A Rare Case of Disseminated Histoplasmosis Mimicking Varicella in A 28-Year-Old Immunocompetent Female

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Abstract

Histoplasmosis is well-characterized as a fungal disease that more commonly occurs in North America, mostly endemic in Ohio and Mississippi river valleys. [1] The clinical spectrum of histoplasmosis ranges from asymptomatic infection to a fatal disease. Progressive disseminated histoplasmosis is typically seen in immunocompromised individuals and presents with non-specific systemic symptoms associated with cutaneous manifestations of papules and nodules.[2] We report a case of a 28-year old Filipino female with a history of exposure to soil activities months before consult. The patient presented with a 3-week history of erythematous macules, vesicles, and pustules over the face, arms, and trunk, which evolve into papules and plaques with hemorrhagic crusting. Patient was initially diagnosed and treated as a case of varicella but had no improvement with initial management. Histopathologic findings were consistent with histoplasmosis. The patient was started with oral itraconazole, but unexpectedly expired before any improvement in cutaneous symptoms were noted.

Key Words: *Disseminated histoplasmosis, Itraconazole, Nonendemic area*

INTRODUCTION

Histoplasma capsulatum is a dimorphic fungal organism found most in fertile soil contaminated by bird or bat droppings. It is most endemic in certain parts of North, Central and South America, particularly in Mississipi and Ohio River Valleys when more than 80% acquire the infection asymptomatically. [2] Transmission occurs via inhalation of spores from the soil, and infections may range from asymptomatic to the disseminated fatal type. In immunocompromised individuals, disseminated histoplasmosis occurs when cellular immunity is impaired and the organism continues to reproduce intracellularly and disseminate via lymphatic and hematogenous circulation. Patients usually present with weight loss, fever, respiratory symptoms and cutaneous lesions with different morphologies such as papules, nodules or ulcers. Untreated disseminated histoplasmosis is fatal within a few weeks of inappropriate treatment. Therefore, a prompt diagnosis and initiation of therapy is very important.[3]

Here, we present the case of a young patient with no evidence of existing immunosuppression from a nonendemic area infected by *H. capsulatum*, initially treated as a case of varicella due to its clinical presentation at the time of referral. One of the few cases of disseminated histoplasmosis in the Philippines.

CASE REPORT

A 28-year old female was admitted under the service of Internal Medicine service due to community acquired pneumonia and was referred to the service of Dermatology due to the presence of papules and plaques with hemorrhagic crusting over the face, trunk, upper and lower extremities. The patient's history started 3 weeks prior to referral when the patient had erythematous macules, vesicles, and pustules over the arms, spreading to the face and trunk which were non-pruritic and non-tender, associated with undocumented fever but no consult for the skin lesions were done. Patient claims to have exposure to a farm they visited months prior to the appearance of the lesions. During the interim, the patient noted spontaneous crusting of

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the lesions, no topical medications were applied and still no consult was done. Three days prior to referral, the patient was admitted under the service of Internal Medicine with an assessment of community acquired pneumonia, moderate risk and to consider pulmonary tuberculosis. Upon review of systems, patient had easy fatigability, generalized body weakness, unintentional weight loss, productive cough, shortness of breath, hemoptysis and low back pain. Past medical history revealed that the patient has been treated with unrecalled antibiotics as a case of Community Acquired Pneumonia, moderate risk three months prior to admission and was treated for two months with Anti-Koch's therapy for clinically diagnosed pulmonary tuberculosis. Laboratories upon admission revealed normocytic and normochromic anemia with hazy opacities in the right upper lobe on the chest xray. The patient was initially assessed by the service of Dermatology as a case of varicella based on the clinical history of vesicles and pustules over an erythematous base which spontaneously evolved into crusted papules, and was given Acyclovir 800 mg five times a day for one week with noted no progression of the lesions, Hence, team then signed out from the case. However, one month interval history showed no evolution of some the lesions to crusted nodules and plaques, hence, patient was referred back to Dermatology.

The initial cutaneous examination revealed multiple, well-defined, erythematous papules with hemorrhagic crusting over the face and trunk. (Figure 1) associated with slightly pale palpebral conjunctiva. The rest of the physical examination was unremarkable. The patient had symmetric chest expansion with clear breath sounds, as well as a normal neurologic examination. Upon the 2nd referral, patient now had multiple, discrete, crusted papules, nodules and plaques scattered all over the body, predominantly the face, some with erythematous borders (Figure 2)

During admission, complete blood count revealed normocytic normochromic anemia and thrombocytopenia. The chest xray revealed hazy opacities in the right upper lobe, suggesting pneumonia, but could not rule out presence of tuberculosis. Sputum Gram stain, culture and sensitivity revealed gram (+) pairs and tetrads, isolating *Streptococcus sp*. while the acid fast bacilli sputum test turned out negative. HIV screening also tested negative. The rest of the laboratories were unremarkable.

