Case Report

Hydrocephalus in Mexican children with Coccidioidal Meningitis: Clinical, serological, and neuroimaging findings

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ABSTRACT

Background: Coccidioidal meningitis (CM) is a fungal infectious disease that rarely affects children. Even in endemic areas, coccidiomycosis rarely affects the pediatric population. However, 40% of affected children develop hydrocephalus. Here, we describe the clinical, serological, and neuroimaging findings in a series of Mexican children admitted to our neurosurgical service with hydrocephalus and subsequently diagnosed with CM.

Methods: We report a prospective series of pediatric patients with hydrocephalus secondary to CM in an endemic area at the north of Mexico. Our report includes children with CM who were hospitalized from 2015 to 2019 in a regional hospital in Torreón, Coahuila. Clinical evolution was monitored for 1 year after hospital discharge.

Results: Our series include five children with CM (2–17-years-old, three female), who were hospitalized for hydrocephalus and developed intracranial hypertension. The most frequent neuroimaging findings were leptomeningeal enhancement (5/5) and basal arachnoiditis (4/5), followed by asymmetric hydrocephalus (3/5), abnormalities in fourth ventricle morphology (3/5), and cerebral vasculitis (2/5). CM was diagnosed by positive serology or pathology studies. All children were initially managed with fluconazole and a shunt was placed for management of hydrocephalus. Four patients recovered without permanent neurological deficits and one subject developed persistent vegetative state. One year after hospital discharge, none of the subjects died.

Conclusion: This series contributes to the limited number of pediatric CM cases reported in the literature, and describes neuroimaging findings in the pediatric population. The cases here presented show that the identification of *Coccidioides* as causal agent in pediatric meningitis is crucial for targeted treatment and can affect dramatically neurological prognosis. Furthermore, our report stresses that even in endemic areas pediatric coccidiomycosis represents a diagnostic challenge, which is further exacerbated by the limited availability of resources in these regions. Therefore, a positive immunoglobulin G by enzyme immunoassay is enough for diagnosis of CM in endemic areas without access to CF.

Keywords: Coccidioidal meningitis, Diagnosis, Hydrocephalus, Pediatric, Serology

INTRODUCTION

Coccidioidomycosis is a fungal disease with pulmonary origin[15] caused by two species of dimorphic fungi: *Coccidioides immitis* and *Coccidioides posadasii*.[27] This rare disease is endemic of northern Mexico.[13,16] Padua *et al.*[21] reported the 40.2% of positivity in the coccidioidin skin test in Torreón, Coahuila. Approximately, 1% of patients with disseminated coccidioidomycosis will develop Coccidioidal Meningitis (CM). Neuroimaging studies detect hydrocephalus in more than 40% of the cases,[8,15,19] followed by basal meningitis and cerebral vasculitis.[1,7,24,28]

Given that more than 90% of untreated patients die within the 1st year,[2] CM demands an early diagnosis and prompt treatment.[10,15,27] Diagnosis of CM is made by isolation of *Coccidioides* from culture, histopathological, or serological findings.[10,12,27] According to IDSA guidelines for the treatment of Coccidoidomycosis (2016), the diagnosis of CM can be made by the finding of positive immunoglobulin (Ig)G serum antibodies against *Coccidioides* in patients with neurological manifestations (intracranial hypertension, meningism, or neurological focalization) and cerebrospinal fluid (CSF) abnormalities (lymphocytic or eosinophilic pleocytosis, hyperproteinorrachy, and hypoglycorrhachia). Fluconazole, dose of 400–1200 mg daily, is usually the initial treatment in these patients.[15,27]

TCD4+ cells perform an important role in the defense against invasive fungal infection.[14] The low counts of these cells in AIDS patients could explain their predisposition to severe *Coccidioides* infection[9,11] that frequently involves the central nervous system causing CM with brain abscess.[20] Hereditary immunodeficiencies, such as hyperimmunoglobulinemia E syndrome (HIES), have been associated in children with MC.[22] Other authors report elevated levels of IgG in a Mexican children series with CM.[3] Therefore, cellular and humoral immunity are essential for the *Coccidioides* infection control.

Specific genetic mutations that alter the immune response involving Interferon-γ/Interleukin-12 and other cellular immune pathways may predispose to severe Coccidioidomycosis. Patients with these mutations have a higher incidence of disseminated infection by *Coccidioides sp.* in comparison to the healthy population in an endemic area (75% vs. 1%).[10]

The objective of this study was to describe the clinical, radiological, and serological findings in a series of pediatric patients with hydrocephalus secondary to CM in our hospital.

