

Chronic Cerebral Coccidioidomycosis: An unusual case beyond geographic boundaries

Coccidioidomicosis cerebral crónica: Un caso inusual que trasciende las fronteras geográficas

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Abstract

Coccidioidomycosis (CM) is an emerging fungal infection caused by *Coccidioides immitis* and *C. posadasii*, primarily affecting semi-arid regions of the Americas. While pulmonary disease is most common, central nervous system (CNS) involvement—particularly chronic cerebral CM—is rare and presents significant diagnostic and therapeutic challenges. We describe a 64-year-old male from Mexico City with a history of type 2 diabetes and hypertension, who had previously lived and worked for four decades in Salinas, California, an endemic region for CM. Twelve years earlier, he was diagnosed with cerebral CM, treated with intravenous amphotericin followed by oral fluconazole, but prematurely discontinued therapy. He subsequently required placement of a ventriculoperitoneal shunt. He presented with acute neurological decline, including somnolence, gait instability, urinary incontinence, and confusion. Neuroimaging revealed hydrocephalus, prompting shunt revision. CSF cultures confirmed *C. posadasii* reactivation. CNS involvement in CM, though uncommon, can lead to severe complications such as hydrocephalus and arachnoiditis. Reactivation of CM is a concern, especially in immunocompromised individuals. This case underscores the importance of long-term management and monitoring in patients with CNS CM, particularly those with underlying comorbidities. Chronic CNS coccidioidomycosis requires sustained antifungal treatment and vigilant

follow-up to prevent reactivation and associated complications. Increased clinical awareness and early intervention are essential, particularly in endemic areas.

Keywords: coccidioidomycosis, central nervous system, hydrocephalus, chronic infection, antifungal therapy

Resumen

La coccidioidomycosis (CM) es una infección fúngica emergente causada por *Coccidioides immitis* y *C. posadasii*, que afecta principalmente a las regiones semiáridas de las Américas. Aunque la enfermedad pulmonar es la manifestación más común, el compromiso del sistema nervioso central (SNC) –particularmente la CM cerebral crónica– es una entidad poco frecuente que representa un desafío diagnóstico y terapéutico de gran complejidad. Describimos el caso de un hombre de 64 años residente de la Ciudad de México, con antecedentes de diabetes mellitus tipo 2 e hipertensión arterial, quien vivió y trabajó durante cuatro décadas en Salinas, California (zona endémica para CM). Doce años atrás, fue diagnosticado con CM cerebral y tratado con anfotericina B intravenosa seguida de fluconazol oral; sin embargo, suspendió el tratamiento de forma prematura. Posteriormente, requirió la colocación de una derivación ventriculoperitoneal (DVP). El paciente ingresó por un deterioro neurológico agudo caracterizado por somnolencia, inestabilidad de la marcha, incontinencia urinaria y confusión. Los estudios de neuroimagen revelaron hidrocefalia activa, lo que requirió una revisión quirúrgica de la DVP. Los cultivos de líquido cefalorraquídeo (LCR) confirmaron la reactivación de *C. posadasii*. El compromiso del SNC en la CM, aunque poco frecuente, se asocia a complicaciones graves como hidrocefalia y aracnoiditis. La reactivación de la CM es un riesgo latente y crítico, especialmente en pacientes con comorbilidades. Este caso destaca la importancia del seguimiento estrecho y el tratamiento a largo plazo en pacientes con CM del SNC, especialmente cuando existen factores de riesgo o interrupción previa de la terapia. La coccidioidomycosis crónica del SNC exige un tratamiento antifúngico sostenido y una vigilancia médica estricta para prevenir recaídas y complicaciones potencialmente fatales. Incrementar la sospecha clínica y asegurar una intervención temprana son pilares fundamentales, particularmente en pacientes con antecedentes de exposición en zonas endémicas.

