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The (Un)Resolved Case: Blurry vision, left foot drop and brain cysts

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Abstract
This clinical vignette describes the interdisciplinary diagnostic approach to a patient with cystic brain lesions. The scope of this case is to develop the clinical reasoning skills of trainees in clinical neuroscience, taking into account alternative diagnoses and unusual clinical presentations.

Keywords
Multiple sclerosis, metastatic tumor, parasitic infection, evoked potentials/visual, MRI

Step 1

A 50-year-old male patient complained of blurred vision in his right eye worsening over the last 2 weeks. This presentation was accompanied by a lack of sensation and weakness in the left lower extremity as well as right-sided facial numbness. The patient was diagnosed with untreated hypertension and pulmonary tuberculosis 7 years ago. On admission, physical examination revealed normal sinus rhythm and blood pressure. Neurological evaluation showed reduced visual acuity in the right eye (0.5) and reactive and symmetric pupils without a relative afferent pupillary defect. Right-side facial sensation to touch was diminished, while other cranial nerves were not affected. Strength testing showed left tibialis anterior muscle paresis (Medical Research Council grade, 4/5), with muscle strength otherwise preserved in all limbs. The patient showed a slight left foot drop with steppage gait and severely impaired heel walking on the left side. Deep tendon reflexes were brisk and symmetric throughout, with an up-going left toe but no clonus. Muscle tone was normal in all four limbs. Vibration and postural senses were moderately impaired at the left ankle and slightly reduced at the right ankle. No other sensory deficits were observed. Laboratory values for complete blood count, C-reactive protein, electrolytes, and glucose were within normal range.

Questions step 1

What is your differential diagnosis at this point?
Which exam would you perform first?

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Step 2

Differential diagnosis is guided by potential lesion topography as well as the pattern of clinical evolution. A single lesion would hardly explain a clinical picture characterized by progressive right-sided vision loss, contralateral foot drop with pyramidal signs, along with patchy sensory deficits. Indeed, this manifestation could be explained by a concomitant occurrence of a neuro-ophthalmological condition (e.g. retinal disease or retrobulbar optic neuritis) and a right pontine bulbar lesion accounting for the right-sided facial and left lower limb deficits. Alternatively, this crossed sensorimotor pattern could be attributed to two distinct supratentorial brain lesions: one in the left convexity (loss of sensitivity of the right face) and another in the right medial sagittal part of the frontal lobe (left foot paresis). Finally, a lower spinal cord lesion could also account for the left foot drop.

Neuroinflammatory conditions are the main differential diagnosis for a subacute clinical presentation and progressive accumulation of lesions in the central nervous system (CNS). Among brain infections, neurosyphilis, pyogenic brain abscess, or tuberculosis should be considered. Additionally, a possible HIV infection needs to be ruled out, given the increased risk for these patients to develop opportunistic CNS infections such as cryptococcosis, toxoplasmosis, nocardiosis, or mycotic affection. Alternatively, metastases and more rarely primary brain tumors may cause scattered lesions with progressive neurological deficits.

Rapid brain and spinal cord magnetic resonance imaging (MRI) are indicated as pivotal investigations to detect inflammatory disease or tumors. MRI has clear advantages over computerized tomography (CT) to differentiate potential parenchymal lesions. Indeed, brain MRI revealed juxtacortical brain cysts in the corona radiata on both sides and adjacent to the left medial temporal gyrus. Some of these lesions displayed a gadolinium enhancement of the cyst walls and perilesional edema (Figure 1). Furthermore, multiple bilateral ovoid white matter lesions were found in the centrum semiovale and periventricular areas. MRI of the thoracic spinal cord showed two lesions, one of which exhibited gadolinium enhancement (T6–7).