MATERIAL AND METHODS

Pediatric patients with hydrocephalus secondary to CM diagnosed at our center (Hospital de Especialidades N° 71 Mexican Social Security Institute) between January 2015 and January 2019 were included in the study. Our hospital is a regional center in northern Mexico, an endemic region for coccidioidomycosis.

We conducted a prospective case series. Hydrocephalus was diagnosed by clinical signs and simple cranial computed tomography (CT) scan. All the subjects underwent gadolinium-enhanced magnetic resonance imaging (MRI) 1 month after surgery. CM was diagnosed by a positive serology test (IgG in CSF ≥ 0.150 D.0.) performed by enzyme immunoassay (EIA), or by isolation of *C. immitis* in a leptomeningeal biopsy, CSF culture or CSF cytology. Furthermore, IgG and IgM levels against *C. immitis* were measured in serum. Patients with CM underwent serological tests for HIV, Hepatitis B and C. Ig levels (IgA, IgE, IgG, and IgM) were also measured to rule out secondary and humoral immunodeficiencies; blood lymphocytes levels were tested in only one case. As part of the differential diagnosis, a polymerase chain reaction (PCR) for tuberculosis in CSF was performed in all subjects.

Approval for this study was obtained from the Institutional Review Board of our Center (R-2020-501-020). Before enrollment, informed consent was signed by parents or tutors of the patients.

RESULTS

Five pediatric patients (including three female and two male) with ages ranged from 2 to 17 years old (average 9-years old). At admission all the patients presented hydrocephalus, and a ventriculoperitoneal shunt (VPS) was subsequently placed. Physical examination revealed low weight in one subject and moderate malnutrition in two cases [Table 1].

Clinical manifestations

All patients showed signs of endocranial hypertension on admission. Sixth nerve palsy was identified in three children and central facial palsy in one case. Seizures were documented in one child, while in another case the patient developed ataxic gait. Three children debuted with hemiparesis; two patients had Parinaud's sign and meningeal signs on admission. Papilledema was found in three patients on fundoscopy. Fever was recorded in only three cases [Table 2].

Neuroimaging findings [Table 3]

Preoperative CT scan showed an Evans´ index greater than postoperative control MRI (average of 0.39, ranges 0.31–0.58, and 0.30, ranges 0.15–0.31, respectively). Three cases presented asymmetric hydrocephalus (AH) [Figure 1] and abnormalities in the fourth ventricle morphology (cases 2, 4-5). Case 2 developed a isolated fourth ventricle (IFV) [Figure 2]. Case 5 developed compression and displacement of the fourth
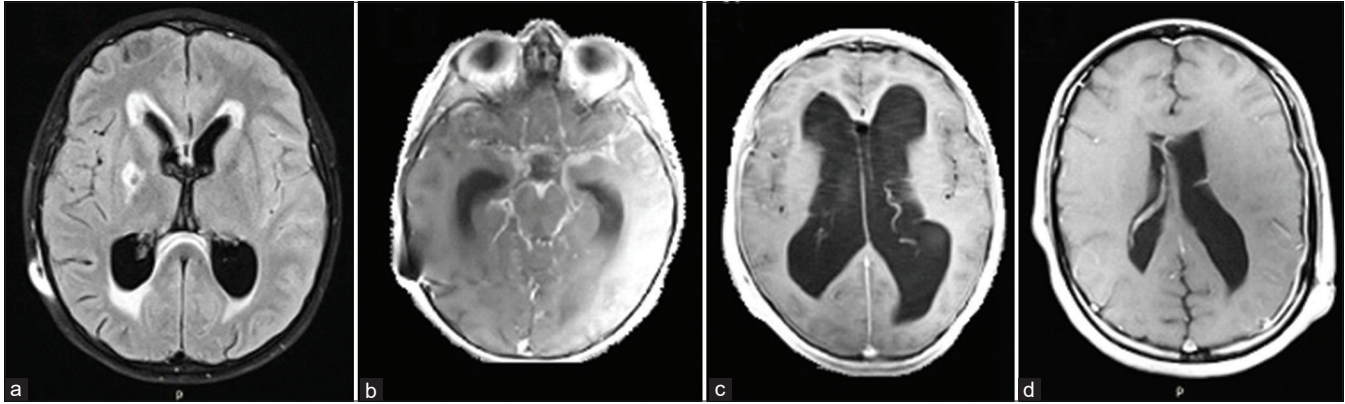
Figure 1: (a) T2-FLAIR-weighted magnetic resonance imaging (MRI) showing ischemic stroke in the right head of the caudate nucleus and anterior limb of the internal capsule, (b) Gadolinium-enhanced T1-weighted MRI with basal arachnoiditis, (c) Gadolinium-enhanced T1-weighted MRI showing asymmetric hydrocephalus (AH) and leptomeningeal enhancement, (d) Gadolinium T1-weighted MRI showing AH and left frontoparietal leptomeningeal enhancement.

