Disseminated histoplasmosis in an HIV-positive Filipino

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Introduction: Histoplasmosis is a granulomatous infection caused by the fungus, *Histoplasma capsulatum*. The disseminated type can be the initial manifestation of HIV/AIDS. It may affect the lungs, skin, gastrointestinal tract, liver, spleen, genitourinary tract, heart, bone marrow, adrenal glands, lymph nodes, and the central nervous system. Cutaneous findings are diverse and most present with few nodules and ulcerative lesions with involvement of the mucosal surface.

Case summary: This article describes the case of a 42-year-old male who presented fever, cough, oral ulcers, and multiple brownish nodular papules and plaques on the lips, face, trunk and extremities. Skin biopsy with tissue culture and sensitivity revealed *Histoplasma capsulatum* which was resistant to the recommended treatment, Amphotericin-B and Itraconazole. The patient was seropositive for HIV.

Conclusion: The incidence of HIV in the Philippines is rapidly increasing and we are expected to encounter more cases of opportunistic infections, such as in this case. Having a high index of clinical suspicion is important in establishing a diagnosis. In patients with HIV/AIDS or presumed to have AIDS presenting with multiple cutaneous lesions, skin biopsy for identification, culture, and sensitivity studies are valuable in determining the diagnosis and initiating treatment. Furthermore, the stigma of being diagnosed with HIV/AIDS prevents people from having HIV tests done. This causes delay in the diagnosis and treatment, and results in higher mortality. Public education and patient counseling are therefore vital in addressing the HIV epidemic.

Keywords: *Histoplasma capsulatum, Disseminated histoplasmosis, HIV, AIDS*

INTRODUCTION

Histoplasma capsulatum is a dimorphic fungus which is the etiologic agent of Histoplasmosis. It has a worldwide distribution that can affect both immunocompromised and immunocompetent individuals. The infection is acquired by inhalation of spores from soil contaminated by bird and bat excreta.[1]

Histoplasmosis is mostly asymptomatic and self-limiting in immunocompetent persons. Among immunocompromised patients with an acquired or congenital cellular immunodeficiency, histoplasmosis can cause significant morbidity and mortality. It is mostly fatal in the absence of appropriate treatment.[2]

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Histoplasmosis may be classified into three types: acute pulmonary, chronic cavitary, and disseminated histoplasmosis.[3] The disseminated or extrapulmonary form is an AIDS-defining infection.[4] Primary cutaneous histoplasmosis is very rare and occurs due to penetrating injuries.[5]

Mucocutaneous lesions were present in about 20% of human immunodeficiency virus (HIV)-infected patients with disseminated histoplasmosis (DH). Most commonly, the lesions noted were papules and nodules, macules and patches, and/or ulcers located on the face, extremities, and/or trunk.[3] The mortality from DH in AIDS patients was reported at 30.2%. Poor compliance to highly active antiretroviral therapy (HAART) was associated with both mortality and relapse in DH.[6] Early diagnosis of HIV infection is critical to reduce the morbidity and mortality of patients, and the survival rate increases upon introduction of antiretroviral therapy.[1]

CASE REPORT

A 42-year-old, male, who had a reactive HIV screening test one month prior, was admitted for oral ulcers and fever. He was referred to the Section of

Dermatology for the evaluation of multiple brownish nodular papules and plaques on the face, trunk, and extremities. The patient initially noted the appearance of erythematous, scaly, and mildly pruritic plaques on the nasolabial folds one month before, which gradually increased in number, becoming generalized and brownish in color. During this time, the patient also had fever, cough and unquantified weight loss. Confirmatory tests for HIV and CD4 count were requested but the patient was not able to have the tests done. He was admitted at another hospital where a skin punch biopsy showed Nodular dermatitis and Lobular panniculitis. Differential diagnoses included Deep fungal infection vs Subcutaneous T-cell Lymphoma vs Atypical mycobacterial infection. Patient then opted to be transferred to our institution. The patient is single and worked as a call center agent for 10 years. He had unprotected sex with multiple female partners. He had a history of Pulmonary Tuberculosis one year prior, and was treated with anti-TB medications for 6 months. He had no history of recent travel or illicit drug use.