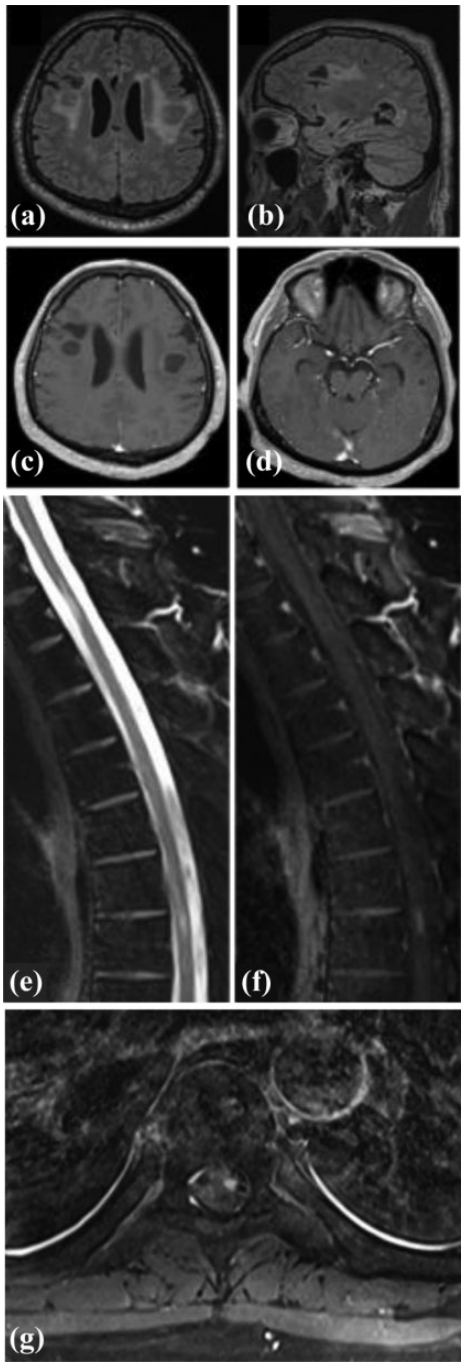

Figure 1. Brain and spinal MRI. 3-D FLAIR brain MRI sequence revealed (a) juxtacortical cysts with perilesional edema within corona radiata on both sides. (b) A cavity was located anterior to the right frontal cyst, and ovoid hyperintense lesions were present around the posterior horn of the right lateral ventricle. (c) The cyst walls exhibited gadolinium enhancement on a T1-sequence. (d) Another contrast-enhancing cyst was found adjacent to the left medial temporal gyrus. (e) On spinal cord MRI, T2-hyperintense lesions were seen at the level of T1 and T6–7, (f) one of which showed gadolinium enhancement (T6–7). (g) The enhancing lesion at the level of T6–7 was lateralized to the left. 3-D FLAIR: 3-D sagittal Fluid Attenuated Inversion Recovery; MRI: magnetic resonance imaging.

Questions step 2

What are the most common causes of cystic brain lesions?

Which exams are needed to rule out these conditions?

Step 3

The diagnostic workup of cystic brain lesions is extensive. Despite the pivotal role of brain MRI, cystic image features alone are not sufficient to determine an etiology.[1–3] The most common causes for brain cysts are neurocysticercosis (NCC) and metastases. However, other autoimmune CNS conditions can also result in cavitary lesions: multiple sclerosis (MS), acute disseminated encephalomyelitis, sarcoidosis, and Behçet disease.[3] NCC is the most common parasitic infection of the CNS,[2] particularly in endemic areas in Central and South America, sub-Saharan Africa, and Asia. Definite NCC diagnosis requires direct histopathological, imaging (MRI), or fundoscopic evidence of the parasite.[4] Additional major criteria include specific antibody immunoblot, response to anticysticercal drugs and spontaneous lesion resolution.[4] NCC usually affects the basal subarachnoid space, periventricular or juxtacortical areas.[2] Lesion appearance depends on infection stage: vesicular, degenerating, or residual with calcifications.[2,3,5] Overall, the average diameter of NCC cysts tends to be 8–10 mm (range 4–20 mm), although larger cysts are identified in the ventricles.[5] In this case, serology was negative for both NCC and HIV. Screening for other infections causing cystic brain lesions such as tuberculosis, echinococcosis (serology), or cryptococcosis (serum antigen) were also negative.

Breast and lung adenocarcinoma and melanoma are the most common tumors causing cystic brain metastases.[2,3,6] However, cystic glioblastoma and lymphoma can also occur. Total body CT looking for a primary mass outside the CNS was unremarkable.

Additionally, ophthalmological examination and fundoscopy did not reveal any retinal affection (e.g. papilledema, parasites). However, visual evoked potentials (VEPs) showed an absent P100 response in the right eye and a P100 latency at 130 ms (normal <114 ms) on the left side.

Questions step 3

How do you interpret the ophthalmological and visual evoked potentials findings?

Would you consider a lumbar puncture indicated and safe?

