Journal of Neuroimmunology 330 (2019) 1–4

Contents lists available at ScienceDirect

Journal of Neuroimmunology

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

Short Communication

Atypical presentation of fulminant primary central nervous system angiitis

Sean Spence[a], Denise Ng[b], Colin Casault[a,*]

[a] Department of Critical Care Medicine, University of Calgary, Calgary, AB T2N 1N4, Canada
[b] Department of Pathology & Laboratory Medicine, University of Calgary, Calgary, AB T2N 1N4, Canada

ARTICLE INFO

Keywords:
Primary CNS angiitis
Viral encephalitis
PACNS
Primary CNS vasculitis

ABSTRACT

Background: Primary Angiitis of the Central Nervous System (PACNS) is a rare cause of CNS vasculitis that should be included as part complete differential diagnosis, especially in cases with suggestive imaging findings and an absence of secondary causes for CNS vasculitis.
Case presentation: We describe a case of a 47-year-old previously healthy Caucasian male presenting with rapid progression of encephalopathy and fevers. Extensive infectious, autoimmune, and imaging workups were unrevealing. A diagnosis of PACNS was made posthumously on histopathology.
Conclusions: PACNS is a challenging diagnosis owing to frequent discrepancies between radiologic and histopathologic findings. Tissue biopsy is key to diagnosing PACNS.

1. Case report

A 47-year-old Caucasian male drywall installer with no past medical history presented to hospital with acute onset of confusion and subsequent obtundation. Prior to presentation, he reported 7 days of malaise, with interval evolution of fevers, nausea, vomiting, and severe headache. His wife brought him to the emergency department (ED) after finding him aphasic and ataxic resulting in a ground level fall. He had no history of recent travel, insect bites, or sick contacts. The patient's immunization schedule was up-to-date, and he was a lifetime non-smoker, who consumed less than 10 alcoholic drinks per week. There was no history of illicit or injection drug use or high-risk sexual activity. Moreover, he did not endorse signs or symptoms of autoimmunity such as arthralgias or rashes previously.

Upon ED presentation, he experienced a 30-s generalized tonic seizure which aborted spontaneously. He was severely hyperthermic at 42 degrees Celsius, and had a GCS of 8T (E3VTM4). His cranial nerve, gross motor, and sensory examinations were normal. There were no signs of meningsmus. His skin demonstrated a diffuse petechial rash involving his chest and arms. Postictally, he remained stuporous and required intubation. Language could not be evaluated due to intubation.

Based on the patient's clinical presentation, there was strong concern for meningoencephalitis of either viral or bacterial aetiology. Consequently, antimicrobial treatment with intravenous ceftriaxone, vancomycin, acyclovir, and dexamethasone was initiated. Anticonvulsive treatment was provided with a phenytoin load followed by maintenance doses. The patient was kept intubated, and was brought to the ICU for monitoring, further workup, and physiologic support.

2. Investigations

A lumbar puncture was performed and cerebrospinal fluid (CSF) analysis demonstrated an elevated protein of 1.92 g/L, 16 white blood cells (WBC) per mm^3, 4 red blood cells (RBC) per mm^3 and a normal CSF-serum glucose ratio. The pleocytosis was mixed, with lymphocytic, neutrophilic, and monocytic differentials of 20%, 16%, and 18% respectively. CSF gram stain demonstrated heavy neutrophils but no organisms. CSF direct 165 rDNA NAT/PCR demonstrated no evidence of bacterial infection. Similarly, cultures of the blood and urine were all negative. Viral studies of the serum and CSF for HIV, HSV, VZV, respiratory viruses, enteroviruses, parechovirus, and West Nile virus were all negative. Serum studies of autoimmunity including ANA, C3/4, dsDNA, ANCAs, Anti MPO/PR3 and anti-GBM were all normal.

