Case report

CNS Histoplasmosis as a Gliosarcoma mimicker: The diagnostic dilemma of solitary brain lesions

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A B S T R A C T

Histoplasmosis is usually a benign, self-limited disease with lungs predilection. However, it might manifest as a disseminated disease in immunocompromised individuals. The involvement of the central nervous system (CNS) accounts for about 5–10% of cases with disseminated disease. Isolated histoplasmosis of the CNS is rare, and the literature shows only a few reported cases. By imaging studies, it usually presents as an isolated ring-enhancing lesion. Its spectrum of symptoms ranges from acute severe infection to progressive chronic meningitis, which delays the initial diagnosis, correct work-up and initiation of appropriate therapy. We present a case of a 57-year-old man from the Midwest of the United States who misdiagnosed with Gliosarcoma in 2019, for which he underwent appropriate management for Gliosarcoma. Presented for follow-up after new neurological symptoms; worsening in ring-enhancing brain lesions was found on magnetic resonance image (MRI). After a re-examination of surgical pathological cases, histoplasmosis of the CNS was diagnosed. Failure of diagnosis CNS histoplasmosis early can lead to poor outcome and decrease chances of recovery.

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Introduction

Histoplasma is a dimorphic thermal fungus that changes its active phase based on ambient temperature [1]. Histoplasma capsulatum is the etiology of the most common endemic mycosis known as histoplasmosis, which occurs worldwide, but is endemic in North and Central America [2]. The infection occurs mainly after inhalation of microconidia, which transforms into yeast in the alveolar spaces and multiply within the cytoplasm of the alveolar macrophages, making lung histoplasmosis the most commonly reported form of the disease. Later, after approximately two weeks of exposure, adaptive cellular immunity develops in the presence of sensitized T lymphocytes, Tumor necrotic factor and interferon gamma, which will lead to activation of fungicidal effect of macrophages to help eradicate the infection. [3] Histoplasmosis, and specifically CNS histoplasmosis have been reported in immunocompetent as well as immunocompromised hosts. [4–6].

The clinical presentation could range from completely asymptomatic (e.g. incidental mediastinal lymphadenopathy in Computed Tomography (CT) scan during cancer staging) to severe disseminated disease after spreading through lymphatics and blood. The symptoms depend mainly on the amount of fungal spores, while the extent of organ involvement depends on the immune status of the host.[7] On average, 70% of asymptomatic cases occur in immunocompetent patients. [8,9].

Disseminated histoplasmosis is by definition a fungal infection caused by Histoplasma capsulatum, which spreads outside the lungs into the bloodstream and reaches other parts of the body. [7] After the end of the incubation period (approximately 14 days after exposure), the acute phase of infection begins. The first reported symptoms usually relate to the pulmonary system, which can go unnoticed, mainly because they mimic all other simple respiratory viral infections. Cellular immunity is expected to develop against similar infections, especially in immunocompetent individuals, which limits the spread of disease. [10] However, hematogenic spread will follow one in 20,000 Histoplasma infections [7], 5–10% of which have CNS involvement [11,12], especially in patients with a suppressed immune system. [11,13].

Case report

A 57-year-old male from the Midwest of the United States who presented for worsening brain lesions follow-up. His past medical history includes compensated cirrhosis secondary to chronic untreated hepatitis C virus infection with an unknown genotype, and
familial adenomatous polyposis syndrome status post colectomy with colostomy placement. Twelve months earlier, the patient had seizure-like symptoms, in addition to progressive facial spasms and tinnitus in his right ear. Five months later, he sought medical attention and was found to have a right frontal lobe solitary 1.4 x 1.8 cm mass, surrounding by vasogenic cerebral edema on magnetic resonance image (MRI) of the brain.

A craniotomy with resection of the mass was performed. The submitted tissue for the frozen section demonstrated extensive tissue necrosis with a rim of viable tissue with increased cellularity with surrounding gliosis. At the time of frozen section, the findings were consistent with Gliosarcoma. Immunohistochemistry studies for GFAP and vimentin, Snook’s reticulin stain, as well as molecular analysis such as IDH1 and IDH2 genes and methylation of the MGMT promoter were performed on permanent sections. The cells appeared to be glial in H&E stains, although they mostly were GFAP immunonegative (they were vimentin immunopositive). As the outer "shell" around the necrosis appeared collagenous, a Snook’s reticulin stain was done, which showed a heavy deposition of reticulin in that shell and among most highly cellular tissues, as well as extensively within the necrosis. With the mindset that this was a malignant glioma, the histomorphologic findings, the intense reticulin, and positive vimentin results, in conjunction with the patient’s clinical history and radiologic findings of a solitary mass, were more supported of a CNS malignant neoplasm. Molecular genetic studies directed at this high grade glioma diagnosis revealed wild-type IDH1 and IDH2 genes, and no methylation of the MGMT promoter. No tissue culture was obtained at that time.