Table 1: Demographic findings, CSF characteristics, treatment, and follow-up of our pediatric series.

Case	Age (months), Sex	IMC	CSF initial parameters©	Hospitalization (days)	Shunts (n)	Medical treatment	Outcome
1	24, M	12.34 LW	Normal	42	3	Fluconazole Ⱦ	No neural deficit
2	84, F	11.8 MM	Normal	426	9**	Caspofungin, Fluconazole, Corticosteroids	Persistent vegetative state
3	108, M	15.6	Low glucose levels, pleocytosis	73	1	Fluconazole Ⱦ	No neural deficit
4	156, F	14.3 MM	Normal	22	1	Fluconazole	No neural deficit
5	204, F	16.4	Normal	40	1***	Fluconazole	No neural deficit

CSF: Cerebrospinal fluid, M: Male, F: Female, LW: Low weight, MM: Moderate malnutrition, **Isolated fourth ventricle, ***Chiari II malformation, Ⱦ Initial misdiagnosis of meningeal tuberculosis, ©(see Annex I)

Table 2: Clinical findings.

Clinical manifestation	N (*n*=5)
Headache	5
Nausea	5
Vomit	4
Weakness	3
Seizure	2
Meningism	1
Cranial nerve paralysis (VI, VII)	4
Fever	3
Ataxia	1
Parinaud	2
Papilledema	3

ventricle secondary to tonsillar displacement and Chiari II malformation [Figure 2c]. In control MRI studies, two children presented cerebral vasculitis (case 2-3). Postsurgical control MRI showed leptomeningeal enhancement (5/5) and basal arachnoiditis (4/5) (involving perimesencephalic cisterns and medial portion of the Sylvian cisterns).

**Serological and histopathological studies [Table 4]**

Serological tests in CSF revealed IgG levels from 0.150 to 0.495 D.0. (mean 0.845 D.0. across subjects) while in serum IgG titers ranged from 0.005 to 2.16 D.0. (mean 0.8344). Children with CM diagnosed by serology presented serum IgG levels against *Coccidioides* >0.500 D.0 with an upper limit of 2.16 D.0. (case 1, 3-4). In contrast, in patients diagnosed by histopathology (cases two and five) titers were <0.150 D.0. and therefore considered negative for systemic coccidiomycosis. Only two patients, with serological diagnosis of CM, presented positive serum IgM titers for *Coccidioides* (≥0.150 D.0)*.

Mean IgE levels ranged from 25 to 173.UI/ml (mean 0.845 D.0.). Case 5 (patient with Chiari II malformation, who underwent myelomeningocele repair at birth), presented high levels of IgE but did not meet the criteria for Job Syndrome. One patient presented high levels of IgM and in 40% (*n* = 2) high levels of IgG were observed. The average IgG titers ranged from 1219 to 1858 mg/dl (mean 1522.4 mg/dl). Despite having the highest serum IgG titers, Case 4 antibodies against *Coccidioides* were not

Table 3: Neuroimaging findings.

| N Case | Presurgical findings (CT) | Postsurgical findings (MRI) | | | |
	Evans index	Evans index	Asymmetric hydrocephalus	Morphology of the fourth ventricle	Others
1	0.377	0.26	-	Normal	BM, BA, LE
2	0.3125	0.311	+	Severe dilation (IFV)	BM, BA, LE, CV
3	0.38	0.29	-	Normal	BM, BA, LE, CV
4	0.58	0.5	+	Moderate Dilation	BM, BA, LE
5	0.33	0.15	+	Not visible*	LE