A CT Angiogram of the head demonstrated no arterial or venous abnormalities, with no luminal irregularities of the intracranial vessels (Fig. 1). Same day gadolinium enhanced MRI brain demonstrated multifocal T2/FLAIR hyperintensities involving the splenium, bilateral thalami and periventricular parenchyma, and bilateral cortical gray matter with increased signal interdigitating within the sulci. Additionally, disseminated foci of restricted diffusion and microhemorrhage within the splenium were noted (Fig. 1). Two routine EEGs and a limited continuous EEG montage demonstrated moderate generalized slowing with no evidence of electrographic seizures or

* Corresponding author at: Department of Critical Care Medicine, University of Calgary, PLC - 3500 - 26th Avenue NE, Calgary, AB T2N 1N4, Canada.
E-mail address: Colin.Casault@albertahealthservices.ca (C. Casault).

https://doi.org/10.1016/j.jneuroim.2019.01.019
Received 27 November 2018; Received in revised form 14 January 2019; Accepted 30 January 2019
0165-5728/

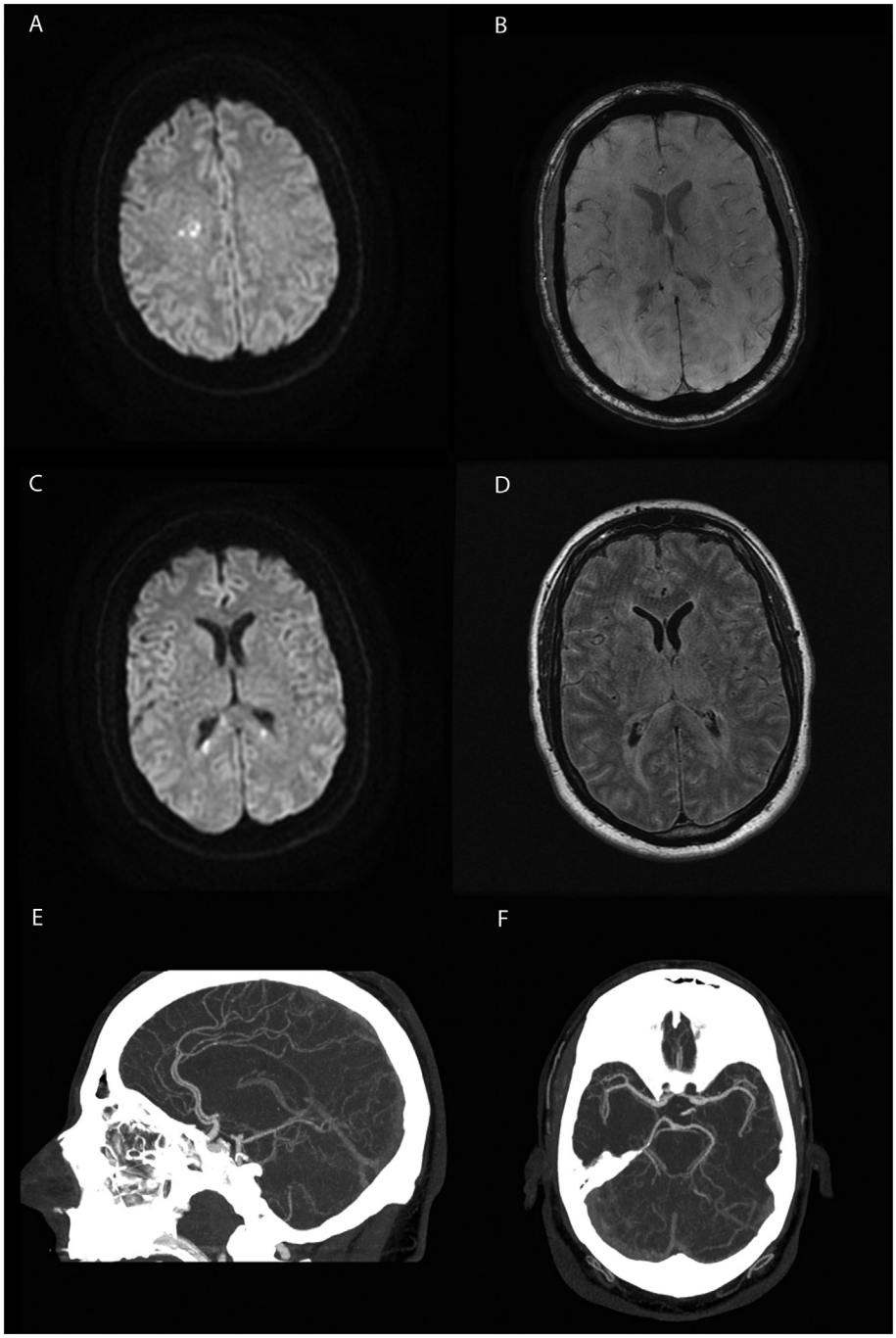

Fig. 1. (A) Axial MR Brain with multifocal foci of restricted diffusion in the centrum semiovale. (B) Susceptibility Weighted Imaging with areas of microhemorrhage in the splenium. (C) Areas of diffusion restriction in the splenium. (D) Multifocal increased signal of the bilateral thalami, periventricular parenchyma, as well as bilateral cortical gray matter. (E & F) Sagittal and axial Multiphasic CT Angiogram demonstrating no evidence of intracranial stenosis.

epileptiform discharges.

3. Clinical case follow up

Within 24 h of admission, the patient developed fulminant cerebral edema refractory to maximal medical management resulting in cerebral herniation and neurologic death. The patient's wife provided consent for a complete academic autopsy. Pathologic examination of all visceral organs, including lungs, liver, heart, spleen, and kidneys, revealed no evidence of systemic vasculitis or disseminated infection. Gross neuropathological examination demonstrated diffuse cerebral edema with herniation and softening of tissue found throughout the centrum semiovale, bilateral cerebral cortices, bilateral caudate nuclei, and throughout the brainstem. Microscopic evaluation identified multifocal early infarction and diffuse lymphocytic vasculitis (Fig. 2) involving the leptomeninges, cerebral cortex, central gray