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CASE REPORT

Disseminated histoplasmosis in a 53-year-old HIV-negative Filipino male: A case report

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ABSTRACT

INTRODUCTION Histoplasmosis is a disease of global distribution with diverse manifestations caused by the dimorphic fungus *Histoplasma capsulatum*. It is frequently described in severely immunocompromised and Human Immunodeficiency Virus (HIV)-positive individuals. Despite being widely reported in Southeast Asia, few cases have been reported in the Philippines.

CASE REPORT A 53-year-old Filipino male who presented with umbilicated papules resembling molluscum contagiosum, and a previous history of a left lung mass with initial complaints of cough and hemoptysis. Gram stain of his sputum revealed the presence of fungal elements, otherwise not specified. In relation to this, a fine-needle aspiration biopsy of the suspected lung mass was done. However, findings were negative for malignant cells and fungi.

Dermoscopy revealed central ulceration and necrosis with faint peripheral arborizing telangiectasia and surrounding superficial scaling. Histopathologic analysis revealed a diffuse granulomatous dermatitis, and Periodic acid-Schiff (PAS) and Grocott methenamine silver (GMS) stains showed numerous small yeast-like structures measuring approximately 3.74µm in diameter. Tissue culture of the skin lesion on the right thigh isolated fungal elements but was not specified. As histoplasmosis is an AIDS-defining infection and often found in immunocompromised states, screening for HIV was done which revealed negative results. Interestingly, disease distribution of histoplasmosis in the Philippines was frequently found in HIV-negative patients. Due to persistent serum creatinine elevation of over 300 µmol/L, renal biopsy was also done and revealed similar fungal elements. With these findings, a diagnosis of disseminated histoplasmosis was made. After a month of treatment with oral itraconazole, there was marked improvement of the patient's skin lesions.

CONCLUSION This case highlights the importance of recognizing cutaneous manifestations and maintaining a high index of suspicion for histoplasmosis in HIV-seronegative patients.

KEYWORDS systemic fungal infections, disseminated histoplasmosis, molluscum-like lesions, itraconazole

INTRODUCTION

Histoplasmosis is a systemic mycosis caused by the thermally-dimorphic saprophytic fungus *Histoplasma capsulatum* and is frequently described in severely immunocompromised and Human Immunodeficiency Virus (HIV)-positive individuals. Although histoplasmosis is globally distributed, it is thought to occur more commonly in North America and is primarily endemic in Ohio and the Mississippi River Valley. It thrives in soil enriched with bird or bat guano, and humans are infected via inhalation of spores. Histoplasmosis has been widely reported in Southeast Asia; however, only 14 cases have been reported in the Philippines.[1-7]

We present a case of a 53-year-old HIV-seronegative Filipino male who presented with discrete umbilicated lesions on his face, trunk, and limbs. A tissue culture of the skin lesions on the right thigh showed the growth of fungi elements which prompted the investigation of an underlying infectious process. Histopathologic examination of the skin was consistent with cutaneous histoplasmosis. A biopsy of the renal interstitium confirmed the presence of fungal elements. The patient was thus managed as a case of disseminated histoplasmosis.

CASE SUMMARY

Three (3) months prior to consult, a 53-year-old Filipino male residing in Bulacan, a province located in the region of Central Luzon in the Philippines, presented with productive cough with minimal whitish sputum and he-