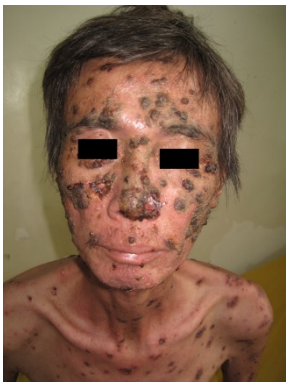

Figure 1. Multiple erythematous papules and plaques with thick brownish crusts on the face

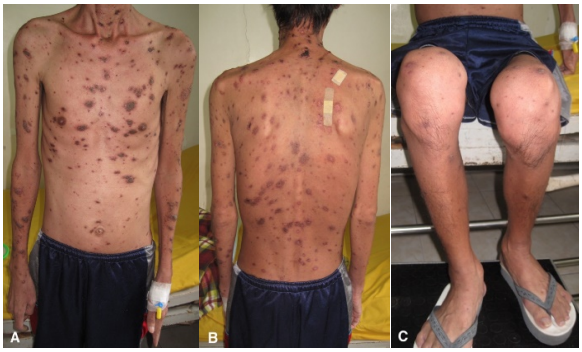

Figure 2. Multiple erythematous papules and plaques with thick brownish crusts on the chest, abdomen, arms (A), back (B), and lower extremities (C).

Dermatologic examination revealed multiple erythematous papules and plaques with thick brownish crusts on the face, trunk, arms and on the lower extremities (Figures 1-2). He had few brownish papules on the lips and nasal mucosa, erosions on the hard palate, and whitish plaques on the tongue (Figure 3). Based on the history and dermatologic findings, Deep fungal infection vs Subcutaneous T-cell Lymphoma vs Atypical mycobacterial infection, and Oral Candidiasis were considered. The patient was started on Fluconazole 200mg/tablet once a day.

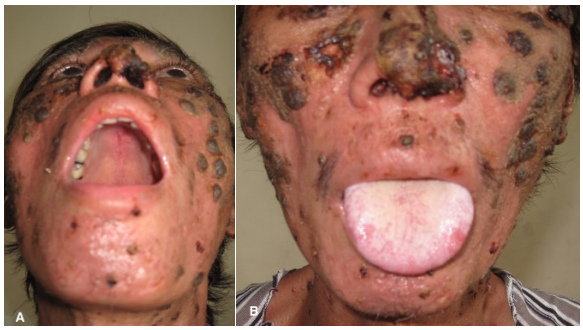

Figure 3. (A) Brownish papules on the lips and nasal mucosa, erosions on the hard palate, and (B) whitish plaques on the tongue.

Chest X-ray showed few fibrotic infiltrates in the right upper lobe ascribed to PTB. Sputum AFB smear was negative. Ultrasound of the abdomen showed mild hepatomegaly with fatty changes. Skin punch biopsy for Hematoxylin and eosin (H&E) stain, Periodic-acid Schiff (PAS) stain, Acid fast bacilli (AFB) stain, and tissue culture were done and were sent out.

The patient's symptoms improved and he was discharged. Fluconazole 200mg/tablet once a day was continued as his home medication. He was advised to follow-up at the Dermatology OPD after 2 weeks.

A 4-mm punch biopsy was done on the brownish nodular plaques on the left thigh. H&E showed parakeratosis overlying irregular epidermal hyperplasia with mild spongiosis, focal areas of hypergranulosis, and liquefaction degeneration of some areas of the basal layer. Lymphocyte exocytosis was also observed. There was marked dermal edema, especially at the papillary dermis. Throughout the entire dermis, there were dense collections of interstitial infiltrates comprised of lymphocytes, histiocytes, and nuclear dust. Throughout the dermis, there was infiltration with moderately dense thick-walled spores mostly within the histiocytes (Figure 4). PAS stain was positive (Figure 5). AFB stain was

negative. Histopathologic diagnosis was consistent with a cutaneous deep fungal infection.

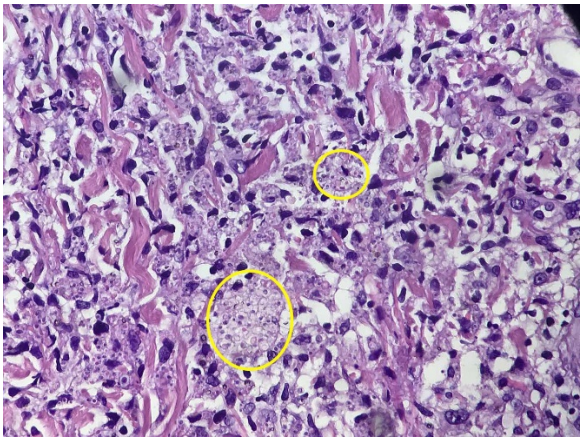

Figure 4. Hematoxylin and eosin stain showing dense collections of interstitial infiltrates in the dermis, comprised of lymphocytes, histiocytes, nuclear dust, and thick-walled spores mostly within the histiocytes (x 400).

