CASE REPORT

Cryptococcal eosinophilic meningitis in a patient with sarcoidosis

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SUMMARY

A 51-year-old African-American man with underlying pulmonary, hepatic and splenic sarcoidosis, reported a 3-day history of headache, neck stiffness and photophobia. He was not using medication for chronic sarcoidosis. Physical examination was significant for nuchal rigidity. Lumbar puncture revealed marked eosinophilia in the cerebrospinal fluid, which, on further analysis, demonstrated a positive cryptococcal antigen. HIV antibody and PCR tests were negative. Bronchoscopy and fungal blood cultures were also negative. The patient was started on amphotericin B and flucytosine, with significant clinical improvement. He recovered well without any neurological sequelae and remained symptom-free at 2-week follow-up. Cryptococcal central nervous infections are uniformly fatal if left untreated. Prompt diagnosis and treatment is essential, to prevent the associated high morbidity and mortality.

BACKGROUND

Eosinophilic pleocytosis of the cerebrospinal fluid (CSF) is a rare, distinctive finding that is often indicative of certain helminthic infections of the central nervous system. Non-helminthic causes are rare but well documented in the literature. Cryptococcosis is an opportunistic infection that typically affects immunocompromised patients. Cryptococcal eosinophilic meningitis is unusual, with few cases reported. Sarcoidosis is an idiopathic, systemic, granulomatous disorder that has been described as an independent risk factor for cryptococci infection. The impairment of cell-mediated immunity, and treatment with steroids and other immunosuppressive medications, are thought to be the main culprits for the increased risk of acquiring opportunistic infections in these patients. We report a unique case of a patient in whom an uncommon infection was manifested by an atypical presentation (eosinophilic pleocytosis) in the setting of an unusual, but well-described, risk factor (sarcoidosis).

CASE PRESENTATION

A 51-year-old African-American man presented with a 3-day history of nausea, vomiting, neck stiffness, photophobia and a gradually progressive, diffuse, throbbing headache. The patient's medical history was significant for hypertension and a seizure disorder secondary to bleeding cavernous malformations that were resected two decades earlier. The patient also had a history of biopsy-proven lung, liver and spleen sarcoidosis diagnosed 10 years previously during a hospitalisation for bile

duct obstruction. Owing to financial and compliance issues, the patient never started any chronic treatment for his sarcoidosis. The patient's social history was negative for alcohol, tobacco, and over-the-counter and recreational drug use. His long-term medications included levetiracetam 500 mg twice daily and atenolol 50 mg daily. He had no significant travel history in the past year; however, 2 years prior, he had travelled to multiple states, including Georgia, Louisiana, California and Alabama. He was employed as a truck driver and denied any recent sick contacts or contact with any animals or wildlife. The patient was not on any immunosuppressive medications and denied any risk factors for HIV. He had no previous exposure to tuberculosis and no history of incarcerations. On physical examination, the patient had vital signs within normal limits. Neurological examination was significant for nuchal rigidity. Kernig's and Brudzinski's signs were negative. His mentation was intact and there was no evidence of focal neurological deficits. Routine blood work revealed a complete blood count and comprehensive metabolic panel within the normal reference range. A non-contrast CT scan of the head showed no acute pathology.

INVESTIGATIONS

Lumbar puncture revealed normal glucose of 44 mg/dL, elevated protein of 108 mg/dL, a red blood cell (RBC) count of 1969 cells/mm³ and a white cell count of 1826 cells/mm³ with a corresponding differential of 76% eosinophils, 14% neutrophils, 7% lymphocytes and 2% monocytes. Opening pressure was not obtained during the initial lumbar puncture. CSF and blood cultures were collected, along with ACE levels. CSF samples were analysed to rule out tuberculosis, fungal infections, viruses, parasites, syphilis and Lyme disease. Although the patient had no abdominal symptoms, given the marked eosinophilia in the CSF, stool samples were obtained to rule out parasitic infections. Owing to the xanthochromic appearance of the CSF, CT angiography of the brain, followed by MRI of the brain and entire spine, was performed. HIV, aspergillus galactomannan and complement test results were normal. The cryptococcal antigen was positive. Subsequent ophthalmology examination revealed no ocular involvement. Immune cell function assays as well as T-helper/suppressor cell analysis were also obtained. CT of the chest and bronchoscopy were performed to determine if there was any cryptococcal pulmonary

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involvement. Fungal blood cultures were collected to rule out disseminated infection.