Palabras clave: coccidioidomycosis, sistema nervioso central, hidrocefalia, infección crónica, terapia antifúngica, reactivación

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INTRODUCTION

Coccidioidomycosis, also known as Valley fever, is an emerging systemic mycosis caused by the thermally dimorphic fungi *Coccidioides immitis* and *Coccidioides posadasii*. These species are endemic to arid and semi-arid regions of the Americas, particularly the southwestern United States and northern Mexico, where environmental conditions such as alkaline soils, drought, seasonal rainfall, and soil disruption favor fungal growth and aerosolization of infectious arthroconidia. Recent epidemiologic studies have shown increasing incidence and marked seasonal variability, with climate-driven hydroclimatic swings increasingly recognized as important determinants of transmission (Camponuri et al., 2025; Heaney et al., 2024).

Human infection occurs after inhalation of airborne arthroconidia, followed by transformation into tissue spherules. Although most infections are asymptomatic or self-limited pulmonary illnesses, coccidioidomycosis can progress to severe pulmonary disease or extrapulmonary dissemination involving the skin, soft tissue, bones, joints, and central nervous system. The true burden of disease is probably underestimated, as recent modeling suggests that symptomatic cases may be substantially higher than those captured by routine surveillance (Williams et al., 2025). Diagnostic delay remains common because clinical manifestations are nonspecific, laboratory confirmation may require combined serologic, microbiologic, histopathologic, and molecular approaches, and clinical suspicion depends heavily on recognition of epidemiologic exposure (McHardy et al., 2023).

Central nervous system involvement is the most severe form of disseminated coccidioidomycosis. Coccidioidal meningitis is the most frequent neurologic manifestation, but parenchymal granulomas, hydrocephalus, arachnoiditis, spinal cord involvement, vasculitis, ischemic stroke, and intraparenchymal “shotgun” lesions have also been described (Rajmohan et al., 2024; Sharifi et al., 2022). Contrast-enhanced magnetic resonance imaging is preferred when neurologic disease is suspected because it improves detection of meningeal enhancement, vascular complications, hydrocephalus, and granulomatous lesions. Before the availability of antifungal therapy, coccidioidal meningitis was almost uniformly fatal; despite modern treatment, it remains associated with substantial morbidity, frequent neurosurgical complications, prolonged therapy, and risk of relapse (Rajmohan et al., 2024).

Azole therapy is the cornerstone of treatment. Fluconazole remains the preferred first-line agent for coccidioidal meningitis because of its central nervous system penetration, oral bioavailability, and tolerability profile. However, management is often prolonged and complicated by treatment failure, toxicity, drug interactions, adherence challenges, and pharmacokinetic variability. Alternative triazoles, including itraconazole, voriconazole, posaconazole, and isavuconazole, have been used in refractory or chronic disease, but evidence remains limited and largely based on observational experience (Heidari et al., 2023; Peçanha-Pietrobon et al., 2023). These challenges underscore the importance of reporting severe and atypical neurologic presentations, particularly in patients with remote epidemiologic exposure or delayed diagnosis.

General objective

The primary objective of this study is to report and analyze an atypical clinical presentation of chronic, recurrent central nervous system (CNS) coccidioidomycosis caused by *Coccidioides posadasii* in a non-endemic urban setting, 12 years after initial diagnosis and primary exposure. Furthermore, this report aims to contextualize this singular clinical course through a comprehensive chronological review of literature pertaining to atypical or complex neuro-coccidioidomycosis, highlighting the critical roles of environmental risk factors, long-term latency, biological features triggering reactivation, and the absolute necessity of sustained long-term antifungal compliance.

METHODOLOGY

Study Design and Context

This is a descriptive, retrospective, observational single-case report paired with a comprehensive chronological review of the medical literature. The clinical and diagnostic evaluation was entirely conducted at the "Dr. Bernardo Sepúlveda" Specialty Hospital, National Medical Center (CMN) Siglo XXI, within the Mexican Social Security Institute (IMSS) in Mexico City, a non-endemic region for systemic mycoses.

