Clinical case

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Central nervous system histoplasmosis , a neurologic challenge: Report of two cases

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Abstract

Introduction: Histoplasmosis in the central nervous system is a fungal infection that affects 5% to 25% of patients with disseminated disease, being more common in immunocompromised patients.

Clinical cases: We examined two different cases: Case 1. A 62-year-old male presented with abdominal pain and weight loss. *Histoplasma* capsulatum was confirmed by colonic biopsy. He later presented convulsions and medullary syndrome with multiple supratentorial and infratentorial abscesses. CD4+ low was found; desnutrition and alcohol intake were the only explanations, as HIV tests were negative. The selected therapeutic scheme was amphotericin induction plus itraconazole for one year. Follow-up showed clinical improvement.

Case 2: A 51-year-old male presented with a 7-month clinical picture of weight loss, fever, dyspnea, and focal epilepsy. He had a recent HIV-positive diagnosis. Cerebrospinal fluid revealed hypoglycorrhachia and elevated protein levels, while brain resonance showed pachymeningeal enhancement. Histoplasmosis was confirmed by bone marrow biopsy, and other causes of pachymeningitis were ruled out. Treatment with amphotericin was initiated, leading to clinical improvement.

Discussion: Histoplasmosis typically presents as chronic basal meningitis, while abscesses, pachymeningitis, or spinal involvement are infrequent. Altered consciousness and headache are the main symptoms. The diagnosis is delayed in 60% of cases. Cerebrospinal fluid (CSF) findings include hyperproteinorrachia (77%), hypoglycorrhachia (53%), and lymphocytic pleocytosis (50%). Although culture and antigen studies are useful, they have limited performance; therefore, imaging and histopathological studies are fundamental. Treatment with amphotericin and itraconazole is necessary and reduces mortality.

Conclusion: Central nervous system infection by *Histoplasma* is an important challenge due to its variable clinical presentation and the complexity of diagnosis. Evidence remains limited; our cases are atypical and constitute the fourth and fifth cases reported in Colombia.

Keywords: Histoplasmosis, Central nervous system, Brain abscess, Pachymeningitis, Fungal meningitis, Myelitis.

Histoplasmosis en el sistema nervioso central, un desafío neurológico: reporte de dos casos

Resumen

Introducción: la histoplasmosis en el sistema nervioso central es una infección fúngica que afecta del 5 % al 25 % de los pacientes con enfermedad diseminada, siendo más común en pacientes inmunocomprometidos.

Casos clínicos: examinamos dos casos diferentes: Caso 1. Hombre de 62 años con dolor abdominal y pérdida de peso, se confirmó infección por *Histoplasma capsulatum* por biopsia colónica. Presentó convulsiones y síndrome medular con múltiples abscesos supratentoriales e infratentoriales. Se encontraron CD4+ bajos; la desnutrición y el consumo de alcohol fueron las únicas explicaciones, ya que las pruebas de VIH fueron negativas. Se seleccionó un esquema de inducción con anfotericina seguido de itraconazol por un año. El seguimiento mostró mejoría clínica.

Caso 2. Hombre de 51 años con cuadro clínico de 7 meses de pérdida de peso, fiebre, disnea y epilepsia focal. Tenía un diagnóstico reciente de infección por VIH. El líquido cefalorraquídeo presentó hipoglucorraquia y elevación de proteínas, mientras que la resonancia cerebral mostró realce paquimeníngeo. Se confirmó histoplasmosis por biopsia de médula ósea, descartándose otras causas de paquimeningitis. Se inició tratamiento con anfotericina, con posterior mejoría clínica.

Discusión: la histoplasmosis suele presentarse como meningitis basal crónica; los abscesos, la paquimeningitis o el compromiso espinal son manifestaciones infrecuentes. La alteración de la conciencia y la cefalea son los síntomas principales. El diagnóstico es tardío en el 60 % de los casos. Los hallazgos en líquido cefalorraquídeo (LCR) son hiperproteinorraquia (77 %), hipoglucorraquia (53 %) y pleocitosis linfocítica (50 %). Aunque el cultivo y los estudios antigénicos son útiles, tienen un rendimiento limitado, por ello, los estudios imagenológicos e histopatológicos son fundamentales. El tratamiento con anfotericina e itraconazol es necesario y reduce la mortalidad.