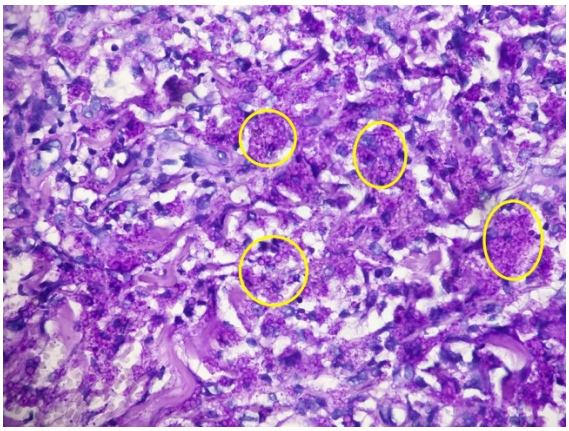

Figure 5. PAS stain showing yeast cells (x 400)

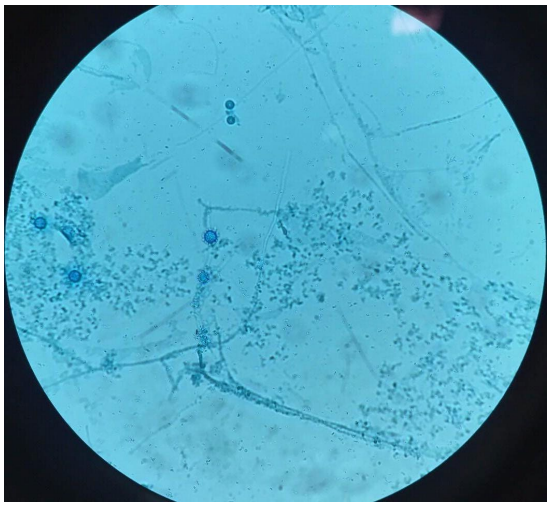

Figure 6. Microscopic identification of *Histoplasma capsulatum* from tissue culture

Fungal culture of the biopsy tissue revealed *Histoplasma capsulatum* (Figure 6). Sensitivity testing for filamentous fungi was requested and revealed *H. capsulatum* sensitive to Anidulafungin, Capsofungin, and Micafungin; and resistant to Amphotericin-B, Itraconazole, and Fluconazole.

The patient, however, was lost to follow-up. His relative later revealed that he passed away 2 months after he was discharged. He was able to have the confirmatory test for HIV done and it was positive. His CD4 cell count was 11/mm^3. He was placed on antiretroviral treatment (Lamivudine/ Tenofovir/ Efavirenz), and was given Isoniazid 300mg, Co-trimoxazole 800/160mg, and Azithromycin 500mg, as prophylaxis. He was complaining of weakness and had poor appetite. He eventually passed away at his home.

DISCUSSION

According to the World Health Organization (WHO), the Philippines has one of the fastest-growing HIV epidemics in the world. There were 7,500 cases of HIV reported in 2016 with 26 new cases diagnosed per day.[7] The highest reported incidence of HIV was in May 2017 at 1,098 according to the HIV/AIDS & ART Registry of the Philippines (HARP). There was a 48% increase compared to the same period from the previous year (741) and this was the highest recorded incidence since 1984.[8] A total of 44,010 cases of HIV was reported by the Department of Health from January 1984 to May 2017.

Histoplasmosis is a granulomatous infection caused by the fungus *Histoplasma capsulatum*. It is a dimorphic fungus that exists in mycelial form at 30°C and in a yeast phase at 37°C. The spores of these organisms are found in soil, thorns, and bird droppings. Infection usually results from inhalation of these spores.[3] It is commonly encountered in the endemic regions in the western hemisphere, which include southern Mexico and some areas in the southeastern USA.[9] In the Philippines, a study on the incidence of histoplasmin hypersensitivity was conducted on office workers from Manila, and a positive skin test to histoplasmin was found in 26% of the test subjects. This indicated that *Histoplasma capsulatum* is sufficiently present in the Philippines to come in contact with one-fourth of the test population.[10]

There are reported cases of Histoplasmosis in the Asia-Pacific region; however, the exact numbers are difficult to obtain since endemic fungal infections are not notifiable diseases. In the past, histoplasmosis

was considered rare in this region but the incidence of opportunistic fungal infections, such as what is presented in this study, is expected to increase significantly with the rise in HIV/AIDS cases.[11]

