A 67-Year-Old Man With Headaches, Gait Changes, and Altered Mental Status

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The Neurohospitalist
3(4) 221-227
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DOI: 10.1177/1941874413483756
nhos.sagepub.com

A 67-year-old right-handed man was referred to a tertiary care center for headaches, changes in cognition, and gait imbalance. His symptoms began 3 months prior when he developed an unremitting, left-sided, parietal headache. The headache was unusual for him and was not associated with nausea, photophobia, or phonophobia. He had a history of prior headaches that began after minor head trauma in a skiing accident. However, those headaches were infrequent and invariably resolved after 1 day.

Shortly after the onset of headache, he began experiencing intermittent scotomas and scintillations in the right visual field. The visual phenomenon would resolve after several minutes. Around the same time, he began having word-finding difficulties and deficits in his short-term memory. There were no clear deficits in long-term memory or changes in mood, behavior, or emotional stability.

Within a few weeks, he began to feel unstable when walking. He had several falls due to what he described as a feeling of “being stuck to the floor” and then falling forward when he was finally able to move. His family noted a shuffling gait but no listing to either side. He had to start using a walker.

Two months after the onset of symptoms, his visual phenomenon resolved without any intervention. However, he then developed stereotyped, olfactory hallucinations consisting of 20-second episodes of smelling a foul odor. His gait also continued to decline with increased bradykinesia and shuffling. The headaches were still persistent.

He was seen at a local hospital 2 weeks after the onset of symptoms, where he underwent a lumbar puncture as part of his workup. Following the lumbar puncture, his gait temporarily improved.

His past medical history was significant for diabetes, hyperlipidemia, and hypertension. There was no significant family history. He had smoked 1 pack per day for 37 years, but quit 5 months prior to presentation. There were no systemic symptoms including fevers, night sweats, or rashes.

Neurologic Examination

On general examination, the patient was well appearing. He was afebrile. Blood pressure was 130/75 mm Hg. Heart rate

was 68 beats/min and respiratory rate was 12 breaths/min. On mental status testing, he was fully oriented and attentive with a digit span of 7 forward and 5 backward. Naming and repetition were intact. He could name only 3 D-words and 13 animals in 1 minute (normal = ≥ 16 D-words and ≥ 23 animals). There was no neglect. He scored 30 of 30 on the Mini-Mental Status Examination. The cranial nerve examination was normal including visual acuity, visual fields, and funduscopy. On motor examination, there was mild spasticity in the bilateral upper extremities. He had a subtle right pronator drift. Power was full on confrontational testing in all the 4 limbs. Sensation was intact to all modalities with a negative Romberg. Reflexes were symmetrical and 2+ in the biceps, triceps, brachioradialis, and patellas. Ankle jerks were absent bilaterally. Plantar responses were flexor. He had a shuffling, wide-based gait, and could not tandem.

Investigations

Imaging

Two months into the course of the illness, magnetic resonance imaging (MRI) of the brain with contrast was done (Figure 1). It showed sulcal fluid-attenuated inversion recovery (FLAIR) hyperintensity and leptomeningeal enhancement within the left parietal, temporal, and occipital lobes along with mild ventriculomegaly. A follow-up MRI, done 1 month later, showed progression of the leptomeningeal process with 3 new foci of reduced diffusion in the left parietal, temporal, and occipital lobes (Figure 2). Computed tomography (CT) of the brain and CT angiography of the head and neck did not show any vascular abnormalities.

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Figure 1. Initial magnetic resonance imaging (MRI) of the brain. A and B, Sulcal fluid-attenuated inversion recovery (FLAIR) hyperintensity within the left hemisphere (particularly the parietal, temporal, and occipital lobes). There is slight cortical expansion and effacement of the sulci along with mild hydrocephalus. C, Gyriform leptomeningeal enhancement within the left hemisphere (particularly the parietal, temporal, and occipital lobes).

Additional imaging included, a CT of the chest, abdomen, and pelvis which showed a 3 × 2 cm calcified, right upper lobe lung mass most consistent with a hamartoma (unchanged from a CT chest done prior to 10 years). There was no hypermetabolism on positron emission tomography (PET) in the lung mass or elsewhere.