Conclusión: la infección del sistema nervioso central por *Histoplasma* es un reto importante debido a su presentación clínica variable y a la complejidad del diagnóstico. La evidencia disponible es limitada; nuestros casos son atípicos y constituyen el cuarto y quinto caso reportados en Colombia.

Palabras clave: histoplasmosis, sistema nervioso central, absceso cerebral, paquimeningitis, meningitis fúngica, mielitis.

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Introduction

Histoplasmosis is a systemic infection and part of the fungal germs that can affect the central nervous system (CNS) (1–4). It is commonly seen in immunocompromised patients, but it can also occur in immunocompetent people (5–8). The involvement of the CNS by this agent has been reported in 5% to 25% of patients with disseminated disease (9–11). Some cases have also been reported in the pediatric population, with the first description of the disease documented in an infant in 1934 (9–13). Risk factors for brain involvement include human immunodeficiency virus (HIV), solid organ transplantation, immunosuppressive drugs, and advanced age (14–19). However, between 16% and 36% of patients present without predisposing conditions (7,20,21). We report two histoplasmosis cases in the CNS with atypical presentations.

Case 1

A 62-year-old male with a history of alcohol and cigarette consumption consulted for a two-month history of abdominal pain and 14 kg of weight loss. He was hospitalized by endoscopic/colonoscopic finding of polymorphous ulcers of 9–25 mm with a histopathologic report positive for *Histoplasma capsulatum*. Thorax and abdominal images proved a probable pulmonary and suprarenal involvement. On the second day of hospitalization, he presented an episode of loss of consciousness with tonic posture of the four limbs, gaze supraversion, right cephalic version, and abnormal movements; this event was interpreted as a focal motor seizure. A cranial tomography revealed right temporoparietal vasogenic edema (Figure 1A). Levetiracetam was started as an anticonvulsant treatment, and no focal deficit signs were found.

After 24 hours, the patient presented gait instability and sphincter compromise, the physical examination found flaccid paraparesis with L1 sensitive level, bilateral extensor plantar responses, and left-sided dysmetria. A spinal and cerebellar compromise was suspected. A total neuroaxis magnetic resonance image (MRI) with gadolinium was done. Fungal hematogenous dissemination with multiple abscesses formation was found in the brain (Figure 1B) and spinal cord (Figures 1C, 1D).

For differential diagnoses evaluation, serum and cerebrospinal fluid (CSF) tests were requested. In serum, HIV tests (ELISA and Western Blot) were negative. The IgG for toxoplasmosis, non-treponemal (RPR dilution 1:1) and treponemal (FTA-ABS) tests for syphilis were positive. CSF showed discreet pleocytosis with an altered glucose ratio (inferior to 0.5). Common staining studies were negative, and neither *Histoplasmanor Treponema pallidum* were identified. *Histoplasma* urine antigen was also negative. A summary of the principal paraclinical findings is shown in Table 1.

The IgG for Toxoplasma was positive, however, the images in the MRI were not typical of this infection, and the patient did not have HIV. The PCR (polymerase chain reaction) in CSF for this pathogen was not available in our country. Concerning syphilis tests, the abscesses are unusual in this disease. Moreover, the VDRL in CSF was negative, with inflammatory hallmarks discreet and serum dilutions low. All the mentioned elements and histological confirmation of *Histoplasma make* these differential infectious diagnoses unlikely. Evidence of positive *Histoplasma capsulatum* in colon biopsy is shown in Figures 2A and 2B .

