Case Report
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When No More Investigations are Left: A Probable Case of Primary Angiitis of the Central Nervous System

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Abstract

Primary angiitis of the CNS (PACNS) is a distinct form of cerebral vasculitis, the former being confined to the central nervous system (CNS) with no systemic involvement. Diagnosing PACNS is challenging due to its varied presentation and rarity. We describe a case highly suggestive of PACNS which despite extensive investigation could not be confirmed even on histology but responded to immunosuppression. We present a 69-year old man who presented to the emergency department (ED) with acute confusion. Initial magnetic resonance (MR) imaging of the head had shown ischaemic infarcts and haemorrhages. Cerebrospinal fluid (CSF) analysis and serological work-up had ruled out a systemic vasculitis and an infectious disease to account for the presentation. Computerised tomography (CT) angiography nor digital subtraction angiography had reported any evidence of vasculopathy. The brain biopsy had failed to show features of vasculitis. Although the diagnosis of PACNS was not definitive, immunotherapy was commenced. A significant cognitive improvement was noted and correlated by resolution of the initial imaging changes.

Keywords: Primary angiitis of the CNS • Cerebral vasculitis • Angiography • Immunotherapy • Cyclophosphamide • Vasculopathy

Introduction

PACNS is a rare form of vasculitis that affects blood vessels supplying the brain, spinal cord, and peripheral nerves. PACNS can result in vascular sequelae that include aneurysms, haemorrhage, and ischaemia. Cerebral vasculitis can have a varied presentation, and is the result of, or mimicked by, a multitude of different disorders including systemic vasculitis, infections, and malignancy. Therefore, extensive investigation is required to secure a diagnosis of PACNS, a situation complicated by the fact that there are no neuroradiological or serological tests that definitively confirm the diagnosis [1-3]. Early recognition and treatment are essential in PACNS due to disease severity and ensuing morbidity and mortality. The rarity and heterogenous presentation of PACNS present diagnostic challenges for clinicians.

Case Presentation

We report the case of a 69-year-old man who presented with acute confusion following a prodrome of frontal throbbing headaches for a few days prior. He had a notable background of ulcerative colitis, prostate cancer (locally extensive with no lymph node involvement), atrial fibrillation, hypertension, remitting psoriasis and hypertension. Initial CT imaging of the brain showed no acute changes, and a presumptive diagnosis of delirium was made given a mildly raised neutrophil count (8.3 × 109/L [normal range 2.0-7.5]), although all other basic laboratory investigations were normal. He was discharged from hospital but readmitted the following week with worsening confusion. MR imaging of the head had revealed a new large left parietal haemorrhage not present in the prior CT scan, as well as multiple small infarcts throughout the cortex bilaterally, innumerable microhaemorrhages and cortical subarachnoid blood (Figures 1-4).

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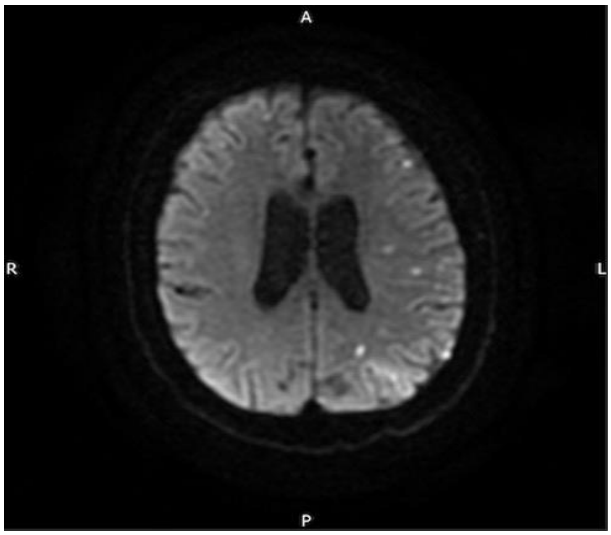

Figure 1. MR imaging demonstrating multiple bilateral cortical infarctions.

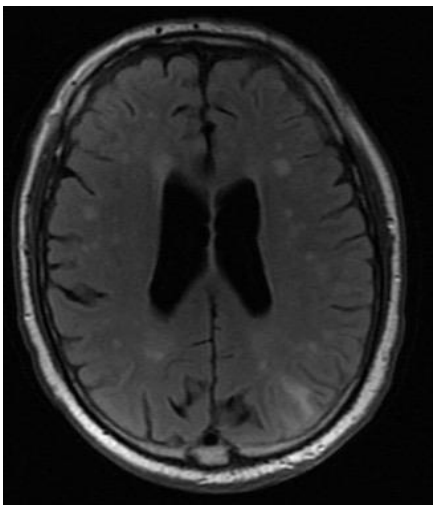

Figure 2. MR imaging demonstrating numerous white matter lesions on fluid-attenuated inversion recovery (FLAIR).