Laboratory Studies

Cerebrospinal fluid (CSF) studies were significant for elevated protein (161), a normal cell count (3 white blood cells [WBCs], 100% lymphocytes), normal glucose (74), and an elevated immunoglobulin G (IgG) index (0.88). Extensive

laboratory testing was unrevealing as reported in Tables 1 and 2. A diagnostic test was performed.

Case Analysis

Discussant: S. Andrew Josephson. When working through a difficult case, it is best to begin by identifying the key elements of the history. In this patient's case, it includes the new onset of unremitting headaches, visual changes, and olfactory hallucinations, with an insidious decline in cognition and gait.

Let us begin by focusing on the headaches. The main question is whether they are just an exacerbation of his previous posttraumatic headaches or if they represent a new primary or secondary headache syndrome. Their unremitting character

Figure 2. Magnetic resonance imaging (MRI) of the brain 2 months later. A, Progression of left cerebral leptomeningeal disease. B, New involvement of the right anterior cingulate sulcus. C, New focus of reduced diffusion in the left parietooccipital lobe.

Table 1. Serum and Urine Laboratory Tests With Normal Results.

Metabolic	Infectious	Inflammatory	Hypercoagulable	Neoplastic
CBC; electrolytes; creatinine; BUN; LFTs; TSH; vitamin B12; MMA	HIV 1 and 2; RPR; FTA-Abs; Hepatitis B; Hepatitis C; lyme antibodies; coccidioides antibody and complement fixation; cryptococcal antigen West Nile IgG and IgM; TB skin test; Urine histoplasmosis antigen	ESR; ACE; C3/C4; ANA; anti-dsDNA; anti-Smith; RF; anti-RNP; anti-SSA/Ro; anti-SSB/La; anti-MPO; anti-PR3	Lupus anticoagulant; anti-cardiolipin	LDH; SPEP; UPEP; serum IFE

Abbreviations: CBC, complete blood count; BUN, blood urea nitrogen; LFTs, liver functional tests including alanine transaminase, aspartate transaminase, alkaline phosphatase, and total bilirubin. TSH, thyroid-stimulating hormone; MMA, methylmalonic acid; HIV, human immunodeficiency virus; RPR, rapid plasma reagin; FTA-Abs, fluorescent treponemal antibody-absorbed; TB, tuberculosis; ESR, erythrocyte sedimentation rate; ACE, angiotensin-converting enzyme; C3/C4, complement 3/complement 4; ANA, antinuclear antibody; anti-dsDNA, anti-double-stranded DNA antibodies; RF, rheumatoid factor; anti-RNP, anti-ribonucleic protein antibodies; anti-MPO, anti-myeloperoxidase antibodies; anti-PR3, anti-proteinase 3 antibodies; LDH, lactate dehydrogenase; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; IFE, immunofixation electrophoresis.

Table 2. CSF Laboratory Tests With Normal Results.

Infectious	Neoplastic
VDRL; coccidioides antibody and complement fixation; cryptococcal antigen; HSV 1 and 2; CMV PCR; VZV PCR; bacterial cultures; AFB cultures; fungal cultures	Cytology $\times 3$; flow cytometry $\times 2$

Abbreviations: VDRL, venereal disease research laboratory test; Cocci, coccidioides, CrAg, cryptococcal antigen; HSV 1 and 2, herpes simplex virus 1 and 2; CMV, cytomegalovirus; PCR, polymerase chain reaction; VZV, varicella zoster virus; Abs, antibodies; AFB, acid-fast bacilli; CSF, cerebrospinal fluid.

and the fact that they heralded a number of other neurological deficits are much more consistent with a secondary headache due to an intracranial process. The cause could be a new parenchymal lesion, a meningeal process, or elevated intracranial pressure, although the latter is less likely in the face of a normal examination of the optic disks.

The visual and olfactory changes may also provide an important clue. Although scintillations and scotomas can be frequently seen with migraine, they can also be a sign of cortical irritation in the occipital cortex or temporoparietooccipital junction. The appearance of the stereotyped, brief olfactory hallucinations shortly after the appearance of visual symptoms supports the presence of cortical irritation and possibly seizure as the most likely cause, perhaps secondary to a structural lesion. Taken together, the cognitive problems (language and memory dysfunction), visual phenomena, and possible seizures are suggestive of multifocal cortical involvement, perhaps more on the left, given the language dysfunction. The patient's unstable gait with magnetic features (characterized as "sticking to the floor"), which improved after lumbar puncture raises concern for the presence of hydrocephalus affecting subcortical frontal lobe regions.