An immunosuppression by CD4+ low levels (79 cells) was detected, however, HIV was negative in multiple exams, and hematologic or solid neoplasm, autoimmune, and systemic conditions were excluded; alcohol intake and malnutrition were the unique factors associated with this finding. After a week of antifungal treatment with liposomal amphotericin B, the patient showed movement improvement and the absence of convulsive events. An induction phase extension with this antifungal for 6 weeks was recommended, and itraconazole use for one year was contemplated by CNS compromise. The patient remains under clinical follow-up, finishing the treatment with partial improvement of his symptoms and lesion resolution, though with mild motor sequelae. A control MRI demonstrating lesion resolution is visible in Figure 2F.

Case 2

A 51-year-old male patient with no significant past medical history was admitted to the emergency department with 7 months of weight loss, approximately 8 kg in the last month, associated with asthenia, adynamia, hyporexia, subjective fever, dyspnea, and apparent urinary incontinence. Admission ancillary testing was done with a normal metabolic panel and a complete blood count with leukopenia (2.700 cells/L) and lymphopenia (486

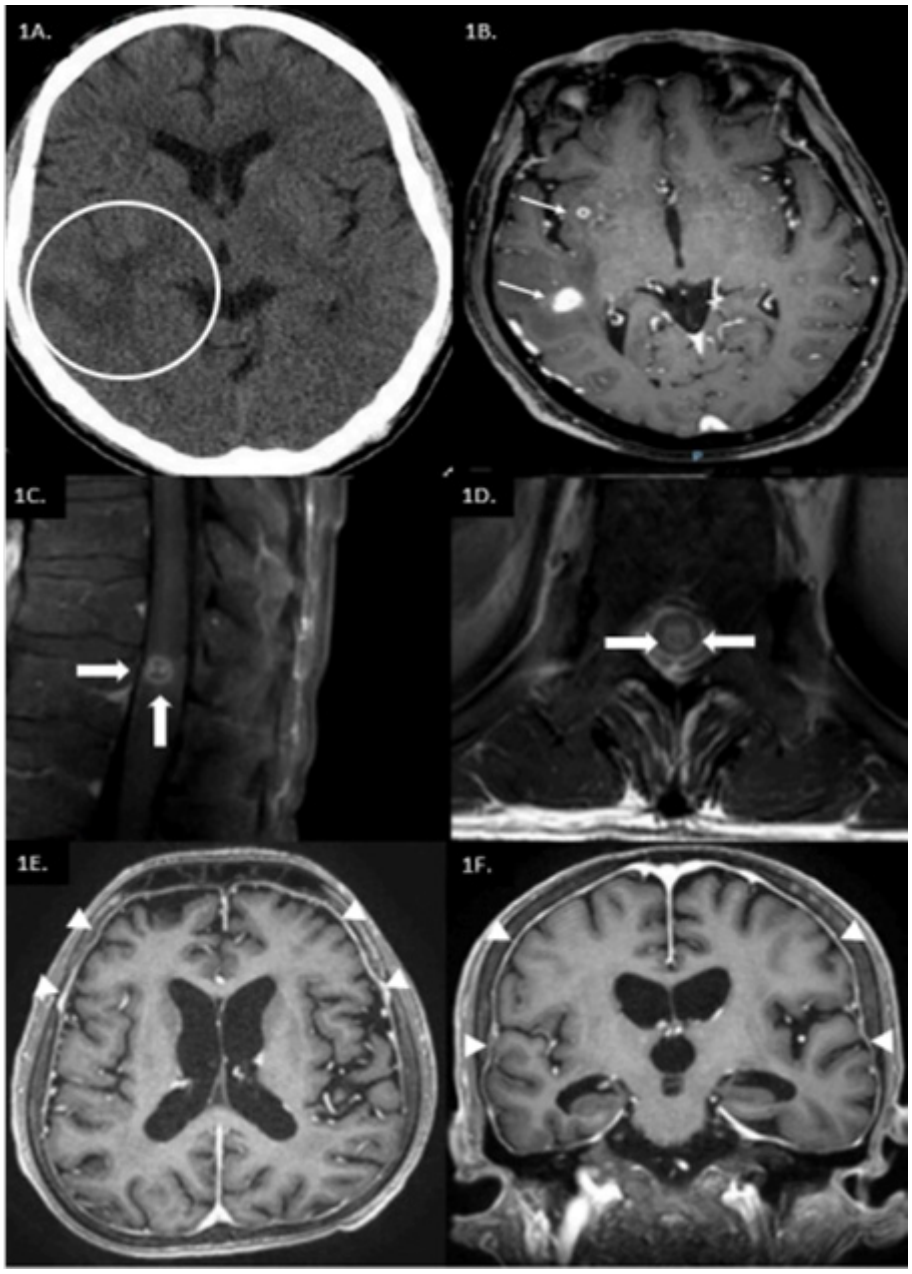

Figure 1. Diagnostic CNS Images

Note. Patient 1: 1A) Skull Tomography (Axial). Right temporal hypodensity with associated vasogenic edema (White circle). **1B) Simple and contrasted Brain MRI (Axial).** Multiple supratentorial abscess with ring contrasted enhancement (Thin white arrows). 1C/1D) Simple and contrast thoracic spine resonance. Spinal cord lesion between T10-T11 with enhancement of the contrast medium and mild associated edema, compatible with myelitis and medullary abscess (Thick white arrows). **Patient 2: 1E) Magnetic Resonance Image (T1 Contrast - Axial).** Diffuse pachymeningeal enhancement is evident, less leptomeningeal compromise. **1F) Magnetic Resonance Image (T1 Contrast - Coronal).** Pachymeningeal enhancement including basal compromise is visualized. (White arrowheads).

Source: Own elaboration.

Table 1. Paraclinical studies

Diagnostic Tools	Patient 1	Patient 2
