



(CASE REPORT)



## African histoplasmosis – an underdiagnosed tropical disease in Ghana

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### Abstract

African histoplasmosis is a mycotic infection mostly confined to Madagascar, Western and Central Africa with a few rare cases reported outside these endemic areas. Despite being in the endemic zone, few cases have been reported from Ghana. A 36 year old woman developed inexplicable left knee pain and four months later noticed nodular eruptions at the posterior aspect of her neck which subsequently spread to involve other body areas. She had associated generalized lymphadenopathy but no constitutional symptoms and screening for human immune-deficiency virus was negative. Biopsy confirmed African histoplasmosis and after fourteen months treatment with itraconazole during which she experienced periods of remission and relapse, symptoms resolved. Clinicians in African histoplasmosis endemic regions need to consider this diagnosis in patients presenting with systemic mycosis. Though treatment is generally rewarding, prolonged periods of treatment are required as well as long term follow up due to frequent relapse.

**Keywords:** Systemic mycosis; Endemic; Itraconazole; Remitting; Relapsing

### 1. Introduction

African histoplasmosis also known as large histoplasmosis or large form histoplasmosis is a systemically invasive deep mycotic infection caused by *Histoplasma capsulatum* var *duboisii* which is endemic in West Africa, Central Africa and Madagascar hence its name [1]. Infections outside these geographic areas have been reported in India, Japan, Arabia and parts of Asia but almost all can be traced back to the endemic areas with the exception of a case from Kerala India [1]. It is one of two varieties of histoplasma known to infect humans. The other *Histoplasma capsulatum* var *capsulatum* is more common with a worldwide distribution and tends to occur in the immune-compromised. Physicians in endemic areas often misdiagnose and hence mismanage cases of African histoplasmosis largely due to lack of awareness about the disease and unavailability of appropriate investigative tools. [2, 3]

### 2. Patient and observation

A 36 year old woman was referred to the dermatology clinic of the Komfo Anokye Teaching Hospital on account of a generalized skin lesion associated with generalized lymphadenopathy. No specific diagnosis or differentials were made by the referring doctor and the only investigation carried out was for human immune-deficiency virus (HIV) which came out negative. She had an eight month history of inexplicable pain of the left knee joint associated with a skin rash. There was no history of trauma to the knee and no associated swelling or systemic symptoms. Her skin lesions had started as asymptomatic nodules at the posterior aspect of her neck which later became pruritic and spread to involve other body parts. Spontaneous rupture of the nodules produced a creamy-white discharge and resulted in scalloped ulcers. She had

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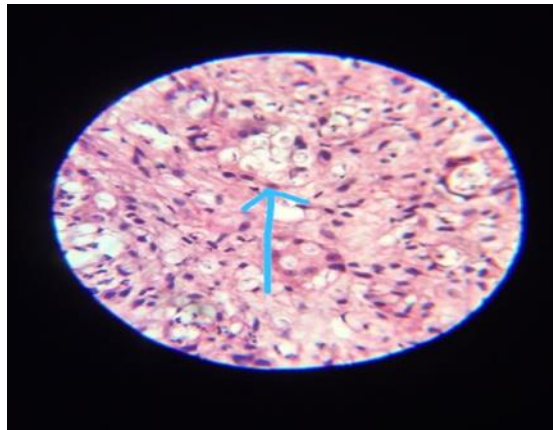
no associated constitutional symptoms. There was no history of contact with any persons with a similar skin lesion and patient could not recall exposure to chicken runs or bat faeces. On examination, patient appeared generally well except for the variably sized tender subcutaneous nodules with scalloped ulcers which were well demarcated on her face, neck, upper trunk, arms, pubic area and legs (figure 1). She also had generalized lymphadenopathy.



**Figure 1** Variably sized subcutaneous nodules on posterior aspect of neck (Blue arrow: ulcerated nodule)

A clinical diagnosis of histoplasmosis was made and x-ray of the left knee, full blood count, erythrocyte sedimentation rate, swab for culture and sensitivity and an excisional biopsy requested.

Biopsy confirmed the diagnosis of histoplasmosis (figure 2) and patient was started on itraconazole 200 mg twice daily with a five day course of analgesics. X-ray of the left knee was normal.



**Figure 2** Histology finding (Blue arrow: Cluster of Histoplasma spores)

Patient was reviewed after 45 days of itraconazole and appeared to be responding to treatment but complained of anorexia and vomiting. She was prescribed an additional two week course of 200 mg itraconazole twice daily and metoclopramide 10 mg three times daily.

The dosage of Itraconazole was halved (100 mg twice daily) during her 4<sup>th</sup> review on account of breakthrough vomiting. Patient had also noticed the eruption of new nodules. (figure 3).



**Figure 3** Examination findings during treatment (old nodules resolving with eruption of new nodules, Thick blue arrow: new subcutaneous nodule, Thin blue arrow: Post inflammatory hypopigmentation following resolution of nodule.)

On her 5<sup>th</sup> review two weeks later, vomiting had resolved but patient still had eruption of breakthrough nodules that soon responded to on-going therapy. She was thus prescribed 60 days of 100 mg itraconazole twice daily.

On subsequent review two months later, she complained of pain in the lumbar spine and knee joints and the eruption of subcutaneous nodules that ruptured to release a whitish cream substance. Full blood count showed a white cell count of  $6.5 \times 10^9 / L$  with 66% neutrophils, 17.2 % lymphocytes and eosinophils 5.4%. She had severe microcytic hypochromic anaemia with haemoglobin level 8.8 g/dL, mean cell volume 71 fL and mean cell haemoglobin of 20 pg. Platelet count was  $295 \times 10^9 / L$ . She was prescribed iron supplements and analgesics and the dosage of itraconazole increased to 200 mg twice daily for four weeks. Lesions had resolved at her subsequent review. Itraconazole was suspended for four weeks and patient was to report for review after a month. She however turned up for review two months later with painful nodules and complaints of anorexia and generalized bodily pains. Itraconazole 200 mg twice daily was restarted for a month. She also received analgesics and vitamin B complex. She was discharged from the clinic 6 months later after a 5 month symptom free period off medication.

