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Authors

Ngo, Angeline

McGehrin, Kevin

Di Loreto, Christina

et al.

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Clinical Reasoning: A 67-Year-Old Man With Multiple Intracranial Lesions

Angeline Ngo, MD, Kevin McGehrin, MD, Christina Di Loreto, MD, Rajan Arora, MD, and Jamie Nicole LaBuzetta, MD, MSc, MPhil

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Correspondence

Dr. Ngo
ann011@health.ucsd.edu

Abstract

A wide variety of diseases present with intracranial lesions. In this case report, a 67-year-old man initially presented to an outside hospital with nausea, headache, and ataxia and was found to have multiple intracranial lesions. Diagnostic workup was ultimately unrevealing, and his condition improved after a course of steroids and antibiotics. Unfortunately, symptoms returned 3 months later. MRI of the brain revealed progression of his intracranial lesions. This case highlights a diagnostic approach and general management strategy for patients presenting with undifferentiated intracranial pathology. A final diagnosis is ultimately reached and raises further discussion.

From the Department of Neurosciences (A.N., K.M., J.N.L.), University of California San Diego; Office of the Coroner Ada County (C.D.L.), Boise, ID; and Department of Neurology (R.A.), Keck School of Medicine of USC, Los Angeles, CA.

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Section 1

A 67-year-old Hispanic man presented with 2 weeks of headache, dizziness, nausea, vomiting, and ataxia. He had similar symptoms 5 months earlier, at which time he was admitted to an outside hospital. Prior MRI of the brain revealed contrast-enhancing lesions in his occipital cortex and cerebellum, and biopsy showed lymphocytic microvasculitis, although ultimately nondiagnostic. Broad infectious workup, including CSF studies, was negative. After a course of steroids and broad-spectrum antibiotics, including vancomycin, cefepime, and metronidazole, his symptoms had improved over 2

months. He was able to return to his occupation as a ranch manager, which included training horses. Unfortunately, he was lost to follow-up because of a lack of health insurance until his symptoms returned 3 months later, at which time he was admitted to our hospital. Examination showed a right monocular abduction defect and dense right homonymous hemianopsia.

Questions for Consideration:

1. Where do the presentation and examination localize?
2. What is the differential diagnosis?
3. What testing should be completed?

GO TO SECTION 2

Section 2

The presentation and examination localize to multiple areas within the CNS. The right homonymous hemianopsia localizes anywhere along the left optic tract, lateral geniculate nucleus, parietotemporal optic radiations, or calcarine fissure. The right lateral ophthalmoparesis is suggestive of a peripheral right cranial nerve (CN) VI nerve palsy, either from a pontine lesion or from elevated intracranial pressure (ICP) causing downward traction on the nerve. Dizziness and ataxia localize to the cerebellum or brainstem.