CSF	Leucocytes 8 cells /mm3. Glucose 51 mg/dL. Glucose ratio 0.48. Protein 42.8 mg/dL. Gram, Chinese ink, VDRL, Cryptococcal antigen and culture: Negatives. Cytology: Negative.	Leucocytes 0 cells /mm3. Glucose 32 mg/dL Glucose ratio 0,38. Protein 48 mg/dL. Gram, Chinese ink, VDRL, Cryptococcal antigen and culture: Negatives. Cytology: Negative.
CSF TBC Studies	ZN: negative. PCR Negative. Culture: Negative	ZN: negative. PCR Negative. Culture: Negative
Infectious studies	Histoplasma antibodies urine: Negative. HTLV 1: Negative. Mantoux: Negative, Ac IgG CMV 131 (Positive), IgM: Negative, Ac IgG Epstein Barr 20.3 (Positive), IgM: Negative, HIV Negative	Histoplasma fecal antibodies: Negative Treponemal test for Syphilis: Negative. HIV: Positive (ELISA and Western Blot). Mantoux: Negative.CMV and Epstein Barr Antibodies: Negative.
Other serum studies	CD4+: 79, CD8+: 168, IgG 2604 (RV: 600-1800) IgM: 119: (RV: 50-283), C3: 162, C4: 62 ANAS: negative, ENAS: Negative, ACE: Negative. TSH: 6.68, Albumin: 2.06, Protein electrophoresis: Normal.	CD4+: 58 cels, CV: 125.429 copy/mL, ANAS: Negative. ENAS: Negative. Rheumatoid Factor: Negative ACE: Negative. TSH: 2,01 T4L: 1,36. Protein Electrophoresis: Normal, Serum tumor markers: Negative.
Images	CNS MRI: Multiple supra- and infratentorial abscesses with contrast enhancement. Myelitis and thoracic spinal cord abscess. Thorax CT: Randomly distributed micronodules predominantly involving the upper lobes in relation with military pattern. Contrast abdominal CT: slight hepatosplenomegaly showing a regular increase in the volume of the adrenal glands which show finely hypodense. Echocardiogram: Normal. No endocarditis signs.	CNS MRI: Global atrophy changes in relation to HIV encephalopathy. Non-nodular global dural enhancement (Pachymeningitis), mild lepto-ningeal involvement. No abscess or focal lesions. Thorax CT: Normal. No signs of pleural effusion or consolidations. Thoracic spine MRI: vertebral body fracture L1 by compression pathological Echocardiogram: Normal. Abdominal ultrasound: Liver fatty.
Histopathologic	Gastric and colonoscopy: PAS and Grocott positive for mycotic structures. *Histoplasma capsulatum* Bone marrow: Normal, negative to precursor hematology neoplasia.	Bone marrow: Normal, negative to precursor hematology neoplasia. Myelogram: Histiocytes with inclusions compatible with *Histoplasma capsulatum.*