matter, and brainstem, consistent with a diagnosis of Primary Angiitis of the CNS (PACNS). No venous abnormalities were noted on microscopy, and no features consistent with either bacterial or viral infection were present. Immunologic testing was negative for lymphocyte receptor gene rearrangement, thereby excluding clonality among the population of T-cells tested.

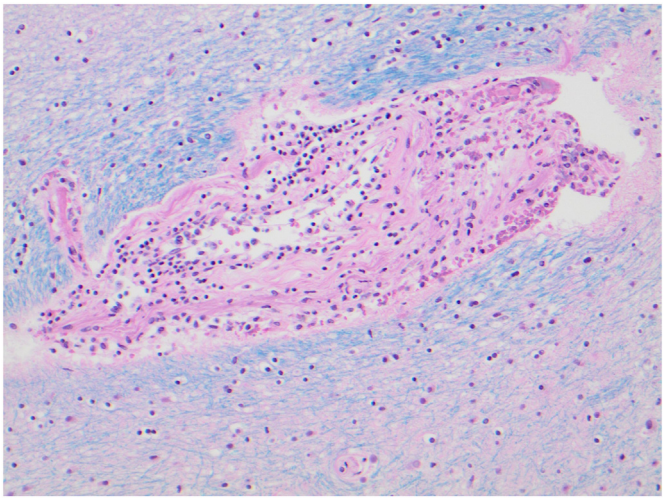

Fig. 2. Throughout the brain parenchyma, arterioles demonstrated mural thickening with diffuse lymphocytic infiltration, fibrinoid necrosis. Edema, and reactive fibroplasia, diagnostic of angiitis. Minimal perivascular lymphocytic cuffing was identified. Rare intravascular fibrin thrombi were seen. Sparing of venules and capillaries were noted. Infarcts showed acute chronology with no evidence of older lesions, supportive of an isolated precipitous presentation.

4. Discussion

PACNS is a rare vasculitis occurring in the medium to small vessels of the brain, spinal cord, and meninges. Despite increased recognition, PACNS remains a rare condition with an annual incidence of 2.4 cases per 1,000,000 person-years, and a median age of diagnosis of 50 (Salvarani et al., 2007). There appears to be a predilection for males, with a male to female ratio of 2:1 noted among affected individuals. PACNS typically presents subacutely, with patients developing headaches, altered cognition, focal neurologic deficits, and seizures in a progressive manner over several months (Hajj-Ali et al., 2011). An associated petechial rash has been infrequently reported, but data delineating the precise rate of occurrence of this finding is not present in the current body of medical literature. Ruling out secondary causes of CNS vasculitis is crucial to establishing a diagnosis of PACNS. Secondary causes of CNS vasculitis are myriad, and can be dichotomized into infectious and non-infectious aetiologies. Infectious causes can be further subdivided into viral, bacterial, fungal, and parasitic organisms, whereas common non-infectious aetiologies include systemic vasculitides, connective tissue disorders, and other autoimmune disorders. Key viruses to consider include Varicella Zoster, HIV, Hepatitis C, Parvovirus B19, and cytomegalovirus. Chief causative bacteria include *Treponema pallidum*, *Mycobacterium tuberculosis*, *Borrelia burgdorferi*, *Rickettsia* species, and *Bartonella henselae*.