His immediate postoperative MRI showed only postoperative changes without additional lesions. After surgical resection, he underwent adjuvant radiotherapy and maintenance chemotherapy with temozolomide and OPTUNE device. The patient was not compliant with either maintenance chemotherapy or the OPTUNE device. After the surgical treatment, the patient’s previous symptoms of facial spasms resolved, but he continued to complain of weakness of the left upper limb.

Four months after his initial presentation, his weakness worsened, he developed nausea and vomiting. He denied seizures, paraesthesia, syncope, vision, or hearing alterations. The patient claimed to have lost 20 lb of weight after his surgery without fever, fatigue, or night sweats.

A repeat brain MRI (Fig. 1), seven months after craniotomy, showed two new rim-enhancing lesions, measuring 11 and 5 mm in the greatest dimension. The largest mass was in the left cerebellar region, while the smaller lesion was in the left temporal lobe. After the patient complained of new episodes of morning dizziness, a follow-up MRI (six months after the new findings) (Fig. 2) showed both lesions continued to grow, increasing from 11 to 21 mm for the cerebellar lesion, and 5–6 mm for the left temporal occipital lesion. Positron emission computed tomography (PET CT) was performed, showing fluodeoxyglucose (FDG) avid brain lesions in the left cerebellum and posterior left temporal lobe, correlating with previous MRI results.

The patient underwent a second left-sided craniotomy for the cerebellar cortex mass resection. The frozen evaluation showed necrosis, fibrosis, inflammation, and few atypical cells, and a fragment of the cerebellum, and the final diagnosis was deferred to permanent H&E sections (Fig. 3A and 3B). The neuropathologist who first reviewed the case in the patient’s second resection (TJP) provided a final diagnosis of Histoplasma infection, after which cultures were performed for confirmation. Sections show cerebellum with patchy necrosis and extensive chronic lymphohistiocytic and plasmacytic inflammation with focal acute inflammation. The inflammation is vaguely granulomatous, but without compact, well-formed granulomas. No tumor is identified. (Fig. 3C and 3D) Within the histiocytes, clustered numerous small (2–4 mm) round-to-ovoid fungal yeast forms were found, with a mucicarmine-negative capsule. There are also many degenerate fungal yeast forms in the necrosis. Narrow-based budding is noted. The fungal organisms were most suggestive of Histoplasma species. Tissue culture grew Histoplasma capsulatum in three different samples, which were finalized on day 26 of culture. The anaerobic culture of the brain tissue had no growth. Fungal smear from brain tissue was negative for hyphae or yeast.

That prompted reevaluation of the pathological slides from his first surgery. It was noted that there were similar small round organism-like structures in or around some of the cells in a few foci, prompting the production of a Crockett Methenamine Silver (GMS) stain, which confirmed the initial diagnosis of Gliosarcoma was incorrect. That showed that the necrotic tissue as well as the viable tissue were filled with thousands of small round regular yeasts. There were no pseudohyphae or hyphal forms.

Serum histoplasma quantitative antigen enzyme immunoassay (EIA) was positive (0.56 ng/mL; reference interval: None Detected). However, Urine Histoplasma antigen EIA was negative (0.00 ng/mL). Studies were done while the patient had been on fluconazole for three days at that time. The [1,3] Beta-glucan was found to be (190 pg/mL; reference normal value: <60 pg/mL). Hepatitis C viral load of 3.9x 10^6 copies. The HIV test was negative. Other laboratory workups shown in (Fig. 4).

Fig. 1. Cranial Histoplasmosis lesions: Initial magnetic resonance image of the brain at seven months after the first craniotomy; showed two new rim-enhancing lesions, measuring 11 and 5 mm in the greatest dimension. The largest mass was in the left cerebellar region, measuring 11 and 5 mm in the greatest dimension. The largest mass was in the left cerebellar region, while the smaller lesion was in the left temporal lobe. Picture on the left: 6 x 4.2 x 3 mm in left cerebellar (white arrow). Picture on right: left posterior inferior temporal lobe approximately 5 mm in diameter (orange arrow). (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)
Fig. 2. Magnetic resonance image of the brain thirteen months after his first craniotomy. Left: 17 x 21 x 15 mm ring enhancing lesion in left cerebellar (white arrow). Right: same 6 mm rim-enhancing lesion in the left temporal occipital region (green arrow). (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)