### 3. Discussion

*Histoplasma duboisii*, the causative agent of African histoplasmosis is a diamorphic saprophytic fungus with a thick galactomannan and B-(1, 4) - glucan cell wall. It causes a rare invasive deep mycotic infection and is endemic in West Africa, Central Africa and Madagascar. The first case was reported in 1942 from Africa and the first natural reservoir of infection was a bat cave in Nigeria. A few cases have since been reported in India, Japan, Arabia and parts of Asia but almost all can be traced back to the endemic areas with the exception of a case from Kerala India.[1] It is one of two varieties of histoplasma known to infect humans. The other *Histoplasma capsulatum var capsulatum* is more common with a worldwide distribution and tends to occur in the immunocompromised unlike *Histoplasma duboisii* which for unknown reasons tends to occur in immunocompetent persons.[4] The route of acquisition is still unclear but most authorities believe it is acquired by inhalation of soil contaminated with microconidia or hyphae. Bat faeces, chicken runs and two species of baboons from Senegal and Guinea, namely *Papio* and *Papio cynocephalus* have been identified as potential sources. A few authorities also propose direct inoculation as a potential source. Our patient was immunocompetent and no possible source of infection could be found. Depending on the host immune response and the size of inoculum, infection could either manifest clinically as disseminated disease, osteolytic or cutaneous lesions. Most immune-compromised patients present with mucocutaneous, subcutaneous and bone lesions. [5] Our patient was immune-competent presented with only disseminated subcutaneous lesions. Some infected immune-competent persons may remain asymptomatic for many years. Disseminated histoplasmosis can also be unearthed as part of immune reconstitution response syndrome in acquired immune deficiency syndrome (AIDS) patients. [5] Superficial cutaneous lesions present as painless papules which may be transformed into nodules, plaques or cold abscesses that may breakdown and ulcerate while subcutaneous lesions are firm, warm and tender. Exfoliative erythroderma, cellulitis, acneiform eruptions and molluscum-like cutaneous lesions have also been noted. [3] Cutaneous lesions may heal spontaneously, develop granulation tissue or invade the bone beneath. A painless nodular rash was the initial cutaneous manifestation in our patient but spontaneous rupture of the subcutaneous nodules produced a creamy-white discharge and resulted in scalloped ulcers. She also had numerous subcutaneous nodules. Although she complained of severe left knee pain, x-ray was normal. In cases where the bone is invaded, x-ray shows lytic bone lesions.

The skin lesions of histoplasmosis are nonspecific thus making the diagnosis virtually impossible based on physical examination alone as a number of conditions such as cryptococcosis, blastomycosis and *H. capsulatum* infection present

similarly. Microscopic examination of biopsy or secretions shows the typical hourglass appearance of budding cells. The saprophytic phases of *H. capsulatum* and *H. duboisii* are however indistinguishable. Microscopically, *H. duboisii* is about twice the size of *H. capsulatum* and unlike *H. capsulatum*, it does not produce urease. No serologic tests can specifically identify *H. duboisii* as serologic tests available for *H. capsulatum* cross-react with antigens of *H. duboisii*. Disseminated histoplasmosis in the immune-compromised and patients with high titres is mostly diagnosed by Histoplasma antigen testing using Enzyme linked immunosorbent assay of urine or blood despite cross reaction between Histoplasma antigen and aspergilosis, coccidiomycosis, paracoccidiomycosis and blastomycosis. Most African countries however rely on culture and histology. [3]

No clinical trials have been performed on the effectiveness or otherwise of drugs such as itraconazole, fluconazole and amphotericin B in the treatment of African histoplasmosis. Amphotericin B is however generally recommended for the initial treatment of disseminated histoplasmosis with itraconazole reserved for the treatment of cutaneous lesions and for maintenance therapy. Fluconazole has been found by most authorities to be less effective in the management of histoplasmosis compared to amphotericin B, itraconazole and ketoconazole.[6] Posiconazole has also been used in disseminated infection resistant to amphotericin B.[7] Patients require months of antifungal therapy where itraconazole monotherapy is used as the disease tends to run a remitting and relapsing course as was the case in our patient.[6] Many patients like our patient experience side effects such as anorexia, vomiting, blurred vision, diplopia, dizziness and abdominal bloating. Treatment has to be continued except in cases where side effects are persistent or serious side effects such as toxic epidermal necrolysis develop. Decreasing the dosage may also be necessary to control side effects but flares are usually noticed as occurred in our patient.

Even when patients are symptom free, prolonged follow up is compulsory due to potential for relapse several years after the initial infection.

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#### 4. Conclusion

Physicians in endemic areas need to consider African histoplasmosis in the management of patients with systemic mycosis. Research is also needed to come up with rapid, sensitive and specific tests for *H. duboisii* as well as effective treatment regimens.

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#### Compliance with ethical standards

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##### *Disclosure of conflict of interest*

Authors declare no competing interest.

##### *Statement of ethical approval*

Ethical approval was given by the Committee on Human Research, Publication and Ethics of the School of Medicine and Dentistry/Komfo Anokye Teaching Hospital.

##### *Statement of informed consent*

Informed consent was obtained from the patient.

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