Initially, during the course of admission, the patient was noted to be stable without subjective complaints. However, despite treatment with Meropenem, anti-Koch's therapy, blood transfusion and ferrous sulfate, she became febrile again with associated tachycardia, crackles over the right lung field and grade I bipedal edema. On further workup, she still had normocytic, normochromic anemia with the peripheral blood smear revealing mildly hypochromic and slightly anisopoikilocytic erythrocytes with decrease platelets. In addition, fecal occult blood test turned positive, she had increased total and direct bilirubin, and her chest xray suggested progression of the pneumonia bilaterally with consolidation to the right.

Skin punch biopsy was done over the face and abdomen revealing diffuse granulomatous infiltrates composed of multinucleated giant cells, lymphocytes, plasma cells, and neutrophils. Interspersed within these infiltrates are small, round spherules with an artefactual halo. The dermatopathology report was signed out as diffuse granulomatous infiltrate suggestive of systemic mycosis, specifically histoplasmosis (Figure 3). Other stains were requested to confirm the diagnosis. Periodic acid-Schiff stain turned out to be negative for visualizing the fungal cell wall (Figure 4) while Giemsa and Gomori's Methenamine Silver stains turned out to be positive for intracellular clusters of budding yeast and fungal capsule, respectively. (Figure 5 and 6)

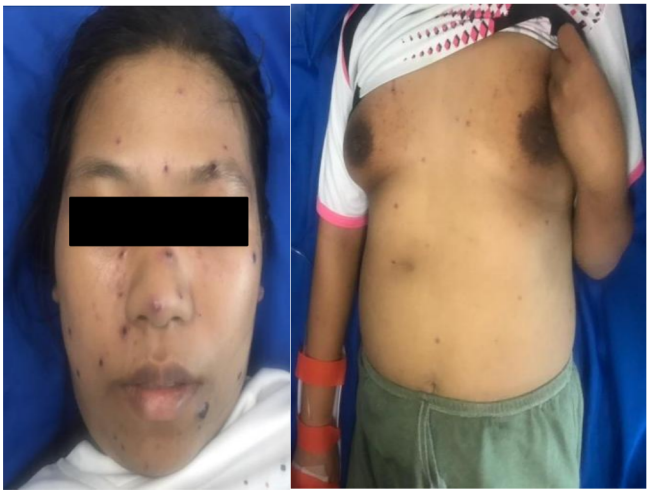

Figure 1. First Referral (February 26, 2020) Patient presenting with multiple, well-defined, erythematous papules with hemorrhagic crusting over the face and trunk

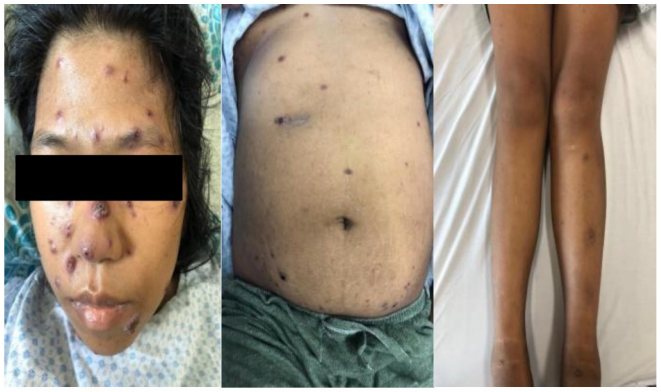

Figure 2. Second Referral (March 21, 2020) Patient with multiple, discrete, erythematous to violaceous papules, nodules and plaques with hemorrhagic crusting, scattered all over the body, predominantly the face, some with erythematous borders

