15]

In most cases, a clear temporal relationship between EGPA, asthma, and eosinophilia with the presence of MPO-ANCA autoantibodies is seen.[16] These individuals usually have a history of allergies and show an increased frequency of renal, lung, and CNS involvement.[17] EGPA usually develops in three phases: allergic phase (e.g., asthma, allergic rhinitis), eosinophilic phase, and vasculitic phase (e.g., peripheral neuropathy).[18] Interestingly, our patient had no history of asthma or allergies nor did she have any involvement with other organs. Given our patient had no tissue that could be biopsied, we cannot confirm the subtype of her AAV. The diagnosis of EGPA can be established using the Lanham Criteria, which encompasses asthma, peak blood eosinophilia of more than 1500 cells/μl, and systemic vasculitis involving two or more extra-pulmonary organs. All three criteria must be observed. Our patient, who did not suffer from asthma, therefore fails to meet these criteria for the diagnosis of EGPA.[19]

Standard treatment of AAV includes three to 6 months of high-dose glucocorticoids and cyclophosphamide (either oral or intravenous) to induce remission.[20] Azathioprine or methotrexate are used thereafter to maintain remission whilst glucocorticoids are gradually reduced and withdrawn.[20] Recently, rituximab has been found to induce remission in AAV patients[20]; however, our patient was commenced on azathioprine, which has maintained remission.

Our case gives an important reminder that acute ischemic stroke can be the presenting manifestation of AAV.

AUTHOR CONTRIBUTIONS

John Chuan Nguyen Tran conceived, designed the case study, and wrote the abstract, introduction examination, investigations, and treatment. Joshua Haron Abasszade completed the discussion and learning points. Yew Li Dang edited and provided revision of all aspects of the manuscript. Douglas Crompton edited and provided revision of all aspects of the manuscript.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author

ETHICAL APPROVAL

Written consent was obtained from the patient for publication of this case report and any accompanying images overseen by the Northern Health Ethics & Research Governance. This study protocol was reviewed, and the need for approval was waived by the Northern Health Ethics & Research Governance.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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