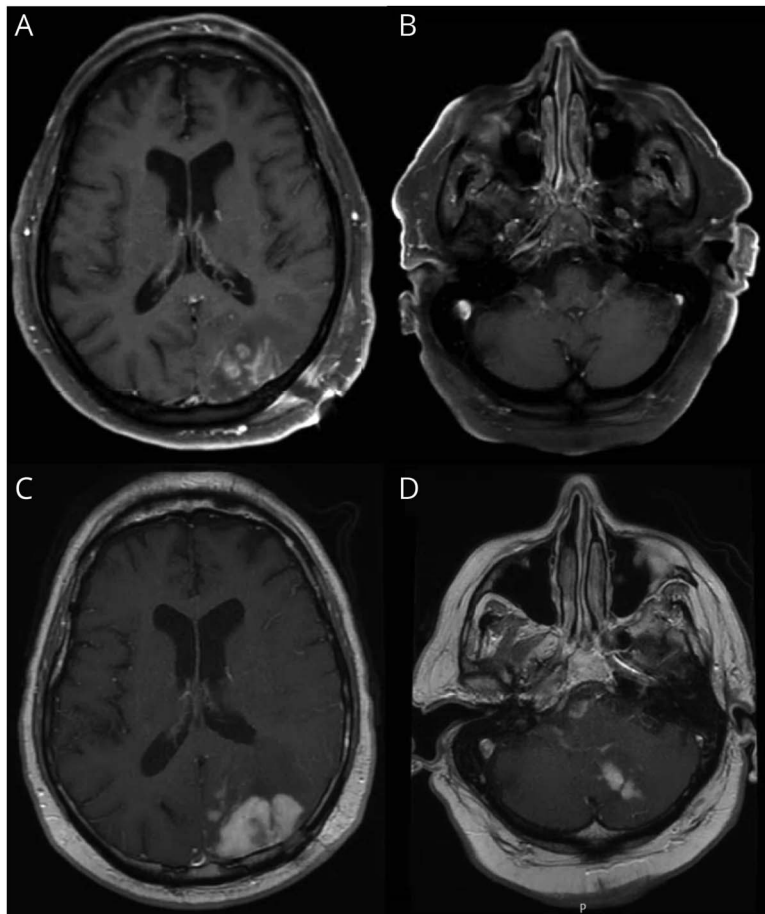
The main differential categories for multifocal, contrast-enhancing intracranial lesions are infectious and neoplastic, but vascular, autoimmune, and inflammatory diagnoses should also be considered. Possible infectious agents include bacteria, viruses, fungi, and parasites. Zoonotic illnesses should be considered given this patient's occupational exposures as a ranch manager. Chronic infections include tuberculosis, Brucella, John Cunningham (JC) virus, HIV,

Cryptococcus, toxoplasma, neurocysticercosis, Echinococcus, and Lyme.

Malignant etiologies that can relapse include primary tumors, particularly CNS lymphoma, and metastatic brain cancers. Although this patient's age is atypical for autoimmune and inflammatory disorders, tumefactive demyelinating diseases, Behcet disease, lupus, and neurosarcoidosis can present as discrete, relapsing CNS lesions. Vasculitis, including CNS primary angiitis, can also present with recurring mass-like lesions.¹

MRI of the brain with contrast is an important initial test. HIV status is crucial to determining immunocompetency and refining the differential. The patient's prior tests were equivocal, so lumbar puncture should be repeated. CSF studies should include infectious panels, cytology, and flow cytometry. Repeat brain biopsy will be necessary if CSF studies are unrevealing. Additional studies include angiography for vasculitis and MRI of the spine for clinically silent cord lesions. Malignancy scans should include chest, abdomen, and pelvis.

Figure 1 MRI of the Brain



MR T1-contrasted axial slices from (A, B) initial presentation compared with (C, D) current presentation, showing interval enlargement of the left posterior parieto-occipital lesion and new cerebellar and pontine lesions.

Results

Imaging

MRI of the brain showed interval enlargement of known occipital and cerebellar lesions, as well as new enhancing pontine lesions (Figure 1). MRI of the spine showed no abnormal cord enhancement. MR angiography showed no evidence of vasculitis. There was no evidence of primary malignancy on CT body scans or testicular ultrasound.

CSF

Opening pressure was 34 cm H₂O; 300 white blood cells (77% lymphocytes, 2% neutrophils, and 21% macrophages); 3 red blood cells; 99 mg/dL glucose; 211 mg/dL protein; gram stain negative; bacterial, fungal, and acid-fast cultures are pending; bacterial/viral/yeast panel

(eTable 1, links.lww.com/WNL/C797), and JC virus PCR negative; Cryptococcal antigen test negative; angiotensin-converting enzyme (ACE) 8 U/L; venereal disease research laboratory negative; and cytology and flow cytometry results are pending.

Serum

Results include HIV nonreactive, rapid plasma reagin negative, antinuclear antibodies positive/titer negative, antineutrophil cytoplasmic antibodies negative, ACE negative, Coccidiomycosis screen negative, and QuantiFERON-gold negative.