Our patient also has several key findings on his neurological examination. The presence of bilateral upper motor neuron signs (bilateral arm spasticity) once again indicates a diffuse process. The wide-based, shuffling gait and the ability to name only 3 words beginning with the letter "D" both point to frontal lobe dysfunction, perhaps due to ventricular enlargement or another structural lesion. Imaging supports this multifocal condition with the findings of sulcal FLAIR hyperintensity and leptomeningeal enhancement, involving multiple areas of the left hemisphere along with mild ventriculomegaly that could be secondary to a leptomeningeal process. The presence of reduced diffusion consistent with infarction on the MRI suggests associated vascular involvement.

Once the region of involvement has been localized, we can concentrate on the differential diagnosis. Leptomeningeal enhancement on the MRI is suggestive of an inflammatory process, which is further supported by elevated protein and IgG index in the CSF. Notably, there is no evidence of systemic inflammation on the remaining serological workup, suggesting the process is likely confined to the central nervous system (CNS).

Several diagnoses come to mind when dealing with an isolated CNS inflammatory process of insidious onset, resulting in diffuse cerebral and leptomeningeal involvement. Common culprits to consider include carcinomatous meningitis, sarcoid, lymphoma, primary angiitis of the CNS (PACNS), and atypical infectious etiologies such as coccidioidomycosis, tuberculosis (TB), and some viral encephalitides. Although cerebral infarction has been reported in association with each of these diseases, it is most commonly observed in the setting of CNS angiitis and meningitis due to tuberculosis and coccidioidomycosis.

Carcinomatous meningitis is unlikely in this patient as it is extremely rare to have isolated carcinomatous meningitis in the absence of a systemic primary. Our patient had a normal PET/CT scan, a test often used to exclude systemic involvement in suspected malignancy, sarcoid, and paraneoplastic syndromes. The normal CSF glucose and negative cytology also point away from this etiology, although neither is sufficiently sensitive to exclude the diagnosis.

Infectious etiologies such as coccidioidomycosis and TB were addressed by negative cocci antibodies and complement fixation (serum and CSF) and negative CSF AFB cultures, respectively. The TB meningitis remains very difficult to exclude in these types of cases, since CSF testing is notoriously insensitive. However, most cases do have more prominent CSF findings including a low glucose and leukocytosis, neither of which is present in this case.

Sarcoidosis remains an important consideration; however, isolated neurosarcoidosis is rare, and since the patient had no evidence of systemic disease with a normal chest CT, PET scan, and serum angiotensin-converting enzyme level, this diagnosis is less likely.

A diagnosis of CNS vasculitis seems most likely in this case. There are several important misconceptions regarding PACNS. Although it is commonly thought that PACNS progresses in a stepwise fashion and evolves quickly over days to weeks, in reality, its onset can be quite insidious and progress in a slow, continuous fashion over months. Clinical manifestations of PACNS are not limited to parenchymal disease due to strokes, and meningeal disease occurs commonly; in fact, a purely isolated meningeal syndrome occurs in up to 15% to 20% of the cases.

The diagnosis of PACNS is best made by tissue biopsy. The yield of biopsy is highest when tissue demonstrating enhancement on postcontrast MRI is sampled. In this case, given the range of diagnoses being considered and the negative serologic and systemic workup, the most appropriate next step would be a brain and leptomeningeal biopsy.