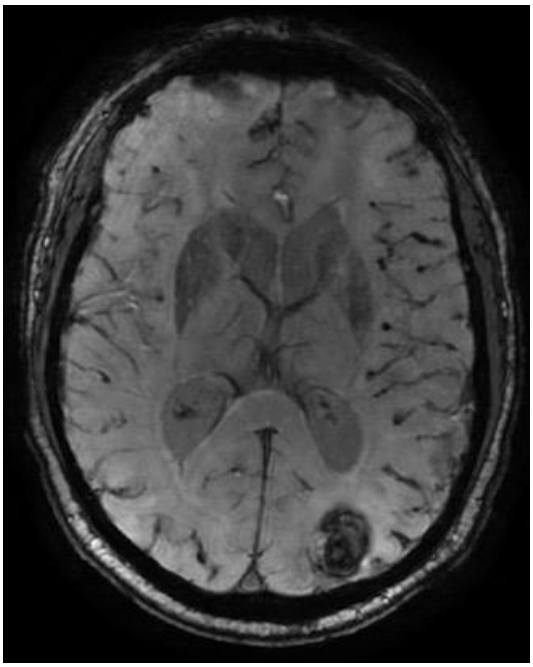

Figure 3. A large parietal haemorrhage shown from MR imaging.

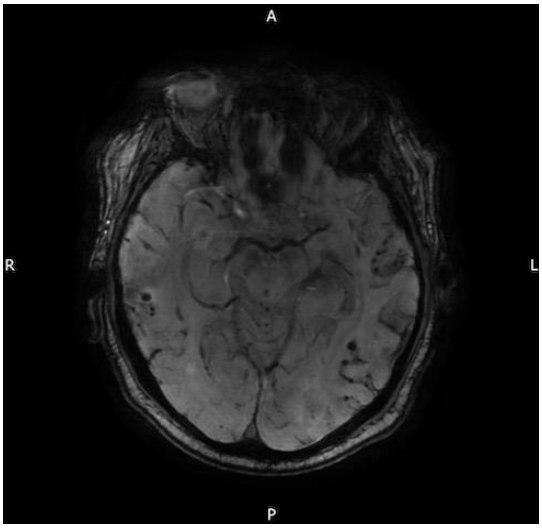

Figure 4. Widespread microhaemorrhages noted from MR imaging.

Cerebrospinal fluid analysis revealed a lymphocyte pleocytosis (34 × 10^6/L; confirmed on flow cytometry as being 96% T cells with a CD4:CD8 ratio of 4:1) but with a borderline protein concentration (0.89g/L) and no evidence of unpaired intrathecal oligoclonal band synthesis; polymerase chain reaction (PCR) for herpes simplex, varicella zoster and enteroviruses were negative, as was cytology. CT chest, abdomen and pelvis showed no evidence of malignancy driving the process, nor of infarctions in other organs. There was no evidence of valvular disease or endocarditis on echocardiography. There remained no acute-phase reaction in the blood, and antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), rheumatoid factor (RF), and paraneoplastic antibodies were all negative. Lupus anticoagulant was not detected. Serum complement levels were normal. Hepatitis B and C, human immunodeficiency virus (HIV), Borrelia, and syphilis serology were all negative. Interval CT imaging showed a further cortical haemorrhage, suggesting an ongoing disease process but CT angiography did not reveal vasculopathy.

The patient was then transferred to the regional neuroscience centre for invasive vascular imaging and further management. Digital subtraction angiography again failed to show evidence of vasculopathy, despite the strong suggestion from the serial CT and MR imaging studies.

