

CASE REPORT

Hiding in plain sight: a case of chronic disseminated histoplasmosis with central nervous system involvement

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SUMMARY

A 64-year-old man presented with gradual onset of confusion, ataxia and 25-pound weight loss over 3 months. MRI of the brain revealed two enhancing cerebellar lesions suspicious for metastases. Positron emission tomography-CT showed enhancement of cervical and axillary lymph nodes. Left axillary lymph node biopsy showed no evidence of malignancy but instead showed fungal organisms morphologically consistent with *Histoplasma* spp. Disseminated histoplasmosis with central nervous system involvement was suspected. Further history revealed that the patient had been having subjective fever for the past several months. He has had mild pancytopenia for about 2 years, which had not been further evaluated. Additionally, he had an oesophagogastroduodenoscopy 3 months prior to admission, which had shown granulomatous gastritis. Subsequently, the diagnosis of disseminated histoplasmosis was confirmed by serological testing and bone marrow biopsy. The patient was started on liposomal amphotericin B. Unfortunately, the patient had a catastrophic stroke and was transitioned to comfort care measures.

BACKGROUND

Disseminated histoplasmosis is rare and is generally seen in immunocompromised hosts. However, it has also been reported in immunocompetent middle-aged men.¹ It often presents with indolent multisystem involvement with seemingly unrelated symptoms, as illustrated in our case. Hence, several opportunities to diagnose disseminated histoplasmosis can be easily overlooked.

CASE PRESENTATION

A 64-year-old man, who is a Michigan resident, presented in the outpatient clinic with gradual onset of confusion, ataxia and 25-pound weight loss over 3 months. He had a medical history of type 2 diabetes mellitus, hypertension and peripheral artery disease. Family history was significant for diabetes mellitus in the brother. The patient worked at a storage facility and helped move the articles. He also enjoyed doing yard work at his house. On clinical examination, the patient's body temperature was 99.5 °F, and his neurological evaluation revealed left upper limb dysdiadokokinesia and gait ataxia. He was alert and oriented to place and person but not to time. An MRI scan of the brain

was ordered, which revealed two enhancing cerebellar lesions suspicious for metastases (figure 1).

At this point, the patient was referred to oncology with a presumed diagnosis of metastatic cerebellar malignancy. A positron emission tomography-CT scan was ordered by the oncologist, which showed enhancement of cervical and axillary lymph nodes. Lymphoma was suspected and lymph node biopsy was planned. However, the patient's mental status deteriorated over the next few days and he became progressively more confused. Per family, the patient would start making coffee late at night thinking it is early morning. He also had rapidly progressing ataxia and had several bruises from frequent falls. Due to these changes, the patient had to be admitted to the hospital.

INVESTIGATIONS

In the hospital, the patient underwent CT scan of the head, which showed stable cerebellar lesions. The cerebellar lesions were thought to be responsible for the patient's worsening ataxia and confusion. The patient did not complain of headache and was afebrile at the time when he was admitted to the hospital. The oncology service was consulted and they requested left axillary lymph node biopsy. Interestingly, the biopsy showed no evidence of malignancy. Instead, the Grocott's methenamine silver (GMS) staining revealed fungal organisms that were morphologically consistent with *Histoplasma* spp (figure 2). At this point, disseminated histoplasmosis with central nervous system (CNS) involvement was suspected to be the cause of the patient's cerebellar lesions. Infectious disease service was consulted for further management.

It was learnt that the patient had been having intermittent subjective fever for the past several months. His laboratory data showed that he has had mild pancytopenia for about 2 years, which had not been further evaluated. During this admission, his reticulocyte index was 0.74, suggestive of suppressed marrow response. Furthermore, he had an oesophagogastroduodenoscopy (OGD) 3 months prior to admission for work-up of melena and anaemia (his haemoglobin at that time was 6.9 g/dL). The OGD revealed a gastric ulcer, the biopsy of which showed 'granulomatous gastritis'. No further work-up was done for this peculiar pathology. The patient also had an erythematous papular rash of unclear aetiology in the lower extremities for 1 year. Finally,



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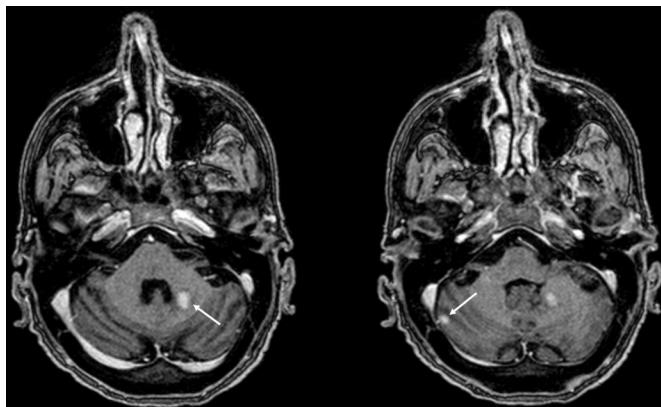


Figure 1 T1-weighted MRI images showing two enhancing lesions in the cerebellum.

prior abdominal imaging had shown masses in both adrenal glands.