DIFFERENTIAL DIAGNOSIS

Given the significant RBCs in the CSF, there was initial concern for an intracranial bleed from cavernous angiomas. CT angiography of the brain did not reveal any acute bleeding. Owing to the patient's history of cavernous angiomas of the brain and his high risk for vascular malformations in the spine, MRI revealed several small non-bleeding cavernous angiomas of the thoracic spine. Although there was high concern for an active bleed, evidence did not suggest bleeding from any of the malformations and further work up was not warranted. We also had a high index of suspicion for neurosarcoidosis as the cause of this patient's symptoms; however, MRI of the brain refuted this possibility. ACE level in the CSF and blood were within the acceptable reference range. Given the marked eosinophilia in the CSF and the lack of a plausible explanation, we attempted to identify possible alternative causes. Stool and CSF samples ruled out helminthic infection. CSF samples ruled out viral, bacterial, mycobacterial and fungal infections. Given that the patient was not on any new medications, the possibility of drug-related eosinophilic reaction was eliminated. CSF India ink prep was negative and no organisms were seen. On day 2, cryptococcal antigen came back positive at a titre of 1:2. Given this atypical presentation and the presence of an opportunistic infection, an immunodeficiency work up was conducted. Total helper CD4 count was found to be 328 cell/ μ L (%T-helper CD4 of 31%), with CD4:CD8 ratio of 1. Immune cell function assay was found to be severely low at 24 ng/mL ATP (<225 ng/mL ATP signifies low immune response). Disseminated cryptococcal infection due to T-cell immunodeficiency from underlying sarcoidosis was the concluding diagnosis. Fungal blood cultures remained negative. Despite the lack of respiratory symptoms in our patient, disseminated cryptococcal infection from a primary lung source was considered. A CT of the thorax showed diffuse, tiny nodular opacities in the lungs bilaterally in a tree-in-bud configuration, with relative sparing of the lower lobes. Although these findings were similar to previous imaging obtained many years prior,

bronchoscopy with biopsy was performed to rule out primary lung cryptococcal infection. Final results were consistent with sarcoidosis with no evidence of infection.

TREATMENT

After obtaining the initial lumbar puncture, the patient was empirically started on broad spectrum coverage with vancomycin, ceftriaxone and acyclovir. The patient remained symptomatic and required large amounts of narcotics to control his symptoms. He refused a repeat lumbar puncture to alleviate symptoms and to measure the opening pressure. When the cryptococcal antigen proved positive, treatment was tailored with amphotericin B at a dose of 5 mg/kg/day and 5-flucytosine at a dose of 25 mg/kg/dose every 6 h. The patient remained in significant discomfort from continued headaches and agreed to undergo successive therapeutic lumbar punctures. The second lumbar puncture was performed on hospital day 4 (opening pressure of 35, closing pressure of 19) and the third lumbar puncture on day 8 (opening pressure of 22, closing pressure of 5), the latter of which was negative for cryptococcus antigen (table 1). Eosinophilia in the CSF trended downward with treatment but had not resolve completely when the patient was discharged. Interestingly, his RBC count in the CSF significantly diminished, raising the hypothesis that the elevated RBC count was related to the active infection. With successive lumbar punctures and antifungal treatment, the patient showed significant clinical improvement and had a complete resolution of his symptoms and headache after 1 week of treatment.

OUTCOME AND FOLLOW-UP

After several days of amphotericin B, the patient's creatinine increased 30% from baseline and remained elevated despite adequate fluid therapy. Given his complete resolution of symptoms, low initial cryptococcal titres and no remaining evidence of cryptococcal antigen, the decision was made to proceed to consolidative therapy. The patient was transitioned to high-dose fluconazole (1000 mg/day) for 10 weeks, followed by maintenance therapy with 200 mg/day for 6–12 months. The patient remained asymptomatic and was discharged home on hospital

Table 1 Analysis of cerebrospinal fluid samples obtained from the patient on hospital days 1, 4, and 8.

	Hospital day 1	Hospital day 4	Hospital day 8
Tube #	4	4	5
Volume	3.0	2.5	5.0
Colour	XANTHOCHROMIC	RED	Colourless
Clarity	HAZY	Hazy (A)	Clear
Spun appearance	XANTHOCHROMIC	Clear	Clear
Glucose, CSF (40–80 mg/dL)	44	51	50
Protein, CSF (15–55 mg/dL)	108 (H)	66 (H)	60 (H)
RBC (0/cu mm)	1969 (H)	5074 (H)	33 (H)
WCC (0–5/cu mm)	1826 (H)	301 (H)	133 (H)
Neutrophils (0–6%)	14 (H)	15 (H)	6
Basophils (0%)	1 (H)	0	1 (H)
Eosinophils (0%)	76 (H)	61 (H)	64 (H)
Lymphocytes 40–80%)	7 (L)	18 (L)	28 (L)
Macrophages (0%)	0	0	0
Monocytes (15–45%)	2 (L)	6 (L)	1 (L)
Mononucleates (15–45%)	0 (L)	0 (L)	0 (L)
	Crypto antigen positive	Crypto antigen positive	Crypto antigen negative

