



Primary Angiitis of Central Nervous System

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Abstract

Primary angiitis is a rare disorder and is difficult to diagnose. A 45 year old female presented with headache and slurred speech with bilateral pyramidal signs. There were lesions in the cranial imaging bilaterally with minimal enhancement. She was put on antitubercular treatment along with steroids by which there was substantial recovery. As the steroids were tapered five months later there was recurrence of symptoms as slurred speech and seizures. Repeated brain imaging showed recurrence of the lesions. An open brain biopsy was suggestive of vasculitic pathology with transmural inflammation of the vessels and fibrinoid necrosis at a few places. A thorough work up for systemic vasculitic disorders was negative. Immunosuppression was initiated with corticosteroids and cyclophosphamide was instituted.

Keywords: Primary Angiitis of Nervous System, Transmural Inflammation, Immuno Suppression

Introduction

Primary angiitis of central nervous system (PACNS) is a rare disorder causing inflammation and destruction of central nervous system (CNS) without evidence of inflammation in tissues outside CNS. The disease is poorly understood and is difficult to diagnose. There are no useful animal models for this disease. Though there are some neuroradiological findings they are not very sensitive or specific.

The diagnostic criteria for PACNS include[1]:

1. The presence of an acquired unexplained neurological or psychiatric deficit
2. The presence of classic angiographic or histopathological features within CNS
3. No evidence of systemic vasculitis or any other disorder that can mimic the angiographic or histological features of the disease

The clinical presentation of PACNS is varied and no specific symptoms exist. Headache is one such symptom though the nature and severity of headache may vary. Presence of thunderclap headache is unusual and may suggest a different pathology. There may be cognitive impairment of insidious onset. Occasionally there can be strokes or transient ischemic attacks accounting for 30% to 50% of the cases. If there are constitutional symptoms, weight loss or visceral target organ damage, a systemic illness may be considered as the cause of vasculitis. Occurrence of ocular motor nerve involvement, ataxia, myelopathy and seizures are described as case reports only as features of PACNS.

The Magnetic Resonance Imaging (MRI) and angiographic abnormalities which are seen in PACNS are not specific to that disease. Reversible vasoconstriction syndrome, posterior reversible encephalopathy syndrome and brain neoplasms are common entities and are common mimics of the disease (Table 1)[2].

Case Presentation

A 45 year old female patient with, no known comorbidities was admitted on 28th March 2017, with diffuse holocranial low grade headache of one month duration, facial deviation to left and slurring of speech of one day duration. On examination right upper motor neuron facial paresis and mild dysarthria were noted. There was spasticity in all four limbs. Mild (MRC grade IV) hemiparesis was present on right side. The deep tendon jerks were brisk bilaterally with extensor plantar responses bilaterally. The cranial MRI showed hyperintense lesions on diffusion weighted images and fluid attenuated inversion recovery (FLAIR) images with minimal contrast enhancement in bilateral parietal areas, bilateral capsuloganglionic regions and in the brainstem (Figure 1,2). In

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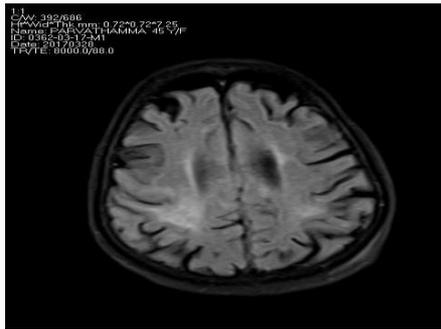


Figure 1: FLAIR image (28-03-2017).

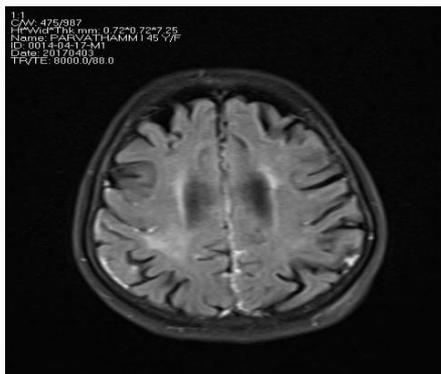


Figure 2: Contrast enhanced FLAIR image (28-03-2017).