In addition to excluding secondary causes of CNS vasculitis, the diagnostic criteria for PACNS include the presence of a compatible neurologic syndrome accompanied by compatible angiographic or histologic findings (Calabrese and Mallek, 1988). Typical angiographic findings include a “beaded” appearance of medium and small intracranial arteries, reflecting staggered regions of arterial stenosis and dilatation. Circumferential or eccentric irregularities of vessel walls may also occur. Despite being regarded as the “classic” imaging pattern for PACNS, such findings are non-specific, and can be seen in reversible vasoconstriction syndrome, posterior reversible encephalopathy syndrome, arterial vasospasm from subarachnoid haemorrhage, and many other conditions (Calabrese et al., 2007). Consequently, indiscriminate reliance on imaging may lead to incorrect diagnoses of PACNS being made. The diagnosis of PACNS can be equally challenging when relying on histologic criteria. Histopathologic patterns seen in PACNS include granulomatous, lymphocytic, or necrotizing arterial inflammation. The classic finding of segmental granulomatous vasculitis with Langerhans cells is encountered in less than half of biopsies (Lie, 1997). Furthermore, given the focality of PACNS to discrete segments of the CNS vasculature, a positive biopsy can serve to confirm the diagnosis, whereas a negative biopsy does not definitively exclude it (Lie, 1997).

Interestingly, the rate of diagnosis of PACNS has increased dramatically over the past 50 years. This may reflect increased recognition of the diagnosis, establishment of diagnostic criteria, greater availability of non-invasive cerebral vascular imaging, or a combination of these factors. Of 701 reported cases of PACNS included in a recent systematic review, 82.9% had catheter angiography, whereas pathologic examination was only performed in 50.2% of cases (McVerry et al., 2017). McVerry et al. demonstrated the frequent discrepancy between angiography and pathology in the diagnosis of PACNS, wherein 10.6% of cases with abnormal angiography had normal pathology on brain biopsy (McVerry et al., 2017). This may reflect sampling error, as previously mentioned, but may also stem from incorrect application of diagnostic criteria. This same review found in patients with abnormal angiography, biopsies were twice as likely to be normal than abnormal, thereby demonstrating a high risk false positive rate when relying on angiography. Equally disconcerting is angiography was three times more likely to be normal than abnormal in cases with classical histopathology (McVerry et al., 2017). This latter finding may reflect the limitation of currently available imaging modalities to adequately visualize the affected medium to small vessels of the brain. These diagnostic challenges are clearly present in our clinical case, and serve to highlight the importance of obtaining tissue samples in making the diagnosis of PACNS. In the authors' opinion, this provides support for the preferential use of the Birnbaum and Hellmann diagnostic criteria, wherein histopathologic findings are treated as the “gold standard”, rather than being regarded as equivalent to angiographic findings as proposed by Calabrese and Mallek in 1988 (Birnbaum and Hellmann, 2009).

