

Received: 2026.05.07

Accepted: 2026.10.13

Available online: 2026.10.21

Published: 2026.XX.XX

Cryptococcal Meningitis in an Apparently Immunocompetent Patient With a Ventriculoatrial Shunt: Diagnostic Challenges of Negative Serum Cryptococcal Antigen

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Corresponding Author: Steve Carlan, Graduate Medical Education Administration, 1335 Sligh Blvd, Orlando, FL 32806, USAFax: 321-481-0182, Phone: (321) 841-8934, e-mail: stevecarlan@gmail.com**Financial support:** None declared**Conflict of interest:** None declared**Patient:** **Male, 60-year-old****Final Diagnosis:** **Cryptococcal meningitis****Symptoms:** **Headache****Clinical Procedure:** —**Specialty:** **General and Internal Medicine****Objective:** **Rare disease****Background:** Cryptococcal meningitis usually occurs in people with impaired cellular immunity, but it can also affect patients without a recognized immunodeficiency. Cerebrospinal fluid (CSF) shunts complicate recognition because symptoms may be subtle and serum studies may be unrevealing. We describe a case of a patient with a longstanding ventriculoatrial (VA) shunt whose CSF findings established the diagnosis despite a negative serum cryptococcal antigen result.**Case Report:** A 60-year-old man with a remote ventriculoperitoneal shunt subsequently converted to a VA shunt developed persistent headache and an episode of seizure-like activity 3 days after robotic cholecystectomy. He had no focal neurological deficit, and electroencephalography showed no epileptiform activity. Brain magnetic resonance imaging showed no mass lesion or hydrocephalus. Lumbar puncture revealed lymphocytic pleocytosis (101 cells/ μ L), CSF protein of 61 mg/dL, and glucose of 44 mg/dL. Serum cryptococcal antigen was negative, whereas CSF cryptococcal antigen was positive at a titer of 1: 40 and CSF culture grew *Cryptococcus neoformans*. The discordant serum result has an uncertain mechanism because assay-platform details and repeat or dilution testing were unavailable. He received liposomal amphotericin B and flucytosine, underwent VA shunt removal and external ventricular drainage, and later had shunt revision. Following clinical and microbiologic improvement, he received fluconazole consolidation and maintenance therapy and remained clinically well at 4-week follow-up.**Conclusions:** A negative serum cryptococcal antigen result did not exclude meningitis in this patient with a CSF shunt. Persistent unexplained neurological symptoms warrant CSF evaluation when cryptococcosis remains clinically plausible. This case also illustrates the importance of antifungal therapy and coordinated neurosurgical management for suspected shunt-associated infection.**Keywords:** **Cerebral Cortex • Cryptococcus • Meningitis****Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/954036> 2355 4 2 18

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Introduction

Cryptococcosis is an opportunistic, potentially deadly invasive fungal disease caused by 2 main species: *Cryptococcus neoformans* (*C. neoformans*) and *Cryptococcus gattii* (*C. gattii*) [1]. The primary route of infection is inhalation of *Cryptococcus* spores from contaminated soil and bird droppings. After successful inoculation in the lungs, the fungus can spread to other parts of the body, remain dormant, or cause acute illness [2]. The reported incidence of cryptococcosis in the United States is estimated at 0.4 to 1.3 cases per 100 000 people, with a much higher rate among immunocompromised individuals [3]. *C. neoformans* accounts for most cases of cryptococcosis and tends to infect immunocompromised hosts [4]. Cryptococcal meningitis (CM) is a rare but severe infection, with a 1-year mortality rate estimated at 20% to 30%, even with long-term antifungal treatment [5]. Up to 30% of cases occur in immunocompetent individuals [6,7].