Step 4

Altered right visual acuity without visual field deficits and unremarkable retinal findings indicate acute optic neuritis, confirmed by an absent P100 response that reflects substantial acute inflammation including axonal damage. The P100 amplitude recovers with time, but its latency remains prolonged due to persistent demyelination. Therefore, the VEPs point toward a previous left optic neuritis in this patient.

At this stage, the clinical picture, MRI findings (Figure 1), and electrophysiology clearly suggest the diagnosis of MS, fulfilling the McDonald's criteria for spatial and temporal dissemination.[7] Nonetheless, a lumbar puncture (LP) was performed, given the unusual appearance of the lesions and that a tumor, an infection, or another neuroinflammatory disease was not formally ruled out. In the presence of brain cysts, an LP is considered safe when no signs of intracranial hypertension are seen and the cysts are located outside bottlenecks of the cerebrospinal fluid (CSF) system. The LP showed CSF protein at 1101 mg/L (normal: 150–450 mg/L), 10 cells (all lympho-mononuclear cells), and an intra-thecal synthesis of immunoglobulin G (IgG; oligoclonal bands, type II). CSF glucose and lactate levels were not measured. Anti-MOG (myelin oligodendrocyte glycoprotein) and anti-NMO (neuromyelitis optica) antibodies were negative. No malignant cells were found by CSF flow cytometry.

Question step 4

Would you retain multiple sclerosis as the only diagnosis or perform an additional exam? If yes, which?

Step 5

Taken together, these findings strongly suggest a diagnosis of MS, although cavitary or cystic lesions only very rarely occur in these patients.[8–10] However, concurrent lymphoma or cysts of infectious origin were not formally excluded. Intravenous (IV) administration of methylprednisolone and subsequent immunomodulatory treatment were indicated for the presumptive diagnosis of MS. Since, these treatments may exacerbate an infectious disease or lead to subsequent false-negative biopsy findings in the case of CNS lymphoma, an interdisciplinary panel recommended brain biopsy. After thorough discussion of risks and benefits and informed patient consent, a right frontal supratentorial craniotomy was performed to access the more posterior of the two right frontal lesions (Figure 1). Neuropathological examination showed an inflammatory and demyelinating lesion, compatible with MS, without other abnormalities (Figure 2). The patient fully recovered after a course of IV methylprednisolone 1000 mg daily over 5 days. During outpatient follow-up, the disease-modifying MS treatment fingolimod was initiated.

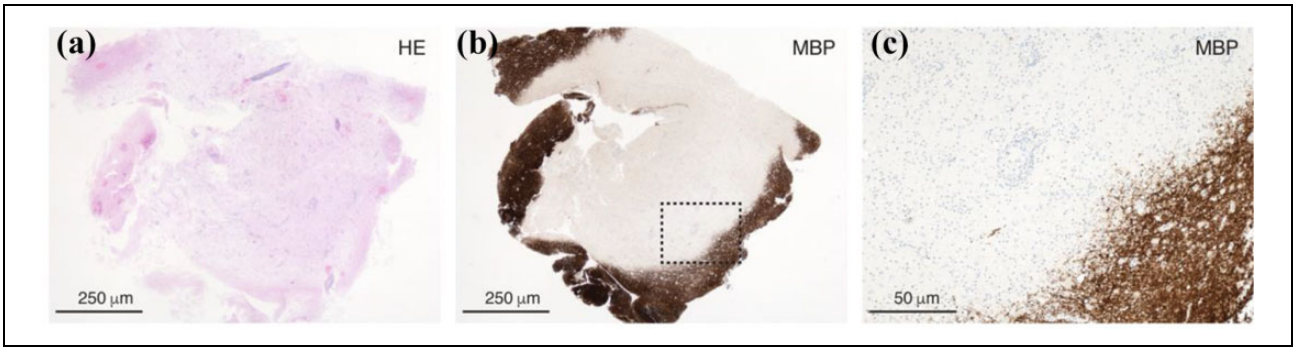

Figure 2. Neuropathological evaluation of the lesion. The histological analysis of the brain biopsy reveals a well-demarcated white matter lesion with a nodular focus of demyelination, as illustrated on (a) HE coloration and (b) MBP immunohistochemistry. Scale bar, 250 μm. (c) Magnified inset of the region highlighted in (b) showing the lack of MBP at the center of the lesion, while the borders show normal myelination. Scale bar, 50 μm. HE: hematoxylin and eosin; MBP: myelin basic protein.