This constellation of abnormalities including low-grade fever, weight loss, pancytopenia with suppressed marrow response, granulomatous gastritis, adrenal masses and erythematous rash were all identified as potential manifestations of disseminated histoplasmosis. A lumbar puncture was performed on day 4 of admission. Serological testing for *Histoplasma capsulatum* was positive in both serum and CSF. CSF analysis showed no white blood cells, CSF protein of 44 mg/dL and CSF glucose of 105 mg/dL. The CSF bacterial culture was negative. On day 5, a bone marrow biopsy was performed, which showed hypocellular marrow and scattered interstitial granulomas with fungal organisms most consistent with *Histoplasma* spp (figure 3). HIV testing was negative. The patient's history of diabetes was the only factor that may have caused an immunocompromised state.

DIFFERENTIAL DIAGNOSIS

The outpatient working diagnosis for the patient's cerebellar lesions was cerebellar metastases. However, convincing evidence of disseminated histoplasmosis was obtained during inpatient work-up, including blood and CSF serology, lymph node and bone marrow biopsy, as well as aforementioned other prior clinical data. Hence, the major differential for the cerebellar lesions was CNS histoplasmosis.

TREATMENT

Thereafter, the patient was started on liposomal amphotericin B therapy at a dose of 5 mg/kg (276.5 mg) once a day.

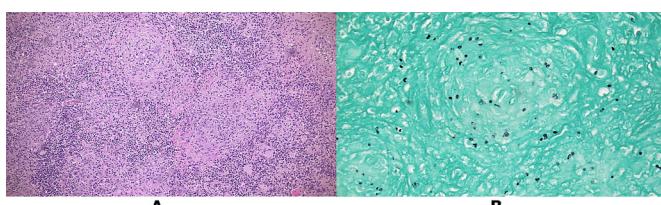


Figure 2 (A) A 10× magnification view of H&E staining of the lymph node showing confluent granulomas. (B) A 40× magnification view of Grocott's methenamine silver staining of the lymph node showing scattered yeast-like organisms morphologically highly consistent with *Histoplasma* spp.

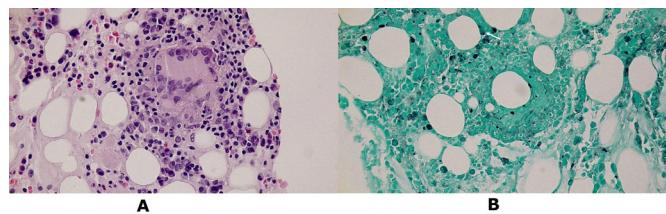


Figure 3 (A) A 40× magnification view of H&E staining of the bone marrow showing an interstitial granuloma. (B) A 40× magnification view of Grocott's methenamine silver staining of the bone marrow showing fungal organisms morphologically highly consistent with *Histoplasma* spp.

OUTCOME AND FOLLOW-UP

Unfortunately, 2 days after antifungal therapy was started, the patient developed multiple ischaemic strokes involving the left middle cerebral artery territory, right basal ganglia and deep right frontal lobe, as seen on the CT scan of the head (figure 4). There was no evidence of intracranial haemorrhage on the CT. The aetiology of these strokes was unclear but was thought to be embolic in nature due to their heterogeneous distribution. Apart from thrombotic emboli, infected (fungal) emboli were considered as a potential cause. The patient's mentation acutely worsened and he was suspected to have non-convulsive status epilepticus. An electroencephalogram was ordered and the patient's family was counselled that the patient needs to be transferred

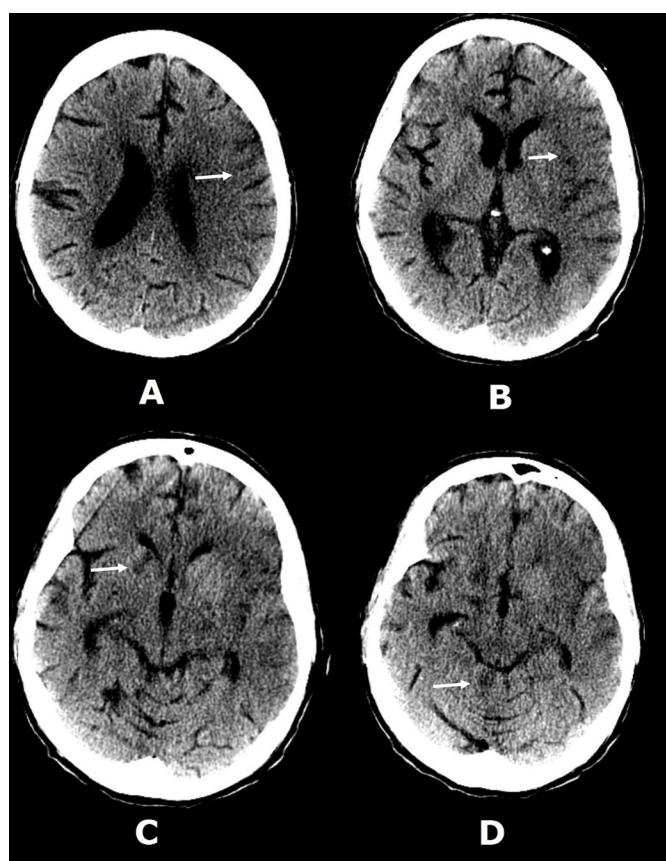


Figure 4 CT scans of the head showing loss of grey-white matter differentiation (A) and loss of insular ribbon (B) on the left side suggestive of acute middle cerebral artery infarct. Also seen are small hypodensities involving right basal ganglia (C) and superior cerebellum (D) suggestive of acute strokes.

