The majority of immunocompetent infected individuals have either no symptoms or a very mild illness. CNS involvement is observed in 5% to 10% of patients, mostly in case of disseminated histoplasmosis and/or in association with immunocompromising conditions. Radiologic differential diagnosis of a ring-enhancing intraparenchymal brain mass lesion should include also histoplasmosis. Biopsy remains the gold standard for diagnosis, but non-invasive strategies, such as detection of fungal antigens in cerebrospinal fluid, may be helpful. Liposomal amphotericin B followed by itraconazole for at least 1 year is recommended, but often associated with significant side effects.

We present a case of isolated CNS histoplasmosis, presenting with multiple ring-enhancing bilateral lesions, in a young Ecuadorian immunocompetent host, successfully treated with oral voriconazole for twelve months.
enhancing lesion in the left frontal region. Magnetic resonance imaging (MRI) confirmed the presence of a cystic lesion with mass effect in the frontal left lobe and found two other smaller ring-enhancing lesions in the right post-central sulcus and in the left parietal sulcus.

Considering the country of origin of the patient and the type of brain lesions, empirical treatment for neurocysticercosis with albendazole 400 mg bid was started in association with anti-epileptic and anti-edema therapy. After 28 days, treatment was discontinued and control MRI was performed. An increase in volume of the known lesions and the presence of two new ring-enhancing bilateral lesions were documented (Figure 1). Lumbar puncture was performed: cerebral spinal fluid (CSF) examination was normal, culture was negative, but CSF (1,3)-β-D-glucan (BG) was 282 pg/ml. Serum BG, cryptococcal antigen and galactomannan in CSF and serum, serum antibody assays for *H. capsulatum* and *Coccidioides immitis* were all negative. Stereotactic-guided craniotomy and total excision of the left frontal lesion was performed in June 2010. The biopsy specimens was culture-negative, Ziehl-Neelsen stain for Mycobacteria was negative, but Gomori-Grocott methenamine silver stain identified numerous yeast-like roundish structures of variable size and DNA of *H. capsulatum* was detected in tissue sample by real-time PCR.

This patient was immunocompetent and serology for human immunodeficiency virus (HIV) was negative. He did not have any history suggestive of a deficient cellular immunity. His absolute lymphocyte count was normal. He denied involvement in any recreational activities that could have predisposed him to *Histoplasma* infection, or exposure to bat or bird droppings.

Considering his good clinical conditions, oral voriconazole was started on July 2010 with loading dose of 400 mg twice daily and later 300 mg bid orally. After one month of treatment, MRI showed a decrease of size and contrast enhancement of left frontal lesion. Therapeutic drug monitoring (TDM) was performed once a week to ensure trough concentration levels between 1 and 5 µg/mL by adequate dose adjustments. After one month of therapy, the patient experienced hepatic toxicity which led to voriconazole dose reduction at 200 mg bid. TDM, performed one week later, showed low drug levels (0.638 µg/mL). Antifungal dose was modified with prescription of 200 mg tid that the subject tolerated well with adequate trough concentration levels (1.5 µg/mL). Voriconazole was discontinued after twelve months. MRI performed at the end of treatment and six months later demonstrated significant reduction of left frontal ring-enhancing lesions with a remaining scar area and disappearance of the smaller lesions. The patient remained in good clinical conditions and seizure-free on 1000 mg of levetiracetam twice daily. Clinical follow up was ended three years after the onset of treatment.

**DISCUSSION**

Isolated central nervous system (CNS) histoplasmosis in immunocompetent patients, such as in our patient, who presented with a non-specific ring enhancing brain lesion, is highly uncommon. Differential diagnosis of such lesions include not only parasitic, mycobacterial or fungal agents which may be more common in certain endemic areas, but also other causes of intraparenchymal mass such as bacterial abscess or necrotic tumor, all of which are often difficult to distinguish from fungal granuloma with MRI. Indeed, living in an area endemic for mycoses should be considered as an important epidemiological factor even if clinical presentation is not suggestive for histoplasmosis.

In Italy, histoplasmosis is considered a very rare disease and diagnostic tools, such as serology and antigenic detection, are not available in all laboratories, although autochthonous cases have been described, especially in recent years in Northern Italy. The gold standard for diagnosis remains positive fungal culture of *H. capsulatum* in CSF, parenchymal tissue, or other sites. Obtaining an
adequate sample for culture, however, may be difficult and dangerous and requires qualified laboratory staff due to low sensitivity and a long turn-around time of fungal cultures. Therefore non-invasive strategies may be helpful: serum BG test has shown a sensitivity of 87% for infection caused by *Histoplasma spp.* and it has been recently demonstrated that BG detection in CSF is useful for the diagnosis of different cerebral fungal infections, including histoplasmosis.

Response to therapy is lower in CNS histoplasmosis than in other localizations. Current treatment recommendations, in either HIV-positive or HIV-negative subjects, indicate polyenes as first-line therapy: liposomal amphotericin B (5.0 mg/kg daily for a total of 175 mg/kg given over 4-6 weeks) followed by itraconazole (200 mg 2 or 3 times daily) for at least 1 year is recommended. However, administration of liposomal amphotericin B is still burdened with nephrotoxicity and, rarely, infusion reactions. Moreover, lack of an oral formulation imposes hospitalization with increased costs and risk of healthcare-associated complications. The use of itraconazole is limited by several well-recognized problems such as variable intra- and inter-individual digestive absorption, poor tolerability and low cerebral penetration.

In this patient, considering his good clinical conditions, voriconazole was preferred because of its excellent oral bioavailability and ability to reach fungicidal concentrations within the CNS. It is recommended for invasive aspergillosis and candidiasis, and has been used in histoplasmosis in AIDS patients or in patients failing itraconazole. In particular, in the case reported by Srini-vasan et al, the use of voriconazole for histoplasmosis brain abscess resulted in a clinical and radiological improvement with good tolerability in a patient with undefined immunodeficiency disorder experiencing liver toxicity after itraconazole administration.

Voriconazole has not been studied in animal models of histoplasmosis. The *in vitro* inhibitory effects of the drug on *H. capsulatum* and its high bioavailability suggest its utility for treating histoplasmosis. Variable and unpredictable metabolism related to genetic factors, age, compliance, gastrointestinal absorption during oral treatment or drug interactions may result in an insufficient exposure of the fungal pathogen to voriconazole or excess drug concentrations with potential toxicity. For these reasons, monitoring of voriconazole serum levels has been advocated as a method for ensuring adequate drug exposure in treating invasive mycoses. In our patient TDM was performed weekly to ensure trough concentration levels between 1 and 5 µg/mL, with the aim of avoiding side effects and maximizing antifungal activity. The patient experienced hepatotoxicity that was initially considered as related to voriconazole, although other causes, including anti-epileptic drugs, may have played a role; indeed, the patient tolerated well the subsequent antifungal dose increase. As reported for other azoles, the use of voriconazole is burdened with many drug interactions, in particular with most of the anti-epileptic medications. Therefore, levetiracetam was chosen for seizure control, due to the absence of hepatic metabolism and interactions with voriconazole.

**CONCLUSIONS**

Isolated cerebral histoplasmosis in an immunocompetent host may be challenging for clinicians. BG testing in CSF might help confirming the presence of a fungal infection, although definite diagnosis should be rapidly confirmed by either culture or biopsy. Voriconazole is a viable alternative for treating cerebral histoplasmosis due to confirmed *in vitro* activity, excellent CNS penetration and availability of both intravenous and oral formulation.

**CONFLICT OF INTERESTS:**

The Authors declare that they have no conflict of interests.

**REFERENCES**


