A 25-year-old man with progressive left-sided weakness and a mass lesion on brain imaging

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Grand Rounds Case

Medical History and Clinical Examination

A 25 year old left handed man presented with progressive left sided weakness for two to three days. On the day of admission, the patient reported that his left lower extremity buckled beneath him and that he had to drag his left leg in order to walk. The patient was healthy and denied any constitutional symptoms, joint pains, rash or seizures. There was no recent trauma.

On physical exam, the patient appeared his stated age and was in no acute distress. Vital signs were normal. Heart, lung and abdominal exams were normal. There was no rash, skin lesions or joint swelling. On neurological exam his mental status was intact, with normal speech, comprehension and mental status. There was no neglect or visual field cut. Cranial nerve testing was normal except for mild left nasolabial fold flattening. There was no papilledema or optic atrophy. A mild 4/5 left-sided hemiparesis was present with increased tone in both the arm and the leg. The patient demonstrated marked slowing and impairment of fine motor coordination in the left hand but finger to nose testing revealed no dysmetria. Sensation of the left lower extremity was intact. However, two-point discrimination was mildly impaired in the left upper extremity. Left-sided reflexes were hyperactive with clonus at the ankle, with a positive Babinski. He walked with a wide based gait, circumducting the left leg during the swing phase with flexion of the left arm.

What are the possible diagnoses in this patient?—Most importantly when evaluating this patient, one must first localize the lesion so appropriate studies can be performed. His clinical course is quite acute. The facial weakness implies a central lesion, and as his weakness is on the same side as his arm and leg weakness, this suggests that the lesion is above the brainstem. He has signs of upper motor neuron dysfunction (corticospinal tract) with increased reflexes and clonus. There are some sensory changes in the upper extremity suggesting that the lesion is not limited to the motor tracts. He has no cortical
signs (ie., aphasia, neglect or visual field loss) and his mental status was intact. This implies primarily a subcortical lesion in the right hemisphere.

1. Multiple sclerosis or demyelinating disease
2. Vascular event. In an older patient with risk factors this would be the most likely, although this clinical syndrome would usually not have sensory changes and could represent a “pure motor stroke” in the internal capsule. A dissection, hypercoagulable state or a patent foramen ovale should be considered in a young patient with focal findings.
3. Infection. His HIV status would be critical to evaluate, as well as any history of intravenous drug use.
4. Tumor. Although the clinical presentation seems quite acute, often a mass lesion can present with minimal symptoms until hydrocephalous, seizure, or weakness occurs.

What diagnostic test would you perform?—Neuroimaging would be the first step in the evaluation. His symptoms localize to the CNS and facial weakness on the same side as the arm and leg weakness suggests that the lesion is in the brain above the facial nerve nucleus (in the pons). CT scanning could be considered as an initial step, although MRI with gadolinium is likely to be much more sensitive, especially for demyelinating disease. This has to be done prior to any consideration of obtaining spinal fluid. Although he had no papilledema, this can often be hard to determine with a non-dilated eye exam, and if the process is relatively acute, optic disc swelling may not have developed.

MRI showed a large ill defined heterogeneous enhancing mass along the margins of the right lateral ventricle with diffuse associated signal abnormality consistent with white matter edema (Figure 1). No hemorrhage was seen. The 4th ventricle was patent. The differential at this point was a demyelinating disease, an infection, or most likely a glial tumor. His exam was surprisingly benign for the degree of edema and the size of the mass. This is consistent with a primary CNS tumor, which can often grow to large sized before clinical symptoms appear.

Other Investigations—A lumbar puncture was performed. The CSF was negative for malignant cells and oligoclonal bands. Cytology and flow cytometry were performed on the small number of cells present. These were negative for monoclonal cell populations such as would be seen in lymphoma. Protein, glucose and opening pressure were all within normal limits. CSF PCR for HSV, JC virus, and TB were negative. Serology was remarkable for a positive ANA. However, further rheumatologic evaluation showed negative titers for specific antibodies and the diagnosis of a systemic vasculitis was excluded. Infectious causes were ruled out with serology that was negative for Bartonella, HIV, Toxoplasmosis (IgG and IgM) and CMV. An electroencephalogram was within normal limits without any seizure activity.

