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Educational Case

Educational case: Brain abscess

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see https://www.journals.elsevier.com/academic-pathology/news/pathology-competencies-for-medical-education-pcme.[1]

Keywords: Pathology competencies, Organ system pathology, Central nervous system infection, Brain abscess, Clinical microbiology

Primary objective

Objective NSC2.1: Infections of the CNS. Compare and contrast the clinical, gross, and microscopic manifestations of common bacterial, viral, and fungal infections of the central nervous system.

Competency 2: Organ system pathology; Topic: nervous system: Central nervous system (NSC); Learning goal 2: Infection

Secondary objective

Objective M1.3: Identification. Give examples of the types of testing, and their optimal usage, performed in microbiology to identify an infectious disease.

Competency 3: Diagnostic medicine and therapeutic pathology; Topic: Microbiology (M); Learning goal 1: Pathogenesis, diagnosis, and treatment of infectious disease

Patient presentation

A 22-year-old woman presents to a community hospital after having a generalized seizure at work, which lasted for 5 min and was associated with incontinence of urine. She has an unremarkable past medical history and denies using alcohol, tobacco or illicit drugs. She works as a nursing assistant in a nursing home. She is married and lives with her husband and four young children.

Diagnostic findings, Part 1

At the hospital, the patient's temperature is 98.4 °F, pulse 134 beats per min, blood pressure 131/70 mmHg and respirations 28 per min. On examination, she is drowsy, staring blankly, unresponsive to verbal stimuli but without focal neurological findings. Ten minutes after her arrival, she has a second seizure characterized by unresponsiveness, rigid extremities, head turned to the side and cyanosis.

Questions/discussion points, Part 1

What are the most common causes of new onset seizures?

The most common causes of seizures vary greatly by age group.[2] Fever is the most common cause of seizures in children. Between 2% and 5% of children have febrile seizures.[3] Cerebrovascular disease is the most common cause of seizures in adults over 35 years of age.[2] In young adults such as this patient, the new onset of seizures does not have a single predominant cause. Trauma is the most common cause, but tumor is a close second most common cause.[2] Gliomas and meningiomas often present with seizures. Drugs, especially alcohol withdrawal, are an important cause of seizures in young adults. Autoimmune encephalitis, including anti-NMDR encephalitis in young women with ovarian teratomas, can present with seizures.[4] Infections, including herpes simplex virus encephalitis or neurocysticercosis, can present with seizures. The cause of new onset seizures is idiopathic in many young adults.[2]

The most common causes of recurrent seizures unprovoked by fever or drug toxicity (epilepsy) also varies by age. Recurrent seizures in a neonate, within 48 h of a difficult birth, are usually due to severe anoxic brain injury.[2] Recurrent unprovoked seizures in an infant are often due to congenital malformations, for example, cortical plate malformations such as focal cortical dysplasia, which can exist alone or in association with hippocampal sclerosis or an adjacent lesion (e.g., glial or glioneuronal tumor, vascular malformation, etc.). Epilepsy beginning in

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early childhood may be benign, without intellectual impairment, and may cease in adolescence. The most common causes of recurrent unprovoked seizures in later childhood and adolescence shade into those in young adults and include arteriovenous malformations.[2]

The new onset of seizures can be due to underlying treatable disease, making recognition of the cause important. Hyponatremia, hypernatremia, hyperglycemia, hypoglycemia, hypocalcemia, uremia, and thyrotoxicosis are among the many metabolic derangements that can cause seizures, which resolve with successful treatment of the underlying medical disease.[2] Seizures can be an adverse effect of medications such as cefepime, imipenem, linezolid, tramadol, bupropion, and many others.[2] Illicit drugs such as methamphetamine, cocaine or high-potency synthetic cannabinoids can cause seizures. Bacterial meningitis can cause seizures, which will be associated with fever, headache and stiff neck. In immuno-compromised patients, central nervous system primary lymphoma or opportunistic infections such as *toxoplasmosis* can present with the new onset of seizures.[2] The most likely cause of new onset seizures in each patient depends on their age, immunological status, and other conditions.

Diagnostic findings, Part 2

The patient's white blood cell count is 11,900/cu mm (70.6% granulocytes, 22.6% lymphocytes, 6.8% monocytes), hemoglobin 13.1 g/dL, platelets 192,000/cu mm, sodium 138 mEq/L, potassium 3.8 mEq/L, chloride 104 mEq/L, carbon dioxide 19 mEq/L, blood urea nitrogen 7 mg/dL, creatinine 0.8 mg/dL and glucose 106 mg/dL. Following her second seizure, the patient's pulse increases to 145 per min. She is given supplemental oxygen and a loading dose of phenytoin. Computerized tomography (CT) of the head shows a single 1.5 cm ring-enhancing lesion in the high left parietal lobe with less density in the center of the lesion and moderate surrounding edema.