Case Selection and Eligibility Criteria

A single patient was selected based on the following explicit inclusion criteria:

- A confirmed, documented historical and microbiological diagnosis of central nervous system coccidioidomycosis.
- Subsequent long-term clinical latency followed by neuro-structural or microbiological reactivation.
- Complete availability of institutional clinical, radiological, and microbiological records.

Data Collection and Clinical Monitoring

Clinical variables, including detailed epidemiological history, past medical comorbidities, pharmacological adherence, physical examination findings, and baseline biochemical parameters, were gathered retrospectively from the patient's physical and electronic institutional medical records. Complete monitoring was conducted daily over a 10-day active hospitalization period, tracking targeted therapeutic response and structural outcomes.

Radiological and Microbiological Analysis

Neuro-structural changes and ventriculoperitoneal shunt placement were evaluated using single-phase cranial computed tomography (CT) scans with axial sections and secondary coronal and sagittal reconstructions. Microbiological confirmation was achieved via cerebrospinal fluid (CSF) and cerebral tissue biopsy direct examination using potassium hydroxide (KOH) preparation and lactophenol blue staining to evaluate distinct fungal structures (hyaline, septate hyphae, and tissue arthroconidia), incubated over a standard 6-day evaluation window.

Literature Review Strategy

To contrast our findings, a structured chronological literature search was executed across international scientific databases (PubMed/MEDLINE, Embase, and Google Scholar) spanning from 1952 to 2024. The search syntax incorporated target medical subject headings (MeSH) including "Coccidioidomycosis", "Central Nervous System", "Hydrocephalus", and "Meningitis". Atypical, chronic, or complex disseminated cases with explicit descriptions of clinical presentation, neurological outcomes, and therapeutic regimens were selected and summarized chronologically (Table 1).

Ethical Considerations and Consent

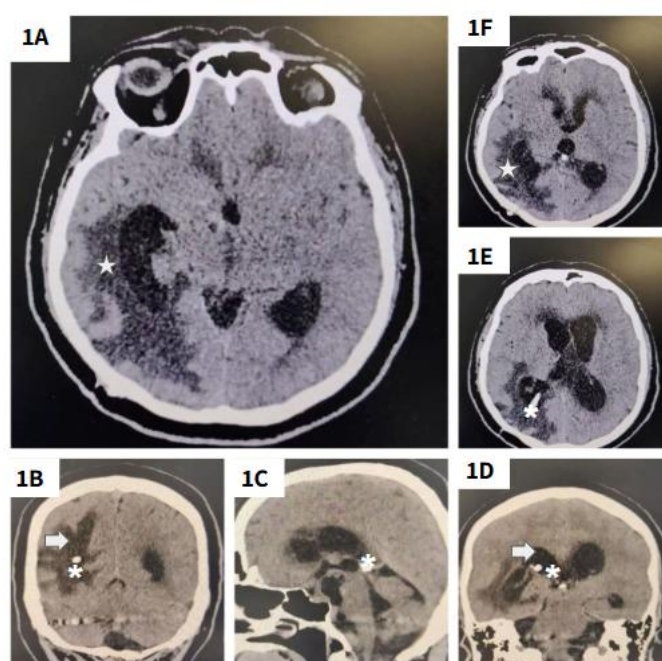
This study was conducted in strict adherence to the ethical principles of the Declaration of Helsinki. According to the institutional guidelines of the National Medical Center Siglo XXI, formal ethical approval from a board committee is not mandatory for isolated, non-interventional case reports that do not compromise patient safety. Comprehensive written informed consent was explicitly obtained from the patient and his legal representatives, authorizing the use of anonymized clinical data, historical records, and imaging findings for scientific publication.

Case

We present the case of a 64-year-old man from Mexico City with chronic cerebral coccidioidomycosis. He had spent 40 years working as a baker in Salinas, California. His medical history included type 2 diabetes and hypertension. According to his family, he had been diagnosed with cerebral CM 12 years earlier and was initially treated with intravenous amphotericin B, followed by oral fluconazole. However, he discontinued antifungal therapy prematurely. A ventriculoperitoneal shunt was later placed due to hydrocephalus (Figure 1).

