The key is in the details: a case of disseminated histoplasmosis

Abstract

Case description: A 39-year-old HIV-positive Hispanic gentleman presented to the emergency department with a four-day history of altered mental status, pyrexia, mild non-productive cough, nausea and vomiting on a background of night sweats, chills, weight loss and diarrhoea. The patient had a history of non-compliance with his antiretroviral therapy, and of tobacco, alcohol and cocaine use. He was a lifelong gardener, born in Mexico but living in southern California for 19 years. On examination he was febrile, wasted and disoriented. A number of skin lesions were appreciated throughout his body. Laboratory studies demonstrated pancytopaenia and severe immunosuppression; however, imaging, serology, cultures and a bone marrow biopsy were unremarkable. Despite antibacterial, antiviral and antifungal treatment, he continued to deteriorate clinically. Thirteen days into his admission, his blood and bone marrow fungal cultures tested positive for *Histoplasma capsulatum*. His final diagnosis was disseminated histoplasmosis involving multiple organ systems, which responded rapidly to treatment with intravenous liposomal amphotericin B.

Discussion: This case illustrates the challenges faced in the diagnosis of disseminated histoplasmosis in a patient with advanced HIV, including vague symptomatology, the presence of multiple HIV-related comorbidities, non-reactive serology, and delay due to slow-growing fungal cultures. Most importantly, this case highlights the importance of a thorough history and examination in eliciting the clues to diagnosis in the face of these challenges.

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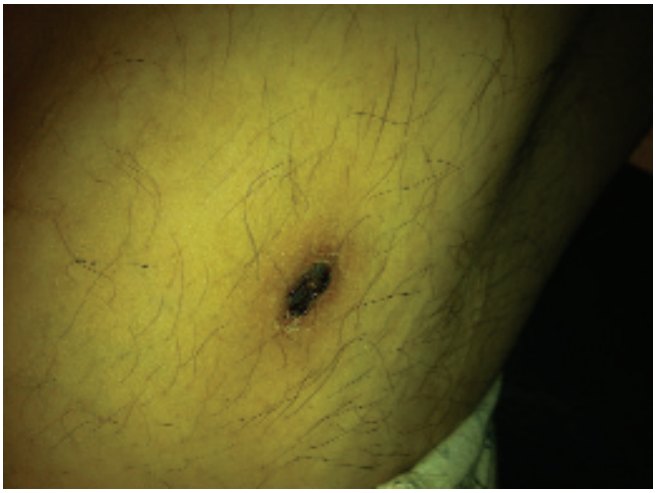

FIGURE 1: Multiple circular, depressed, firm and non-tender plaques surrounded by erythema and with a central haemorrhagic crust were present bilaterally in his lower extremities.

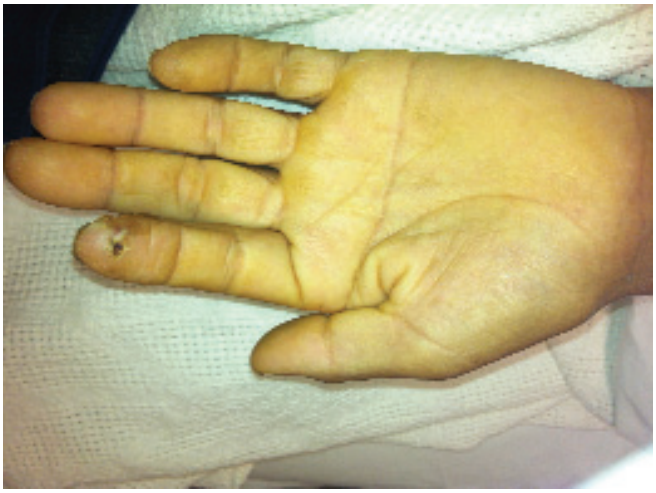

FIGURE 2: Multiple similar lesions were present on his hands, shoulders, legs, head and neck.