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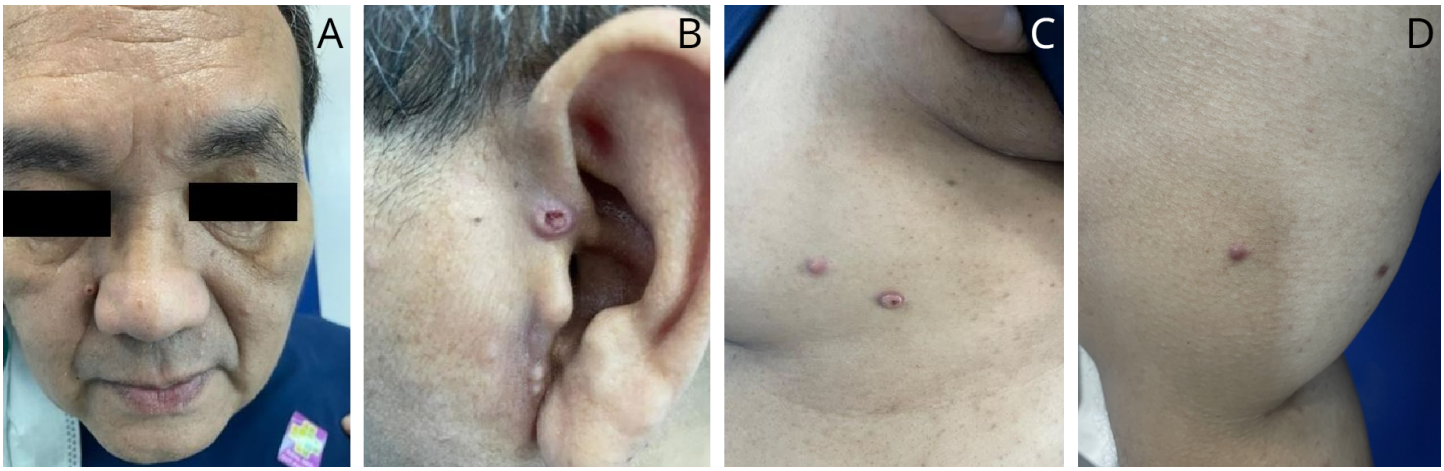

Figure 1. Pretreatment image of multiple, well-defined skin-colored to slightly erythematous umbilicated papules on the (A) face, (B) ears, and (C) trunk measuring approximately 1.0-1.5cm x 0.8cm x 0.4-0.5cm.

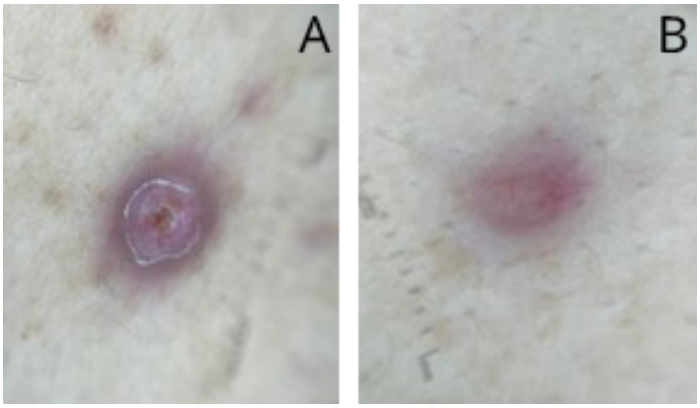

Figure 2. A. Dermoscopy of the ulcerated lesions on the face and trunk revealed central ulceration and necrosis, faint arborizing telangiectasias on the periphery of the lesions with surrounding superficial scaling. B. Red homogenous areas with overlying arborizing telangiectasias were more prominent on the right thigh.

moptysis, with associated exertional dyspnea, prompting hospitalization at a private institution. During this time, *Mycobacterium tuberculosis* infection was considered due to its endemicity in the Philippines. GeneXpert testing of a sputum sample was negative. A sputum sample was also sent for Gram stain which revealed fungal elements. No sputum culture was done at the time. A differential diagnosis of invasive candidiasis was considered, and an Aspergillus galactomannan antigen test was requested, which revealed a positive result of 5.0. Further evaluation of pulmonary findings with a computerized tomography scan of the chest revealed an ill-defined heterogeneously enhancing mass lesion with central air-fluid level and satellite lesions within the left lung. Fine-needle aspiration biopsy of the suspected lung mass was done which revealed findings negative for malignant cells and fungi. Physicochemical stains for microorganisms, such as Brown and Brenn, Periodic Acid-Schiff (PAS), and Ziehl-Neelsen, were done and were unable to isolate bacterial colonies, fungal elements, and acid-fast bacilli. Fungal culture of the lung mass also yielded a negative result. Serial complete blood count testing during this hospitalization showed persistent anemia and thrombocytopenia without associated symptoms such as fatigue, tachycardia, or pallor. Due to the persistence of his pulmonary symptoms, and positive Aspergillus galactomannan antigen test, he was empirically treated with sultamicillin 750mg and fluconazole 200mg daily. Eltrombopag 25mg daily was also given for persistent thrombocytopenia and the patient was subsequently discharged. Whilst taking fluconazole, the patient experienced nausea and was unable to tolerate the medication. Consequently, the medication was shifted to itraconazole 200 mg daily after two (2) weeks. Approximately a month after his initial admission, the patient presented with multiple, non-pruritic and non-painful papules on the face. The lesions increased in number to involve the trunk and extremities, with spontaneous ulcerating and crusting of lesions (Figure 1).