Figure 1

Single-phase cranial CT scan with axial sections and coronal sagittal reconstructions shows marked right temporal hypodensity and malaise zone (star in the figura 1A and 1F), suggestive of ischemic disease



Note: In addition, there is increased width of the sulci, fissures, ventricular system, and basal cisterns (arrow in the figure 1B and 1D) associated with ventricular shunt zones (asterisk in the figure 1B, 1C, 1D, and 1E), with a terminal in the anterior horn of the right lateral ventricle.

Three days before admission, the patient developed progressive drowsiness, gait instability with falls, urinary incontinence, and disorientation. Within 48 hours, he experienced severe headaches, nausea, and vomiting, raising concern for increased intracranial pressure. Imaging confirmed hydrocephalus, and CSF cultures revealed *Coccidioides posadasii* after 6 days of incubation, characterized by hyaline, septate hyphae with arthroconidia (Figure 2 and 3).

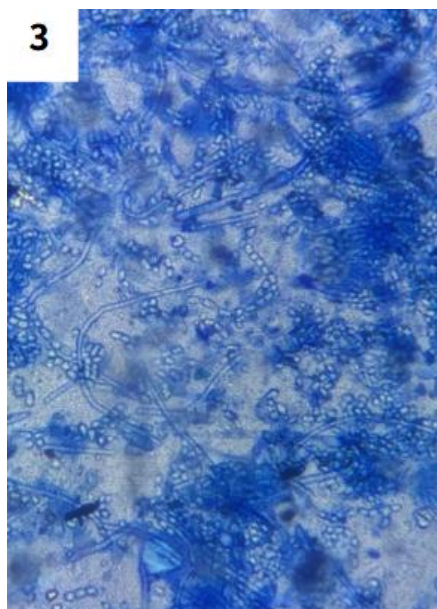
Figure 2

KOH: Arthroconidia in cerebral tissue biopsy



Figure 3

CM: arthroconidia with lactophenol blue stain



The patient was treated with intravenous liposomal amphotericin B for two weeks, showing clinical improvement. He was discharged on long-term fluconazole therapy. Despite persistent neurological sequelae, gradual neurological recovery is anticipated with sustained treatment adherence.

RESULTS

Patient follow-up was conducted over a 10-day hospitalization period. Following the initiation of target antifungal therapy, there was a complete resolution of the acute febrile syndrome and meningeal signs. From a neurological standpoint, the progressive drowsiness and acute disorientation cleared completely, allowing the patient to achieve full awareness and baseline cognitive engagement.

However, objective neurological sequelae persisted at the time of discharge, characterized by residual gait instability (ataxic features) and mild urinary incontinence. Control neuroimaging demonstrated adequate positioning and mechanical patency of the revised ventriculoperitoneal shunt, with a secondary reduction in the acute ventricular mass effect. The patient was discharged under a strict long-term oral triazole maintenance regimen, with a coordinated interdisciplinary outpatient monitoring plan to assess gradual neurocognitive and motor rehabilitation.

DISCUSSION

The central nervous system (CNS) represents the most severe, debilitating, and devastating clinical manifestation of disseminated coccidioidomycosis, historically associated with near-uniform mortality prior to the introduction of modern systemic antifungals (Rajmohan et al., 2024). While coccidioid meningitis accounts for the vast majority of these neurological presentations, the development of chronic cerebral coccidioidomycosis—frequently complicated by hydrocephalus, basilar arachnoiditis, and focal ischemic events—presents an extraordinary diagnostic and therapeutic challenge (Phelps et al., 2020). This clinical scenario is further magnified when it occurs outside traditionally recognized geographic boundaries, obscuring immediate diagnostic suspicion (Laniado-Laborín et al., 2019).