Background

Cases of histoplasmosis have been reported on nearly every continent; however, it is endemic in areas of the USA such as the Mississippi, Ohio and St Laurence river valleys. The infection is caused by the dimorphic saprophytic fungus *Histoplasma capsulatum* (*H. capsulatum*), found most commonly within 20cm of the surface of soil contaminated with bird or bat excreta. Transmission occurs via inhalation of *H. capsulatum* spores and persons at risk include those engaged in agriculture, outdoor construction and spelunking.[1] It is the most common endemic mycosis in AIDS patients and is the AIDS-defining illness in more than 50% of patients.[2]

More than 90% of primary infections are asymptomatic or result in a mild influenza-like illness. Those who become symptomatic usually present with fever, headache, a non-productive cough, chills, chest pain, and also rarely with malaise, weakness, fatigue, myalgia and rheumatologic manifestations. Most symptoms resolve spontaneously, but in one out of 2,000 cases the organism grows relentlessly and affects multiple organ systems leading to disseminated histoplasmosis (DH). Most cases of DH are observed in immunosuppressed patients who are more likely to develop systemic symptoms, pancytopaenia, fungaemia and hepatosplenomegaly.[3]

While primary infection with *H. capsulatum* is not uncommon, DH is rare and, left untreated, the mortality rate is 100% in the HIV population. The challenge to diagnosis is the time it takes for fungal cultures to grow, which could take up to two weeks. It is therefore recommended that if there is an index of suspicion, the clinician should start appropriate antifungal treatment without delay.

The case

This is the case of a 39-year-old HIV-positive Hispanic gentleman who presented to the University of California Irvine Medical Center complaining of a four-day history of altered mental status, pyrexia, mild non-productive cough, nausea and vomiting on a two-week background of night sweats, chills, weight loss and diarrhoea. His wife noted that four days prior to presentation, he began "acting drunk". He progressed to becoming agitated, exhibiting repetitive behaviours such as turning the lights on and off, and expressing somatic delusions of anosmia, blindness and nihilistic delusions of being "dead inside". Further questioning revealed that he had been behaving oddly for several weeks, having lacerated his own scrotum two weeks ago for no apparent reason.

The patient had been diagnosed with HIV in 2004 and had a history of antiretroviral therapy (ART) non-compliance, and of tobacco, alcohol and cocaine use. He denied any recent travel, sick contacts or intravenous drug use. He had no other past medical or surgical history, and was not on any medications.

He was a lifelong gardener who was born in Mexico but moved to California in 1993. His last visit to Mexico was one year prior to presentation and he had never travelled outside southern California and Mexico.

On examination, he was febrile (temperature of 38.5°C), tachycardic, wasted and disoriented. A white plaque was appreciable on his tongue and a number of circular, depressed, firm and non-tender plaques with a central haemorrhagic crust and surrounding erythema were present throughout his body (**Figures 1** and **2**). All other systems examinations were unremarkable and he demonstrated no focal neurological deficits or meningism.

Laboratory studies demonstrated pancytopaenia, severe immunosuppression (**Table 1**), and extensive serology and imaging findings were negative (**Table 2**). A lumbar puncture was contraindicated due to severe thrombocytopaenia but a bone marrow biopsy performed on day two of admission demonstrated a normocellular marrow, budding yeast-like structures on fungal stain that failed to grow on fungal culture, and no evidence of acute lymphoma or leukaemia.

Table 1: Diagnostic data.

Complete blood count		Urea and electrolytes		Liver function		T-cell subsets and viral load	
Hb	2.9g/dl Low	Na^+	133mEq/L Low	T. Prot.	7.0g/dl	White cell count	2,900/mcL Low
Hct	28.3% Low	K^+	3.1mEq/L Low	Albumin	2.8g/dl	Lymphocytes	100/mcL Low
WCC	10.2g/dl Low	Cl^-	100mEq/L	Alk Phos	91IU/L	CD3+CD4+ count	3/mcL Low
Plt	26,000 Low	BUN	16mg/dl	AST	238IU/L High	Viral load	1,730,000 copies/mL High
		Creat	1.0mg/dl	ALT	86IU/L High		
		Mg_2^+	2.1mEq/dl	T. Bili.	1.7mg/dl High		
		Inor. Phos.	3.8mg/dl				
		Corr. Ca_2^+	8.6mg/dl				

Hb, haemoglobin; Hct, haematocrit; WCC, white cell count; Plt, platelets; Na^+, sodium; K^+, potassium; Cl^-, chloride; BUN, blood urea nitrogen; Creat, creatinine; Mg_2^+, magnesium; Inor. Phos., inorganic phosphate; Corr. Ca_2^+, corrected calcium; T. Prot., total protein; Alk Phos, alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; T. Bili., total bilirubin.

Table 2: Serology and imaging.