Cryptococcal CM has been reported in patients with preexisting cerebrospinal fluid (CSF) shunts, which can serve as a nidus for chronic infection and complicate diagnosis and management [8]. However, VP shunt-associated cryptococcal meningitis in immunocompetent hosts remains very rare [9], and VA (ventriculoatrial) shunt cryptococcal meningitis in immunocompetent patients has been reported only twice [9,10]. Cryptococcal meningitis associated with ventriculoatrial (VA) shunts is rarely reported, with only limited cases described in the literature.

Cryptococcus neoformans possesses a polysaccharide capsule that can form a biofilm on the shunt, resulting in resistance to antimicrobial agents and host defense mechanisms, causing significant morbidity and mortality. The main difference is that VA shunts drain directly into the bloodstream [11]. The cryptococcal antigen (CrAg) test is often the first and most reliable diagnostic step when evaluating for *C. neoformans*. It has nearly 100% sensitivity and specificity and can be detected in serum, plasma, whole blood, and cerebrospinal fluid (CSF). A positive serum CrAg result has been found to precede the onset of cryptococcal symptoms by an average of 22 days [3]. False-negative CrAg LFAs are rare but have occurred [12].

The present case adds to this small body of evidence by describing cryptococcal meningitis in an apparently immunocompetent patient with a longstanding VA shunt who presented with subtle clinical findings and negative serum cryptococcal antigen testing despite positive CSF studies. This report highlights an important diagnostic consideration in shunted patients and reinforces the value of early CSF evaluation and multidisciplinary management when clinical suspicion for central nervous system infection persists.

Timely recognition is crucial given the risk of severe morbidity [13]. Here, we present a case of *C. neoformans* VA

shunt-associated meningitis in an immunocompetent individual with a longstanding ventriculoperitoneal (VP) shunt, later converted to a ventriculoatrial (VA) shunt, that developed days after robotic cholecystectomy for cholecystitis.

Case Report

A 60-year-old man with a history of normal-pressure hydrocephalus underwent VP shunt placement about 10 years before admission, then conversion to a ventriculoatrial (VA) shunt 4 years later because of recurrent obstruction. Six years later, he presented to the emergency department with several days of sudden-onset abdominal pain, fatigue, and generalized weakness and on hospital day 1 underwent robotic cholecystectomy for suspected phlegmon in the gallbladder fossa. Pathology showed acute and chronic cholecystitis and cholelithiasis without obstruction. He received postoperative piperacillin-tazobactam (3.375g IV every 6 hours) for 2 days. Before surgery, he denied recent trauma, headache, mental status changes, or cranial nerve palsy. He had no gait disorder or diplopia. His medical history was otherwise unremarkable aside from his shunt and oral sertraline for endogenous depression. He did not smoke, drink, or use drugs. Diabetes mellitus, malignancy, and corticosteroid or immunosuppressive medication use were excluded.

He frequently hunted quail as a hobby, suggesting environmental exposure to bird droppings as a potential source of *Cryptococcus*. However, he had not hunted quail in over a year.

On hospital day 3, the patient developed persistent headaches and intermittent episodes concerning for seizures. At that time, his vital signs were stable: blood pressure 123/87, heart rate 92 (regular), low-grade fever of 37.6°C, and respiratory rate 12 breaths per minute. A brain magnetic resonance imaging without contrast showed the VA shunt but was otherwise normal (Figure 1). The brain image revealed no mass lesion or hydrocephalus. A neurological assessment and physical examination were unremarkable. Electroencephalography (EEG) was performed and did not demonstrate epileptiform activity. No focal neurological deficits were documented. Fundoscopic examination was not performed. There was no nystagmus, facial weakness, or abnormal reflexes. Kernig and Brudzinski signs were negative. There was no neck rigidity, and the physical exam was otherwise unremarkable. He was given acetaminophen for his low-grade fever and headache. His routine laboratory test results were normal except for anemia (Table 1). He tested negative for HIV (human immunodeficiency virus) using 4th-generation Ag/Ab (antigen/antibody) screening and was also negative for hepatitis B core total antibody, hepatitis C antibody, and RPR (rapid plasma reagin) test.

