From Diplopia to Disseminated Cryptococcosis

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Introduction

Cryptococcus neoformans is a ubiquitous pathogen, usually transmitted by inhalation of spores from the environment. C. neoformans is not dependent on a host for survival. Key features like its polysaccharide capsule and cell wall ensure its resilience to destruction – making it an “accidental human pathogen”.

In an immunocompetent host, infection is commonly asymptomatic and limited to the lungs. However, with increasing utilization of immunosuppressants, the incidence of invasive opportunistic infections has increased multifold.

Before the emergence of the AIDS pandemic, Cryptococcosis was a rarely seen disease. However, people with HIV are not the only ones at risk. In a large epidemiological study done over 12 years, with 30,840 hospitalizations identified for Cryptococcal Meningitis, 21.6% of the patients admitted to the hospital were HIV negative.

C. Neoformans causes significant morbidity and mortality in the US, and the proportion of HIV negative persons with Cryptococcus infection is on the rise.

Case Description

A 42-year-old female, who had been diagnosed with Lupus Nephritis with renal biopsy in 2019, maintained of Mycophenolate Mofetil (MMF), and prednisone, presented to the emergency room on May 1, 2020 due to progressive dyspnea and near syncope prior to arrival. She described a 5-week history of diplopia, bifrontal headaches, associated with progressive generalized weakness. For the past 5 weeks she has been usually closing 1 eye to correct the diplopia which is been persistent for her. She denies any vision loss or changes in visual fields otherwise. She denied exposure to pigeon droppings. She was homebound for past several months.

Physical Exam on arrival was significant for tachycardia in the 170s, tachypnea in the 30s, on 2L of oxygen, lungs were clear to auscultation. Labs showed leukocytosis with lymphopenia, and lactic acidosis.

Chest X Ray on admission was read as mild atelectasis of the right lung base. CT head without contrast was negative for hemorrhage.

She was admitted with Severe Sepsis and was started on broad spectrum antibiotics. In the hospital, she developed progressively worsening hypoxia and was placed on a non-rebreather mask, developing a left sided infiltrate on repeat chest xray.

The patient was considered to have moderate risk for pulmonary embolism, based on tachycardia, and knowing that the patient was on oral contraceptives. Therefore, she was started empirically on a heparin drip in the acute setting. CT with contrast was deferred at the time given history of chronic kidney disease.

Further imaging revealed evidence of left internal jugular vein thrombus on brain MRI, with deep venous thrombosis of the left popliteal vein on lower extremity doppler ultrasound, so heparin was continued.

She underwent lumbar puncture on May 4th, India ink staining revealing budding yeast consistent with C. Neoformans (first image), and was started on amphotericin and flucytosine.

CT of the chest showed ground glass opacities and areas of consolidation in both upper and lower lobes.