The patient was referred to our dermatology service for assessment of his skin lesions. On physical examination, the patient had stable vital signs and had no apprecia-

ble lymphadenopathy. Dermatologic examination revealed multiple discrete skin-colored to slightly erythematous, monomorphic umbilicated papules measuring 1.0-1.5 x 0.8 x 0.4-0.5 cm, on the face, ears, trunk, and extremities (Figure 1A, 1B, 1C, and 1D). Red homogenous areas with overlying arborizing telangiectasia were more prominent on the right thigh. Some of the lesions had superficial ulcerations. Dermoscopy of the ulcerated lesions on the face and trunk revealed central ulceration and necrosis with faint peripheral arborizing telangiectasia and surrounding superficial scaling (Figure 2A-B).

The past medical history was significant for pulmonary tuberculosis wherein the patient completed six (6) months of treatment with anti-Kochs therapy in 2016. The patient is a known hypertensive, and dyslipidemia is maintained on amlodipine, losartan with hydrochlorothiazide, and rosuvastatin (10mg, 50mg/125mg, 10mg, orally). He also has diabetes mellitus maintained on glimepiride and pioglitazone/metformin (2mg, 15/500 mg). The patient was compliant with his medications with blood pressure and fasting blood sugar controlled. Previous surgical history included a cholecystectomy and hernia repair in the 1990s. He provided no history of smoking or alcoholism. Upon further inquiry, he revealed that he had owned birds for 11 years and was an avid participant in local cockfighting: a traditional pastime in most provinces in the Philippines. He denied trauma or exposure to excavation or landscaping. History of travel included the Middle East including Israel, Jerusalem, and Egypt in 2017, and the United States, including San Francisco, Nevada, and New Jersey, in 2019. The patient is in a monogamous relationship with his wife and denies previous history of sexually transmitted infections.

Further workup was done with serial blood tests revealing asymptomatic microcytic hypochromic anemia and thrombocytopenia. As bone marrow infiltration with fungi was considered, peripheral blood smear and bone marrow aspirate were done which revealed hypochromasia and anisocytosis of red blood cells, and normocellular marrow for the patient's age (50-60%). No evidence of fungal invasion was seen. However, stains to isolate fungal organisms were not done. Serologic testing for HIV was negative. Tests to rule out other sexually transmitted infections were not requested.

Due to persistent serum creatinine elevation of over 300 µmol/L, the patient was referred to nephrology service.