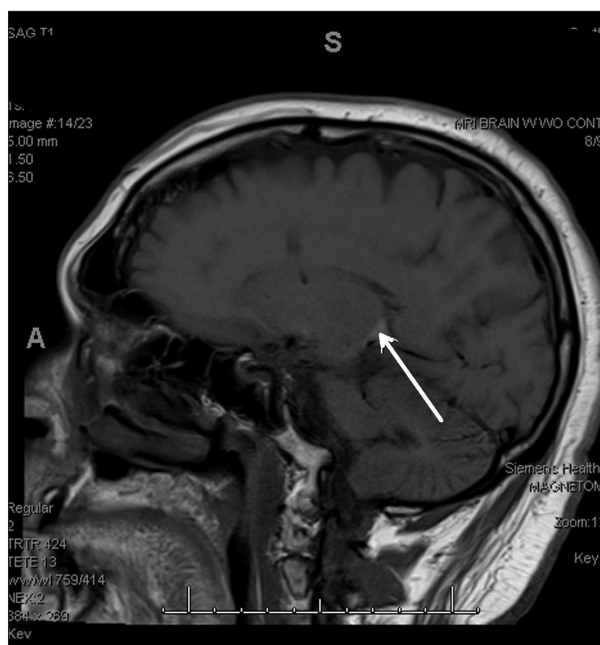


Figure 1. Brain magnetic resonance imaging without contrast. Demonstrates no mass lesion, hydrocephalus, or other structural abnormality, supporting exclusion of alternative causes of the patient's neurologic presentation. The tip of the VA shunt can be seen at the white arrow.

A lumbar puncture performed on hospital day 4 showed CSF lymphocytic pleocytosis, with CSF white blood cells (WBC) of 101 and 92% lymphocytes, along with elevated protein at 61 mg/dL (milligrams per deciliter) and low glucose at 44 mg/dL (**Table 2**). The CSF cryptococcal antigen test was positive (titer 1: 40), and *C. neoformans* was subsequently isolated in culture, while serum cryptococcal antigen was negative. The polymerase chain reaction (PCR) Meningitis/Encephalitis Pathogen Panel on the CSF was negative. The patient had a CD4+ T-lymphocyte count of 989 cells/ μ L, along with normal Ig levels. The serum and CSF cryptococcal antigen assay platforms were not available in the records reviewed. The diagnostic CSF sample was collected on hospital day 4, when antifungal therapy was initiated; the exact collection times of the serum and CSF samples relative to the first antifungal dose could not be verified. No repeat serum cryptococcal antigen or dilution testing to assess antigen-excess interference was documented. The negative serum result therefore represents an observed assay finding of uncertain mechanism. The multiplex CSF meningitis/encephalitis PCR platform was also not identified in the available record. Its negative result did not exclude cryptococcal meningitis because CSF cryptococcal antigen and culture were positive.

On hospital day 4, antifungal therapy was initiated with liposomal amphotericin B (3 mg/kg every 24 hours) and flucytosine

(2000 mg every 6 hours). The patient was transferred for neurosurgical evaluation on hospital day 10, when the VA shunt was removed and a left external ventricular drain was placed. Computed tomography of the head showed a small parenchymal hematoma along the right caudate body at the shunt-removal site (**Figure 2**). Serial CSF samples obtained through the drain showed improving inflammatory indices and subsequent culture clearance. A new VA shunt was later placed; the exact hospital day of placement requires confirmation against the operative record because the dates in the supplied materials conflict.

Liposomal amphotericin B induction was reported as completed by hospital day 31. Following clinical improvement and negative CSF cultures, fluconazole 800 mg daily was prescribed for consolidation, with an intended duration of 8 weeks. The reported end date of hospital day 59 is inconsistent with an 8-week course beginning after day 31 and therefore requires verification. QTc monitoring was planned because the patient also received sertraline (baseline QTc 465 ms). Fluconazole 200 mg daily was then prescribed for maintenance for 6 to 12 months. The exact discharge date and dates of transition between antifungal phases were not ascertainable from the supplied materials. He was neurologically stable at discharge and remained clinically well at 4-week follow-up. A formal modified Rankin Scale assessment was not performed. Throughout his antifungal therapy, the patient remained afebrile and hemodynamically stable, with improving laboratory values (**Table 3**).