Figure 3: Normal MR Angiogram (28-03-2017).

view of the punctuate enhancing lesions the radiologist opined 'as small granulomatous lesions consistent with tuberculous etiology with a differential of vasculitic etiology'. The vascular imaging was normal (Figure 3). The laboratory work up was negative for any underlying systemic disease. Cerebrospinal fluid (CSF) analysis showed lymphocytic cellular response (total cells 64/HPF-20% neutrophils and 80% lymphocytes, protein 196 mg/dl, and 58 mg/dl of glucose with a corresponding blood glucose value of 112 mg/dl). Gram staining and culture were negative.

The patient was started on 4-drug antituberculous regimen (rifampicin, isoniazid, ethambutol and pyrazinamide) along with corticosteroids in the form of oral prednisolone 1mg/Kg/day, in the first week of April, 2017. She had hepatotoxicity and skin rash due to which the medicines were stopped for about 20 days in May, 2017 and restarted at a low dose under cover of steroids (Prednisolone) twenty days later. In July she was reviewed, able to walk independently.

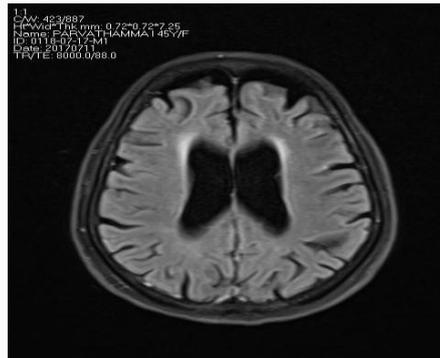


Figure 4: Contrast enhanced FLAIR image showing good improvement (11-07-2017).

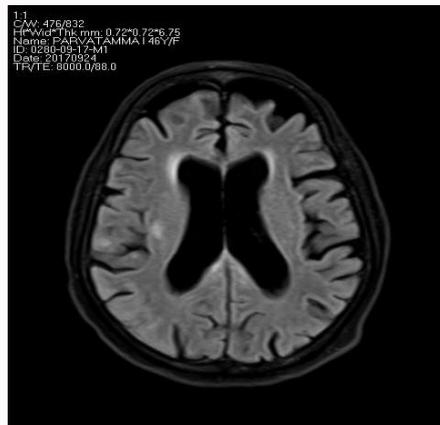


Figure 5: Flair image (24-09-2017).

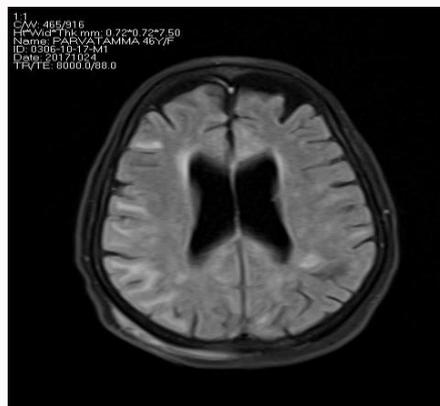


Figure 6: Contrast enhanced FLAIR image showing the enhancing lesion and subgaleal hematoma (24-10-2017).

There were hyperreflexia and up going plantar responses bilaterally. Cranial MRI scan showed significant improvement (Figure 4). Antituberculous treatment (ATT) was continued; steroids were gradually tapered and stopped in first week of September 2017. On 24th September she had transient slurred speech for about 10 min. The cranial MRI scan showed reappearance of a small lesion in the right periventricular region (Figure 5). She refused admission to the hospital for further work and continued same treatment at home.