Positive serology	Negative serology	Positive imaging	Negative imaging	Other negative findings
HBsAg	Anti-HBs Ab	CT head: prominent central cerebral atrophy	Plain film chest and abdomen x-ray	Tuberculosis blood culture
	HBV DNA			Tuberculosis sputum cultures
	HBeAg		CT chest, abdomen and pelvis	
	Anti-HBe Ab			Sputum acid-fast bacilli x 3
	Anti-HCV Ab		MRI brain	Stool, urine and sputum cultures
	Anti-HAV Ab			
	T. pallidum		MRI L-spine	Urine histoplasma antigen
	Cryptococcus			
	Histoplasma		MRI T-spine	Sputum *Pneumocystis jirovecii*
	Coccidioides			
	EBV, CMV, HSV		Ultrasound scan: Liver/ gallbladder/bile ducts/ pancreas/spleen	Blood and bone marrow bacterial, viral and fungal cultures
	Toxoplasma			

HBsAg, hepatitis B surface antigen; HBs Ab, hepatitis B surface antibody; HBV DNA, hepatitis B virus DNA; HBeAg, hepatitis B extracellular core antigen; HCV Ab, hepatitis C virus antibody; HAV Ab, hepatitis A virus antibody; EBV, Epstein-Barr virus; CMV, cytomegalovirus; HSV, herpes simplex virus.

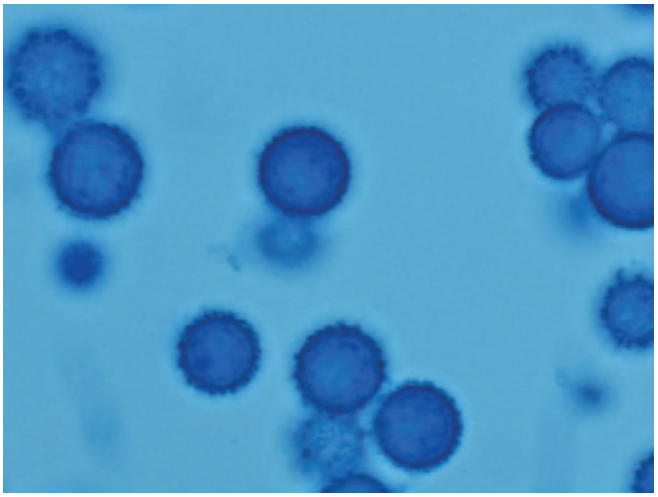

FIGURE 3: Fungal cultures on bone marrow demonstrating H. capsulatum.

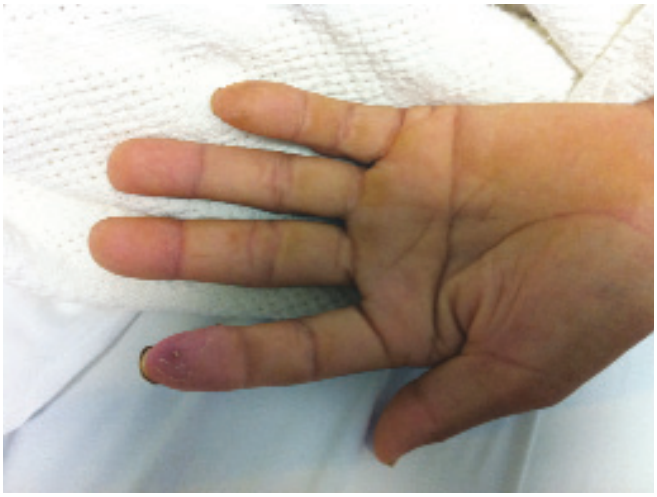

FIGURE 4: A dramatic improvement in the patient's skin lesions was appreciated after just two days of treatment with liposomal amphotericin B.

Despite being on aggressive treatment with broad-spectrum antibiotics, antivirals and antifungals (**Table 3**) he continued to spike daily fevers greater than 40°C and he deteriorated clinically. He required near daily blood and platelet transfusions and developed frank psychosis with visual and auditory hallucinations. On day 10 of admission, he began complaining of severe neuropathic pain on the soles of his feet, which debilitated him further. With no diagnosis and a worsening clinical picture, a family meeting was called for a discussion regarding palliative care. Thirteen days into his admission, the first set of blood and bone marrow fungal cultures became positive for *H. capsulatum* (**Figure 3**). Guidelines by the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH) and Infectious Diseases Society of America recommend initiation therapy with intravenous liposomal amphotericin B and maintenance therapy with oral itraconazole.[4] DH does not respond to micafungin and responds poorly to fluconazole.[5] He was therefore started on a high dose of liposomal amphotericin B and became afebrile one day into treatment. From day two of treatment, the clinical picture had improved significantly (**Figure 4**). Not all of this patient's symptoms could be explained by DH. While he began to improve clinically after treatment with amphotericin B, his psychosis, pancytopaenia and peripheral neuropathy failed to respond. These conditions were attributed to HIV and he was started on ARTs. While waiting for the patient to respond to ART, his HIV psychosis, pancytopaenia and peripheral neuropathy were managed with antipsychotics, packed red blood cell and platelet transfusions, and gabapentin, respectively, and responded adequately to symptomatic management.