Note. Patients' cerebrospinal fluid, serum, imagenological and histopathological complementary studies.

Ab: Antibody; ACE: angiotensin converting enzyme; ANAS: Antinuclear Antibodies; CSF: Cerebrospinal fluid CMV: Cytomegalovirus; ENAS: Extractable Nuclear antibodies; HTLV1: Human T-cell lymphotropic virus; PCR: Polymerase chain reaction; RV: reference value; TBC: Mycobacterium tuberculosis; TSH: thyroid stimulating hormone; VDRL: Venereal Disease Research Laboratory; ZN: Ziehl Neelsen.

Source: Own elaboration.

cells/L). There were also hypokalemia (3,4 mg/dL) and hyponatremia (128 mg/dL), HIV test (ELISA) was positive, with no history of antiretroviral therapy.

After 48 hours the patient presented bilateral seizures (without previous episodes or epilepsy diagnosis) and gait instability, the physical exam did not show cranial nerve, motor, or sensitive compromise, but bilateral extensor response and hyperreflexia in low limbs were found. An MRI was performed, diffuse pachymeningeal enhancement images were described (Figures 1E and 1F), and a lumbar puncture was done with the presence of hypoglycorrhachia and hyperproteinorrachia without pleocytosis. The patient did not have any respiratory symptoms, had negative smear microscopy, had normal contrasted thoracic tomography, and had CSF with PCR negative for *Histoplasma*. However, our country is endemic for tuberculosis, so the more probable differential diagnosis was tuberculous pachymeningitis. An intensive phase with four-drug anti-TB treatment was initiated, and levetiracetam was started for seizure control. Other differential diagnoses were considered but CSF, serum, and image studies excluded other infectious, malignant, or autoimmune diseases (Table 1). The patient did not show improvement with empirical tuberculous management, considering pachymeningeal infiltration by hematologic malignancy, the haemato-oncology team performed a bone

