Case report

Cerebral vasculitis in rheumatoid arthritis

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Case

This case is of a 52-year-old lady, who presented with a 7-day history of headache associated with nausea and vomiting. On physical examination, she was afebrile, and neurological examination was unremarkable. She had a history of seropositive rheumatoid arthritis diagnosed 20 years previously. During this time, she had been treated with multiple anti-rheumatic drugs, including Gold, Sulphasalazine, Methotrexate, Penicillamine and Leflunomide, in addition to several arthroplasties and arthrodeses. No extra-articular manifestations of rheumatoid disease were documented since diagnosis.

Laboratory investigations on admission showed haemoglobin of 135 g/l, white cell count of 9.7 × 10⁹/l, platelets of 171 × 10⁹/l, C-reactive protein of <5 mg/l and erythrocyte sedimentation rate of 36 mm/h. A CT scan of her head was reported as a normal unenhanced CT brain (Figure 1A), with no focal infarct or haemorrhage. She was discharged home the following day, her headache improved, the provisional diagnosis being migraine. She re-presented 7 days later with the same three symptoms of headache, nausea and vomiting, in addition to a new right visual field defect, ataxia and expressive dysphasia. A further CT scan revealed appearances consistent with left occipital infarction (Figure 1B). High-dose oral glucocorticoids (1 mg/kg) were commenced as it was felt that temporal arteritis could not be excluded clinically. Seven days later, and with no clinical improvement, she suffered a recurrence of symptoms with sudden onset of left-sided weakness, left visual field defect and confusion. CT scanning revealed multiple large, new right parieto-occipital, right high frontal and smaller left centrum semiovale non-haemorrhagic infarctions. In addition, the previously noted left occipital infarction was noted to be larger in size (Figure 1C).

Cerebrospinal fluid analysis showed normal appearance, white blood cells 5 × 10⁶/l and red blood cells 2 × 10⁶/l; glucose was mildly elevated at 4.8 mmol/l and total protein was 0.21 g/l with no xanthochromia. No oligoclonal bands were seen. Gram staining and subsequent cultures were both negative.

HIV testing and syphilis serology were negative; serial blood cultures showed no growth. ANCA and ENA were negative. ANA titre was positive at 1/80; C3 and C4 levels were normal. Anti-dsDNA was borderline positive on two occasions reading at a maximum of 18.7 IU/ml (normal range 0–15). Anticardiolipin and lupus anticoagulant were

Figure 1. (A–C) Serial CT scanning showing progressive infarcts.
Negative. Cyclic citrullinated peptide was 190 U/ml (normal range 0–3).

Cerebral angiography 19 days following initial presentation revealed widespread proximal cerebral vessel stenosis bilaterally, with beading and stenosis of distal anterior cerebral arteries (Figure 2). Wedge perfusion defects in the capillary phase were seen in corresponding territories to those regions of occipital infarct noted on CT scanning. MRI with Gadolinium enhancement demonstrated extensive vascular beading and stenosis, particularly prominent in the anterior circulation.

Biopsies of cerebral parenchyma and dura mater showed lymphocytic infiltration and focal vessel wall disruption consistent with a small vessel leukocytoclastic vasculitis (Figure 3). Gram and Grocott fungal staining was negative, with no evidence of an infective process.

Cerebral vasculitis was diagnosed, and treatment was initiated with three fortnightly pulses of IV Cyclophosphamide therapy (15 mg/kg) followed by a further three 3-weekly pulses, all accompanied by Methylprednisolone 500 mg. Oral prednisolone was reduced by 5 mg with each pulse treatment followed by Azathioprine 25 mg once daily, uptitrated to 25 mg three times daily, dosed according to her TPMT levels, which were low at 35 mU/l (normal range 68–150).

Although no further neurological event occurred, her neurological features have shown little improvement clinically, with persistent left-sided hemiparesis. She has made limited progress with physiotherapy. Her visual acuity has shown no improvement, with persistent bilateral hemianopia, complete on the left side, less extensively on the right. Visual acuity was measured at N36 bilaterally, and she is registered blind. Primary retinal pathology was ruled out.

Four months after her initial presentation, she remained an inpatient under stroke rehabilitation and suffered a recurrence of the original headache symptoms without further neurological deficit. Repeat CT scanning showed further evolution of the original occipital infarcts with an extensive area of right frontoparietal hypodensity also consistent with infarct evolution. No lesion was identified which could be reasonably attributed to a progressive vasculitic process.

She remained an inpatient under stroke rehabilitation for 10 months following the initial infarcts, whereby she was discharged home with no further problems to date. She continued treatment with Azathioprine and followed a reducing regime of prednisolone. Baclofen was prescribed for hypertonia. Her visual defect is likely to persist, despite treatment due to extensive cerebral infarct, and the possibility of deterioration cannot be ruled out.

Discussion

RA-associated cerebral vasculitis is the most likely culprit for neurological symptoms in our case. RA cerebral vasculitis is typically a small vessel necrotizing vasculitis characterized microscopically by lymphocytic infiltration and fibrinoid deposition and necrosis of all vessel wall layers, resulting in the radiological changes of beading and stenosis, which in turn give rise to haemorrhagic and ischaemic phenomena.1 Presentations are highly variable, depending entirely on the vessels and territories involved. Most commonly seen are headache, stroke and encephalopathy but myelopathies, cranial nerve palsies, dementia and seizures are also recognized.1,2

Figure 2. Cerebral angiography, demonstrating arterial beading and stenosis.

Figure 3. Cerebral biopsy, demonstrating a small vessel with inflammatory infiltration of the vessel wall (black arrow) as seen in a leukocytoclastic vasculitis, leading to destruction of the form of the vessel wall.
Methods used in diagnosis are highly variable, particularly regarding the importance placed upon cerebral angiography. CT scanning is useful only in detection of cerebrovascular sequelae of cerebral vasculitis, not in its diagnosis. Laboratory tests may confirm an underlying inflammatory process and are required to exclude other differentials such as infective aetiologies. Cerebrospinal fluid analysis and MRI (specifically FLAIR weighted MRI) have often been key in diagnosis of cerebral vasculitis in the literature, however, were seen to add little in the case presented (although FLAIR MRI was not available).

One recent case reported good treatment outcome, in the absence of histopathology, where the diagnosis was suspected on CSF analysis and imaging studies alone. However, in the case presented, it was characteristic findings on cerebral angiography together with brain biopsy, which provided evidence of the aetiology. Of note, cerebral angiography has long been shown to lack both sensitivity and specificity in addition to exhibiting variable correlation with histopathological findings. None of the investigations employed here has high sensitivity or specificity for RA-associated cerebral vasculitis, all liable to show positive results to an array of infective, inflammatory and neoplastic aetiologies.

As is the case regarding diagnosis, no consensus has been reached concerning treatment of the condition. Pons et al. carried out a recent literature review detailing the diagnosis, treatment and outcomes for cases of rheumatoid associated vasculitis involving the cerebral parenchyma dating from 1951. It was seen that prior to 2006, published cases received solely glucocorticoids and had exclusively fatal outcomes. Two cases since 2006 reported better outcomes with combination glucocorticoid and cyclophosphamide therapy, their own case achieving good symptom remission with early administration of IV glucocorticoid, with mortality of unrelated cause at three years with no evidence of ongoing vasculitis, cerebral or systemic, at post-mortem. Mrabet et al present a further case where suspected RA cerebral vasculitis was treated with monthly IV glucocorticoids alongside pulsed cyclophosphamide with good 5 month outcome, in the absence of histopathological diagnosis.

Conflict of interest: None declared.

References