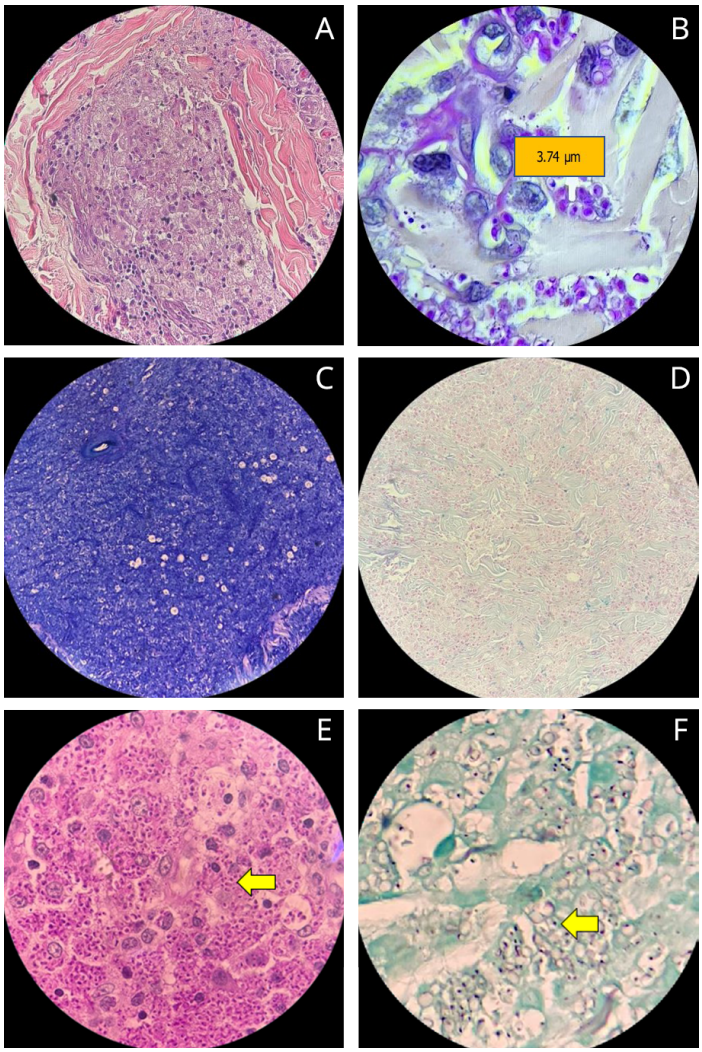

Figure 3. A. Histopathologic findings of 6-mm skin punch biopsies from the trunk and B. right thigh showing diffuse granulomatous infiltrates composed of multinucleated giant cells, foamy histiocytes, lymphocytes, plasma cells, and neutrophils with numerous small yeast-like structures, both extracellular and within the histiocytes and giant cells, seen as basophilic dots measuring approximately 3.74 micrometers with surrounding artefactual halo. C. Giemsa and D. Alcian Blue were negative. E. Periodic acid-Schiff and F. Grocott (GMS) methenamine silver stains positively highlighting yeast forms of Histoplasmosis.

Viral hepatitis was excluded and an antineutrophil cytoplasmic antibody test (p-ANCA) was found to be negative. A renal biopsy was performed revealing IgA nephropathy with 5% cellular crescents and 24% global glomerulosclerosis. Acute interstitial nephritis was also noted with acute tubular injury, mild interstitial fibrosis, tubular atrophy, and mild hyaline arteriosclerosis. PAS staining highlighted

fungal elements within the interstitium. Through collaborative efforts with infectious disease, hematology, nephrology, and dermatology services, a diagnosis of disseminated histoplasmosis was made.

6-mm skin punch biopsies were done on lesions from two (2) sites on the papule on the trunk and right thigh (Figure 3A). The dermatopathology reports from both sites with hematoxyline and eosin (H&E) staining were signed out as diffuse granulomatous infiltrates composed of multinucleated giant cells, foamy histiocytes, lymphocytes, plasma cells, and neutrophils with numerous small yeast-like structures, both extracellular and within the histiocytes and giant cells, seen as basophilic dots measuring approximately 3.74 micrometers with surrounding artefactual halo, suggestive of systemic mycosis (Figure 3B). Histopathologic differentials such as cryptococcus, coccidioidomycosis, penicilliosis, and blastomycosis were considered. We performed both Giemsa stain and Alcian Blue stain tests as they could confirm the presence of deep fungal mycoses other than histoplasmosis (Figure 3C-3D). However, the results were negative in both cases. PAS and GMS stains highlight the characteristic morphology and size of histoplasmosis described as intracellular, round-to-oval spores with narrow-necked budding and the presence of pseudocapsule described as an artefactual halo. In our patient, PAS and GMS stains aided in the visualization of yeast forms of *H. capsulatum* (Figure 3E-3F). Tissue culture and sensitivity of the skin lesions on the right thigh done in another institution showed growth of fungi. (as it did not specify organism/sensitivity). In summary, the presence of yeast forms in both PAS and GMS stains measuring approximately 3.74 micrometers, the positive results of fungal culture from the papule on the right thigh, the presence of unspecified lung mass, PAS-positive fungal elements from the kidney, and symptoms such as prolonged cough, were highly suggestive of disseminated histoplasmosis.