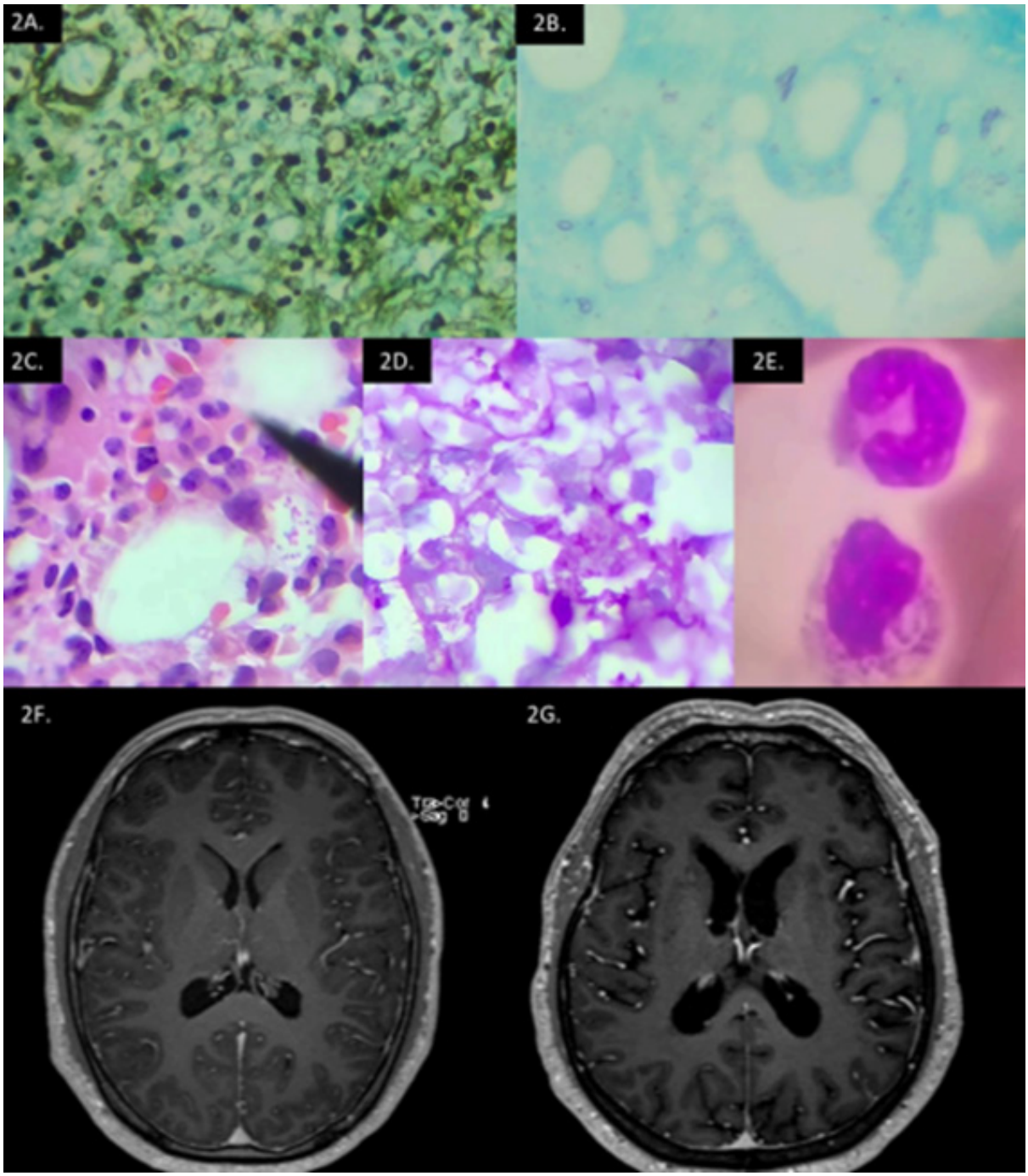

Figure 2. Histological findings and control images

Note. Patient 1: 2A) Colon biopsy (Grocott staining). Lymphocytic infiltrate with evidence of fungal structures is observable. **2B) Colon biopsy (Grocott-Gomori methenamine silver stain).** Structures consistent with histoplasmosis are observed. **Patient 2: 2C) Bone marrow biopsy (Hematoxylin and eosin).** Mononuclear, lymphocytic, and macrophage infiltrates are associated with chronic disease. Some histiocytes are observed. **2D) Bone marrow biopsy (Hematoxylin and eosin).** Rounded, pink intracytoplasmic structures within macrophages suggestive of yeast (Leishman-Donovan inclusion bodies). **2E) Peripheral blood.** Combination of binuclear cells (neutrophils) and mononuclear cells (activated macrophages) with systemic inflammatory activity. **Patient 1: 2F) MRI Axial T1 Contrasted:** Decreased edema and supratentorial lesions resolution are observed. **Patient 2: 2G) MRI Axial T1 Contrasted:** Improvement in the pachymeningeal enhancement observed initially.

Source: Own elaboration.

marrow biopsy, which revealed *Histoplasma capsulatum* by immuno-histochemistry (Figures 2C and 2D). Serum studies also demonstrated a systemic response generated by activated neutrophils and lymphocytes (Figure 2E). Antifungal amphotericin B management was started, and after six weeks, adequate clinical evolution and improvement of neurological symptoms were observed. Itraconazole could not be administered due to its unavailability in our country at the moment. The patient was remitted to another hospital and continued his treatment. At follow-up, the patient was alive with mild sequelae and continued medical antifungal treatment. The CNS control image showed a slight improvement in pachymeningeal enhancement (Figure 2G).