Our case highlights a critical and underrecognized phenomenon: the long-term latency and subsequent reactivation of *Coccidioides* species. The patient's epidemiological history is definitive, having spent four decades working as a baker in Salinas, California, a highly endemic valley. However, the onset of acute neurological decline occurred 12 years after his initial diagnosis and long after returning to Mexico City, where environmental exposure is absent. This dramatic timeline underscores that *Coccidioides* spherules can remain quiescent within host tissues for over a decade. The structural trigger for reactivation in this patient was likely a combination of long-standing metabolic dysregulation from type 2 diabetes mellitus and, pivotally, the premature discontinuation of his primary antifungal therapy years prior. This observation strongly reinforces the current consensus that CNS coccidioidomycosis requires lifelong, uninterrupted triazole suppression, as true microbiological eradication is rarely achieved (Peçanha-Pietrobom et al., 2023; Rajmohan et al., 2024).

To contextualize the singularity of this presentation, we performed a comprehensive chronological review of atypical, chronic, or complex neurological and organ-specific coccidioidomycosis cases reported globally over the last several decades (Table 1).

The literature illustrates a broad spectrum of neuro-coccidioidomycosis presentations that mimic other pathologies or carry catastrophic vascular risks. For instance, Sim et al. (2024) described disseminated disease presenting as atypical parkinsonism with parenchymal enhancement of the globus pallidus and subsequent ischemic stroke in the insular cortex, emphasizing the vasculitic nature of the fungus. Similarly, Kleinschmidt-DeMasters et al. (2000) documented a fatal case of *C. immitis* meningitis complicated by massive sagittal sinus thrombosis and tissue arthroconidia.

Chronic localized or dural forms can also act as structural space-occupying lesions. Komotar and Clatterbuck (2003) reported chronic dural lesions mimicking plaque meningiomas in a patient with a

history of poor treatment adherence—a clear parallel to our patient’s non-compliance. Furthermore, dural involvement causing communicating hydrocephalus and severe papilledema was observed by Garoon et al. (2017) following a history of chronic alcoholism.

Extrapulmonary tissue destruction can occasionally form distinct intraparenchymal abscesses rather than diffuse meningitis, as demonstrated by Mendel et al. (1994) with a multiloculated right frontal lobe abscess requiring ultrasound-guided surgical aspiration. Even in historical cohorts before advanced biological therapies, such as the cases reviewed by Reeves (1968) from the 1950s and 1952, the development of dense arachnoid bands, fourth ventricle occlusion, and extensive cerebellar granulomas highlights the unrelenting fibrotic response the host generates against the encapsulated spherules, invariably resulting in obstructive hydrocephalus.

Our patient’s presentation with a classic triad of normal-pressure hydrocephalus mimics (gait instability, urinary incontinence, and dementia-like confusion) was directly tied to the mechanical failure or obstruction of his existing ventriculoperitoneal shunt due to persistent low-grade fungal arachnoiditis. The isolation of *Coccidioides posadasii* from the cerebrospinal fluid culture confirmed active microbiological replication. While induction therapy with intravenous liposomal amphotericin B remains the standard of care for acute neurological deterioration or refractory disease, the transition to high-dose oral fluconazole is the absolute cornerstone for preventing subsequent relapses (Rajmohan et al., 2024). This case demonstrates that even after a prolonged period of treatment cessation and severe acute neuro-structural compromise, aggressive induction followed by strict therapeutic adherence can halt fungal replication and promote meaningful clinical recovery.

Table 1

Similar cases reported in the medical literature (chronological order)