On 24th October she was brought with a history of headache of one week duration and two seizures of left focal onset and secondary

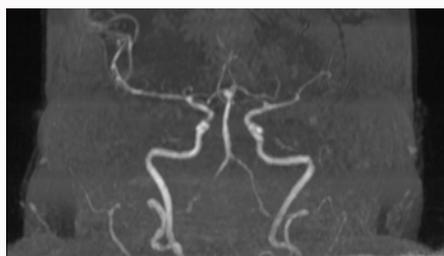


Figure 7: MR angiogram beaded appearance of right middle cerebral artery (24-10-2017).

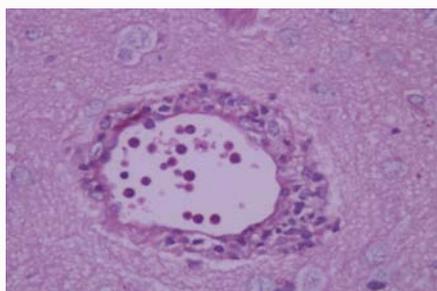


Figure 10: H&E stain. Transmurial inflammation.

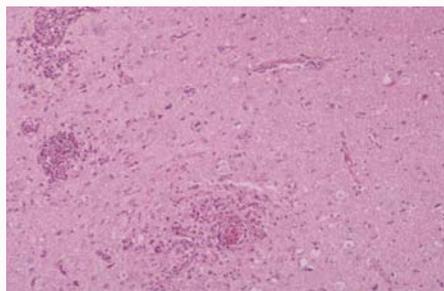


Figure 8: H&E stain. Vessel with transmurial inflammation and fibrinoid necrosis 10X.

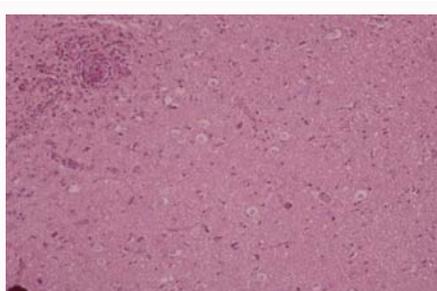


Figure 11: H&E stain. Gliosis.

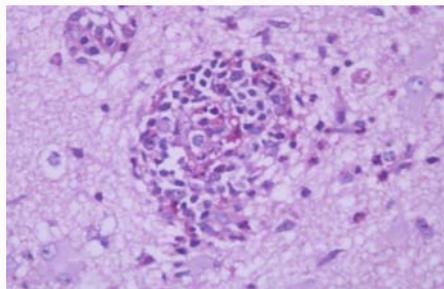


Figure 9: H&E stain. Vessel with transmurial inflammation and fibrinoid necrosis 40X.

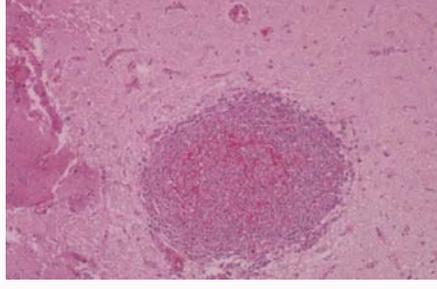


Figure 12: PAS stain 10X.

generalization. She was drowsy on admission, but arousable, moving all four limbs in response to pain with mild paucity of movements on left side. The cranial MRI scan showed hyperintense signal in the right temporoparietal areas (Figure 6), right thalamus, midbrain and pons with hyperintensity on the brain surface in the same regions. Magnetic resonance angiogram showed beaded appearance of right middle cerebral artery and its branches with stenotic segments between the beads (Figure 7). The laboratory work up showed mild neutrophilic leukocytosis. The chest x-ray was normal. The CSF analysis was almost similar to the one in March, 2017, showing lymphocytic pleocytosis (38 cells/cu mm and 90% lymphocytes and protein of 68 mg/dl and normal glucose levels). A complete work up for collagen vascular diseases including cytoplasmic and peripheral antineutrophil cytoplasmic antibodies, rheumatoid factor, anti nuclear factor, anti-double stranded DNA antibodies and other antibody profile was negative. Urine test for Bence-Jones protein was also negative.