Disseminated histoplasmosis (DH) in endemic areas is the first manifestation of AIDS in up to 50–75 % of patients. Ninety percent of cases have occurred in patients with CD4 cell counts below 200/mm^3.[1]

Most patients have asymptomatic hematogenous spread of *H. capsulatum* in the reticuloendothelial system through parasitized macrophages. The cell-mediated immunity is activated to control the infection. T lymphocytes gain immunity to *H. capsulatum* antigens by activating macrophages and eliminating the organism. As time passes, viable *H. capsulatum* may still remain viable in various organs, like what occurs in infection with *Mycobacterium tuberculosis*. Reactivation of the disease can occur years after. It is difficult to discern whether histoplasmosis in endemic areas is due to a new infection or the reactivation of a previous infection.[13]

Patients with disseminated histoplasmosis can present with fever, cough, dyspnea, malaise, anorexia, and weight loss. On physical examination, hepatosplenomegaly and lymphadenopathy are usually appreciated, and pallor and petechiae are seen if pancytopenia is present.[1,3,13]

Our patient presented with generalized cutaneous lesions including the oral mucosa. Most reports in literature involve a few lesions, mainly nodules and ulcerative lesions.[9] Mucocutaneous lesions are seen in nearly 20% of HIV-infected patients with DH.[3] Its cutaneous manifestations are diverse and non-pathognomonic. Clinical lesions include papules, plaques, umbilicated papules, comedo-like papules, psoriasiform plaques, verrucous plaques, crusted plaques, nodules, and ulcers. It has marked tropism for the oral mucosa and often involve mucosal surfaces.[14]

Chest radiograms show diffuse infiltrates, usually in a miliary reticulonodular pattern.[1] However, in one study, only 52% had infiltrates on their initial chest x-ray.[15] Other clinicians suspect that DH may be a clinical reality that is probably overlooked or misdiagnosed as other granulomatous-inducing disorders such as tuberculosis or “drug-resistant” tuberculosis.[10] Our patient’s chest x-ray showed few fibrotic infiltrates, and it was uncertain whether this could be attributed to his previous PTB infection or if it was due to pulmonary histoplasmosis since sputum fungal culture was not done.

Disseminated Histoplasmosis can also involve the gastrointestinal tract, liver, spleen, genitourinary tract, heart, bone marrow, adrenal glands, lymph nodes, and the central nervous system.[16]

The diagnosis of DH requires a high index of clinical suspicion. Diagnosis can be based on the culture and isolation of *Histoplasma capsulatum* from any site of infection. Specimen for culture can be obtained from infected tissue or body fluid like blood, bone marrow, liver, and skin lesions.[13] The organism has been isolated in culture from blood, bone marrow, respiratory secretions, or localized skin lesions in more than 85% of cases.[1] Skin biopsy of mucocutaneous lesions with special staining (Periodic acid-Schiff or Gomori methenamine silver stain) can help establish the diagnosis of a fungal infection. Culture and identification of the organism is confirmatory; however, it may take several weeks. Fungal culture using Sabouraud’s dextrose agar media is incubated for 1-6 weeks between 25 °C and 30 °C.[2] Antigen detection in body fluids by radioimmunoassay or enzyme immunoassay with polyclonal antibodies to *H. capsulatum* provides a rapid diagnosis of DH in patients with AIDS.[1] However, antigen detection is not readily available. In our patient, the result of the fungal culture and sensitivity study took about 6 weeks to be completed. Having access to diagnostic tests to rapidly diagnose histoplasmosis could allow early diagnosis and treatment of DH and decrease overall mortality from the disease.

The difficulty that we anticipated in this case was the treatment. The recommended treatment of DH involves two phases: an induction phase to produce a clinical remission and a maintenance phase to prevent relapse.[1] Liposomal amphotericin B at 3.0mg/kg/day is given for 1–2 weeks during the induction phase. This is followed by oral itraconazole at 200mg three times a day given for three days, and then 200mg twice a day for at least twelve months. Lifelong suppressive therapy with itraconazole at 200mg a day may be required for immunocompromised patients if immunosuppression cannot be reversed, and for patients who relapse despite receiving appropriate therapy.[17] Our patient’s infection was resistant to both Amphotericin-B and Itraconazole. Sensitivity testing for filamentous fungi is important especially now that resistant strains are emerging.