Synopsis

The patient was affected by MS mainly presenting with cystic brain lesions. The current relapse consisted of a right optic neuritis, an acute, gadolinium-enhancing T6–7 spinal lesion likely explaining the left foot drop, and several acute cystic lesions, of which the one located in the left corona radiata caused the sensory deficit of the right side of the face. Cavitary or cystic lesions have been rarely described in MS (Table 1). The cystic phase appears to represent acute inflammatory processes, whereas cavities such as the one observed within the right anterior frontal lesion in our patient (Figure 1) reflect old, chronic lesions, analogous to the so-called 'black holes'.

In MRI, cystic and even more so cavitary lesions do not only differ from "black holes" in size: both are T1-hypointense and T2-hyperintense, but cavitary lesions exhibit hypointensity on fluid attenuated inversion recovery (FLAIR) sequences, whereas 'black holes' are FLAIR-hyperintense (Figure 1 and Table 2). The long inversion time of FLAIR suppresses extracellular water signal, such as CSF or intracavitary fluid.[10] Juxtacortical cavitary MS lesions are frequent, but in contrast to the present case, they tend to predominantly affect parieto-occipital areas. Disease onset in patients with cystic MS is usually delayed (median age: 37 years).[10] Furthermore, these patients tend to exhibit a progressive course of the disease[8–11] with significant cognitive impairment.[8]

Across various etiologies, cystic or cavitary brain lesions are more often found in children and adolescents than in adults. Here, congenital cytomegalovirus infection, neonatal hypoxic-ischemic encephalopathy, childhood ataxia with CNS hypomyelination syndrome, mitochondrial leukoencephalopathy, and cystic megalencephalic leukoencephalopathy have to be taken into account.[10]

In conclusion, in a patient with cystic brain lesions, major differential diagnoses are NCC and brain metastases (Table 1). However, thorough clinical assessment, correlation of radiological with clinical findings and interdisciplinary evaluation may reveal much rarer causes of cystic lesions, such as MS.

Table 1. Differential diagnosis of cystic brain lesions.

Etiology	Neoplastic	Parasitic			Fungal	Bacterial	Autoimmune			
Major causes of brain cysts	Metastases/primary brain tumors	Neurocysticercosis	Echinococcosis	Toxoplasmosis	Cryptococcosis	Tuberculosis	MS	ADEM	Neurosarcoidosis	Behçet disease
Complementary investigations	Retinal exam: abnormalities, for example, papilledema	Retinal exam: for example, parasites	Retinal exam: for example, parasites	Retinal exam: for example, parasites	Retinal exam: for example, choroiditis	Retinal exam: for example, uveitis	Retinal exam: generally normal	Retinal exam: generally normal	Retinal exam: for example, uveitis	Retinal exam: for example, uveitis
	CT total body for primary tumor	Specific serology	Specific serology	Specific serology HIV serology	Specific serum antigen HIV serology	Specific serology HIV serology			CT total body	
Visual evoked potentials	Normal	Normal	Normal	Normal	Normal	Normal	Abnormal	Rarely abnormal	Rarely abnormal	Abnormal
CSF	OCB: <5% incidence	OCB: can be present	OCB: can be present	OCB: can be present	OCB: can be present	OCB: can be present	OCB: 95% incidence	OCB: variable Anti-MOG can be present	OCB: 40% incidence	OCB: 20% incidence
Neuropathological findings	malignant cells	Presence of cysticerci according to their stage	Presence of echinococcal cyst	Multiple basophilic dot-like parasites can be seen in cysts.	Granuloma containing cryptococcus	Granuloma	Demyelination	Demyelination	Granuloma	Perivascular infiltration of neutrophils

ADEM: acute disseminated encephalomyelitis; MS: multiple sclerosis; CSF: cerebrospinal fluid; FLAIR: fluid attenuated inversion recovery; CT: computerized tomography; OCB: oligoclonal bands.

Table 2. Distinctive MRI features of black hole and cystic/cavitary lesions.

	Black hole	Cystic/cavitary lesion
T1	Hypointense	Hypointense
T2	Hyperintense	Hyperintense
FLAIR	Hyperintense	Hypointense
Morphological correlate	Area of axonal loss and edema	Intracavitary fluid

FLAIR: fluid attenuated inversion recovery.

Author contributions

GDL, IAR, and AAS analyzed data and drafted this manuscript. IAR and AAS acquired data. RADP, JNC, MS, NBB, PM, JPB, and RTD revised the manuscript for content. AAS supervised this case discussion.

Declaration of conflicting interests

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