Fig. 3. Histopathological specimen and stain from the patient’s 2nd craniotomy samples. A. Hematoxylin & Eosin (H&E) stains show cellular foci composed of fibroblast, histiocytes, and glial cells with hyperchromatic nuclei, originally concerning for glioma. B. Hematoxylin & Eosin (H&E), stains serpentine basophilic necrosis originally concerning for palisading necrosis of a glioblastoma. In B (inset), tissue voids within histiocytes were suspicious for occult yeast fungal forms. C, D Grocott methenamine silver (GMS) and Periodic Acid Schiff Stain for fungus (PAS-F) highlights the walls of numerous small oval-to-round yeast forms growing in clusters within regions of necrosis (C) and within histiocytes within regions of inflammation (D). Additionally, mucicarmine stain was ordered and confirms the absence of capsule, as would be seen in Cryptococcus neoformans. Tissue cultures grew Histoplasmosis capsulatum.
The patient was started on fluconazole, which was switched to amphotericin liposomal B after three days, dose 3 mg / kg daily, completed four weeks of induction therapy with amphotericin, had a week (the fourth week) overlap with itraconazole induction dose of 200 mg three times daily for three days, followed by a maintenance dose of 200 mg twice daily. The follow-up to the infectious disease clinic was planned to check itraconazole levels in 7 days after itraconazole began, but the patient never showed up. Four months later, he presented with progressive left-sided weakness to the neurosurgery clinic. Brain MRI (Fig. 5) at that time showed a new lesion within the right posterior centrum semiovale, extending to the posterior horn of the right lateral ventricle and into the body of the corpus callosum. The largest portion of this lesion measured approximately 1.7 x 1.2 x 2.2 cm. The previously identified lesion within the left inferior temporal gyrus was stable, measuring approximately 0.5 cm in diameter. The lesions previously observed in the left superior cerebellum were no longer identified. The patient reported taking his itraconazole tablets with food as prescribed, and had not missed any doses. The proposed etiology of the new lesions was either non-compliance with itraconazole, subtherapeutic levels or failure of itraconazole. Brain MRI with spectroscopy confirmed this lesion appears similar to previous histoplasmosis lesions. Itraconazole levels were therapeutic. He was reinstated on amphotericin, with plans for four weeks of induction therapy, followed by the start of isavuconazole with one week of overlap with amphotericin. The patient did not return to the ID clinic for follow-up. Our outpatient parenteral antimicrobial therapy team was informed that the patient passed away in an outside hospital after two weeks of combined isavuconazole and amphotericin therapy.

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**Fig. 4.** Basic blood work up obtained at thirteen months after the first craniotomy.

**Fig. 5.** Magnetic resonance image of the brain five months after finishing 1st round of amphotericin induction, and while being on therapeutic itraconazole, pictures show a new right-side lesion at posterior centrum semiovale (white arrow) extending to the posterior horn of the right lateral ventricle (green arrow) and into the body of the corpus callosum (blue arrow). (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)
Discussion

Our patient was misdiagnosed with CNS gliosarcoma in 12/2019. He survived over a year to 2021, when he subsequently showed progressively worsening neurological symptoms and radiological evidence of CNS masses over at least 12 months, though the average survival rate of CNS gliosarcoma is less than 6 months [14]. In his case, CNS gliosarcoma relapse was top on differential given his poor adherence with recommended treatment (patient was started on adjuvant chemotherapy with temozolamide and OPTUNE device (it is a device that can be worn on the head to send electrical signals to interrupt the cancer cells) [15]). Upon examination of his second lesions histologically, findings were similar to the original resection. This prompted a re-evaluation of the slides of right frontal lesions obtained 13 months earlier. Organisms concerning for fungal (yeast) infection were noted. GMS stain was applied; this showed that the necrotic tissue, as well as the viable tissue, were filled with thousands of small round regular yeasts. The case was amended from the original diagnosis of Gliosarcoma, WHO Grade IV, to a non-neoplastic diagnosis of chronic CNS fungal brain lesions, likely Histoplasma.

There are many locations where disseminated histoplasmosis occurs, and it can rarely reach the central nervous system (CNS) [16]. Similarly, isolated cases of CNS histoplasmosis without involvement of other organs were also reported [78]. According to a review by Staffonali et al. that CNS manifestations were only detected in 2% of acute histoplasmosis cases [10]. The affected areas in the CNS may be located superficially in meninges, deep in the brain tissue, as focal lesions [7] or even as ischemic stroke [13], and therefore radiological findings and clinical presentation may vary. The clinical picture of a CNS fungal disease is too unspecific and depends mainly on the location involved. Radiological presentation of CNS histoplasmosis ranges from cortical ring-enhancing lesions, large masses or enhanced meningeal signals [7].