Oral itraconazole 200mg twice daily was continued following the diagnosis of histoplasmosis, with ongoing monitoring of liver function. Notable improvement in skin lesions were seen four (4) weeks after initiation of itraconazole and subsequently during follow-up visits (Figure 4).

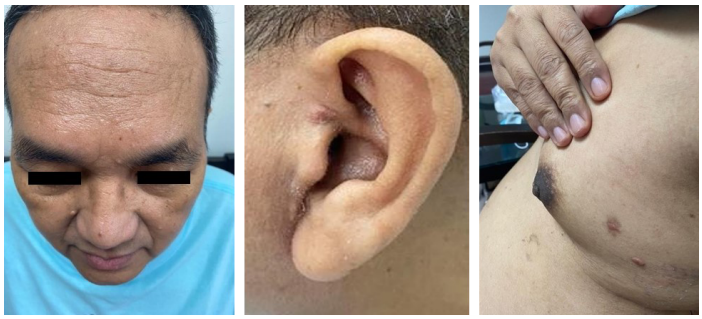

Figure 4. Post-treatment image of skin papules on the face and trunk showing reduction in size after 4 weeks of treatment with Itraconazole 200 mg/capsule daily.

DISCUSSION

Histoplasmosis is primarily a pulmonary disease that can be acquired from inhalation of soil contaminated with bird and bat droppings. It may present as an acute or chronic pulmonary, cutaneous, or progressive disseminated disorder. Histoplasmosis encompasses a wide range of clinical manifestations, with the disseminated type being the most serious and fatal. Disseminated histoplasmosis encapsulates extrapulmonary involvement in various organs such as the lymph nodes, liver, spleen, skin, or bone marrow. It is normally seen in patients with progressive illnesses such as HIV-positive individuals, or those who are in immunocompromised states. This may arise from previous reactivation of latent histoplasmosis by residing in areas where histoplasmosis is endemic or may occur from recent exposure to high fungal load.

Histoplasmosis is considered hyperendemic in the Philippines based on high histoplasmin sensitivity (26%), which is considered as above the global histoplasmin rate.[8] Histoplasmin skin sensitivity is a measure of immunity of individuals that may have been exposed to *H. capsulatum*. The prevalence rate of sensitivity may aid in the determination of endemicity of histoplasmosis in certain regions. Thus, a high histoplasmin sensitivity may indicate high incidence of exposure to this fungus, increasing the likelihood that the total number cases of histoplasmosis may be underreported.

In one study of mapping histoplasmosis in Southeast Asia, it was concluded that in the Philippines, histoplasmosis is common in HIV-negative individuals. However, few cases of disseminated histoplasmosis with cutaneous manifestations have been reported in the Philippines to date.[1-7]

It is possible that the disseminated type of histoplasmosis is underreported in the Philippines due, in part, to its overlap in features with tuberculosis. *Mycobacterium tuberculosis* infection is also endemic in the Philippines and may also present with similar pulmonary findings, as well as similar diffuse granulomatous inflammation on histology.

Cutaneous manifestations of histoplasmosis may be

polymorphous and non-specific. The diagnosis of cutaneous histoplasmosis may not be achieved based on clinical findings alone as it may exhibit significant overlap with other fungal infections. Cutaneous manifestations may occur in 4-11% of cases and result as a secondary invasion of the skin due to hematologic dissemination of infected macrophages.

In this case, an HIV-negative, and possibly non-immunocompetent individual (as he is having diabetes and dyslipidemia) developed unusual cutaneous lesions following a history of prolonged cough and lung lesions and was diagnosed as a case of disseminated histoplasmosis. This is an AIDS-defining disease and one of the major causes of mortality among HIV/AIDS patients. This case highlights the possibility of disseminated histoplasmosis in an HIV-negative individual.