Questions for Consideration:

1. What are the next steps in management?
2. What are some considerations before starting empiric treatment?

GO TO SECTION 3

Section 3

The patient exhibited signs of elevated ICP including headache, vomiting, and CN VI palsy. At high risk for acute decompensation and herniation, he warranted close monitoring. Clinical symptoms that indicate an emergent ICP crisis are depressed mental status, irregular breathing, and fixed pupils. In this situation, airway protection must be considered along with other interventions including elevating the head of bed, brief hyperventilation, and hyperosmotic therapies.²

High-potency glucocorticoids can be used to treat vasogenic edema. Dexamethasone acts in astrocytes and pericytes to upregulate angiopoietin-1, a blood-brain barrier–stabilizing factor, and downregulate vascular endothelial growth factor, a

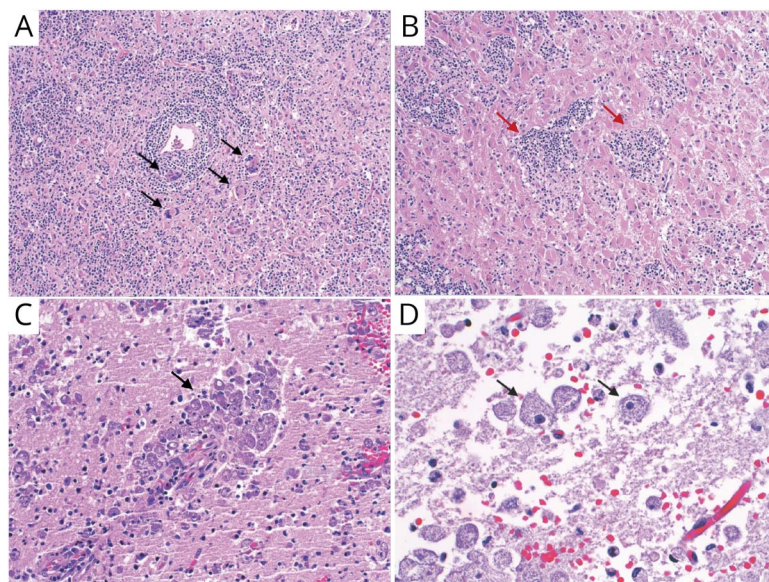
permeabilizing factor.³ The decrease in edema can contribute to a decrease in ICP over time. However, steroids should be ideally deferred until a brain biopsy can be repeated, as steroids may decrease sample yield given the possibility of lymphoma or demyelinating disease.⁴ The patient received a short course of dexamethasone. Antibiotics were not administered because of high concern for malignancy.

While pending results and biopsy, the patient developed worsened cerebral edema and hydrocephalus and quickly decompensated. Within 9 days of admission, he experienced a clinical herniation event and died. Brain autopsy was performed (Figure 2).

Question for Consideration:

1. What is the final diagnosis?

Figure 2 Autopsy Results



Hematoxylin and eosin–stained sections demonstrated (A, B) scattered multinucleated giant cells (black arrows) and clusters of epithelioid histiocytes and lymphocytes (red arrows) among sheets of swollen, reactive astrocytes (100× magnification). Meninges were involved. Areas of gross hemorrhagic necrosis disclosed fibrinoid vasculitis and microthrombosis, with focal hemorrhagic coagulative necrosis. On 200× magnification, (C) perivascular aggregates of large cells were seen among the inflammatory infiltrates (black arrow). (D) High-power (400× magnification) view of these cells demonstrated granular cytoplasm, low nuclear-to-cytoplasmic ratios, and small, round nuclei with prominent nucleoli. The cells were identified as *Balamuthia mandrillaris* trophozoites.

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Section 4

The diagnosis is amoebic meningoencephalitis, an exceedingly rare infectious encephalitis caused by the free-living protozoa, amoeba. Two distinctive clinical amoebic syndromes exist: (1) primary amoebic meningoencephalitis, an acute hemorrhagic meningoencephalitis caused by *Naegleria fowleri*, and (2) granulomatous amoebic encephalitis, a subacute chronic infection caused by *Acanthamoeba* and *Balamuthia mandrillaris*.