Diagnosis is challenging for many reasons, including hosts who are not necessarily always immune-compromised, fungal infections are not considered, and when considered, there is no appropriate approach with the most effective high-yield studies [11]. The approach to suspected cases typically begins with brain imaging. Deep brain histoplasmosis infections usually appear as ring-enhancing lesions on CT scan or MRI. These lesions have a broad differential diagnosis, including brain abscesses, toxoplasmosis, and other infectious, inflammatory and neoplastic etiologies that vary in likelihood with the immune status of the patient. [8] Therefore, Histoplasma has been frequently presumed neoplastic, and extensive metastatic work-up for primary tumor and initiation of radiation therapy has been also reported. [17] Lumbar puncture is another important step in the diagnosis. The expected findings in histoplasmosis meningitis are similar to all other fungal meningitis findings with high protein, low glucose content and mild mononuclear leucocytosis [7]. Cerebrospinal fluid (CSF) tests with Histoplasma antibodies and antigen are considered the most sensitive tests for the detection of CNS histoplasmosis [11]. Anti-histoplasma serum antibodies, as well as urine and serum antigens, are considered a main part of the diagnostic workup [6,12]. The correlation between cerebrospinal fluid, serum and urine studies is imperfect. [6] In one study of patients with CNS Histoplasmosis, CSF Histoplasma antigen test sensitivity reached up to 78% [18]. In another multicentric study, Urine and serum Histoplasma antigen sensitivity were 73% and 50% respectively [11]. In one study, Clearance of Histoplasma antigens in disseminated histoplasmosis was monitored over time, initial follow up was obtained in 4 weeks after treatment [19]. Our patient had been on fluconazole for three days only at the time of obtaining his antigens test.

It is indicated to treat all cases of disseminated histoplasmosis. Untreated chronic disseminated histoplasmosis has a high mortality rate [12,20]. Survival rates ranged from 55% to 80% in various reports [11]. Treatment options depend on the severity of the disease and the affected organs. CNS histoplasmosis is considered the most challenging due to the poor penetration of most antifungals. According to the IDSA guidelines, it is recommended to start with amphotericin-liposomal lipid-soluble form, mainly due to its high CNS effectiveness compared to other amphotericin formulations, followed by itraconazole for at least one year [12]. Itraconazole is known to be active against histoplasmosis, although it has not been well studied in terms of CNS penetration in humans [6, 21, 22], except for cryptococcal meningitis [23,24]. The other azole proposed in the studies is fluconazole. Fluconazole has better CNS bioavailability at the expense of weaker histoplasmosis activity. Maintenance therapy with either is acceptable with a desirable outcome [7–9]. Poor results are associated with the use of non-lipid-soluble amphotericin formulations, age, non-compliance with therapy and immunosuppression [11].

Infection recurrence is an expected problem, with an estimated incidence of 6–50% in various reviews. These cases are mainly related to non-compliance with treatment, so patients must remain under medical supervision for at least one year after completion of therapy to ensure a resolution of the infection by radiological and/or CSF antigen / serological studies. Immune-compromised patients may require a longer course of therapy, which may extend to lifelong treatment as long as their immune system is suppressed [6, 8, 11]. Even with prolonged therapy, cases of relapsed CNS histoplasmosis have been reported in immunocompromised patients during maintenance therapy [25]. Our patient his compensated cirrhosis secondary to chronic untreated hepatitis C virus infection. He was also noted to be leukopenic and lymphopenic repeatedly on multiple blood checks. He had thrombocytopenia, likely secondary to liver cirrhosis, but no other signs of decompensation were found. Patients with liver cirrhosis are considered immunocompromised, and at risk of multiple infections, mainly bacterial and fungal infections due to multiple mechanisms [26,27].

Conclusion

Our case illustrates a patient who initially presented with concerns for CNS tumor, underwent craniotomy and resection. Patient was misdiagnosed with Gliosarcoma, after which he had a relapse of symptoms with radiological evidence of multiple enhancing lesions in the brain, which was strongly suspicious of recurrence of malignant lesions in the setting of his misdiagnosis. A subsequent craniotomy and biopsy were decisive in demonstrating multiple yeasts and thus, establishing Histoplasmosis. In the context of the previous diagnosis of gliosarcoma, a new biopsy diagnosis of histoplasmosis led to a re-evaluation of previous slides, noted to have thousands of small round regular yeasts, and corrected to histoplasma. Clinicians should be vigilant regarding histoplasmosis as an etiology of CNS pathology in patients living in endemic areas, regardless of their immune status or presentation. Early suspicion helps avoid delay in diagnosis by ordering an appropriate workup, which will allow early treatment and, therefore, prevent fatal consequences. The duration of treatment for CNS histoplasmosis is prolonged. Discontinuation of therapy depends mainly on proving the resolution of the infection. Nevertheless, relapses can still occur.

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CRediT authorship contribution statement

Suha Abu-Khalaf: Conceptualization, Writing – original draft. Paragkumar Patel: Writing – review & editing. Carla R. Caruso: Supervision, Writing – review & editing. Timothy Parrett: Diagnosis of Histoplasmosis, Supervision, Providing histopathology pictures, Writing – review & editing. Andres Brann: Supervision, Writing – review & editing.
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