Discussion

This case is important for 2 reasons. First, CM or VP shunt-associated infection due to *C. neoformans* is extremely rare in immunocompetent individuals [1,7,8], and our patient had no recognized immunocompromising conditions and tested negative for HIV, hepatitis B, hepatitis C, and syphilis. His CD4+ T-lymphocyte count was 989 cells/ μ L, supporting preserved cellular immunity. Immunoglobulin levels were normal (IgG 900 MG/DL, IgM 200 mg/dl), indicating preserved humoral immunity. Although cryptococcal disease is classically associated with impaired cellular immunity, up to 30% of cases have been reported in individuals without obvious immune compromise [6,7].

Cryptococcal infection associated with ventriculoatrial (VA) shunts has been reported only twice previously [9,10] (**Table 4**). One reason VA shunt-associated infections may be particularly uncommon is that fewer than 5% of ventricular shunts terminate in the atrium [14]. The case most similar to ours involved a 28-year-old man with a VA shunt in place for 1 year who presented with headache, slurred speech, confusion, and vomiting. CSF cultures grew *C. neoformans*, and he was treated

Table 1. Serial laboratory test results and treatment summaries throughout the hospital stay.

Test	Reference range	Serial labs, treatment by date of hospital									Day 31	Day 59
		Admission	Hospital day 1	Hospital day 3	Hospital day 4	Hospital day 7	Hospital day 10	Hospital day 14	Hospital day 21	Hospital day 29		
Hemoglobin	Men: 13.5 to 17.5 g/dL	11.6		10.8		10.1		9.9	9.5			
White Blood Cell count	4,500-11,000 cells/ μ L	5 900	Cholecystectomy	6 300	Lumbar puncture performed - Liposomal amphotericin B and flucytosine *	8 400	Removal of the VA shunt and placement of a left external ventricular drain	7 890	9 000	Discharged home	Completed induction therapy and started consolidation with fluconazole 800 mg daily for 8 weeks	Completed consolidation therapy and started on fluconazole 200 mg for 6-12 months
Platelet count	100,000-400,000/L	212 000		200 000		198 000		217 000	189 000			
Fibrinogen	200-400 mg/dL			231		200		256	250			
Creatinine	0.6-1.1 mg/dL	0.8		1		1.14		1.25	1.18			
BUN/Cr ratio	10: 1-20: 1	14.8		16		18.3		19.1	22.2			
Sodium	135-145 mEq/L	141		142		139		144	137			
Potassium	3.5-5.0 mmol/L	4.3		3.9		4.6		4.1	3.7			
Corrected Calcium	8.80 and 10.70 mg/dL	9.4		8.1		9.2		9.4	8.5			
Magnesium	1.7-2.2 mg/dL	2.3		1.9		2.3		1.9	2.5			
Thyroid stimulative hormone (TSH)	1.7-2.2 mg/dL	2.1										
Glucose mg/dL	70-140 mg/dL	114		117		134		122	119			
Blood pressure		123/87		119/78		127/81		115/72	135/70			
Systolic blood pressure		123		119		127		115	135			
Oxygen saturation	95-100%	98		99		96		95	97			
Alanine aminotransferase (ALT)	31 U/L (Units per liter)	7-55 U/L										
Aspartate aminotransferase (AST)	35 U/L	8-48 U/L										
Total bilirubin	1.0 mg/dL	0.1-1.2 mg/dL										

Abbreviations: g/dL, grams per deciliter; cells/ μ L, cells per microliter; L, liter; mg/dL, milligrams per deciliter; mEq/L, milliequivalents per liter; mmol/L, millimoles per liter.