Hematologic abnormalities such as anemia and thrombocytopenia may be found in patients with histoplasmosis. In a study by Smith and Utz, among 21 adults with disseminated histoplasmosis, 38% were thrombocytopenic and anemic. In cases of severe infection, *H. capsulatum* can infiltrate the bone marrow and cause thrombocytopenia, anemia, and leukopenia.[9] Similar to this patient who exhibited the exact same features, a high index of suspicion of bone marrow infiltration with fungi should be considered. Moreover, isolation and growth of *H. capsulatum* from blood or bone marrow samples via culture is the gold standard for the detection of disseminated histoplasmosis. However, bone marrow culture to isolate the organism was not done due to financial constraints.

Histoplasmosis can be detected by various laboratory-based techniques, including H&E and PAS stains of tissue.[7] Classic findings of histoplasmosis in H&E stains reveal the presence of small (2-4mm) budding oval yeasts that are frequently present in macrophages or in the tissues. Through histological examination, *H. capsulatum var. capsulatum* can be misidentified as various other fungi, including *Talaromyces marneffei, Cryptococcus neoformans, Candida glabreta, and Blastomyces dermatitidis*.[7] Careful examination of salient features such as spore size, spore shape, presence of capsule, structures/patterns formed (budding vs traverse septum vs binary fission), reactivity to PAS, cell wall thickness and type of inflammation (granulomatous and neutrophil infiltrate) are pivotal to differentiate *H. capsulatum var. capsulatum* from the aforementioned fungi.

Traditional mycological techniques are the current gold standard for confirming disseminated histoplasmosis; however, non-culture-based tests have been shown to enhance the detection of Histoplasma species. A recent meta-analysis for assay analytical efficiency in histoplasmosis discovered that test sensitivities for culture was 77% with varying sensitivity linked to sample type and laboratory treatment, for antigen detection assays, it was 95%; and for polymerase chain reaction (PCR)-based DNA detection analysis, the efficiency was 95%.[8]

Histoplasma antigen tests were found to be the most reliable approach for diagnosing histoplasmosis. Another study found that the diagnosis of disseminated histoplasmosis in hospitalized patients was facilitated by the combined use of Histoplasma blood PCR and Histoplasma urine antigen.[9] The World Health Organization (WHO) recently made recommendations for the identification, treatment, and control of disseminated histoplasmosis.[10] The antigen Histoplasma detection method is the recommended diagnostic technique in this recommendation. However, in the Philippines, PCR-based analysis and Histoplasma antigen tests are not available locally for the diagnosis of histoplasmosis.

Consensus guidelines on the management of moderate to severe histoplasmosis recommend the use of liposomal amphotericin B at 3.0 mg/kg daily for 1-2 weeks, followed by oral itraconazole 200 thrice daily for three (3) days, followed by 200 mg twice daily for 12 months. Itraconozole may be used as the treatment of choice for non-life-threatening histoplasmosis. The patient described in this case responded well to itraconazole 200 mg/day with lesions improving after four (4) weeks on itraconazole.

CONCLUSION

Disseminated histoplasmosis remains an important differential diagnosis in patients presenting with molluscum-like lesions. Due to possible fatality, if not managed promptly, it is important to have a high index of suspicion for its non-specific cutaneous lesions. Skin biopsies should always be considered in patients with cutaneous lesions of systemic mycoses, as disseminated histoplasmosis can mimic other systemic fungal infections.[11] A comprehensive workup for any possible underlying systemic disease, monitoring disease course, and a thorough understanding of morphological features of various applications of fungal culture and serological procedures may prevent delays in diagnosing disseminated histoplasmosis. In conclusion, disseminated histoplasmosis remains an important consid-

eration, even in non-endemic areas.

Histoplasma urine antigen and PCR assay are complementary to standard mycologic procedures and crucial in our clinical setting.[12] Therefore, further research should be explored in terms of newer diagnostic modalities to establish their efficacy and applicability in the local setting.

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