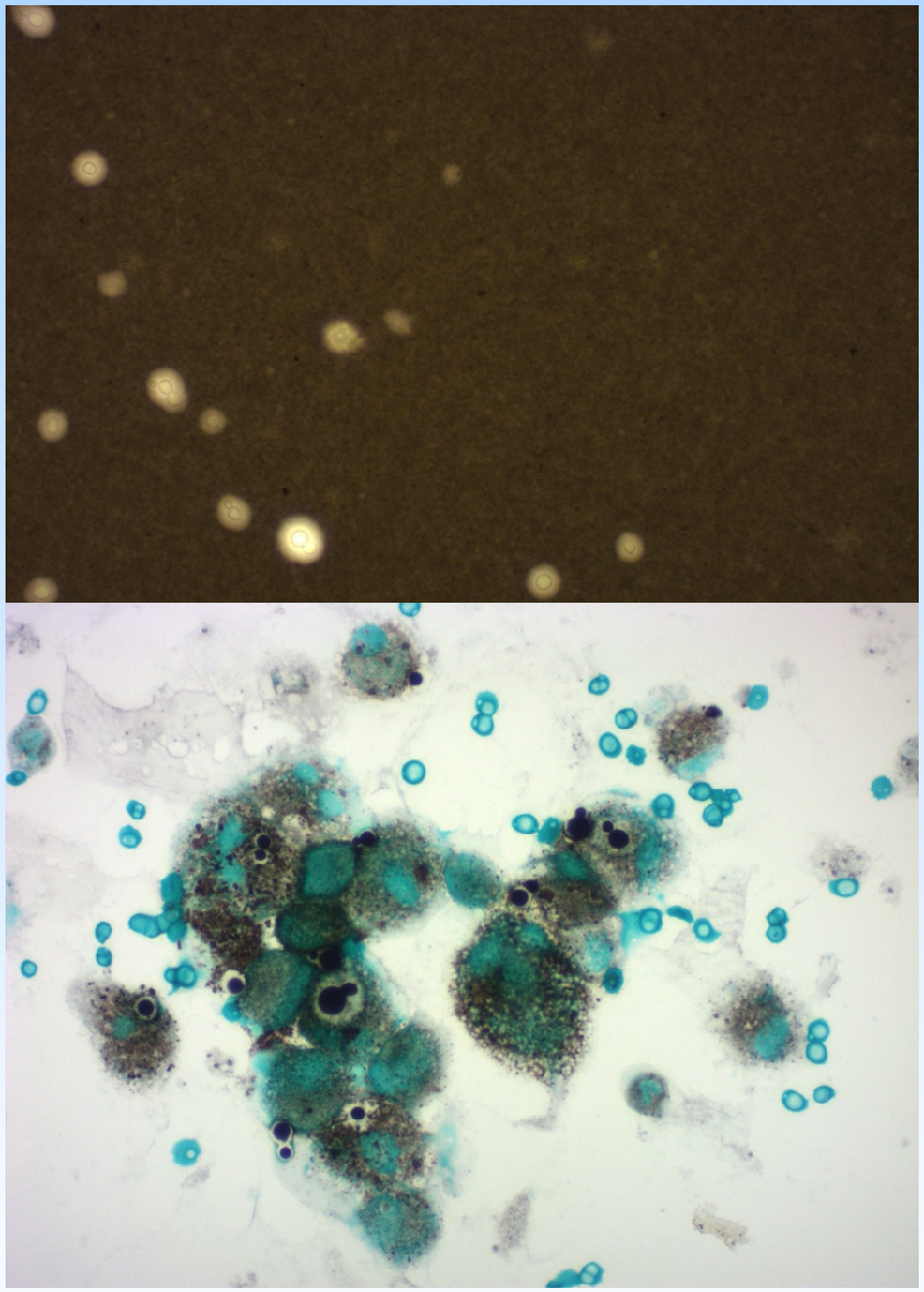
Since her hypoxia was not resolving, she was intubated on May 6th, to obtain samples from broncho alveolar lavage and rule out PCP co infection. The image on the right is a picture of the GMS fungal stain of the BAL showing narrow based budding yeasts with halos, consistent with Cryptococcus.

At this point, her blood cultures from admission became positive for encapsulated organisms as well.

She underwent serial lumbar punctures, with persistently elevated opening pressures without signs of dropping.

The decision was made to transfer her to a tertiary center, for ventriculoperitoneal shunt placement and closer monitoring of intracranial pressure. Before the plan was put into motion, she developed a cerebral venous sinus thrombosis (a rare complication of cryptococcal meningitis), resulting in anoxic brain injury. Despite aggressive treatment, the patient succumbed to the burden of her disease.

Pathology



Discussion

Invasive fungal disease is an uncommon, but frequently fatal infection in the immunocompromised. In comparison to HIV infected persons, non-transplant HIV negative individuals have higher all-cause mortality Furthermore, it was reported in a small retrospective study, that HIV negative patients with CM and concomitant lung involvement, were more likely to have worse outcomes.

Those with rheumatic disorders are a small but significant proportion of HIV negative patients with cryptococcosis, with a majority of data focusing on systemic lupus erythematosus. Those with SLE have an increased risk of infections, when compared to the general population. In addition, concurrent advanced CKD portends poor outcomes in disseminated cryptococcal disease.

A study investigating risk factors for invasive C. Neoformans deemed autoimmune disease an independent risk factor, regardless of dosage of suppressive medications. The same study identified an interesting observation that people on immunosuppressive regimens (including mycophenolate and prednisone), without calcineurin inhibitors, were at increased risk of cryptococcemia. This correlates with the fact that the virulence of C. neoformans depends on fungal calcineurin, and drugs like cyclosporine and tacrolimus could confer host protection with in vitro anti fungal activity. However, the number of subjects on these medication in this study was limited, and requires more research.

Glucocorticoids are the mainstay of treatment of SLE, especially in those with renal involvement like our patient. A systematic review of SLE patients showed a prevalence of 0.5% of CM, also identifying higher doses of prednisone conferring worse prognosis. In the same study, 38.2% of these SLE-CM patients were initially misdiagnosed.

Regardless of what medications they are on, those with autoimmune disorders should be taught to guard against well-known sources of C. Neoformans like pigeon droppings, hollow trees and loose soil. On the other hand, as physicians we should always keep invasive fungal diseases on our differentials for an acutely ill patient with SLE. Neurological symptoms can often be the herald for disseminated disease. Early recognition can lead to timely initiation of anti-fungal therapy, which can be lifesaving.

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