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HISTOPLASMOSIS IN AN IMMUNOCOMPROMISED CHILD- HOW TO DIAGNOSE AND TREAT?

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Clinical Problem:
A 12-year-old boy, diagnosed with acute myeloid leukemia(AML) in February 2024 and on venetoclax and azacytidine therapy, presented to us in April 2024 with high-grade fever, wet cough and loss of weight and appetite for 2 months. Non-contrast computerized tomography(NCCT) chest in February 2024 showed consolidation along the right mediastinal pleura, adjacent ground-glass opacities in the right upper lobe and two small nodules in the right lung, suggestive of fungal pneumonia. At our centre, he was initially admitted to the pediatric intensive care unit for the management of compensated septic shock and septic cardiomyopathy requiring inotropic support. He received intravenous antibiotics and voriconazole. During admission, he had an episode of violent coughing followed by blood-streaked sputum. Contrast-enhanced CT with angiography of the thorax showed an ill-defined and heterogeneously-enhancing mediastinal mass in the right paratracheal region. The mass was biopsied and the histopathological examination revealed an abscess with granulation tissue but no granulomas. Bacterial and fungal cultures of the biopsied tissue did not grow any organism. Xpert MTB/RIF of the biopsied tissue and serum interferon-gamma release assays were negative. Urinary histoplasma antigen was positive and serum ß-D-glucan levels were high (Table 1). He was started on liposomal amphotericin-B(L-AMB)(3mg/kg/day) for 2 weeks followed by oral voriconazole(Table 1). Urinary histoplasma antigen levels decreased in May 2024. NCCT thorax in May 2024 showed almost complete regression of the previously seen right paratracheal mass with subtle foci of fibroatelectatic changes.

How to diagnose and treat histoplasmosis in an immunocompromised child?

Table 1. Investigations of the patient.

Investigations	March 2024	April 2024	May 2024	Reference Range
Hemoglobin (gm/dL)	-	9.9	11.6	11.5-15.5
White blood cell count (cells/cumm)	-	11210	12700	5000-13,000
Platelet count (106cells/cumm)	-	4.43	3.23	1.50-4.50
Voriconazole trough levels (µg/mL)	4.43	0.94	1.02	1-5.5
Urine histoplasma galactomannan (ng/mL)	-	1.3	1.06	<0.9

Discussion:
Histoplasmosis, caused by *histoplasma capsulatum*, is the most common endemic mycosis of the United States, commonly reported in the Midwest and Southeast regions of the country.[1,2] While histoplasma has been isolated from the soil and caves in India and sporadic cases have been reported in various parts of the country, it is an uncommon and under-recognised disease.[2,3,4,5] The diagnosis of histoplasma relies on radiological and laboratory findings. Radiological findings of acute pulmonary histoplasmosis are non-specific and include poorly-defined, diffuse, bilateral lung opacities, resembling bacterial pneumonia, with or without mediastinal or hilar lymphadenopathy. Subacute disease usually appears as focal calcified lung opacities with calcified lymph nodes.[6] Chronic pulmonary histoplasmosis may be cavitatory (40%) or non-cavitatory on imaging.[1] Cavities are usually located in the apical or posterior segments of the upper lobe and are associated with adjacent volume loss and pleural thickening.[6] Non-cavitatory disease includes nodules, which may resemble miliary tuberculosis or hematogenous pulmonary metastases and infiltrates.[1,6] Disseminated histoplasmosis is seen as diffuse lung micronodules, resembling miliary tuberculosis or hematogenous metastases.[6] Laboratory tests include culture and microbiological staining, histopathology, antigen detection, serology and molecular assays.[7] The gold standard method is culture and staining. Culture and staining, however, has a comparatively lower sensitivity in the diagnosis of the various clinical presentations

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of histoplasmosis.[7] Histopathology, while having a slightly better sensitivity than culture, may not be feasible in all cases. Ovoid yeast cells with narrow-based budding are observed phagocytosed within macrophages and histiocytes in the tissue sample. Gomori-methenamine-silver (GMS) and periodic acid-Schiff (PAS) stains can be used to identify the cell wall of histoplasma and help in differentiating it from other yeasts.[7] Histoplasmosis antigen detection via an enzyme immunoassay-based method, has a high sensitivity in all forms of histoplasmosis except subacute pulmonary histoplasmosis.[7] Urine antigen detection is most preferred, followed by serum detection, however, it can also be applied to BAL and cerebrospinal fluid(CSF). Combined urine and serum antigen detection has been shown to increase the sensitivity. A major caveat of histoplasma antigen detection, are the false-positive results from cross-reactivity with antigens of *blastomyces dermatitidis, paracoccidioides brasiliensis,* and *talaromyces marneffei*.[7] The definitive diagnosis of histoplasmosis requires positive culture or histopathological findings, however, a positive histoplasma antigen along with a suitable clinical picture can be used to make a probable diagnosis. Serological assays for histoplasmosis, including the complement fixation assay, immunodiffusion assay and enzyme immunoassay, are suitable for the diagnosis of subacute and chronic pulmonary histoplasmosis.[7] Serology is useful in endemic areas and can be used to diagnose histoplasma meningitis if antibodies are found in the CSF. In acute infections, a fourfold rise in antibody titres over 2 weeks or a single titre of =1:32 can be used to diagnose histoplasmosis. Combined antigen-antibody testing increases the sensitivity of diagnosis. Limitations of serology include cross-reactivity in patients with other systemic fungal infections and granulomatous diseases such as tuberculosis or sarcoidosis and false negative results, particularly in immunocompromised patients.[7] Molecular methods such as nested polymerase chain reaction(PCR)-based assays and real-time PCRs are commonly used and have shown high sensitivity and specificity on various samples including serum, blood, bone marrow, BAL, sputum, CSF and tissue.[7] ß-D-glucan is a component of the histoplasma cell wall whose levels can be estimated in serum. This test has a high sensitivity of about 87% but due to cross-reactivity with other fungal pathogens such as Candida, Aspergillus and Pneumocystis, it has a lower specificity. Thus, it may serve as a supplementary assay for the diagnosis of histoplasmosis.[8]

According to the Infectious Disease Society of America guidelines, the management of histoplasmosis in an immunocompromised child involves AMB deoxycholate(1 mg/kg/day) or L-AMB(3-5 mg/kg/day) for 2-4 weeks followed by itraconazole(5-10 mg/kg/day in 2 divided doses) for a total duration of 3 months of therapy. Immunocompromised patients may require longer durations of therapy with itraconazole, with lifelong therapy in those in whom immunosuppression cannot be reversed or those who experience relapses despite adequate treatment.[9] Histoplasma antigen levels should be checked during therapy and 12 months after end of therapy. Prolonged treatment may be required in those with persistent low-level antigenemia despite no evidence of active disease. The role of prophylaxis in immunocompromised patients receiving chemotherapy is unclear, however, active disease within the past 2 years may warrant itraconazole prophylaxis during immunosuppression.[9] While guidelines suggest itraconazole, multiple studies have shown that voriconazole is well-tolerated, highly efficacious and has milder drug-interactions with drugs used in induction therapy of AML as compared to itraconazole.[10,11,12] In addition, itraconazole shows erratic oral absorption and significant variability in pharmacokinetics in children, thus we used voriconazole in our patient.[13]

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