Discussion

Balamuthia was first isolated in 1986 from brain tissue of a mandrill that died of a necrotizing hemorrhagic encephalitis at the San Diego Wild Animal Park. The first human cases were discovered in 1991, and since then more than 200 cases of *Balamuthia* infection have been diagnosed worldwide, with at least 100 in the United States.^{5,6}

Naegleria is found in warm freshwater and transmitted through inhalation of infested water.⁵ *Balamuthia* enters through inhalation or direct contact of open wounds with contaminated soil or dust. Once infected, *Balamuthia* and *Acanthamoeba* spread to the CNS hematogenously.⁷ *Naegleria* and *Balamuthia* are known to cause disease in healthy humans, and a predominance of reported cases were men in southern and southwestern states, respectively.^{6,8} This demographic matched our patient, a Hispanic male in southern California. *Acanthamoeba*, in contrast, is found throughout the natural environment and causes opportunistic infection in immunocompromised hosts. The incubation period for *Naegleria* averages 5 days, whereas incubation of *Balamuthia* and *Acanthamoeba* can last weeks to months.⁷ Patients often present with headaches, meningismus, seizures, and lethargy. Symptoms are initially mild but invariably worsen over weeks to months, with a case fatality rate greater than 95%.⁵

Given its rarity and nonspecific symptoms, diagnosis of amoebic encephalitis is challenging and often made post-mortem. Brain MRI commonly reveals multifocal enhancing and sometimes cystic lesions with hydrocephalus.⁹ Definitive diagnosis of amoebic encephalitis is established by detection of amoeba in the brain tissue or CSF.

Available diagnostic techniques include culture, wet mount microscopy, serology, immunocytochemistry, and electron microscopy. In contrast to the necrotizing, hemorrhagic, fibropurulent meningoencephalitis of *Naegleria* or the granulomatous inflammation of *Acanthamoeba*, histologic findings of *Balamuthia* infection may vary between the 2, showing hemorrhage, necrosis, and inflammation with or without granulomas.¹⁰ Electron microscopy demonstrates triple-walled cysts.¹⁰ Another feature of *Balamuthia* is typically high concentration and specificity of serum antibodies, allowing for noninvasive detection via immunofluorescent antibody staining.¹¹ Newer diagnostic tools include molecular analysis of CSF and tissue using metagenomic

next-generation sequencing or real-time PCR.¹⁰ Unfortunately, effective utilization of these techniques, such as in this case, is often precluded by the delay in diagnostic consideration, rapid disease progression, and resource accessibility.

There are currently no standardized treatments for amoebic encephalitis because of the rarity of cases diagnosed pre-mortem and limited clinical data. Multidrug regimens for the few survivors have included amphotericin B, rifampin, fluconazole, miltefosine, and azithromycin; amphotericin B particularly has demonstrated in vitro activity against *Naegleria*.^{12,13}

After his first hospitalization, this patient's condition had improved for a couple months before worsening, which is unusual for amoebic encephalitis. Although unclear why, his improvement could possibly be attributed to effective activity of the broad-spectrum antibiotics against *Balamuthia* and a subacute to chronic dissemination of disease. Unfortunately, the disease ultimately progressed and proved fatal before diagnosis and any potential targeted treatment.

Many cases of amoebic encephalitis likely go unrecognized, as most providers are unfamiliar with the disease and its presentation. With increased awareness and utilization of rapid screening methods, earlier diagnosis may allow for the determination of effective treatment strategies with the goal of improving chances of survival.

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Appendix Authors

Name	Location	Contribution
Angeline Ngo, MD	Department of Neurosciences, University of California San Diego	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

Appendix (continued)

Name	Location	Contribution
Kevin McGehrin, MD	Department of Neurosciences, University of California San Diego	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design
Christina Di Loreto, MD	Office of the Coroner Ada County, Boise, ID	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Rajan Arora, MD	Department of Neurology, Keck School of Medicine of USC, Los Angeles, CA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Jamie Nicole LaBuzetta, MD, MSc, MPhil	Department of Neurosciences, University of California San Diego	Drafting/revision of the manuscript for content, including medical writing for content

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