Notes: Abnormal laboratory values are indicated in red text, and administered treatments are highlighted in yellow.

The asterisk (*) denotes the therapeutic regimen consisting of liposomal amphotericin B (3 mg/kg every 24 hours) combined with flucytosine (2000 mg every 6 hours). Normal cells within the table reflect the absolute absence of a collected sample rather than missing data points.

Table 2. Serial cerebrospinal fluid laboratory values throughout the hospital stay.

CSF Parameters	Reference range	Hospital day 4	Hospital day 10	Hospital day 12	Hospital day 21	Hospital day 21	Hospital day 29
Appearance	Clear	Hazy	Removal of the VA shunt and placement of a left external ventricular drain	Hazy	Hazy	New VA shunt placed	Discharged
Opening pressure (cm H ₂ O)	5 to 20 (cm H ₂ O)	26 cm H ₂ O					
Protein (mg/dL)	18-45 (mg/dL)	61 mg/dL		27 mg/dL	24 mg/dL		
Glucose (mg/dL)	50-80 mg/dL	44 mg/dL		44 mg/dL	86 mg/dL		
Glucose CSF: Serum Ratio	≥0.6, or > 2/3rds the serum glucose	0.3		0,7	0,71		
Gram stain	Negative	Negative		Negative	Negative		
WBC/uL	0-8 lymphocytes/uL	101 lymphocytes/uL		3	2		
CSF meningitis/encephalitis panel	Negative	Negative					
CSF culture	Negative	<i>Cryptococcus neoformans</i> -positive		Negative	Negative		
Cryptococcal antigen	Negative	Positive titer 1:40)					

Abbreviations: CSF, cerebrospinal fluid; cm H₂O, centimeters of water; mg/dL, milligrams per deciliter; WBC/uL, white blood cells per microliter.

Notes: Abnormal laboratory values are presented in red text. Shunt management procedures and related interventions are indicated by yellow highlights. Normal cells within the table reflect the absolute absence of a collected sample rather than missing data points.

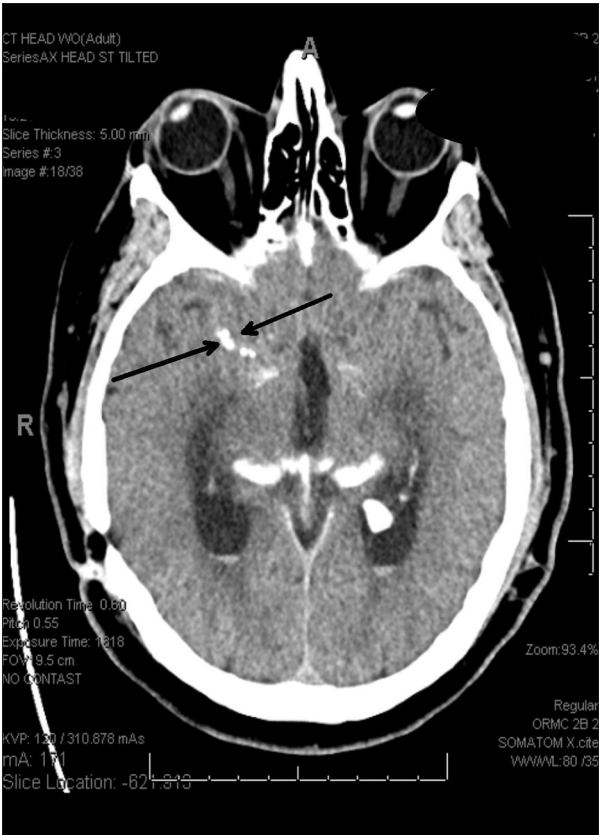


Figure 2. Head computed tomography imaging revealed a small parenchymal hematoma along the right caudate body at the site of shunt removal, (2 black arrows). No new neurological deficits were noted.

with amphotericin B and flucytosine but subsequently died from mixed bacterial ventriculitis and intraventricular hemorrhage. An immunologic evaluation did not reveal an underlying immune deficiency [9]. Another reported case involved a 46-year-old woman with a VA shunt who developed cryptococcal meningitis after prior neuraxis irradiation for malignancy [10]. A review of the literature identified no additional published cases of VA shunt-associated cryptococcal meningitis.