As previously indicated, PACNS is prototypically a subacute, progressive disorder as opposed to a rapidly progressive or fulminant condition. In a large Mayo clinic cohort of 131 patients with PACNS, only 11 had a rapidly progressive course. Among these 11 cases of rapid evolution, only three had duration of illness that was less than 10 days (Salvarani et al., 2011). In all three cases, there was angiographic evidence of large multi-vessel vasculitis, which was conspicuously absent in our case, despite its fulminant progression. Moreover, all three cases demonstrated a granulomatous and/or necrotizing pattern histologically, which stands in stark contrast to the lymphocytic pattern seen in our case. A recent report on a French cohort of PACNS patients found a similar frequency of catastrophic cases. Among patients studied, 11 of 102 (11%) patients met criteria for catastrophic disease course and required admission to ICU. Cases are described within this patient cohort wherein neuroimaging is negative despite positive pathologic findings, but the publication is unclear as to whether any of these patients fell within the catastrophic subgroup (Boysson and Pagnoux, 2018). Similar to the Salvarani cohort, our case demonstrated rapid, unrelenting deterioration. In this case series, prognosis was universally poor, with all 11 patients failing to respond to therapy with high dose corticosteroids and additional immunosuppression with azathioprine or cyclosporine (Salvarani et al., 2011). In light of these findings, experts advocate for high potency combined immunosuppression with biologics and corticosteroids given that randomized controlled trials of therapy are unlikely to be conducted do to the rarity of PACNS (Salvarani et al., 2014).

5. Conclusion

We report a rare case of PACNS with a fulminant presentation with normal angiographic findings and diffuse lymphocytic histopathologic findings. Our case report contributes to the current literature by documenting this atypical combination of rapidly progressive PACNS with

a lymphocytic histological pattern, thereby helping elucidate the incidence rate of this unusual constellation of findings. Additionally, this case highlights the importance of tissue biopsy in PACNS, educates clinicians of the potential discrepancy between histopathologic and angiographic findings in PACNS, and underscores the high degree of clinical suspicion required in making a rare and potentially fatal diagnosis.

Sources of funding

The authors have no sources of funding to declare.

Disclosures

The authors have no conflicts of interest to disclose.

Roles of authors

Sean Spence: Dr. Spence is a Critical Care Medicine Fellow who was involved in patient data collection, literature review, and manuscript preparation.

Denise Ng: Dr. Ng is a Clinical Assistant Professor in the Department of Pathology & Laboratory Medicine at the University of Calgary. She conducted the neuropathological autopsy of the patient described, and also contributed to literature review and manuscript preparation.

Colin Casault: Dr. Casault is a Neurologist who oversaw the admission, diagnostic evaluation, and clinical management of the described patient. He also contributed to literature review, manuscript preparation, and overall supervision of case report preparation.

Acknowledgements

The authors would like to thank the University of Calgary Departments of Critical Care, Clinical Neurosciences, and Pathology & Laboratory Medicine for their on-going support.

References

Birnbaum, J., Hellmann, D.B., 2009. Primary angiitis of the central nervous system. Arch. Neurol. 66, 704–709.

Boysson, H., Pagnoux, C., 2018. Catastrophic primary angiitis of the central nervous system. Eur. J. Neurol. 25, e3. https://doi.org/10.1111/ene.13469.

Calabrese, L.H., Mallek, J.A., 1988. Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine (Baltimore) 67, 20–39.

Calabrese, L.H., Dodick, D.W., Schwedt, T.J., Singhal, A.B., 2007. Narrative review: reversible cerebral vasoconstriction syndromes. Ann. Intern. Med. 146, 34–44.

Hajj-Ali, R.A., Singhal, A.B., Benseler, S., Molloy, E., Calabrese, L.H., 2011. Primary angiitis of the CNS. Lancet Neurol. 10, 561–572.

Lie, J.T., 1997. Classification and histopathologic spectrum of central nervous system vasculitis. Neurol. Clin. 15, 805–819.

McVerry, F., McCluskey, G., McCarron, P., Muir, K.W., McCarron, M.O., 2017. Diagnostic test results in primary CNS vasculitis: a systematic review of published cases. Neurol. Clin. Pract. 7, 256–265.

Salvarani, C., Brown Jr., R.D., Calamia, K.T., Christianson, T.J., Weigand, S.D., Miller, D.V., et al., 2007. Primary central nervous system vasculitis: analysis of 101 patients. Ann. Neurol. 62, 442–451.

Salvarani, C., Brown Jr., R.D., Calamia, K.T., Christianson, T.J., Huston 3rd, J., Meschia, J.F., et al., 2011. Rapidly progressive primary central nervous system vasculitis. Rheumatology (Oxford) 50, 349–358.

Salvarani, C., Brown Jr., R.D., Huston 3rd, J., Morris, J.M., Hunder, G.G., 2014. Treatment of primary CNS vasculitis with rituximab: case report. Neurology 82, 1287–1288.