CSF, cerebrospinal fluid; RBC, red blood cells; WCC, white cell count.

day 11. On follow-up with the infectious diseases clinic 2 weeks postdischarge, the patient appeared well and had no recurrence of symptoms. He was scheduled to follow-up with pulmonary medicine for discussion of starting treatment for sarcoidosis.

DISCUSSION

Eosinophilic meningitis is a subtype of meningitis defined by the presence of 10 or more eosinophils/ μL in the CSF or eosinophilia of at least 10% of the total CSF leucocyte count.¹ The most common cause of this condition is invasion of the central nervous system (CNS) by parasitic infections.^{2–3} Some fungal infections such as *coccidioides immitis* could also present with eosinophilic pleocytosis.⁴ Non-infectious causes such as medications, ventriculoperitoneal shunt malfunction, autoimmune disorders affecting the CNS and haematological malignancies, have also been linked to this disorder.^{5–11} CNS infections with cryptococcal organisms have been rarely associated with eosinophilic pleocytosis.^{12–13} Cryptococcal infections occur most commonly in HIV patients but can also occur in immunocompetent non-HIV individuals. Risk factors for cryptococcosis include inhalation of bird droppings (especially pigeons), immunocompromised status, diabetes and patients with underlying cell-mediated immunodeficiency.¹⁴ Although uncommon, sarcoidosis has been established as an independent and important risk factor for development of CNS cryptococcosis. This association appears to occur regardless of the use of steroids or immunosuppressive drugs, although their use may play a role in facilitating the dissemination of the infection.¹⁵ The diagnosis of CNS cryptococcosis can be made by detecting the encapsulated yeast form of the fungus in the CSF using India ink stain. This method is quick and easy, and immediately available on obtaining the CSF sample; however, it is only 50% sensitive in HIV-negative patients. An alternative method for diagnosis of CNS cryptococcosis can be made by detecting a cryptococcal antigen. The antigen is a sensitive and specific marker, and can be detected in the serum and CSF samples of infected individuals.^{16–17} When cryptococcosis of the CNS is diagnosed, prompt treatment is essential to prevent high morbidity and mortality associated with this disease. Although differences exist in the treatment duration between HIV and non-HIV patients, the general treatment plan is the same, consisting of three stages: induction, consolidation and maintenance therapy. Amphotericin B (5 mg/kg intravenous daily) plus flucytosine (100 mg/kg/day orally in four divided doses) are the mainstay of therapy. This regimen is usually continued for 2–4 weeks, depending on the immune status of the patient, and response and prognosis. This is followed by consolidation therapy with 400–800 mg fluconazole daily. To prevent relapses, maintenance therapy with fluconazole 200 mg/day should be continued for at least 6–12 months.^{18–19} Given the high intracranial pressures usually associated with this infection, consideration should be made to perform successive lumbar punctures to relieve high intracranial pressures associated with this disease and to assess the response to therapy in all individuals.¹⁸ Although these are general guidelines, a balance must be achieved when dosing these toxic drugs between clinical benefits and adverse effects in an individual patient. In our patient, we chose to make the switch to fluconazole early to avoid further kidney toxicity. This strategy was based on our patient's excellent initial clinical response, complete resolution of symptoms, low initial cryptococcal antigen titres, HIV-seronegative status, and his negative CSF and fungal blood cultures. These results signified a low cryptococcal load, making an early switch to oral, less toxic

therapy justifiable, and spared the patient further unnecessary side effects.

Learning points

- ▶ Eosinophilic pleocytosis of the central nervous system is an unusual finding and is usually indicative of invasive parasitic infections. Cryptococcal infections are an extremely rare cause of this condition and should only be considered when other more common causes have been ruled out.
- ▶ Sarcoidosis, if present, should be regarded as an independent risk factor for cryptococcal meningitis in an apparently immunocompetent host, regardless of the use of steroids.
- ▶ Cryptococcal central nervous infections are uniformly fatal if left untreated. Prompt diagnosis and treatment of cryptococcal central nervous system infection is essential to prevent the high morbidity and mortality associated with this disease.

Competing interests None declared.

Patient consent Obtained.

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