The second notable feature of this case was the temporal relationship between recent surgery and the onset of neurologic symptoms. Our patient developed persistent headache and seizure-like activity 3 days after robotic cholecystectomy for acute cholecystitis. The timing of symptom onset is noteworthy because neurological symptoms developed shortly after surgery. However, whether this temporal association reflects progression of a previously unrecognized infection, delayed clinical manifestation of an indolent infection, or simple coincidence cannot be determined from the available evidence.

Table 3. Chronological timeline of clinical, imaging, and management summary.

Day	Clinical, imaging, management summary
Hospital day 1	Robotic cholecystectomy
Hospital day 3	Developed persistent headache and an episode of seizure-like activity
Hospital day 3	Brain MRI demonstrated no mass lesion or hydrocephalus; EEG showed no epileptiform activity
Hospital day 4	Lumbar puncture performed; CSF demonstrated lymphocytic pleocytosis, elevated protein, and low glucose. Serum cryptococcal antigen negative; CSF cryptococcal antigen and culture positive for <i>Cryptococcus neoformans</i>
Hospital day 4	Start induction therapy with amphotericin B
Hospital day 10	Ventriculoatrial shunt removed and external ventricular drain placed
Subsequent hospital course	Serial CSF analyses demonstrated microbiologic and biochemical improvement
Hospital day 21	VA shunt revised
Hospital day 29	Discharged on oral fluconazole for consolidation and maintenance therapy with clinical improvement
Four-week follow-up	Unremarkable neuro exam; reported compliance with the maintenance therapy

Table 4. Comparison of essential available elements among reported cases of VA shunt cryptococcal meningitis.

Characteristic	Case 1 [9]	Case 2 [10]	Current case
Age/Sex	28 M	46 M	60 M
Immune status	No underlying immunodeficiency identified	Prior irradiation for malignancy	Apparently immunocompetent; HIV, HBV, HCV, and syphilis negative; CD4 count 989 cells/ μ L; normal IgG (900 mg/dL) and IgM (200 mg/dL)
Ventriculoatrial (VA) shunt duration	One year	Not reported	Approximately 6 years (converted from VP shunt)
Presenting symptoms	Headache, slurred speech, confusion, vomiting	Meningitis symptoms	Persistent headache and seizure-like activity 3 days after robotic cholecystectomy
Serum cryptococcal antigen	Not reported	Not reported	Negative
Cerebrospinal fluid (CSF) findings	<i>C. neoformans</i> cultured from CSF	Cryptococcal meningitis diagnosed	Lymphocytic pleocytosis, elevated protein, low glucose; CSF cryptococcal antigen and culture positive for <i>C. neoformans</i>
Brain magnetic resonance imaging (MRI)	Not reported	Not reported	No mass or hydrocephaly
Treatment	Amphotericin B + flucytosine	Antifungal therapy with shunt management	Liposomal amphotericin B + flucytosine followed by fluconazole; VA shunt removal. External ventricular drain (EVD) placement, and shunt revision

Several explanations could account for this presentation, including latent cryptococcal colonization associated with the VA shunt, persistence within shunt-associated biofilm, or an indolent infection that became clinically apparent over time. However, these possibilities remain speculative and cannot be established from a single case report. Previous reports have suggested that CSF shunts may provide a surface for microbial adherence and biofilm formation, potentially allowing organisms to persist despite limited clinical manifestations [8]. Whether a similar process occurred in our patient is unknown.

Our patient had no recognized risk factors for immune compromise other than the postoperative state and a remote history of quail hunting, which may have represented prior environmental exposure to bird droppings. However, no direct causal relationship between these factors and the development of cryptococcal meningitis can be established.

