Journal of the African Society for Paediatric Infectious Diseases
Volume 1

CASE REPORT

A case of cutaneous histoplasmosis in a child with HIV infection

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How to cite this article:

Lochan H, Gxolo F. A case of cutaneous histoplasmosis in a child with HIV infection. Journal of the African Society for Paediatric Infectious Diseases. 2022; Volume 1:1-5. DOI: https://doi.org/10.15641/jafspidVol1pp1-5/1697

Article Information
Received: 22 February 2022
Accepted: 11 March 2022
Key words
Cutaneous histoplasmosis; Histoplasmosis species; immunocompromised host; HIV infection; children; Africa

Abstract
Histoplasmosis is an endemic fungal infection that can infect both immunocompetent and immunocompromised individuals. Due to the non-specific clinical symptoms, it can often be misdiagnosed as a more commonly occurring infection such as tuberculosis. In this case report we describe the presentation of a young girl, recently diagnosed with HIV infection, with extensive facial lesions that were found to be positive for histoplasmosis on molecular testing. She responded well to antifungal therapy.

Introduction

Histoplasmosis species that are pathogenic in humans are *H.capsulatum* var *capsulatum* and *H. capsulatum* var *duboisii.* Previously described as being mostly endemic to the United States of America (USA), the fungus now has a worldwide presence with *H. capsulatum* var *duboisii* endemic to western and central Africa[1]. Both species do however occur on the African continent. This dimorphic fungus exists as a mold with hyphae that produces spores or microconidia in the environment. Once a host inhales the microconidia, they transform into budding yeasts in the warmer conditions of the body. The yeasts can then spread through the body resulting in a progressive, disseminated form of the infection[1].

Opportunistic fungal infections can cause significant morbidity and mortality in patients with a compromised immune system such as in human immunodeficiency virus (HIV infection), post solid

organ transplant, haematological malignancies, treatment with immunosuppressive agents as well as in individuals with T-lymphocyte and B-lymphocyte deficiencies[2,3].

In immunocompetent children, the disease can, however, be asymptomatic, self-limiting and may not require treatment[4]. Recent studies have shown that it is at times difficult to distinguish *H. capsulatum* from other dimorphic fungi, namely *Emergomycosis* species and there is considerable clinical overlap between the two infections[5]. We describe the case of a child with an immunocompromised immune system who presented with non-resolving skin lesions.

Case presentation

A 9-year-old girl was referred from a regional hospital to our tertiary level dermatology unit with a one-month history of non-healing facial nodules and ulcers that were unresponsive to treatment with broad spectrum intravenous and oral antibiotic therapy.

Three months prior, the patient was admitted to the regional hospital with pneumonia and seizures. A diagnosis of infection with the human immunodeficiency virus (HIV) was confirmed with a positive HIV-1/2 ELISA. The cluster of differentiation (CD4) T cell count at presentation was 3 cells/uL. Investigations for pulmonary tuberculosis were negative (GeneXpert, auramine and culture); serum cryptococcal latex agglutination test (CLAT) was also negative. She had an elevated cytomegalovirus viral load (CMV VL) of 10 583 IU/ml (log 4). Intravenous gancyclovir was administered for the treatment of CMV-associated pneumonitis and antiretroviral therapy (ART) was commenced (abacavir, lamivudine and efavirenz). Efavirenz was subsequently changed to dolutegravir in accordance with the South African National Department of Health treatment of HIV guidelines[6].

She was referred to the dermatology clinic at our tertiary level hospital for facial skin lesions that had appeared approximately three months after ART initiation. At initial presentation, the skin lesions were assessed to be erythematous papules with central umbilication; nodules with central necrosis; and crusted pus-filled plaques on the face located centrally over nose and the nasal bridge predominantly. The papules with central umbilication resembled large molluscum contagiosum. Similar lesions were also seen on the scalp, neck and arms, **Figure 1a**. The patient at this time was virologically suppressed with an HIV viral load (VL) of 40 copies/mL and an improved CD4 T-cell count of 276 cells/uL. Previous use of broad-spectrum antibiotics resulted in no improvement of the lesions. Deep fungal infection or cutaneous tuberculosis was considered in the differential diagnosis. A biopsy of the facial lesions was taken.

