Patients with advanced HIV-1 disease can present with a vast array of opportunistic infections. Not only is the spectrum of disease more diverse, but the spectrum of presentation can vary significantly from what is expected. In this case report we describe a patient with advanced HIV-1 disease presenting disseminated skin lesions and haematological abnormalities. Upon further investigation, a probable diagnosis of disseminated histoplasmosis was established. The patient was subsequently treated with oral itraconazole and showed marked haematological and clinical improvement within six weeks of therapy. Histoplasmosis is an opportunistic infection endemic to South Africa and, like most opportunistic infections, can present with a myriad of clinical features which can complicate early diagnosis. Although not as prevalent as in other parts of the world, it should always be considered as part of the differential diagnosis, especially among severely immunocompromised individuals.
The skin biopsy revealed numerous histiocytes, containing multiple clusters of PAS-positive, diastase-resistant inclusion bodies consistent with yeast-like organisms. No acid-fast organisms could be demonstrated in the sections. Based on the size and morphology of the organisms, a histological diagnosis of probable disseminated histoplasmosis was made. Although samples were submitted for culture, the fungus could not be grown, which is considered to be the gold standard of diagnosis.

The patient was initiated on oral itraconazole (400 mg daily) with significant clinical and haematological improvement, showing a recovery of his haemoglobin level to 14.1 g/dL within six weeks.

Discussion

*Histoplasma capsulatum* is a dimorphic fungus associated with infection in immunocompromised patients.1-2 *H. capsulatum var. capsulatum* is endemic in some parts of the North and South America,3 as well as South Africa whereas *H. capsulatum var. duboisii* is found in Equatorial Africa, between the Sahara and Kalahari deserts.3 Despite this distribution, most cases described in South Africa have been associated with *H. capsulatum var. capsulatum*4-5 as this organism is found endemically in caves in parts of the country4 as well as in association with settings rich in bird droppings.6 The disease entities associated with the two varieties are significantly different; patients with African histoplasmosis (*H. capsulatum var. duboisii*) present most commonly with cutaneous, subcutaneous, bone and joint lesions and rarely with dissemination to the liver, spleen and gastrointestinal tract.3 Within the South African context, cutaneous manifestations of classical histoplasmosis (*var. capsulatum*) seems to be described.9

Disseminated histoplasmosis (DH) is most frequently described among patients with CD4+ T cell counts below 50 cells/mm³,1 and in endemic areas occur in 5% to 75% of AIDS patients, with mucocutaneous manifestations seen amongst 11% to 25%.2,5 Skin lesions can take a number of forms, from inflammatory folliculitis, rosacea-like eruptions and ulcers, to the nodular lesions2 described in this report.

Laboratory diagnosis is based on microscopy, histology, culture, antigen and antibody detection with varying sensitivities reported for each of these methods.1-2 Although reported sensitivities seem to be poor in general for histology, biopsies of skin lesions in HIV-1-infected patients have been cited to have sensitivities as high as 100%.7 The differential diagnosis once yeasts are visualised in skin sections with the periodic acid Schiff (PAS) stain, include histoplasmosis, cryptococcosis and blastomycosis. The organisms may be distinguished based on morphological features, though this is difficult and requires an experienced histopathologist (Table 1). Further confirmation can be obtained by performing additional special stains including the mucicarmine stain, which specifically stains the capsule. Classically, this stain will provide a positive result for encapsulated forms of *Cryptococcus* spp. and some subtypes of *Blastomyces* spp.; however, non-encapsulated forms will be negative as is *Histoplasma* spp.5

The gold standard for diagnosis is considered microbiological culture with conversion between mould to yeast phase with demonstration of organism-specific precipitins.8 The main limitation of this method remains the prolonged incubation periods required, which can be in excess of four weeks.9-10 Furthermore, culture seems to show limited sensitivity with false negative results obtained in as much as 20% of disseminated cases.8 Microbiological cultures are available at most academic centres in South Africa.

Antigen detection provides a more rapid result, but requires a high fungal burden to render a positive result.10 However, sensitivity seems to be higher among patients with AIDS as compared to patients with other underlying causes of immunosuppression.3 The sample of choice seems to be urine, as it shows improved sensitivity when compared to serum samples.9,11,12 Bronchoalveolar lavage fluid may also be used in cases with pulmonary localisation.12 It is often also utilised in monitoring treatment response in patients with disseminated disease9,10 and monitor for relapse.9 Antigen detection is not available locally.14

Serological detection of antibodies specific to *Histoplasma* serves as an alternative diagnostic tool. Pitfalls with this

<table>
<thead>
<tr>
<th>H. capsulatum</th>
<th>H. capsulatum</th>
<th>Cryptococcus</th>
<th>Blastomyces</th>
</tr>
</thead>
<tbody>
<tr>
<td>var. capsulatum</td>
<td>var. duboisii</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeast size</td>
<td>2-4 µm</td>
<td>12-15 µm</td>
<td>3.5-8 µm</td>
</tr>
<tr>
<td>Shape</td>
<td>Oval</td>
<td>Ovoid</td>
<td>Oval</td>
</tr>
<tr>
<td>Budding</td>
<td>Narrow-based budding</td>
<td>Narrow-based budding</td>
<td>Single budding with narrow neck</td>
</tr>
<tr>
<td>Cell wall</td>
<td>Thin walled</td>
<td>Thick walled</td>
<td>Thick and mucoid</td>
</tr>
<tr>
<td>Mucicarmine stain</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Table I: Morphological characteristics of yeast forms for several mycoses
testing modality include a delay in seroconversion to positivity of about one month, which may be further delayed in immunocompromised individuals. Seroconversion to negative results following successful treatment is also delayed for several years. Furthermore, cross-reaction with other fungal pathogens, including paracoccidioidomycosis, blastomycosis, aspergillosis and rarely coccidioidomycosis has also been described.8,10

Historically, skin tests could be performed but showed a high false positivity rate due to exposure and cross-reaction with other fungal pathogens9,9 as well as false positivity among proven cases of disseminated histoplasmosis.8

Although very promising, molecular testing is not commercially available as yet.9 However, various in-house PCRs are described showing promise to improve both sensitivity and turnaround time for positive identification of histoplasma.9,15,16

Hyperferritinaemia (serum ferritin levels exceeding 1,500 µg/L) has been associated in the past with DH.17 Various authors have alluded to ferritin levels in excess of 10,000 µg/L, as a highly specific marker for DH.17 In the current clinical case, the patient did present with a markedly elevated level, although much lower than described in these reports. Hyperferritinaemia seems to have a significantly different epidemiology in South Africa, where the most common infectious cause seems to be disseminated infection with Mycobacterium tuberculosis.18

The Infectious Diseases Society of America (IDSA) published treatment guidelines in 2007 for the treatment of histoplasmosis. The treatment regimens are determined by disease severity as well as site of infection, associated organ damage and the patient’s immune status.19 In this clinical case of probable disseminated histoplasmosis, the treatment of choice would be a two week course of intravenous amphotericin B (0.7-1 mg/kg/day). Thereafter, the patient should be treated with itraconazole 600 mg for three days, and 400 mg there-after, in divided doses for at least 12 months. If the degree of immunosuppression cannot be improved, lifelong therapy is advocated.19

Histoplasmosis, like most opportunistic infections, can present with a myriad of clinical features which can complicate early diagnosis. Although not as prevalent as in other parts of the world, it should always be considered as part of the differential diagnosis, especially among severely immunocompromised individuals.

References

10. Wheat L. Histoplasmosis: a review for clinicians from non-endemic areas. Mycoses 2006; 49: 274-282