The patient's presentation was subtle. Immunocompetent patients with cryptococcal meningitis can initially present with minimal symptoms, potentially delaying diagnosis [15]. More classic manifestations include fever, cranial nerve deficits, altered mental status, and focal neurologic abnormalities [3]. In this case, there was no neck stiffness, cranial nerve dysfunction, or focal neurologic deficit on examination. Although neck stiffness is absent in approximately 20% of patients with cryptococcal meningitis [16], the relatively mild initial presentation highlights the diagnostic challenge posed by this infection in patients without obvious immunocompromising conditions [17].

The CSF profile was consistent with previously reported cases of shunt-associated cryptococcal meningitis, demonstrating lymphocytic pleocytosis, elevated protein, and low glucose concentrations [8]. Notably, our patient had a negative serum cryptococcal antigen test despite positive CSF cryptococcal antigen testing and culture, highlighting that serum testing alone may not exclude cryptococcal meningitis in patients with shunt-associated disease. The diagnosis was ultimately established through CSF evaluation, emphasizing the importance of lumbar puncture when clinical suspicion for central nervous system infection persists despite nondiagnostic serum studies. The assay platform, exact pretreatment sampling sequence, and repeat or dilution testing were unavailable, so the mechanism of serum–CSF discordance cannot be determined. The negative multiplex PCR result likewise does not override the positive CSF antigen and culture findings.

Management required both antifungal therapy and neurosurgical intervention [18]. The patient received induction therapy with liposomal amphotericin B and flucytosine, followed by consolidation and maintenance fluconazole therapy. On hospital day 10, the ventriculoatrial shunt was removed and an external ventricular drain was placed to achieve source

control while maintaining CSF diversion. Following shunt removal, serial CSF analyses demonstrated progressive microbiologic clearance and improvement in biochemical parameters, after which the patient underwent successful shunt revision. Clinical improvement following antifungal therapy and shunt removal or revision further supported the diagnosis and management approach.

This case demonstrates cryptococcal meningitis occurring in association with a longstanding ventriculoatrial shunt in an apparently immunocompetent patient. The presentation was diagnostically challenging because symptoms were initially subtle and serum cryptococcal antigen testing was negative despite positive CSF studies. Although latent shunt-associated colonization, biofilm persistence, or delayed clinical manifestation may explain this presentation, these mechanisms remain speculative and cannot be confirmed from a single case report. Similarly, while the temporal association between recent surgery, systemic illness, and symptom onset is notable, a causal relationship cannot be established. Accordingly, the principal contribution of this report is not mechanistic but rather reinforces that cryptococcal meningitis can occur in patients with VA shunts despite apparently intact immune status and may require a high index of suspicion when standard serum testing is unrevealing.

Conclusions

This case highlights a rare presentation of cryptococcal meningitis in an apparently immunocompetent patient with a longstanding ventriculoatrial (VA) shunt. Diagnosis was particularly challenging because the patient presented with subtle neurological symptoms and negative serum cryptococcal antigen testing despite positive CSF cryptococcal antigen and culture. This case underscores the importance of maintaining a high index of suspicion for cryptococcal central nervous system infection in patients with indwelling CSF shunts and unexplained neurological symptoms, even in the absence of recognized immunocompromising conditions or positive serum cryptococcal antigen testing. Early CSF evaluation, prompt initiation of appropriate antifungal therapy, and coordinated multidisciplinary management involving infectious diseases and neurosurgical teams are critical to achieving favorable clinical outcomes. Although this report represents a rare clinical presentation, its principal contribution is to reinforce an important diagnostic consideration that may facilitate earlier recognition and treatment of cryptococcal meningitis in similar patients.

Institution Where Work Was Done

Orlando Regional Medical Center, Orlando, FL, USA.

Patient Consent

Consent to publish the case was obtained from the patient. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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