His final diagnosis was DH involving the central nervous system (CNS), liver, skin and bone marrow with concomitant HIV psychosis, pancytopaenia and neuropathy. Two weeks into his treatment, there was a dramatic improvement clinically and we were confident to begin discharge planning.

Table 3: Anti-microbial treatment regimen of patient.

Antibacterial	Antifungal	Antiviral
Vancomycin, ceftriaxone, and piperacillin-tazobactam	Fluconazole initially then switched to micafungin	Aciclovir

Discussion

DH in AIDS patients can present in a wide spectrum of clinical forms and can either be caused by a recent exposure or endogenous reactivation of latent foci. DH in AIDS most commonly presents with fever, weight loss and focal lesions on multiple organ systems including the gastrointestinal tract, endovascular structures, the CNS and the adrenal glands. Cutaneous lesions occur in 10-25% of patients with DH. These are more common in Latin Americans, ranging from 38-85%. They can either be primary, caused by direct inoculation, or secondary, caused by haematogenous spread.[6] The most common cutaneous lesion is a papular eruption with crusting, but other manifestations have been reported, which are summarised in **Table 4**.[7] This patient's lesions (**Figures 1** and **2**) resemble those reported in the literature and responded rapidly to treatment with liposomal amphotericin B.

The most sensitive and specific diagnostic test for DH is the detection of Histoplasma antigen in the serum, urine, cerebrospinal fluid and bronchoalveolar lavage fluid.[8] If there is a high index of suspicion, direct microscopy can be performed for rapid identification on a variety of samples, including bone marrow aspirates. Standard serology has been described to be non-reactive

in HIV-infected patients[9] and was non-reactive in this case. If treated, the prognosis remains poor among the HIV-infected patient population with DH. The overall risk of death is nearly 50%. Fungaemia, renal insufficiency and age are independent predictors of poor prognosis with odds ratios of 12.1, 11.3 and 0.9, respectively. While the vast majority of cases of DH are seen in patients with advanced HIV, defined by a CD4 count less than 50/mcl, a low CD4 count and high viral load are not statistically significant predictors of poor outcomes.[10]

Conclusion

While primary histoplasma infections are common and prevalent globally, only one out of 2,000 *H. capsulatum* infections progress to DH. HIV-infected individuals with low CD4 counts are at increased risk of DH and often present with vague systemic symptoms. A variety of cutaneous manifestations have been described in the literature and multiple organ systems may be involved. Non-reactive serology is not uncommon in this patient population and a definitive diagnosis by way of fungal cultures may not be possible for up to two weeks after presentation. In addition, HIV-positive patients are more likely to present with fungaemia, an independent predictor of poor prognosis despite adequate treatment. The mortality rate is 100% if left untreated, making it essential to recognise and empirically treat at-risk patients. The key to diagnosis in this case was hidden in the details. Since the patient had not visited endemic regions recently, it was concluded that his DH was due to reactivation of latent foci. Retrospective questioning revealed that he was born, raised and worked in the agricultural fields of southern Mexico, the only endemic region in the country, putting to rest the mystery surrounding his unusual diagnosis.

Table 4: Cutaneous lesions of histoplasmosis reported in the literature.[6]

Primary	Secondary	
Painless chancre with regional adenopathy	Papules	Punched-out ulcers
	Plaques with and without crusts	Localised and generalised dermatitis
	Pustules	Panniculitis
	Nodules	Vegetations
	Mucosal ulcers	Polymorphous erythema
	Erosions	Erythroderma syndromes
	Keratotic plaques and papules	Molluscum contagiosum-like lesions
	Purpuric lesions	Pyoderma gangrenosum-like lesions
	Acneiform eruption	Diffuse hyperpigmentation
	Rosacea-like eruption	Abscesses and cellulitis

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