BM: Basal meningitis, BA: Basal arachnoiditis, LE: Leptomeningeal enhancement, CV: Cerebral vasculitis, *Malformation of Chiari II with tonsillar herniation secondary, IFV: Isolated Fourth ventricle
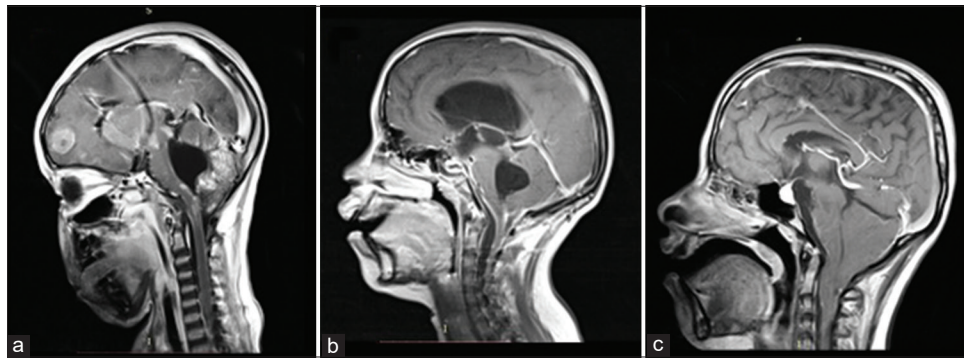

Figure 2: Imaging findings of the fourth ventricle (FV). (a) Severe dilation of the FV (case 2), (b) moderate dilation of the FV (case 4), (c) absence of FV, tonsillar herniation (case 5 with Chiari II malformation).

increased (negative test). Hyper or hypogammaglobulinemia was not detected in the rest of cases. T lymphocyte counts were normal in the tested case. No patient presented with eosinophilia or lymphopenia. Serology tests for HIV, hepatitis B and C were negative in all cases.

CSF cytology was positive in two children [Figure 3]. All leptomeningeal biopsies showed inflammation signs, but no spherules were identified. CSF analysis revealed no abnormalities in four subjects; only in one case low glucose levels and mild pleocytosis was detected (see Annex I). All CSF cultures were negative for fungi. Case 2 presented growth for on the distal shunt catheter.

Medical treatment

Fluconazole at doses of 6–12 mg/kg/day was prescribed as life-long antifungal therapy. Corticosteroids were indicated in case of cerebral vasculitis, or signs of serious illness. Case 2 was treated with caspofungin and cephalosporins initially due to a positive culture for *Pseudomonas aeruginosa* in the distal shunt. The child presented neurological deterioration and poor evolution and MRI showed HA, cerebral vasculitis, and IFV. After a month of hospitalization and multiple shunt
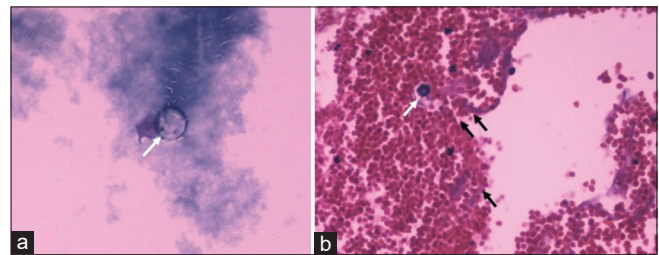
Figure 3: Pathologic findings (a) spherule of *Coccidioides immitis* (white arrow) in cerebrospinal fluid (CSF) cytology (case 2), (b) cell-block form CSF showing a *C. immitis* spherule (white arrow) accompanied by a background of lymphocytes (black arrows) (case 5).

replacements, *C. immitis* was isolated in ventricular CSF [Figure 3a] and treatment with Fluconazole 800 mg/day was started. However, the patient presented cardiorespiratory arrest and evolved to a persistent vegetative state.

Surgical procedures

VPS placement was performed in all subjects. In case of bacterial superinfection, external ventricular drains were also placed (case 2). An average of three surgeries was performed

Table 4: CSF and serum immunoglobulin levels, lymphocyte, and eosinophil count.