Questions/discussion points, Part 2

What is the differential diagnosis for a ring-enhancing lesion in the brain?

The most common causes of a ring-enhancing lesion in the brain can be sorted into five groups: metastases, abscesses, glioblastomas, infarcts (or inflammation) and contusions.[5] Taking the first letter of each, the acronym MAGIC can serve as a memory aide for the most common causes of a ring-enhancing lesion. The acronym is only a starting point. Glioblastomas are only one type of the high grade brain primary tumors that can cause a ring-enhancing lesion. A little clarification of the letter "I" conditions is needed because only infarcts in the subacute phase are likely to produce a ring-enhancing lesion, and multiple inflammatory conditions can cause ring-enhancing lesions. *Cysticercosis*, *toxoplasmosis* and *tuberculosis* are typically associated with ring-enhancing lesions, but demyelinating diseases can also sometimes produce lesions that are ring-enhancing. Metastases are perhaps the most common etiology of a ring-enhancing lesion in the United States, where the annual incidence of tumors in the brain is 46 per 100,000, but only one-third of these are primary brain tumors.[6] Brain metastases and glioblastomas are usually seen in older adults. Brain abscesses are far less common, with reported annual incidence ranging from 0.4 to 0.9 per 100,000.[7] Cerebral infarcts are primarily in older adults with advanced atherosclerotic cardiovascular disease and rarely first detected in a subacute phase associated with a ring-enhancing lesion. The most likely cause of a ring-enhancing lesion depends on the age of the patient. One approach to the differential diagnosis is to first try to put the lesion into one of two broad categories of inflammatory diseases or non-inflammatory diseases. If inflammatory, the next step is to try to put the lesion into the subcategory of infectious diseases or non-infectious diseases. The correct diagnosis is most likely to come from an interdisciplinary collaborative teamwork of radiologists and clinicians.

Diagnostic findings, Part 3

The patient is transferred to a large public hospital, where she is alert, oriented and without focal neurological findings. Her temperature is 97.8 °F, pulse 80 beats/minute, blood pressure 94/64 mmHg and respirations 18 per min. On review of systems, the patient reports having a headache for the previous 3 days. She also reports visiting an emergency room for a severe headache 3 years prior. She denies having any severe headaches since that time. The scan from the other hospital is reviewed by a radiologist at the public hospital and diagnosed as abscess, *cysticercosis* or tumor. The prevalent causes of brain lesions in young adult patients in this hospital are abscesses from endocarditis in intravenous drug users and cysticercosis in recent immigrants. The medical team caring for the patient judges abscess unlikely, and their diagnosis is "rule out glioma." The patient is treated with oral phenytoin and dexamethasone, but no other medications. She is clinically stable, without further seizures.

On hospital day 2, the patient's white blood cell count is 14,300/cu mm (66% segmented neutrophils, 1% bands), hemoglobin 12.2 g/dL, platelets 204,000/cu mm, calcium 8.9 mg/dL, phosphorus 3.7 mg/dL, glucose 97 mg/dL, bilirubin 0.5 mg/dL, alkaline phosphatase 85 U/L, alanine aminotransferase 21 U/L, aspartate aminotransferase 20 U/L, globulin 7 g/dL, albumin 3.9 g/dL, lactate dehydrogenase 129 U/L and creatine phosphokinase 57 U/L. Testing for human immunodeficiency virus infection is negative. On day 3, magnetic resonance imaging (MRI) scan with gadolinium shows a bilobed ring-enhancing lesion with a thick irregular wall in the left parietal lobe, measuring $2.1 \times 1.5 \times 1.5$ cm, with moderate surrounding edema; there is also mild mucosal thickening in the right frontal sinus. The radiologist's diagnosis is: "suspicious for a primary brain tumor." With this presumptive diagnosis, the patient is scheduled for a non-emergency brain biopsy two weeks later. She is clinically stable and discharged home to await her brain biopsy.

Questions/discussion points, Part 3

How does this additional clinical information alter the differential diagnosis?