The overall mortality from DH in AIDS patients is up to 30.2%, according to a study by Damasceno et al.[6] Non-adherence to antiretroviral therapy was the independent risk factor associated with both mortality and relapse in DH.[6] Therefore,

early diagnosis of HIV infection is critical to reduce the morbidity and mortality of patients, and affects survival rate which increases after antiretroviral therapy initiation.[1] One of the barriers that hinder patients to get tested for HIV is stigma and discrimination. UNAIDS cites fear of stigma and discrimination as the main reason why people are reluctant to get tested, disclose their HIV status and take antiretroviral drugs.[19]

CONCLUSION

With the rapid increase in the number of patients with HIV in the Philippines, we are expected to encounter more cases of opportunistic infections, such as in this case. Having a high index of clinical suspicion is important in establishing a diagnosis. In patients with HIV/AIDS or presumed to have AIDS presenting with multiple cutaneous lesions, skin biopsy for identification, culture, and sensitivity studies are valuable in determining the diagnosis and initiating treatment. Furthermore, the stigma of being diagnosed with HIV/AIDS prevents people from having HIV tests done. This causes delay in the diagnosis and treatment, and results in higher mortality. Public education and patient counseling are therefore vital in addressing the HIV epidemic.

REFERENCES

1. Wheat J. Endemic mycoses in AIDS: a clinical review. Clin Microbiol Rev. 1995;8(1):146–59.
2. Adenis AA, Aznar C, Couppié P. Histoplasmosis in HIV-Infected Patients: A Review of New Developments and Remaining Gaps. Current Tropical Medicine Reports. 2014;1(2):119-128. doi:10.1007/s40475-014-0017-8.
3. Cohen, P. R., Grossman, M. E. and Silvers, D. N. Disseminated Histoplasmosis and Human Immunodeficiency Virus Infection. International Journal of Dermatology, 1991;30:614–622.
4. Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. Morbidity and Mortality Weekly Report, December 18, 1992/41 (RR-17), 1993.
5. Nair S P, Vijayahdharan M, Vincent M. Primary Cutaneous Histoplasmosis. Indian J Dermatol Venereol Leprol 2000;66:151-3.
6. Damasceno, L. S., Ramos, A. N., Alencar, C. H., Gonçalves, M. V. F., de Mesquita, J. R. L., Soares, A. T. D., Coutinho, A. G. N., Dantas, C. C. and Leitão, T. d. M. J. S. Disseminated histoplasmosis in HIV-infected patients: determinants of relapse and mortality in a north-eastern area of Brazil. Mycoses. 2014;57: 406–413. doi:10.1111/myc.12175.
7. World Health Organization (2016). HIV and other sexually transmitted infections. Retrieved from http://www.wpro.who.int/philippines/areas/communicable_diseases/hiv_aids/en/
8. Epidemiology Bureau, Department of Health (2017). National HIV/AIDS & STI Surveillance and Strategic Information Unit (NHSSS). Retrieved from http://www.doh.gov.ph/stat_of_the_month
9. Bonifaz, A., Cansela, R., Novales, J., De Oca, G. M., Navarrete, G. and Romo, J., Cutaneous histoplasmosis associated with acquired immunodeficiency syndrome (AIDS). International Journal of Dermatology. 2000;39:35–38.
10. Bulmer AC, Bulmer GS. Incidence of histoplasmin hypersensitivity in the Philippines. Mycopathologia. 2001;149(2):69–71. doi: 10.1023/A:1007277602576.
11. A. Chakrabarti, M. A. Slavin; Endemic fungal infections in the Asia-Pacific region. Medical Mycology. 2011;49(4):337–344.
12. Kauffman CA. Histoplasmosis: a clinical and laboratory update. Clin Microbiol Rev. 2007;20(1):115–32. doi: 10.1128/CMR.00027-06.
13. Kauffman CA. Histoplasmosis: a Clinical and Laboratory Update. Clinical Microbiology Reviews. 2007;20(1):115-132. doi:10.1128/CMR.00027-06.
14. K. Ramdial, P., Mosam, A., Dlova, N. C., B. Satar, N., Aboobaker, J. and Singh, S. M. (2002), Disseminated cutaneous histoplasmosis in patients infected with human immunodeficiency virus. Journal of Cutaneous Pathology, 29: 215–225. doi:10.1034/j.1600-0560.2002.290404.x
15. Johnson PC, Khardor N, Najjar AF, et al, Progressive disseminated histoplasmosis in patients with acquired immunodeficiency syndrome, Am J Med. 1988;85:152-158.