Due to the MRI appearance of the lesion, and the high likelihood of a CNS tumor, the patient underwent a brain biopsy. The biopsy specimen (Figure 2) showed a patchy chronic lymphocytic infiltrate that was mainly perivascular, consistent with CNS vasculitis. All special stains for organisms including TB were negative as was PCR for JC virus, CMV, TB, EBV and HSV. There was no evidence of abscess or noncaseating granulomatous inflammation (suggestive of neurosarcoid). Immunohistochemical analysis showed a mixed lymphocytic infiltrate (CD45, CD3 and CD20), making lymphoma unlikely. There were no perivenular infiltrates or other evidence of demyelinating disease. After a brief course of
steroids his symptoms substantially improved. The patient refused other immune modulating agents. He has remained stable with no clinical symptoms for over a year.

What is the usual clinical presentation of CNS vasculitis?—Primary angiitis of the central nervous system (PACNS) is a term that describes a spectrum of disorders that are rare and of unknown etiology. The disorder most commonly presents in males in the fourth to sixth decades of life, but can be seen at any age in either sex [1-5]. The clinical presentation of PACNS is variable, but most patients present with headache and encephalopathy. Focal neurological signs are rarer, occurring in approximately 20% of cases at the onset of the disease [5]. Non-specific laboratory and imaging findings further obscure the diagnosis. Diagnosis requires an appropriate index of clinical suspicion for a given set of signs and symptoms. Infection, demyelinating diseases, collagen vascular disease and malignancies, which may present in a similar manner, must be excluded by laboratory and imaging studies [1-5].

PACNS is a heterogeneous entity, with two distinct subsets 1) Granulomatous Angiitis of the CNS (GACNS) and 2) Atypical Angiitis of the CNS, which includes patients presenting with mass lesions and those seen in association with cerebral amyloid angiopathy (CAA) (CAL 2007, hell2009). Presentation of PACNS as a solitary tumor-like mass lesion (ML-PACNS) such as in this case [6-9] are becoming increasingly recognized (7-9). This is often seen in younger patients, where PACNS is often not considered in the differential [1]. Interestingly, this patient had significant clinical and radiological improvement within days after a brief course of steroids (Figure 3) and has maintained remission off all therapies. This clinical picture appears to be more typical of younger patients with amyloid negative PACNS who often respond well and quickly to a single treatment [17, 21], suggesting that these patients represent a distinct immunological subset of PACNS. Patients with amyloid positive PACNS are typically older men with more prominent gadolinium-enhanced leptomeningeal lesions on MRI [21]. In the largest case series of biopsy-proven patients presenting with mass-lesions, the median age was 38 when older patients with amyloid positive PACNS were excluded. Importantly, the most common clinical features of patients presenting with ML-PACNS were headache (74%), seizures (47%), and focal neurological deficit (64%), similar to the discussed case. These patients typically present (74%) within 1 month of onset of symptoms (9) rather than the more protracted course (>6 months to presentation) of the more “typical” form of PACNS seen in older men. These clinical differences are important for treating neurologists to recognize, so the appropriate diagnosis is considered.

A substantial number of patients suspected of having PACNS will have signs and symptoms caused by vasospasm rather than vasculitis. In patients younger than 40 years, the diagnosis of reversible vasoconstriction syndrome (RVCS) should be considered. This entity, previously known as benign angiopathy of the CNS, which may not have a benign course, is no longer considered a subset of PACNS and has been reclassified as a vasospastic syndrome (CAL, 2007 review hellman 2009 This is an important distinction as treatment is with steroids and often a calcium channel blocker, rather than cytotoxic agents. RVCS is primarily seen in women aged 20 to 40 years and is associated with migraines, illicit drug use, over-the-counter cold medicines, and the post-partum state (7). The most common presenting syndrome is of a thunderclap headache of sudden onset and sufficient severity to warrant diagnostic evaluation for subarachnoid hemorrhage. Focal symptoms can predominate, with strokes or transient ischemic attack as a presenting feature.

How is PACNS usually diagnosed?—Current diagnostic criteria for PACNS include the following: an unexplained acquired neurological deficit, angiographic or histological features of CNS vasculitis, and no evidence of a systemic condition associated with these
CNS findings [4,9,10]. A brain biopsy is often required to establish the presence of inflammation and exclude infection, neoplasm, atypical multiple sclerosis or an alternative cause of vasculopathy, especially in younger patients with atypical imaging findings.