The patient has a mild and increasing leukocytosis, which suggests the possibility of infection, but also could represent a nonspecific stress response. She has tachycardia without fever, which would fit with a stress response. She has no heart murmur to suggest a cardiac source of emboli to the brain. Some brain abscesses are associated with simultaneous liver abscesses, so the normal liver tests are helpful in making brain abscess less likely. The apparent increase in size of the brain lesion in this case from 1.5 cm on CT to 2.1 cm on MRI a few days later is not interpreted as true growth or progression, but presumably attributed to the differences between the types of scan or the slices scanned. The lesions of *neurocysticercosis* are often multiple and often calcified, making that less likely in this case. Inflammatory brain lesions and tumors may have a similar pattern of ring enhancement around a non-enhancing core of cystic components or necrosis.[8] Glioblastoma tends to be more spherical than brain abscess, which can help differentiating these conditions.[9] Texture analysis of ring-enhancing lesions on MRI based on machine learning approaches are computer-aided diagnostic tools that can assist radiologists in differentiating inflammatory brain lesions from tumors.[8]

Diagnostic findings, Part 4

The patient is re-admitted to the hospital one week later with aphasia and word-finding difficulty. On examination, she also has mild right pronator drift. The patient's white blood cell count is 16,500/cu mm (86% segmented neutrophils, 4% bands), hemoglobin 14.1 g/dl, platelets 327,000/cu mm, glucose 137 mg/dL and lactate dehydrogenase 213 U/L. She is continued on oral phenytoin and dexamethasone therapy. She is clinically stable. She undergoes her previously scheduled stereotactic brain biopsy. The biopsy is evaluated in the frozen section room at the

time of surgery and shows findings such as those in Fig. 1. Normal brain for comparison is shown in Fig. 2.

The pathologist sees the abundant glial cells and knows the diagnoses made by the radiologist and the clinicians. She recognizes that the findings could represent a glioma, but knows they could also represent reactive gliosis in the ring-enhancing margin of the lesion and that a sample from the less dense center of the lesion might be more specifically diagnostic. She asks the neurosurgeon to make another pass, deeper into the lesion, and get another biopsy. This second biopsy shows findings such as those in Fig. 3.

Recognizing the necrotic brain tissue infiltrated by large numbers of neutrophils as an abscess, the pathologist instructs the neurosurgeon what appropriate samples to take for the clinical microbiology laboratory and what tests to order on them.

Questions/discussion Points 4

What pathogens cause brain abscesses?

Brain abscesses can be caused by bacteria (aerobic or anaerobic), fungi, mycobacteria, or parasites (helminths or protozoa).[7] Most brain abscesses are due to bacteria, often from the normal oral flora, and many brain abscesses are polymicrobial, including both aerobes and anaerobes.[10,11] The organisms most commonly isolated are anaerobic bacteria, aerobic and microaerophilic *streptococci*, various *Enterobacteriaceae*, and *Staphylococcus aureus*.[10] *Streptococcus intermedius* has emerged as a frequent pathogen in brain abscesses.[12,13] Among the anaerobes, *Fusobacterium nucleatum* is frequently a pathogen in brain abscesses.[14,15] *Actinomyces* species are sometimes among the anaerobic pathogens in polymicrobial brain abscesses.[16,17] *Mycobacterium tuberculosis* can cause a brain mass with necrosis.[18] *Nocardia* species are an important cause of brain abscess in immunocompromised patients.[19] Fungi such as *Aspergillus* species can also cause brain lesions with necrosis in immunocompromised patients.[20]

What are appropriate samples for the clinical microbiology laboratory to identify the pathogens in a brain abscess?

Aspirate of the liquid center of a brain abscess is usually the best sample for the clinical microbiology laboratory to identify the pathogens causing the infection. Cerebrospinal fluid or blood cultures identify a pathogen in approximately 25% of cases, particularly in patients with meningitis, but the risk of brain herniation must be taken into account and lumbar puncture should be performed only when there is clinical suspicion of meningitis or abscess rupture into the ventricular system and there are no contraindications for lumbar puncture.[7] Gram stain, aerobic and anaerobic cultures are generally the most essential testing. In immuno-compromised patients, smears and cultures should also be done for *mycobacteria*, *nocardia* species, and fungi; nucleic acid molecular testing by polymerase-chain-reaction (PCR) assay for *Toxoplasma gondii* should be performed as well.[7] If a bacterial etiology is strongly suspected but bacterial cultures are negative, PCR-based 16S ribosomal DNA sequencing may provide a definitive diagnosis, enabling targeted antimicrobial therapy. If available and resources allow it, molecular testing can be particularly helpful in identifying anaerobic pathogens in brain abscesses.[21] Molecular diagnostic methods are continuously evolving and next generation sequencing may reveal multiple pathogens as well as expanding the spectrum of pathogens detected.[22] The best specimen for such testing may be frozen and the need for it not evident at the time of collection, so it could be helpful for the pathologist to suggest freezing some of the material collected for possible future use.

