CLINICAL VIGNETTE

Central Nervous System Vasculitis

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Case

A 54-year-old female with hypertension and hyperlipidemia presented to urgent care following an episode of tingling over the right face and hand. Vitals were remarkable only for elevated blood pressure at 148/96, and neurologic exam was normal. She reported experiencing significant stressors, and symptoms quickly resolved and she was sent home with return precautions.

Two days later, she developed new onset, severe headache described as a "jackhammer" sensation behind the eyes and extending over the top of the head, associated with photophobia and intermittent nausea. After five days of these symptoms, she presented to the emergency department, where a CT head showed only areas of microvascular ischemic gliosis. She was treated with intravenous valproate with improvement and was seen in neurology two weeks later and started on as-needed rizatriptan for a presumed diagnosis of migraine.

Three weeks later, she was hospitalized following 15-minutes of numbness affecting the right lower face and right hand with associated slurred speech, mild headache, and confusion characterized as difficulty remembering a friend's name. Brain MRI showed moderate white matter disease, likely sequelae from chronic microvascular ischemic gliosis. CT angiogram of the head and neck was normal. She was discharged with neurology follow up, where she was started on topiramate for complicated migraine unresponsive to triptans.

Her symptoms continued to progress over two weeks with increasing confusion, abnormal behavior, and mood lability. She was eventually unable to talk, write, or tolerate oral intake, and was taken to the emergency department by her spouse. Repeat MRI brain revealed significant progression of confluent white matter disease predominantly involving the frontal lobes with focal areas of enhancement. There was also leptomeningeal enhancement and a focal area of acute infarct within the high left frontal lobe. A lumbar puncture showed a white blood count of 105 with 95% lymphocytes, elevated protein at 123, borderline low glucose at 58. Extensive infectious evaluation including meningitis/encephalitis PCR panel was negative. CSF cytology showed no atypical cells and diagnostic cerebral angiogram was unremarkable.

On day three of hospitalization, she underwent brain biopsy with pathology revealing granulomatous inflammation within the leptomeningeal vessel walls, resulting in fibrinoid necrosis, consistent with primary central nervous system vasculitis. She was started on pulse-dose steroids with dramatic improvement in symptoms and received a dose of intravenous rituximab prior to discharge.

She has been followed by neurology and continued on ritixumab infusions along with a prolonged oral steroid taper. She has reported mild, intermittent recurrence of some symptoms but remains significantly improved from her most recent hospitalization.

Discussion

Primary CNS vasculitis remains rare, with incidence of 2.4 cases per 1 million person-years in one study. It can affect individuals of any age, with similar rates in males and females.[1] Presenting symptoms may be nonspecific and diagnosis can be challenging, leading to a delay in treatment in many cases.[2]

Headache is a common presenting symptom, which may precede or be accompanied by additional neurologic manifestations.[1,3] Other frequent signs include altered cognition, seizure, acute onset focal neurologic deficits, transient ischemic attack, ataxia, or encephalopathy that may progress to drowsiness and coma. Most patients present with multiple manifestations. Less frequently, patients may present with symptoms associated with intracranial hemorrhage. Systemic symptoms such as fever and weight loss are uncommon but have been reported.[1,3,4]

The gold standard for diagnosis remains histologic evidence of vascular-centered, transmural inflammation with vessel wall damage, obtained via brain biopsy. Granulomatous and lymphocytic patterns of inflammation are most common, while necrotizing vasculitis is seen less frequently.[2-4] Given the invasive nature of biopsy, patients frequently undergo imaging with MRI or MRA and/or cerebral angiography. Though findings may be nonspecific, low correlation has been observed between angiography and biopsy findings.[1,5] Common findings on MRI include multiple cerebral infarctions, lesions with parenchymal or leptomeningeal enhancement, and intracranial hemorrhage. MRA may show multifocal and segmental stenoses involving cerebral arteries with occlusions, dilations, and microaneurysms. These findings may be absent in a significant portion of patients.[2,3]

Guidelines from the European Stroke Organization suggest cerebral angiography when clinical suspicion of the diagnosis remains after non-diagnostic MRA.[6] Catheter angiography may have a sensitivity and specificity around 25-35%, which may be related to the subset of presentations involving primarily small cerebral vessels, resulting in normal findings on angiography.[7,8] Biopsy is recommended if suspicion remains for a small vessel vasculitis despite normal angiography.[6]

Many patients undergo lumbar puncture as part of the diagnostic evaluation. CSF findings frequently include nonspecific pleocytosis and elevated protein. The main role for CSF sampling is to evaluate other etiologies that may mimic CNS vasculitis.[1,3,4,6] Ruling out infection is of particular importance, as immunosuppression is the primary mode of management.

The most common treatment approach involves glucocorticoids in combination with an immunosuppressant such as cyclophosphamide or rituximab.[2,4,9,10] Adjunctive use of aspirin is suggested for patients with medium to large vessel involvement.[6] Improved functional status has been reported for patients continued on a maintenance immunosuppressive regimen with mycophenolate, azathioprine, or methotrexate. At least two years of maintenance therapy has been suggested.[6,9,10]

In the largest cohorts, induction immunosuppressive regimens resulted in symptom remission in 68-95% patients. Long-term remission has been reported in 21-66% of patients. Disease flares are common, reported in 12-59% of patients. Good neurologic status with a low level of disability (modified Rankin scale $\leq$ 2) has been reported in 46-73%.[1,2,4,7,9,10] Mortality has ranged from in 6-28% of patients in varying cohorts.[3,10]

Conclusion

Primary CNS vasculitis is a rare condition that can present significant diagnostic challenges. It may be suspected in patients presenting with headache, altered cognition, seizure, focal neurologic deficits, and/or encephalopathy in whom other etiologies such as stroke, infection, or malignancy have been ruled out. Diagnosis may involve MR imaging and/or cerebral angiography, though brain biopsy with histologic evidence of cerebral vasculitis remains the diagnostic gold standard. Treatment consists of immunosuppression, frequently with glucocorticoids followed by maintenance therapy with a non-steroid immunosuppressant. Favorable neurologic outcomes are achievable, though disease flares are common, and a significant mortality rate.

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