to the intensive care unit. However, the family declared that the patient did not want intensive care or any life support. Palliative care was consulted and the patient was eventually transitioned to a comfort care protocol and expired the next day. Autopsy was offered to the family, but they decided not to have that done.

DISCUSSION

H. capsulatum is a dimorphic fungus with a mould (saprophytic/non-pathogenic) form that exists in soil and a yeast (parasitic/pathogenic) form that exists in humans at body temperature.²

The mould form consists of hyphae with small spores called microconidia. Primary infection occurs with inhalation of microconidia from the soil. Histoplasma takes the yeast form in the lungs and is ingested by pulmonary macrophages. These macrophages then cause its silent dissemination via the bloodstream until cell-mediated immunity is activated in immunocompetent hosts and the infection resolves. However, an immunosuppressed state can lead to chronic disseminated histoplasmosis.

Histoplasmosis is endemic in the Midwest region of the USA and Michigan has been identified as an endemic state.³ Up to 50%–99% of patients exposed to Histoplasma remain asymptomatic, and less than 1% develop disseminated histoplasmosis.¹ Among these, only a small fraction have CNS manifestations. The majority of the patients who develop disseminated histoplasmosis either are at extremes of age or are immunosuppressed (eg, patients with AIDS, solid organ transplantation recipients on immunomodulators, and patients on tumour necrosis factor α inhibitors). Subsequently, a third group of middle-aged men with no known immunosuppression has been identified; genetic defect in a component of cell-mediated immunity has been hypothesised to be a risk factor.¹

These patients often have non-specific constitutional symptoms including fever, fatigue and weight loss. Besides, multiple organ systems can be involved with diverse manifestations. Gastrointestinal system is most commonly involved. Hepatosplenomegaly may be present and transaminitis can be noted on routine laboratory investigations. Besides, ulcerated or polypoid lesions can be present in any part of the gastrointestinal tract. This includes the entity granulomatous gastritis, which is characterised by the presence of granulomatous inflammation in the gastric tissue. Apart from histoplasmosis, granulomatous gastritis can be caused by various other infectious and non-infectious causes, including Crohn's disease, sarcoidosis, mucosa-associated lymphoid tissue lymphoma, *Helicobacter pylori* infection and syphilis.^{4,5} Further work-up should be done to identify the aetiology. This may include using the GMS stain to identify fungal organisms. This stain was not performed in our patient when biopsy of the gastric ulcer seen during the outpatient OGD had revealed granulomatous gastritis.

Adrenal involvement in disseminated histoplasmosis has been reported in 80%–90% of autopsied cases, but overt adrenal insufficiency is seen only in less than 10% of the cases.¹ Our patient had bilateral adrenal masses that could have potentially been caused by adrenal histoplasmosis. Their presence can be an important clue in making the diagnosis. Pancytopenia is also

common due to bone marrow infiltration. Our patient had persistent pancytopenia as noted on several outpatient laboratory tests, but bone marrow biopsy was not performed all this time. Various non-specific patterns of skin lesions can be seen.⁶ CNS involvement occurs in only 5%–10% of the cases and can have varied presentation, including meningoencephalitis, stroke syndromes due to infected emboli or focal CNS lesions.⁷ Although infected emboli were considered to be a potential cause of our patient's multiple strokes, it could not be confirmed as no autopsy was performed.

Learning points

- ▶ Disseminated histoplasmosis with central nervous system (CNS) involvement can mimic CNS metastases.
- ▶ Although typically seen in immunosuppressed individuals, disseminated histoplasmosis may also develop in immunocompetent patients.
- ▶ Persistent pancytopenia with suppressed marrow response (defined as low reticulocyte index) should be further investigated.
- ▶ Detection of granulomatous gastritis on biopsy of a gastric ulcer should invoke further work-up. This may include Grocott's methenamine silver staining of the tissue sample.
- ▶ Awareness of the various possible manifestations of disseminated histoplasmosis in both internists and specialists can help in making early diagnosis.

Contributors Both authors contributed to the manuscript as follows: SP was part of the primary team that admitted the patient and GST was on the Infectious Disease team, which was consulted for the patient at that time. Hence, both authors were directly involved with patient care. GST did the literature review and manuscript write-up. SP revised the manuscript critically for important intellectual content. Both authors gave their final approval of the version to be published.

Competing interests None declared.

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