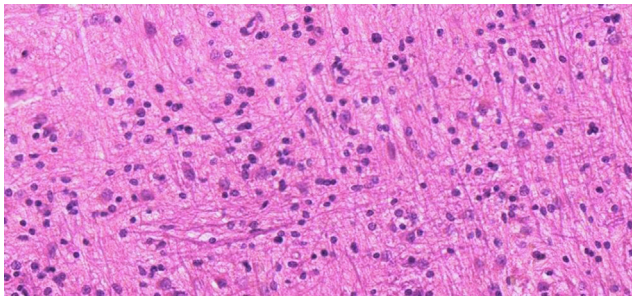

Fig. 1. Gliosis with loss of neurons and increased numbers of glial cells (H&E, X40).

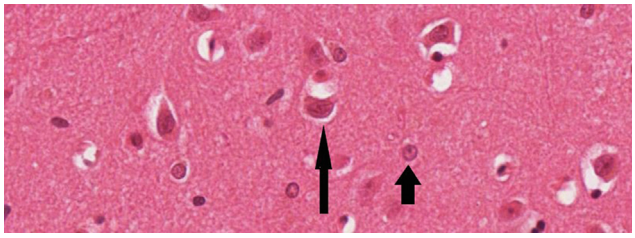

Fig. 2. Normal brain for comparison, with neurons (one indicated by thin arrow), some associated with glial cells (one indicated by thick arrow) (H&E, X40).

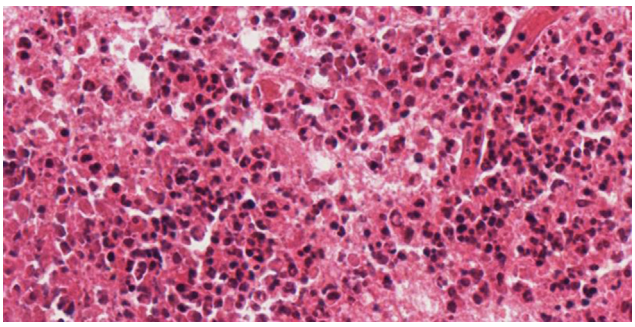

Fig. 3. Necrotic brain tissue with numerous neutrophils recognizable by their multilobed nuclei (H&E, X40).

What is the pathological evolution of a brain abscess?

Intraparenchymal brain abscess starts with spread from a contiguous site of infection in about half of cases.[7] Such contiguous foci include the paranasal sinuses, the nose, mastoid air cells, the ears, the teeth, and sites of trauma or invasive neurosurgical procedures.[23] Brain abscess starts from hematogenous spread of infection in about one third of cases, and from unknown mechanisms in the remaining non-contiguous non-hematogenous cases.[7] Hematogenous brain abscess is often secondary to septic emboli from infective endocarditis. Cerebral abscess evolution can be described in 4 stages: early cerebritis, late cerebritis, early capsule formation, and late capsule formation.[24] Ring enhancement represents the granulation tissue of evolving capsule in the later phases of the host response to contain the infection. The characteristic MRI feature of mature necrotizing brain abscess is fluid hyperintense relative to CSF and hypointense relative to white matter on T1-weighted imaging. T2-weighted imaging showing hyperintensity compared to both CSF and gray matter.[24] The gross and microscopic pathology of brain abscesses do not vary enough with specific pathogens to allow for helpful comparison and contrast.

What are the clinical manifestations of a brain abscess?

The signs and symptoms of a brain abscess are nonspecific, variable and rarely point to a specific pathogen. The reported percentages of various clinical manifestations have a broad range and some are lumped into categories that vary among the reports. As shown in Table 1, the most common presenting symptom is headache, typically generalized.[7,11,23,25] Focal neurological deficits such as hemiparesis, aphasia or

Table 1
Signs and symptoms of brain abscess

Clinical manifestation	Range of frequency
Headache	50–90%
Focal neurological deficit	30–80%
Altered mental status	35–70%
Fever	15–85%
Nausea and vomiting	25–50%
Seizures	5–45%

ataxia might be the second most common clinical manifestation.[7,23,25] Altered mental status, with confusion, lethargy or agitation, may be the next most common manifestation.[11,23,25] Fever was part of the classic triad of clinical manifestations of brain abscess (headache, focal neurological deficit, and fever), but this triad is increasingly uncommon and now present in less than 20% of patients.[11,23] The range of reported frequency of fever as a manifestation of brain abscess is particularly broad, but it is probably less common than focal deficits or altered mental status. Nausea and vomiting can occur in association with increased intracranial pressure. The new onset of seizures can be a clinical manifestation of brain abscess.