Discussion

Nervous system histoplasmosis is unusual, and it is typically expressed as chronic basal meningitis by hematogenous dissemination (10,11,22,23). Acute meningoencephalitis, abscesses, or spinal involvement are infrequent (9,20,24). Our cases show two exceptional presentations: medullary abscess and pachymeningitis.

Clinically, altered consciousness (28%-50%) and headache (24%-60%) are the main symptoms. Focal signs and seizures were present in less than 20% of cases; some of these manifestations were present in the cases reported (21,25,26). Meningitis without systemic involvement is reported in 25% of cases, but only 8%-17% of patients have meningeal signs. Space-occupying lesions occur in a quarter of events (14,27,28). Strokes, aneurysms, ataxia, abnormal movements, and spinal or visual compromise are rare (24,29-34). Some simulating neoplasias have also been described (35,36). HIV and transplant patients are especially vulnerable groups (15-19).

The diagnosis is delayed in 60% of cases due to low suspicion and differential diagnosis (14,21,37,38). The most frequently described CSF findings are hyperproteinorrachia (77%), hypoglycorrhachia (53%), and lymphocytic pleocytosis (50%) (7,14,39). Neutrophils can be identified in 11% of cases, and approximately 17% had normal CSF (9,39). Our patients showed mild inflammatory signs in the cytochemical study. CSF culture is positive in 19%-50% of cases with CNS involvement, antigenic CSF studies are positive in half of patients (39-41), and they are processed by immunodiffusion, complement fixation, or immunoassay techniques, each with a variable sensitivity and specificity (14,21,27,40).

The combined sensitivity of *Histoplasma* antigen plus IgG/IgM antibodies in CSF by fourth-generation enzyme immunoassay is 98%, and its negative predictive value is 100% to rule out CNS involvement, however, their use is not possible in our country (39,40). Additionally, CSF Bd-glucan and PCR have been used but are limited by their poor sensitivity and specificity (41,42). The diagnostic performance of all tests is summarized in Table 2 .

Table 2. Performance of diagnostic tests for histoplasma in CSF

Test	Sensitivity	Specificity
CSF cytopathology	18%	No data
Brain Histopathology	55%	100%
Brain Culture	50%	100%
CSF culture	19%	100%
B-d- Glucan	50%	80%
Immunodiffusion or complement fixation	51%	96%
CSF PCR for Histoplasma	73%	100%
Histoplasma antigen by EIA	78%	97%
IgG or IgM antibody to Histoplasma by EIA	82%	93%
Antigen + Antibody to Histoplasma by EIA	98%	91%

Note. CSF: Cerebrospinal fluid; EIA: Enzyme Immunoassay; Ig: immunoglobulin; PCR: Protein Chain Reaction.

Source: Adapted from (7,9).

Neuroimaging principal findings are abscesses (20%), ventricular enlargement (9%), and meningeal enhancement (8%), although imaging can be normal in up to 28% of cases (3,21,27). Lesions can be identified in multiple regions of the brain, including deep areas with involvement of the basal ganglia (27,32). In the cases described, the images were fundamental to establish the diagnosis. Additionally, positron emission tomography can be useful in the diagnosis of this infectious pathology (21,43).

Treatment for CNS histoplasmosis has no randomized controlled trials or recent clinical practice guidelines, although disseminated histoplasmosis does (44–46). However, the introduction of antifungal therapy has allowed a reduction in mortality with timely diagnosis (27,45,46). The recommended treatment is liposomal amphotericin B at 5 mg/kg/day for 4–6 weeks, which is subsequently replaced by oral itraconazole 200 mg every 8 hours for 3 days and then every 12 hours for 12 months (9,14). We used the principal therapeutic option without any complications in both cases. Other alternative regimens use deoxycholate amphotericin, fluconazole, posaconazole, or isavuconazole (variable results, not consistent) (10,44,45).