Neuroimaging is gaining increasing power as a diagnostic tool [3,5,11-13]. Magnetic Resonance Imaging (MRI) offers a non-invasive strategy with sensitivity of 50-100%, but specificity near 100% in biopsy proven cases [2,3]. MRI features of PACNS vary considerably, but generally consist of bilateral asymmetrical supratentorial lesions predominantly in the subcortical and deep white matter [2-6]. Multiple infarcts of different ages are thought to be suggestive of cerebral vasculitis, especially if the lesions are located in a variety of vascular territories and do not have a typical embolic appearing pattern [11-13]. Multiple infarctions are frequently bilateral and involve both cortical and subcortical areas [5,6,11]. Gadolinium-enhanced intracranial lesions are observed in about one third of patients [11]. Rarely (4-6%), MRI can simulate a mass lesion suggestive of a primary brain tumor [6-8] as in this case, and PACNS is often not considered in the diagnosis. This variant appears to be more common in young patients, and often responds well to steroid therapy.

**Should a cerebral angiogram have been performed?**

Angiographic diagnosis of vasculitis is based on the demonstration of one or multiple stenosis of brain vessels and diffuse vessel caliber changes. Inflammatory changes of very small brain arteries which are below the resolution limits of cerebral angiography will escape detection and cause falsely negative angiograms [9]. While MRA offers a non-invasive diagnosis of PACNS, conventional angiography is somewhat more sensitive than MRA for detecting intracranial vessels. However even conventional catheter angiography has a false negative rate of up to 30% as arteries under 100-200 micrometers are beyond the limit of resolution. The diagnostic value of angiography has been a subject of recent debate [10,15], as the positive predictive value may be as low as 37% as it may not be able to reliably differentiate “vasculitis” from “vasculopathy” [15].

**What are the typical findings on Cerebrospinal Fluid (CSF) Analysis in PACNS?**

In one of the largest case series to comment, CSF evaluation of 110 patients showed 1 or more abnormalities in the vast majority (88%) [4]. Therefore obtaining CSF, if possible, can aid in the diagnosis, especially if MRI or angiogram findings are also consistent with the diagnosis of PACNS. Changes include a mildly increased leukocyte count or total protein concentration, or both. Patients with a diagnosis of PACNS made by biopsy had greater leukocyte counts (up to 17 cells/ml) and greater total protein concentrations (up to 98 mg/dl) [4]. Our patient had a benign CSF profile further obscuring the diagnosis.

**What other studies should be performed?**

PACNS is often a diagnosis of exclusion. Although, most tests are negative in PACNS they are necessary to rule out other possible etiologies which could mimic the clinical picture and imaging of PACNS. Hemoglobin levels, leukocyte counts, platelet counts, and erythrocyte sedimentation rates are typically within reference levels [1,4,10]. Serum test results are usually negative for rheumatoid factor, antinuclear antibodies and anticardiolipin antibodies. Levels of antineutrophil cystoplasm antibodies, complement and human immunodeficiency virus testing are also normal in PACNS [1,4,10]. Weakly positive ANA (with negative dsDNA), c-ANCA, and p-ANCA autoantibodies were found in 14–29% of PACNS patients in one large series, but titres did not exceed 1:40 in any patient, and may be a consequence of polyclonal immune activation associated with the acute phase response in patients [4,8].
What are the typical findings of PACNS on biopsy?

There are no distinguishing features on neuroimaging, angiography or CSF analysis that can differentiate PACNS from other mass lesions, making brain biopsy necessary for diagnosis in these cases [7]. Diagnostic histopathological features of PACNS include transmural vascular inflammation involving leptomeningeal or parenchymal vessels, infiltrating inflammatory cells, the presence of vascular wall fibrinoid necrosis, and parenchymal findings consistent with ischemia. Additionally, vascular amyloid deposition can be seen with immunoperoxidase staining of Beta-amyloid proteins in the amyloid variant of PACNS [4,6,7] Cerebral biopsy is also an invasive procedure which many clinicians attempt to avoid. However, the predictive value of angiography in the setting of normal CSF and an abnormal MRI is not well documented and may be much lower than previously thought [9]. In cases such as ours, biopsy is often the only way to diagnose this disease.

What are the current treatment options for patients with PACNS?