Given the imaging findings and lymphocytic cerebrospinal fluid, and the absence of a demonstrable systemic disease process, a diagnosis of PACNS was felt to be most likely, even in the face of normal angiography. To try to prove this diagnosis before committing to intensive immunosuppression, a brain and leptomeningeal biopsy was taken from the right frontal region; this showed necrosis with histiocytes and rare lymphocytes, but no features of vasculitis or other relevant processes such as amyloid angiopathy or intravascular lymphoma were seen, and the dura mater was unremarkable. Despite extensive investigation, a definitive diagnosis of PACNS could not be made. However, given the presence of what was still clearly an active disease process, immunosuppression was induced using pulsed methylprednisolone (with subsequent prednisolone taper) and five cycles of cyclophosphamide, followed by azathioprine maintenance therapy. This treatment resulted in a marked, but incomplete, improvement in cognition, and corresponding stabilisation of imaging changes, supporting the clinical diagnosis of PACNS. He was subsequently able to return home after a period of neurological rehabilitation.

Discussion

Our case highlighted the difficulty that can occur in confirming a diagnosis of PACNS.

MR imaging of the brain is abnormal in the majority of patients [4,5]. As with our patient, the presence of both ischaemic infarcts and haemorrhages are suspicious for cerebral vasculitis [6], but is by no means specific, occurring in the majority of vasculopathic processes of the central nervous system [7]. Angiography, using CT, MRI, or the gold-standard digital-subtraction angiography, is a key part of the diagnostic work-up for cerebral vasculitis, demonstrating a “beaded” appearance of the medium and small vessels of the cerebral vasculature with multiple stenoses and dilatations when positive. However, angiography has only a moderate sensitivity for cerebral vasculitis of between 50% and 90% [8,9] and so a negative study would not necessarily rule out the diagnosis, as in our case.

Cerebrospinal fluid is usually abnormal in PACNS, in the form of a raised protein content or lymphocytic pleocytosis [7], however again this does not help to differentiate from many of its mimics such as infections or other inflammatory conditions [10].

Brain biopsy is the gold standard investigation for diagnosing cerebral vasculitis, demonstrating transmural inflammation with ensuing damage to the vessel wall. However, as with angiography, the procedure lacks sensitivity, with the distinguishing findings such as lymphocytic cellular infiltrates, acute necrotising vasculitis or granulomatous inflammation absent in up to 50% of cases. This is particularly the case when the biopsy does not target a site of imaging abnormality, as the distribution of changes is often highly focal or segmental [11,12]. However, despite its invasive nature, brain biopsy is a comparatively safe procedure with low risk of morbidity and mortality [10]. In addition, it stands to confirm the diagnosis in a substantial minority, whilst also excluding alternative pathologies such as malignancy or infectious diseases that may resemble cerebral vasculitis clinically.

The diagnosis of primary angiitis rests on demonstrating brain infarcts, a vasculopathy and the underlying aetiology of inflammation. A brain biopsy will demonstrate all of these, but it is often not diagnostic [13]. Subsequently the diagnosis becomes difficult but important to make due to the high morbidity and mortality of cerebral vasculitis. For our patient, the cellular CSF made a strong case that the underlying aetiology was inflammatory with MR imaging reporting clear infarcts. Therefore, it was the criteria of vasculopathy that was missing to make the full diagnosis. To add, an angiogram may well be normal in primary angiitis if the vasculitis affects the small arteries below the calibre of detection in an angiogram.

In this situation, the dilemma concerning this case was whether to expose the patient to the risks of immunotherapy. As reported, cyclophosphamide will cause 90% of vasculitis cases to go into remission as corroborated by Fauci AS, et al. [14]. In this study, ANCA associated vasculitis (AAV) was a fatal disease before the introduction of high-dose glucocorticoids and cyclophosphamide which led to an improvement in survival rates from 20% to over 80%. In addition, cyclophosphamide will be effective in other inflammatory conditions that may be responsible for the presentation, but an array of side effects and implications does exist. On the other hand, if the cyclophosphamide was not effective then an underlying inflammatory aetiology would be ruled out. Indeed, we could have used a less potent and toxic immunotherapy but if it was not effective then we would still be presented with the dilemma of using cyclophosphamide. However,

the positive outcome from the immunotherapy allowed for the right treatment to be instigated.

Conclusion

Our report demonstrated the difficulty in definitively diagnosing PACNS, despite extensive testing. In our case the positive response to immunosuppression helped support the diagnosis and guide further management. Yet, it also highlighted the problems posed to clinicians regarding prompt diagnosis and management of the condition, considering the risks associated with treatment options such as cyclophosphamide.

Conflicts of Interest

None

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Author Contributions

All authors have contributed to the work submitted. The first draft of the manuscript was written by Minesh Patel and all authors commented on previous versions of the manuscript.

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Consent for Publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the relative of the patient/next of kin. A copy of the consent form is available for review by the editor of this journal.

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