ID	Age/Sex	IgG in CSF (D.O.)	IgG in serum (D.O.)	IgM in serum (D.O.)	Lymphocytes K/μL	Eosinophils K/μL	ELISA, HIV	Serology for HBV and HCV	IgE (UI/ml)	IgA (UI/ml)	IgG (UI/ml)	IgM (UI/ml)	Levels of T lymphocytes (LT)
1	24, M	0.495	0.5	0.009	6.72	0.27	-	-	25	53	1661**	114	-
2	84, F	0.011*	0.016	0.0	3.36	0.15	-	-	25	117	1858**	152	-
3	108, M	1.311	1.502	0.812	2.15	0.45	-	-	25	51	1389	100	LT 24%, LT CD3 37%, LT CD4+19%, LT CD8+18%, CD4/CD8 ratio=1.06
4	156, F	2.1	2.16	1.9	3.56	0.13	-	-	25	249	1486	254**	-
5	204, F	<0.012*	0.005	0.005	2.4	0.25	-	-	173.5**	87	1219	115	-

The serological diagnosis was done through immunoenzymatic analysis (EIA) in ventricular CSF and test positive values were ≥0.150 D.0. (optical densities), *Diagnosis by pathology, ** High levels. Serology levels were staged based on the findings of Golubjatnikov[29] and Buckley.[30] LT: T lymphocytes, CSF: Cerebrospinal fluid

per subject (range 1–9). Case 2 developed IFV and it was therefore decided to place a shunt of the fourth ventricle into the subarachnoid space.

Follow-up

Case 2 presented hyponatremia secondary to transient syndrome of inappropriate antidiuretic hormone secretion (SIHAD), with spontaneous resolution. Cases one and three were initially treated as tuberculous meningitis, but CSF PCR was negative for tuberculosis, and CM was later diagnosed by positive IgG serology against *Coccidioides* in ventricular CSF. These two children developed rash and drug related hepatitis due to the interaction of fluconazole and the initial antifimic therapy. The average follow-up was 8 months after discharge. Serum IgG and IgM titers against *Coccidioides* and liver function tests were periodically requested. Control serological tests were reported as negative (<0.150 D.0.). Clinical outcomes were satisfactory in four cases, without evidence of long-term neurological compromise. However, one child (case two) developed a persistent vegetative state. One year after discharge none of the subjects died.

DISCUSSION

According to current Centers for Disease Control and Prevention guidelines, the endemic regions of coccidioidomycosis are found in the Southwestern USA, South-Central Washington state, Northern Mexico, and areas in central and South America. However, Mexico represents the country with the most reported cases in Latin America, with a prevalence of 10–40%.[13,18,21]

We aimed to describe the clinical, radiological, and serological findings in pediatric patients with hydrocephalus due to meningeal coccidioidomycosis in our hospital.

Clinical findings

Headache is the most common symptom documented in CM. Altered personality, impaired cognition, and alterations in the state of consciousness, as well as neurological focal signs (mainly vision disturbances) are symptoms related with severity in CM.[15] All of our patients were hospitalized due to endocranial hypertension syndrome associated with hydrocephalus; a complication that occurs in 40% of cases with CM, as reported in the literature.[10]

Neuroimaging findings

In studies reported from 1981[26] to 2018,[5] hydrocephalus is the most frequently reported neuroimaging finding in CM, with a prevalence of 43–81.8%.[1,7,19,24,28] It is followed in frequency by leptomeningeal enhancement, basal arachnoiditis, and cerebral vasculitis. Brain abscess and fungal aneurysms are less common findings in patients with CM.[7,28] Spinal canal involvement has also been reported in patients

with CM.[5,19] While ventriculitis is frequently described in postmortem studies,[24] fourth ventricle alterations and ventricular asymmetry are rare.[24] All the patients in our series were admitted to the hospital with hydrocephalus; and 60% presented cerebral vasculitis, asymmetry of the ventricular system, and abnormalities in the fourth ventricle morphology.

Shetter *et al.*[24] reported a higher mortality in patients who presented abnormal neuroimaging studies on admission compared to patients with normal studies (31% and 20%, respectively), hydrocephalus being the most common neuroimaging finding reported (62.5%). Subsequently, Arsura *et al.*[1] established a mortality rate of 75% for patients with hydrocephalus and 71.4% for those patients who presented hydrocephalus and cerebral infarction; while patients with normal studies on admission presented a mortality rate of 7.7%. However, in these studies, IFV or ventricular asymmetry were not considered as predictors of mortality; probably due to its low prevalence or because it was not included as a variable in the study.

Shetter *et al.*[24] mentioned that seven of the 15 cases that presented hydrocephalus (46.6%), had alterations of the fourth ventricle, and only in one case asymmetry of the temporal horns (6%) was reported. Shehab *et al.*[23] reported nine pediatric cases with CM and hydrocephalus, with 22% of their patients presenting IFV. About 60% of our patients presented an alteration in the fourth ventricle; however, only one patient reported with IFV who presented a persistent vegetative state; the rest presented normal neurological development in the follow-up period. None patients died.