Although there have been no controlled trials of therapy in PACNS, anecdotal evidence suggests that most patients respond positively to therapy. The standard treatment regimen for CNS vasculitis is a combination of high dose steroids and cytotoxic agents, typically cyclophosphamide [1,4]. The overall response rate to monotherapy with either prednisolone or monotherapy with cyclophosphamide or dual therapy with prednisolone and cyclophosphamide is approximately 80% [4]. Recently, eight cases of PACNS were reported that presented with lesions similar to our case, and these patients also had few CSF abnormalitie. These patients had a good response to a single course of steroid or cyclophosphamide treatment without relapses [14].

Lessons learned from this case

In this case, MRI revealed an ill defined heterogeneously enhancing mass near the right ventricle with diffuse associated signal abnormality likely representing edema and mild associated mass effect, which was highly suspicious of a neoplasm (Figure 1). Tissue characterization was required to make the diagnosis and a brain biopsy was performed to evaluate the lesion. The biopsy provided histological confirmation of vasculitis (Figure 2) with lymphocytic infiltration of small vessels. There was no evidence of demyelinating disease or macrophage infiltration.

PACNS presenting as a mass lesion is an extremely rare presentation of a rare disease (annual incidence 2.4/1,000,000 person-years) and may represent a relatively uncharacterized subset of PACNS [4,6-8]. Interestingly, this patient had significant clinical and radiological improvement within days after a brief course of steroids (Figure 3) and has maintained remission off all therapies. This clinical picture appears to be more typical of younger patients with amyloid negative PACNS who often respond well and quickly to a single treatment [14,16], suggesting that these patients represent a distinct immunological subset of PACNS.

Currently, diagnosis requires an angiogram or brain biopsy with histological analysis [1,4,7]. Early aggressive treatment with steroids can lead to full remission in PACNS, but the disease can be fatal if left untreated. Therefore, prompt diagnosis is critical. While there are some potentially useful imaging modalities employing MR which has high sensitivity, brain biopsy remains the gold standard of diagnosis and should be considered early in the clinical course. Although PACNS rarely presents as a CNS mass lesions (4-6%), it should be considered in the differential diagnosis, especially in young patients so that appropriate treatment can be initiated.
Conclusions

PACNS is a rare inflammatory process affecting mostly medium to small vessels in the CNS. Most commonly, it is a diagnosis of exclusion. Currently, diagnosis requires an angiogram or brain biopsy with histological analysis [1-5]. The diagnostic value of angiography has been a subject of recent debate [11,12, 20]. The positive predictive value may be as low as 37% and it may be unable to reliably differentiate “vasculitis” from “vasculopathy” [21]. Early aggressive treatment with steroids can lead to full remission in PACNS, but the disease can be fatal if left untreated. Therefore, prompt diagnosis is critical. While there are some potentially useful imaging modalities employing MR which have high sensitivity, brain biopsy remains the gold standard of diagnosis and should be considered early in the clinical course. Although PACNS rarely presents as a CNS mass lesions, it should be considered in the differential diagnosis, especially in young patients so that appropriate treatment can be initiated.

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Figure 1. MRI findings
Figure 1a shows an axial FLAIR MRI. Extensive edema involves portions of the frontal, parietal, and occipital lobe of the right hemisphere. An underlying focal area of signal abnormality was seen adjacent to the right lateral ventricle. There was no abnormal signal in the left hemisphere, midbrain or brainstem (not shown). After Gadolinium administration there are obvious ill-defined areas of enhancement in several regions adjacent to the right lateral ventricle which are seen on the axial (Fig 1b), coronal (Fig 1c) and sagital (Fig 1d) images as well as extensive edema. Diffusion imaging was normal. A high grade glioma was suspected.
Figure 2. Surgical pathology specimen from right temporoparietal lobe biopsy
A low power magnification (Fig. 2a) shows hypercellular, gliotic tissue. An inflammatory infiltrate is seen in a perivascular distribution (Fig 2b). Lymphocytes can be seen focally penetrating the walls of small blood vessels (Fig 2c and 2d) consistent with a vasculitis. Lymphoma is unlikely given the chronic symptoms in this case as well as evidence of mixed T and B cell lineage on immunohistochemical staining. No malignant cells or infections were seen.
Figure 3. Repeat MRI approximately one week after high dose steroid administration
Gadolinium-enhanced MRI at approximately the same level shows some resolution in edema and decrease in size of the mass lesion after 1 week of steroid treatment (Figure 3a vs. 3b).