Histology of the biopsied facial lesions showed ulceration and non-necrotizing granulomatous inflammation involving the superficial and deep dermis. The periodic acid-schiff (PAS) stain was negative for fungal elements and on the Grocott stain, a single yeast was seen. Culture of the biopsy was negative for a fungus. The biopsy sample was referred to the National Institute of Communicable diseases (NICD), a reference laboratory in Johannesburg, South Africa where a polymerase chain reaction (PCR) assay test was positive for *Histoplasmosis / Emergomycoses* species. This investigational assay targets the mitochondrial small-subunit gene in the fungal DNA. A normal chest x-ray and abdominal ultrasound excluded internal organ involvement. A presumptive diagnosis of cutaneous histoplasmosis was therefore made.

Intravenous (IV) amphotericin B was started while awaiting the biopsy results and **Figure 1b** shows improvement after seven days on treatment. The facial lesions became less pustular and nodular. As a result of the rapid improvement of the skin lesions, oral itraconazole was initiated after one week of IV therapy. This will be continued for a minimum of 12 months to allow for further immune reconstitution. **Figure 1c** shows the patient having completed 6 months on itraconazole and continuation of ART. Unfortunately, there was appreciable scare formation of the face from the healing lesions.

Figure 1. a – Pre-treatment, b – after 1 week of Amphotericin B, c - 6 months on itraconozole (photographs used with consent of the child's parent)

Discussion

The World Health Organization (WHO) has included the deep mycoses in its list of neglected tropical diseases of which histoplasmosis is an example. In a recent review of childhood histoplasmosis in Africa, only 44 cases, with a median age of 9 years (range: 1-17 years), were described from across the continent over a 70-year period[7]. Similarly, low numbers were described in a global review of paediatric histoplasmosis (83 cases from 2000 to2019) with most cases reported from the USA[3]. Co-infection with HIV was found in 6.8% (3/44) of cases in Africa.

The clinical manifestations of *H.capsulatum*, namely pulmonary disease, disseminated disease, extrapulmonary manifestations involving the skin, abscesses, bone and joint as well as generalised lymphadenopathy are not dissimilar to other more commonly diagnosed disease processes like tuberculosis and malignancies. Symptoms can be non-specific. It is therefore not uncommon for the diagnosis of histoplasmosis to be delayed or misdiagnosed leading to increased mortality[3,7]. Co-infection with tuberculosis also occurs although not as commonly in children[7]. Skin manifestations have been described in infection with *H.capsulatum* var *duboisii*. Localised lesions include swellings, papules, superficial abscesses and ulcers like in our patient. The cutaneous lesions can progress to involve bony structures[7].

The gold standard for the diagnosis of histoplasmosis is microbiological evidence of the yeast form of the organism from blood, bone marrow aspirate, sputum or tissue biopsy samples. The WHO recommends the use of antigen tests (sensitivity: 95%, specificity: 97%) for the diagnosis of disseminated histoplasmosis in adults infected with HIV[8]. Other clinical entities of histoplasmosis require additional investigations such as culture, histopathological analysis or antibody testing. Molecular testing is available but there is a lack of consensus on the technique and availability of services[3,8].

Liposomal amphotericin B for two weeks is recommended for the first one to two weeks of the therapy depending on clinical response. If not available, deoxycholate amphotericin B is an alternative. Side

effects of the drug include infusion-related toxicity, nephrotoxicity (less so with liposomal amphotericin B), electrolyte abnormalities and anaemia. The induction phase is followed by a maintenance phase using itraconozole to complete at least 12 weeks[9]. In patients with disseminated histoplasmosis and those who are immunocompromised particularly with HIV infection, the maintenance phase is prolonged to 12 months[8,9]. Where possible, blood levels of itraconazole should be obtained to ensure adequate drug exposure.

Our patient presented three months after commencing ART and there was virological suppression with some recovery of the CD4 count at the time. This patient may possibly have had a case of unmasking immune reconstitution inflammatory syndrome (IRIS) associated with histoplasmosis. In a French Guiana study among adults living with HIV, the rate of IRIS associated with histoplasmosis was shown to be low at 0.74 cases per 1000 HIV-infected person years. The median time to IRIS symptoms following ART initiation was 11 days (range 7-40) although the literature review revealed a median time of 51 days (range 21-69)[10].

In conclusion, histoplasmosis may be underdiagnosed in children and should be considered if there is not the expected response to therapy for the more commonly diagnosed conditions like tuberculosis.

Author contributions: HL and FG developed the concept and wrote the case report.
Funding Sources: Nil
Ethics approval: Ethics approval was obtained from the Frere and Cecelia Makiwane Hospitals Research Ethics Committee (FCMHREC/A0101/2021).
Consenting statement: Written, informed consent was obtained from the mother of the patient.
Competing interests: The authors declare no competing interests.

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