The most frequent complications in the CNS are hydrocephalus and cranial nerve involvement, the mortality and relapse rates are 20%–40% and 16%, respectively (21,28). It is recommended to re-evaluate the *Histoplasma* antigen in the cerebrospinal fluid once the itraconazole is finished, drug levels should be monitored to avoid toxicity (39,40,44). Incomplete treatment impacts the vital and functional outcomes (4,27,28). Our patients are alive, and mild sequelae are evident, but it is a satisfactory outcome. A brief summary of CNS histoplasmosis cases previously described in our country was included in Table 3 (47,48,49).

Conclusion

Central nervous system infection by *Histoplasma* is infrequent but represents an important challenge due to its variable clinical presentation. Unusual forms, such as those described in our cases, are usually diagnosed by histopathological studies, and the compromise of other organs can be useful for this confirmation. The search for immunosuppression, other infections, and associated diseases is essential in the differential approach. Early diagnosis, although difficult given the performance and difficulty of accessing some diagnostic methods, allows timely treatment with a reduction in mortality. The evidence on this topic is limited to case reports or series. Our cases are important because they are unusual presentations of this disease in the CNS, they are the fourth and fifth cases reported in Colombia.

Authors' contributions. Michael Ariza: conceptualization, formal analysis, research, methodology, writing and revision (original draft); Natalia Sanchez: conceptualization, formal analysis, research, methodology, writing (original draft) and revision; Enrique Hernandez: writing, supervision, writing (review & editing); Patricia Quintero: conceptualization, writing (review & editing); Christian Stevens Labrador: conceptualization, writing (review & editing).

Ethical implications. None.

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Conflicts of interest. The authors declare no financial or personal relationships that could be perceived as influencing the work presented.

Table 3. Comparison CNS histoplasmosis cases in Colombia

COLOMBIAN CASES	CASE 1	CASE 2	CASE 3
Authors	***Potosí, et al. (47)***	***Lizarazo, et al. (48)***	***Osorio N, et al. (49)***
Sex	Male	Male	Male
Age	39 years	10 years	12 years
Reporting area	Popayán	Cúcuta, Norte de Santander	El Bagre, Antioquia
History	HIV	Chickens in the home	None
Time of Onset	3 months	Days of Onset	6 months
Clinical Manifestation	Weight loss, pleomorphic skin lesions. Hypotension, fever syndrome, and cough.	Not described	Vomiting, weight loss. Peak fever and drowsiness one month prior to consultation.
Neurological Manifestation	Tonic-clonic seizures and hetero-aggression	Paresthesias, dysarthria, papille-dema, seizures, drowsiness, ataxia, nystagmus	Severe headache, ataxia, ver tigo, nuchal rigidity.
Clinical Laboratory Tests	Pancytopenia. Low CD4 count (274 cells). LDH: 1.01 (Elevated).	CBC with eosinophilia, negative-PCR.	Mild lymphopenia on CBC.
Chest Imaging	Peribronchial thickening, micronodular infiltrates	Normal (X-ray)	Normal (X-ray)
CNS Imaging	Not reported	Ventriculomegaly, spinal nodular lesions	Obstructive hydrocephalus, basal meningeal enhancement.
Lumbar Puncture	Not reported	Leukocytes: 4 cells, Protein: 20 mg/dL, Glucose: 48 mg/dL	Leukocytes: 21 cells, Protein: 570 mg/dL, Glucose: 12 mg/dL
Diagnostic	Positive culture on bronchoalveolar lavage	Positive serology (IgM)	CSF and serum serology + CSF culture
Treatment	Amphotericin B deoxycholate	Amphotericin B and Fluconazole	Liposomal Amphotericin and Itraconazole
Outcome	Death	Partial improvement	Improvement
Complications	Seizures, respiratory arrest	Optic atrophy (blindness)	Hypokalemia and acute kidney injury

Note. A summary of the cases reported to date in the literature in Colombia with histoplasmosis and central nervous system involvement is presented for comparison with the cases published by the research group (47,48,49).

Source: Own elaboration.

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