Serological studies

The diagnosis of CM is currently made by detection of serum IgG antibodies against *Coccidioides* by complement fixation (CF) test along with clinical manifestations and CSF findings suggestive of CM (eosinophilic pleocytosis, protein level >150 mg/dL and low glucose level);[15] furthermore, antibody titers for FC to *Coccidioides* >1:16 predicted a higher probability of disseminated infection.[25] In the present study, antibodies against *Coccidioides* were measured by EIA as this is the only method available in our hospital setting. While recent studies and guidelines recommend these titers are determined by FC, a few reports suggest that EIA can be considered an acceptable alternative in endemic areas.[6] In support of this claim, Kassis *et al.*[17] reported that EIA is more sensitive than FC as method to measure IgG against *Coccidioides* in CSF (85% vs. 70%), while their specificity is similar (99 and 100%, respectively).

Innate and adaptive immunity plays a critical role in host defense against systemic mycoses. Specifically, TCD4+ lymphocytes that differentiate into Th1 and Th17 are essential in the response against severe Coccidioidal disease.[14] TCD4+ cells activate B lymphocytes, stimulating the production of IgE. IgE levels have been reported to predict the severity of *Coccidioides* infection.[4] Moreover, the decrease in TCD4+ lymphocyte counts observed in patients with AIDS explains their susceptibility to severe coccidioidomycosis.[9,11]

Few studies have investigated immune factors and predisposing conditions in pediatric subjects with coccidiomycosis. Mendel *et al.*[20] reported a case of a 19-year-old male patient with HIV who presented a brain abscess by *C. immitis*. Powers *et al.*[22] described the case of a 17-year-old patient with HIES or Job's Syndrome associated with a mutation of the STAT3 gene, and who developed CM. Cid-Chávez[3] presented a series of 30 pediatric coccidioidomycosis cases from Northern Mexico. Only two of those cases developed CM (6.6%). Elevated IgG levels were found in one-third (33%) of the children in that study, reflecting humoral stimulation by the chronic fungal infection. Primary or secondary immunodeficiencies were documented in only 20% of the patients in that series.[3] In contrast, elevated levels of serum IgG were detected in 40% of our patients. High levels of IgE were detected in only one case, but this patient did not meet criteria for Job Syndrome, despite the CM diagnosis and the presence of Chiari II malformation. Given the limited range of tests performed in our subjects, we could rule out the presence of specific immunodeficiencies or an alteration in the INF/IL 12 axis.

Few pediatric cases with CM have been published. About 1% of pediatrics with coccidioidomycosis are expected to have disseminated disease. The difference between the disease in adults and pediatric patients is unknown, however, is expected a more serious disease in children and often associated with some hereditary or acquired immunodeficiency, while in adults AIDS, pregnancy, and immunocompromised (transplant donors) are well-established risk factors. Despite the efforts for early diagnosis and treatment in children, the IDSA guidelines for coccidioidomycosis (2016) are focused on the adult and neonatal population, and pediatrics have been managed on the criteria established for adults.[15,27]

CONCLUSION

This report is one of the few on pediatric subjects with CM in Mexico. In our series, the most common neuroimage findings were hydrocephalus (5/5) and leptomeningeal enhancement (5/5), followed by basal arachnoiditis (3/5), AH (3/5), abnormalities of the fourth ventricle (3/5), and cerebral vasculitis (2/5). The findings here described support the claim that, in endemic areas without access to CF, a positive IgG in CSF or serum detected by EIA can be useful to diagnose CM.

Ethical approval

All procedures were performed in accordance with institutional ethical standards and with the 1964 Helsinki Declaration and its later amendments.

Acknowledgments

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Conflicts of interest

There are no conflicts of interest.

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ANNEX

Annex I: CSF parameters.

N case/Parameters	Glucose (mg/dl)	Protein (mg/dl)	Appearance/color	Cells	PMN (%)	MNC (%)	Gram stain	Ziehl-Neelsen stain	Bacteria culture	Fungi culture
1	53	30.8	Rock water	0	0	0	-	-	-	-
2	95	14.3	Rock water	0	0	0	-	-	*Pseudomonas aeruginosa*	-
3	49	28.8	Rock water	23	78	22	-	-	-	-
4	64	11.2	Rock water	0	0	0	-	-	-	-
5	71	9.1	Rock water	3	66.6	33.3	-	-	-	-