Year and Country	Age and Sex	Final Diagnosis	Case Presentation and Core Findings	Citation (APA Format)
United States, 2024	64-year-old male	Atypical parkinsonism secondary to disseminated coccidioidomycosis	History of diabetes and hypertension. Presented with lower back pain, gait disturbances, bilateral tremor, and slowed speech. Brain MRI showed abnormal parenchymal enhancement in right globus pallidus. Later developed subacute infarction in the right insular cortex and putamen due to fungal vasculitis. Developed hydrocephalus requiring fluconazole.	(Sim et al., 2024)
United States, 2023	57-year-old male	Chorioretinal coccidioidomycosis + Sarcoidosis	Presented with sudden painless decrease in vision and macular edema. MRI showed left orbital enhancement. PET-CT later confirmed concomitant sarcoidosis; treated with antifungal followed by immunosuppressive therapies.	(Akhavanrezayat et al., 2023)
United States, 2021	44-year-old male	Disseminated coccidioidomycosis + Liver failure	Hispanic inmate with history of alcoholic hepatitis. Presented with weight loss, lingual ulcers, and altered mental status. Brain MRI showed an ischemic event in the corpus callosum. Autopsy confirmed brain tonsillar herniation, hydrocephalus, and diffuse cortical coccidioidal spherules.	(Chee et al., 2021)
United States, 2017	39-year-old male	Chronic dural coccidioidomycosis	History of severe alcoholism. Presented with chronic headache and bilateral papilledema. Brain MRI showed communicating hydrocephalus and extensive leptomeningeal enhancement.	(Garoon et al., 2017)

			Required urgent ventriculoperitoneal shunt and dural biopsy.	
United States, 2010	64-year-old male	Chronic endophthalmitis without systemic involvement	A 1.5-year history of intraocular inflammation unresponsive to steroids. Examination showed vitritis and yellowish chorioretinal lesions. Histopathology confirmed <i>Coccidioides</i> . Progressed to blindness, requiring enucleation.	(Vasconcelos-Santos et al., 2010)
United States, 2003	38-year-old female	Chronic dural coccidioidomycosis mimicking meningioma	History of disseminated coccidioidomycosis with poor treatment adherence. Brain MRI showed multiple dural lesions mimicking plaque meningiomas. Craniotomy and dural biopsy confirmed active granulomatous necrosis with <i>Coccidioides</i> .	(Komotar & Clatterbuck, 2003)
United States, 2000	43-year-old male	Meningeal coccidioidomycosis + Massive cerebral venous thrombosis	Patient with AIDS presenting with altered mental status. CSF grew <i>C. immitis</i> . Developed obstructive hydrocephalus requiring ventriculostomy. Readmitted due to seizures; CT confirmed massive sagittal sinus thrombosis. Fatal outcome.	(Kleinschmidt-DeMasters et al., 2000)
United States, 1994	19-year-old male	Coccidioidomycotic brain abscess	Farmer presenting with generalized seizures. Brain MRI showed a multiloculated intra-axial cystic lesion in the right frontal lobe with ring enhancement. Ultrasound-guided craniotomy and aspiration confirmed <i>C. immitis</i> abscess.	(Mendel et al., 1994)
United States, 1956	15-year-old male	Chronic disseminated coccidioidomycosis	Developed lethargy, papilledema, ataxia, and loss of muscle strength. Suboccipital craniotomy revealed dense arachnoid bands and cerebellar granulomas with <i>C. immitis</i> spores. Autopsy confirmed 4th ventricle occlusion and hydrocephalus.	(Reeves, 1968)
United States, 1952	38-year-old female	Chronic disseminated coccidioidomycosis	Presented with headache, decreased visual acuity, and neck stiffness. Erroneously ruled out initially due to negative skin test. Autopsy confirmed <i>Coccidioides</i> in the brain, spinal cord, and meninges, alongside communicating hydrocephalus.	(Reeves, 1968)

Conclusions

Chronic CNS coccidioidomycosis represents a lifelong clinical commitment. This case highlights that clinicians must maintain a high index of suspicion for fungal reactivation in any patient presenting with unexplained neurological decline or ventriculoperitoneal shunt failure who possesses a remote history of travel or residence in endemic regions, even if the exposure occurred decades prior.

Furthermore, as climate change, ecological disruption, and hydroclimatic swings alter the distribution of "southern" and "northern" fungal species across the Americas, established geographic boundaries can no longer be relied upon for diagnostic exclusion. In countries like Mexico, mitigating the widespread underdiagnosis and subsequent diagnostic delays requires expanding access to serological, molecular, and microbiological tools. Ultimately, minimizing the severe morbidity and high mortality associated with this disease relies on early aggressive intervention, timely neurosurgical shunt management, and the enforcement of indefinite, long-term antifungal compliance.

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