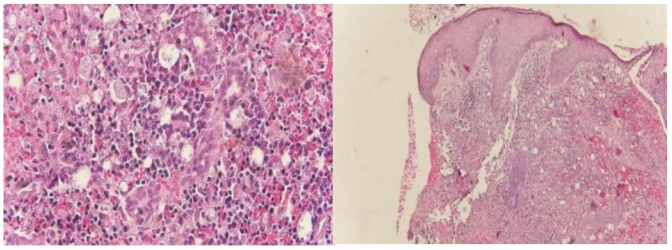

Figure 3. H&E Staining

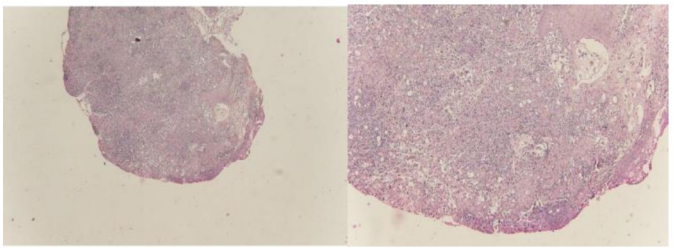

Figure 4. PAS Staining

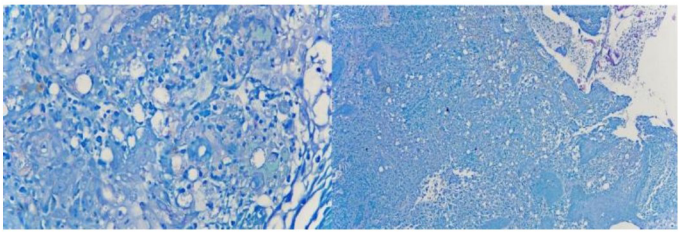

Figure 5. Giemsa Staining

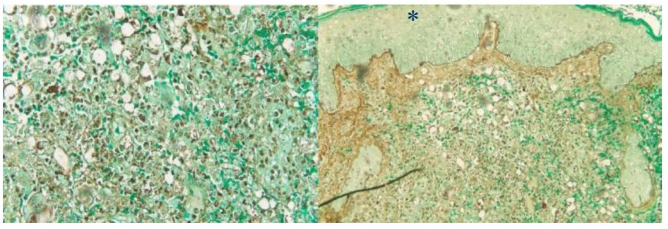

Figure 6. GMS Stain

Overall, based on the history, physical examination, diagnostics, and histopathologic examination, all led to the diagnosis of disseminated histoplasmosis.

The plan was to initiate Itraconazole 200 mg per capsule three times a day and shift to Itraconazole twice a day indefinitely. However, patient expired a day before initiating therapy due to respiratory failure secondary to aspiration pneumonia.

DISCUSSION

Histoplasma capsulatum is a soil saprophytic fungi that usually produces a subclinical infection that may present as asymptomatic, but some may occur as an acute or progressive disorder, disseminated, or chronic disease. [4] Histoplasmosis is globally distributed, although thought to occur more commonly in North America, mostly endemic in Ohio and Mississippi river valleys. In the Philippines, at least nine cases of Histoplasmosis have been reported and presented mainly as papulonodular lesions with umbilication or as ulcerated plaques. [1]

None of the cases reported mentioned a papulovesicular eruption mimicking the lesions of varicella. A study by Bulmer, et al, revealed that atleast 26% of test subjects tested positive for histoplasmin hypersensitivity, revealing that *Histoplasma capsulatum* is sufficiently present in the Philippines to come in contact with one-fourth of the test population.[5] Histoplasma is a dimorphic fungus that is widespread and is able to grow between 15 and 20 ˚C, and when nitrogen content is high. Human infection usually follows

inhalation of fungal aleurioconidia which changes into a pathogen yeast. This causes an asymptomatic or acute, self-limiting respiratory infection. On the other hand, immunocompromised patients infected with *H. capsulatum* may spread through the blood stream involving the reticulo-endothelial system causing a systemic disease. The main risk factors of acquiring histoplasmosis are exposure to sites likely to acquire high levels of *H. capsulatum* mold such as chicken coops, bird roots, and bat droppings, and a concurrent state of immunosuppression such as having HIV/AIDS with a CD4 count of <150cells/uL. For this patient, a history of visit to a farm in Antipolo may be associated with inhalation of the fungi.

The clinical features of disseminated histoplasmosis are usually non-specific, presenting as fever, weight loss, hepatosplenomegaly, lymphadenopathy, cough with pulmonary infiltrates, pancytopenia and hypergammaglobulinemia, and is usually misdiagnosed as visceral leishmaniasis, military tuberculosis, or lymphoproliferative malignancies. Cutaneous involvement usually presents in about 20% of cases.[2] The most frequent disease-related cutaneous manifestations seen in HIV-seronegative patients include exfoliative erythroderma, petechiae, purpura and ecchymoses mostly occurring over the face, arms and trunk.[6] One case of an immunocompetent male with a history of motorcycle accident presented with a solitary nodule that evolved into a nonhealing ulcer revealed to be a case of cutaneous histoplasmosis.[15] Another case report of an immunocompetent male with exposure to bird droppings presented with multiple skin-colored to erythematous papules of varying sizes over the body.[16] There was also one rare case of disseminated histoplasmosis in an HIV positive patient where the patient simulates a case of varicella as papulovesicular lesions.[17] The diverse morphology of histoplasmosis should prompt biopsy in immunocompromised patients presenting with these lesions. [7]