The most likely pathogens in a brain abscess vary with the anatomic source of infection, as does the most likely site of the abscess within the brain. As shown in Table 2, brain abscesses often start with contiguous spread from a paranasal sinus into the frontal lobe and the most likely pathogen is a member of the *Streptococcus milleri* group, which includes *Streptococcus anginosus*, *Streptococcus constellatus* and *Streptococcus intermedius*.[10] Among these *streptococci*, *Streptococcus intermedius* has emerged as the most frequent pathogen in brain abscesses.[12,13] An odontogenic source of infection leading to brain abscess is increasingly recognized.[11] Odontogenic brain abscesses are most often polymicrobial, including oral anaerobes such as *Fusobacterium nucleatum*.[14,15] Otogenic brain abscesses from otitis or mastoiditis are most often in the adjacent temporal lobe and most often with the same pathogens as those from sinusitis. Hematogenous brain abscesses from endocarditis, neurosurgery or trauma are frequently multiple and *Staphylococcus aureus* is a leading pathogen in this context.[10,23,25]

What is the management of a brain abscess?

Management of a brain abscess generally includes both antibiotic therapy and neurosurgery.[7,25] The antibiotics should cover the pathogens, but must also be ones able to cross the blood-brain barrier. If a brain lesion is identified as an abscess, empiric intravenous antibiotic therapy is begun, often with ceftriaxone or cefotaxime combined with metronidazole.[26] Third generation cephalosporins such as ceftriaxone cover the most common *streptococcal*, *staphylococcal* and other bacterial pathogens in brain abscesses. So, for instance, in a study of 47 brain abscess cases, all 29 *streptococcal* pathogens, both *staphylococcal* pathogens, and all but 5 other pathogens were sensitive to ceftriaxone; the only pathogens not covered by ceftriaxone were 3 *Pseudomonas aeruginosa* and 2 *Listeria monocytogenes*.[12] Metronidazole covers the oral flora anaerobic bacteria that are sometimes among the pathogens in brain abscesses.[12,26] Neurosurgery is required for the identification of the causative pathogen, and sometimes drainage to reduce the size of the abscess. With stereotactic neurosurgical techniques, almost any brain abscess 1 cm or larger is amenable to stereotactic aspiration.[7] Endoscopy can aid the visualization of drainage, which can be particularly helpful if an abscess is multiloculated with septated compartments.[27]

Table 2
Most likely pathogens and locations of brain abscess

Anatomic source	Most likely pathogen	Most likely location
Paranasal sinus	*Streptococcus intermedius*	Frontal lobe
Oral cavity	Polymicrobial	Frontal lobe
Ear	*Streptococcus intermedius*	Temporal lobe
Bloodstream	*Staphylococcus aureus*	Multiple lobes

What is the prognosis for a patient with a brain abscess?

The prognosis for a patient with a brain abscess has improved. Mortality has declined from 40% in 1960 to 15% in the recent past.[7] If a brain abscess is promptly identified and treated, the majority of patients have a good outcome. Currently, about 70% of patients recover with minimal or no neurological sequelae.[7] The prognosis may not be as good in some groups of patients. In a recent series of 247 patients from 2009 to 2020, only 43% recovered without neurological deficits, but 35% of these patients had a malignancy, 35% were immunocompromised, 33% had head and neck surgery or traumatic brain injury, and 24% had diabetes mellitus; only 8% died.[25] Prompt diagnosis and combined medical-surgical therapy are the keys to a good outcome.

Teaching points

- The most common causes of new onset seizures vary by age: fever in children, cerebrovascular disease in older adults, and trauma, tumors, drugs, autoimmunity and infections in young adults.
- The most common causes of a ring-enhancing lesion in the brain can be sorted into 5 groups: metastases, abscesses, glioblastomas, infarcts (or inflammation) and contusions, using the first letter of each group to create an acronym MAGIC as a memory aid.
- Most brain abscesses are due to bacteria, often from the normal oral flora, and many brain abscesses are polymicrobial, including both aerobes and anaerobes.
- Aspirate of the liquid center of a brain abscess is usually the best sample for the clinical microbiology laboratory to identify the pathogens causing a brain abscess.
- Gram stain, aerobic and anaerobic cultures are generally the most essential testing of the aspirate of a brain abscess, although it is better to err on the side of ordering too much rather than too little because aspiration of a brain abscess is a difficult and risk-laden procedure.
- Management of a brain abscess generally includes both neurosurgery and antibiotic therapy, with antibiotics that not only cover the pathogens, but also cross the blood-brain barrier.
- If a brain abscess is promptly identified and treated, the majority of patients have a good outcome, with no or minimal neurologic sequelae.

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