Pathology

Discussant: Han Lee. The brain biopsy included portions of cortex and overlying leptomeninges. Within the cortical parenchyma, rare arterioles are associated with granulomatous inflammation, with the inflammation apparent primarily in the perivascular spaces (Figure 3A). Multiple vessels in the leptomeninges,

Figure 3. A, Granulomatous inflammation involving cortical arteriole. Hematoxylin and eosin (H&E) histology of formalin-fixed tissue, with a single intracortical arteriole associated with perivascular granulomatous inflammation (arrowhead). Cortical parenchyma shows scattered reactive astrocytes (arrows). Scale bar = 40 microns. B, Granulomatous inflammation involving leptomeningeal artery. The H&E histology of formalin-fixed tissue showing a small-to-medium leptomeningeal artery caused by granulomatous inflammation within tunica media and adventitia of the artery (arrowhead) and lymphocytes in the intima (asterisk), with intimal thickening. Leptomeninges is fibrotic (upper left corner). Scale bar = 40 microns. C, Granulomatous inflammation involving leptomeningeal artery. Immunohistochemistry for CD68 (clone KPI antibody, Dako) of formalin-fixed tissue highlights the staining of epithelioid histiocytes of the granulomatous inflammation, with involvement of tunica media, adventitia, and intima of the same artery as seen in B. Scale bar = 40 microns.

ranging from arterioles to small and medium arteries, also show involvement by granulomatous inflammation. The inflammation was variably identified within the tunica adventitia, media and/or intima of the vessel walls, and included a lymphocytic component (Figure 3B). The granulomatous component of the inflammation was also confirmed by immunohistochemistry for CD68, highlighting the epithelioid histiocytic composition of the granulomas and demonstrating their involvement in the vessel walls (Figure 3C). The adjacent leptomeninges showed extensive fibrosis, suggesting evidence for chronic injury. The granulomas are nonnecrotizing. Although fibrinoid necrosis of the vessels was not identified, these histologic features are nevertheless diagnostic of a vasculitis that is associated with granulomatous inflammation. Based on the caliber of vessels involved, this is also consistent with a small vessel vasculitis. Although multiple reactive astrocytes are present in the cortical parenchyma, indicating a moderate degree of astrogliosis (Figure 1A), no acutely ischemic neurons are identified. Nevertheless, there may be subtle overall reduction in the density of cortical neurons in this biopsy, suggesting at least the possibility of chronic ischemic injury to the cortex.

Vasculitides may be associated with a variety of infectious etiologies. Given the presence of granulomas, the possibility of an infectious process was considered. However, no evidence of fungal or mycobacterial organisms was identified with Grocott methenamine silver or acid-fast stains, respectively. In addition, a number of systemic vasculitides, including granulomatosis with polyangiitis (formerly known as Wegener) and Churg-Strauss syndrome, may show a granulomatous component in the inflammation. The absence of an eosinophilic component in the inflammation as well as the absence of hallmark findings such as asthma or eosinophilia argues against the diagnosis of Churg-Strauss syndrome. In addition, the presence of well-defined granulomas and the absence of necrosis in this case are features against granulomatosis with polyangiitis, where necrosis and poorly formed granulomas are more typical features. The granulomas of sarcoidosis at times also involve blood vessels, and this possibility is difficult to exclude based on biopsy alone. However, the widely scattered distribution of affected vessels and absence of a microscopically identifiable granuloma-associated mass would be more compatible with a primary vasculitis rather than sarcoidosis secondarily involving blood vessels. As such, in the absence of clinical or laboratory evidence of systemic disease and infection, these pathologic findings are consistent with PACNS.

Primary Angiitis of the CNS

Discussant: Sharon Chung and Yana Kriseman. Primary angiitis of the CNS (PACNS) is a rare vasculitis that affects small and medium vessels of the brain, leptomeninges, and spinal cord. It accounts for 1% of all systemic vasculitides.¹ When left untreated, PACNS can have a progressive and relentless course resulting in severe morbidity or death.

Clinical Presentation

The PACNS tends to affect men twice as often as women. Median age at presentation is 50.¹ Despite reports of PACNS in children and the elderly individuals, the occurrence of PACNS in patients aged younger than 30 years or older than 70 years is rare, and in these cases an alternate diagnosis should be strongly considered.²