Open biopsy was taken from right temporoparietal brain along with meningeal tissue (which was abnormal on cranial MRI scan). On histopathological examination, there was proliferation of capillaries with deposits of eosinophilic material. A blood vessel

showed hyalinization of the wall with transmurial and perivascular infiltrate of neutrophils and lymphocytes (Figure 8-10). Occasional focus of fibrinoid necrosis was seen. There was prominent gliosis around the angiocentric inflammatory foci (Figure 11). There were no granulomas, giant cells or calcification. Periodic-Acid-Schiff stain highlighted the fibrinoid necrosis (Figure 11). Congo red stain was negative for amyloid (Figure 12). The dura showed thick collagenous bundles with dilated thickened blood vessels. The findings were suggestive of angitis of central nervous system.

The antituberculous treatment was stopped. The patient was started on oral prednisolone 1mg/Kg/day along with calcium supplements, proton pump inhibitors. She was given the first dose of intravenous cyclophosphamide 750 mg as per the standard protocol, to be repeated monthly for six months. Follow up after one month showed the patient was doing well, no recurrence of seizures, requiring assistance for activities of daily living and communicative.

Discussion

PACNS can present acutely or subacutely as space occupying lesion (SOL), meningitis, dementia, demyelinating disease or myelopathy. Although mentioned in the differential diagnosis stroke is unusual way of presentation of PACNS[3]. Its confirmation requires

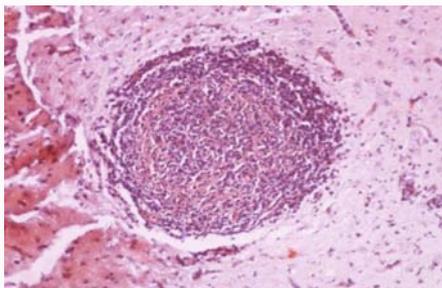


Figure 13: Congo red stain. Negative for amyloid.



Figure 14: Patient after brain biopsy.

extensive investigation to exclude many systemic disorders and other diseases of central nervous system. The patients also need a prolonged follow up, mainly to see whether the disease evolves in to another commoner disease entity. The present case underwent treatment for tubercular meningitis unnecessarily for nearly six months before a proper diagnosis could be made.

The imaging modalities do not have a definite diagnostic appearance in PACNS. There can be contrast enhancing lesions suggestive of granulomas, infarcts in the parenchyma, beaded

appearance of medium or small sized vessels on angiography or even a normal angiogram. The present case had shown normal vessels initially which evolved in to beaded appearance of the involved vessels subsequently. Hemorrhages were also described in a small percentage (10% to 12.5%) of cases[4]. But these cases from literature could be those of reversible vasoconstriction syndrome considering their acute presentation. In a recent metanalysis, Harsha et al tried to define imaging criteria for vasculitis – lesions showing linear/ lace like susceptibility weighted imaging (SWI) blooming with irregular margins, surrounded by FLAIR hyperintensity, and linear/lace/ central dot like enhancement at areas of abnormal SWI blooming[5]. Our present case had not shown blooming in any of the three sets of images obtained during her 9-10 months of illness. In fact blooming may suggest other pathologies like stroke or sinus venous thrombosis.

Brain biopsy may not always be possible. Though histopathological examination is the gold standard for diagnosis of primary vasculitis of central nervous system, it is performed only in 10% to 12% cases during life [6]. Biopsy is mandatory if one intends to treat with cyclophosphamide or other potent immunosuppressive agents which are the mainstay of treatment. Although present in many cases, giant cells are not mandatory to make a diagnosis. Fibrinoid necrosis can occur but eosinophils are not prominently seen.

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