The pathogenesis of disseminated histoplasmosis starts from inhalation of the microconidia. The changes in temperature towards the alveoli facilitates the mycelial-to-yeast phase which is the pathogenic form of *H. capsulatum*, causing the acute disease, or it becomes latent, being able to reemerge once the patient is in a state of immunosuppression. The phagocytised yeasts replicate within macrophages within which they can disseminate hematogenously, utilizing the macrophage's phagosome as a vehicle to translocate to hilar or mediastinal lymph nodes. T cells produce interferon gamma to assist macrophages in killing the organism, while IL-12 and TNF-α play an essential role in cellular immunity. In immunocompetent hosts, granulomas are formed to contain the organism, which eventually fibrose and calcify. While in immunocompromised individuals, the infection is not contained and can disseminate. [11]

Although excellent laboratory methods are widely available, diagnosing histoplasmosis in nonendemic areas in an immunocompetent individual remains a challenge. A proven diagnosis of histoplasmosis is done by confirmation either through histopathology or culture while a probable diagnosis is based on the presence of an appropriate clinical presentation, a predisposing condition and mycological evidence such as presence of antigen in urine. The identification of *H. capsulatum* through culture is the gold standard in the diagnosis of histoplasmosis, however, may take up to 2 weeks to 8 weeks. Histopathology supports the diagnosis and may reveal ovoid yeast cells that have thin, non-refractile cell walls with characteristic narrow base budding, with yeast predominantly found phagocytized within macrophages and histiocytes. The use of histochemical stains facilitates the differentiation of pathogens, with the Gomori methenamine silver (GMS) and periodic acid-Schiff (PAS) stains being used to visualize the cell wall. Antigen testing and serology are also available, with the former proven to be more sensitive and easier to interpret. One of the emerging non-invasive diagnostics is testing the presence of antigen in urine which appears to have a similar specificity and sensitivity with culture.[13] Finally, molecular methods such as PCR may be proving to be more sensitive than fungal culture but is limited by its availability in the laboratories. [9]

The first line agent for patients who have mild or moderately severe symptoms of disseminated histoplasmosis is oral itraconazole 200 mg three times a day for 3 days then twice a day for around 6 to 18 months of treatment in total.[10] In our case, itraconazole 200 mg three times a day was ordered since the patient was

relatively stable without the need for mechanical ventilation at the time of referral.

Generally, acute histoplasmosis has a good prognosis. However, risk factors such as immunosuppression, age >54 years old, or infancy were associated with fatal or disseminated histoplasmosis. One rare case reported of a 13 year old female with no history of immunosuppression was admitted for 16 days and was being worked up for lymphoma died without initiating treatment.[18] Untreated disseminated histoplasmosis has a 90% fatality rate. [12]

CONCLUSION

In summary, we report a case of a 28-year old Filipino female who presented with a 3-week history of vesicles and pustules surrounded by an erythematous base which spontaneously ruptured and dried with crusting over the face, arms and trunk, mimicking a resolving case of varicella, which later evolved into papules, nodules and plaques with crusting. Histopathologic findings revealed findings consistent with histoplasmosis. Unfortunately, the patient expired when the appropriate management was just started. Due to the rarity of the disease and fatality once unable to be managed promptly, it is important to have a high index of suspicion for these kinds of lesions. A complete work-up for identifying any possible underlying systemic disease/s, monitoring disease activity, and most importantly preventing delay in diagnosis such as performing a skin punch biopsy, culture and antigen testing.

RECOMMENDATION

First, histoplasmosis can mimic a common benign disease such as varicella so performing a biopsy should always be considered in patients not showing improvement in the initial mode of treatment.

Second, to address the difficulty in obtaining fungal cultures, which is the gold standard in diagnosing histoplasmosis, urine antigen testing may be done in suspected cases to avoid delay in diagnosis which is proving to be similar in sensitivity and specificity with faster results.

Third, this could be an area of research where further researchers may dwell into performing newer diagnostic modalities available in order to promptly diagnose a patient with histoplasmosis and to prevent delay in the management.

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