Headache and encephalopathy are the most common symptoms of PACNS and are due to diffuse cortical dysfunction. In a large case series presented by the Mayo Clinic, 63% of the patients presented with headaches, while 50% had an insidious onset of encephalopathy sometime during their illness.³ Strokes, TIAs, and intracerebral hemorrhages were also common, occurring in 40%, 28%, and 8% of the patients, respectively. Hemiparesis, aphasia, visual changes, and ataxia were the most common clinical manifestations of the above vascular events, indicating possible large vessel involvement despite the belief that PACNS affects mostly small- and medium-sized vessels. Seizures were relatively infrequent, with 16% of the patients being affected. There was a low occurrence of systemic symptoms, with less than 9% of patients complaining of fevers, chills, or sweats.³ Spinal cord involvement is rare and can precede brain involvement by as many as 10 months. Isolated cord involvement is even more unusual with only 8 documented cases as of 2008.⁴

Studies. The CSF studies are abnormal in 80% to 90% of the patients with PACNS. Inflammatory markers are often present with elevated protein in more than 73% of the patients and oligoclonal bands in 20%.³ Mild to moderate lymphocytic pleocytosis can also be present. Although a range of 0 to 535 cells/ μ L has been seen, the median cell count is only 5 cells/ μ L, and an elevation above 250 cells/ μ L is rare.³ Systemic laboratories are rarely abnormal, with elevations in erythrocyte sedimentation rate in less than 25% of the patients and generally normal levels of antinuclear antibody, C-reactive protein, and rheumatoid factor.^{1,3}

Imaging is also usually abnormal, with 90% to 100% of the patients having findings on MRI. Ischemic infarcts are the most common finding and tend to be bilateral, occur in the distribution of multiple vessels, and involve cortical and subcortical structures.^{3,5} Less common findings include mass lesions (15%) and hemorrhages (10%). Leptomeningeal enhancement is present in 10% to 15% of the patients.³ The MRI angiography (MRA) is generally less helpful. The MRA only detected vasculitic changes in 59% of the patients who were diagnosed with vasculitis by either conventional angiography or biopsy.³ Of the 40% of patients who were not diagnosed by MRA, most had small vessel changes beyond the resolution of MRA.

Diagnosis

Brain biopsy is the mainstay of diagnosis of PACNS. Although conventional angiography is often used, angiography is neither

sensitive nor specific. It shows beading of multiple vessels of various calibers in multiple vascular distributions. The inability to visualize the frequently involved smaller vessels lowers the sensitivity of angiography to anywhere between 10% to 20% and 50% to 90%. Also, findings on angiography can be nonspecific due to the similar angiographic appearance of vasculitis mimics such as reversible vasoconstriction syndrome and CNS infections.^{1,3,6}

Biopsy is the gold standard for diagnosis of PACNS, showing a granulomatous vasculitis with a pleomorphic infiltrate of lymphocytes, plasma cells, and histiocytes. Due to the patchy nature of vasculitis, biopsy is not very sensitive and only approaches sensitivities of 40% to 60% in life and 75% on autopsy.^{1,7,8} Despite its low sensitivity, biopsy remains very useful with 40% of the biopsies establishing an alternate diagnosis such as infection or malignancy.⁷

Treatment

Patients diagnosed with PACNS are initially treated with prednisone at 1 mg/kg/d for a 3- to 6-week course followed by a slow steroid taper. If symptoms are especially severe, initiation of therapy with solumedrol in place of prednisone can be considered. Oral cyclophosphamide is frequently added to the regimen to maintain remission. Due to its toxicity with prolonged use, patients are usually maintained on cyclophosphamide for 3 to 6 months before transitioning to a less toxic immunosuppressant such as azathioprine or methotrexate.^{1,3} This regimen is based on the studies of granulomatosis with polyangiitis in which combined therapy with oral cyclophosphamide and prednisone had successfully induced remission of active disease, and less toxic immunosuppressants were used for remission maintenance.⁹

Serial MRIs should be done every 3 to 4 months in the initial treatment period to monitor disease progression.

Prognosis

Without treatment, PACNS carries a high rate of severe morbidity and mortality. However, up to 81% of the patients respond well to therapy, with decrease in Rankin scores in both the moderately and the severely affected groups. Patients with strokes, cognitive impairment, and large vessel involvement tend to do worse. Better outcomes are seen in patients with

leptomeningeal and cortical lesion enhancement, as these lesions likely have greater response to treatment.^{3,10}

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Keywords

vasculitis, central nervous system, autoimmune diseases of the nervous system, neuroimmunology, clinical specialty, stroke and cerebrovascular disease, clinical specialty

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