Umbilicated papules on the bilateral upper and lower extremities

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Abstract

Cryptococcosis is a rare opportunistic infection with morphologically diverse cutaneous presentations. Primary infection typically occurs in the lungs with subsequent hematogenous dissemination to other organ systems, especially in immunocompromised patients. Herein, we report a woman in her 70's who presented with pruritic, umbilicated papulonodules of the bilateral upper and lower extremities present for many weeks. She was diagnosed with disseminated *Cryptococcus* and subsequently evaluated for potential pulmonary and meningeal disease involvement. She died as a result of multiple medical comorbidities.

Keywords: cryptococcosis, papulonodules

Introduction

Disseminated cryptococcosis is an opportunistic infection, which is common in immunocompromised patients such as individuals living with human immunodeficiency virus [1]. Its cutaneous presentation is morphologically variable, though it may be recognized by notable, umbilicated papulonodules. Histopathology shows a characteristic encapsulated yeast organism. A case of disseminated cryptococcosis is presented.

Case Synopsis

A 72-year-old hospitalized woman with a history of type two diabetes mellitus, stage four chronic kidney disease, and end-stage liver disease related to nonalcoholic steatohepatitis cirrhosis developed a pruritic rash on her lower extremities, upper extremities, and groin. She reported vigorous scratching for many weeks and had been discharged for right upper extremity cellulitis days before this hospital admission. She denied malaise, headache, neck stiffness, photophobia, nausea, or vomiting. She reported living in a rural area and stated she was concerned for mold growth in her basement. She said her basement had recently flooded and the excess water was not cleared. As a result, boxes were friable with significant dirt and debris. She denied a history of chemotherapy or immunosuppression.

Her physical examination was significant for umbilicated, crusted pink papules and papulonodules predominately on the bilateral lower extremities (**Figure 1A)** with few scattered, morphologically identical papulonodules on her bilateral upper extremities (**Figure 1B)**. She also had erythematous plaques on her bilateral arms with bright red, macerated plaques with satellite lesions in the bilateral groin extending onto the mons pubis. A biopsy of the right upper arm was performed, which showed a spare neutrophilic and focally granulomatous infiltrate (**Figure 2A)**. Grocott methenamine silver stain of the specimen revealed pleomorphic yeasts in the area of granuloma formation (**Figure 2B)**. A fungal culture was obtained, which was positive for *Cryptococcus neoformans*. Thus, the patient was diagnosed with disseminated *Cryptococcus* with concurrent *Candida albicans* intertrigo of the groin. The infectious disease service was immediately consulted to discuss systemic treatment. She also underwent chest

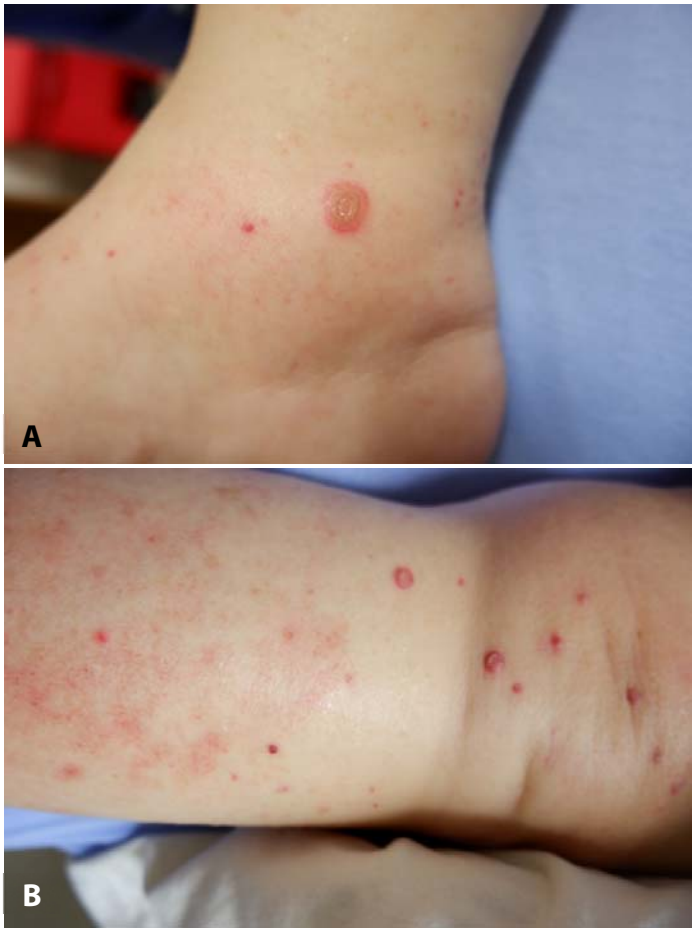

Figure 1. ***A)*** *Umbilicated, crusted pink papules of the lower extremities.* ***B)*** *Umbilicated pink papules of the upper extremities.*

imaging for pulmonary involvement and a potential lumbar puncture to exclude meningeal involvement.

A lumbar puncture was performed, which was positive for cryptococcus antigen in her cerebrospinal fluid (1:640). A chest X-ray was also performed, which showed diffuse patchy and nodular consolidative opacities throughout the bilateral lungs. She was treated with amphotericin B, 3mg/kg for disseminated cryptococcosis. She was also started on lactulose and rifaximin for worsening hepatic dysfunction.

Two days later, she developed acute encephalopathy and respiratory failure. She was transferred to the intensive care unit and required emergent intubation for increased work of breathing and airway protection. At the intensive care unit she developed pulmonary alveolar hemorrhage and her renal function declined; she was started on continuous renal replacement therapy. Her encephalopathy progressed and she developed hypothermia, coagulopathy, and hemodynamic instability, requiring multiple pressor medications. Her code status was changed to do not resuscitate with comfort care and she was extubated. Ultimately, she died 5 days after admission.

Case Discussion

Cryptococcosis is an opportunistic infection caused by the encapsulated yeast, *Cryptococcus neoformans*. Primary infection typically occurs in the lungs with subsequent hematogenous dissemination to the central nervous system, bone, and skin, especially in immunocompromised individuals [1]. Primary cutaneous cryptococcosis with skin lesions but without systemic involvement is uncommon but may occur when patients are exposed to environments with soil or vegetative debris contaminated with bird feces in the setting of skin wounds [2]. Our patient's flooded basement with abundant dirt and debris represents a significant environmental risk factor for the development of cryptococcosis. Twede et al. reported the case of a 28-year-old, immunocompetent Iraq war veteran

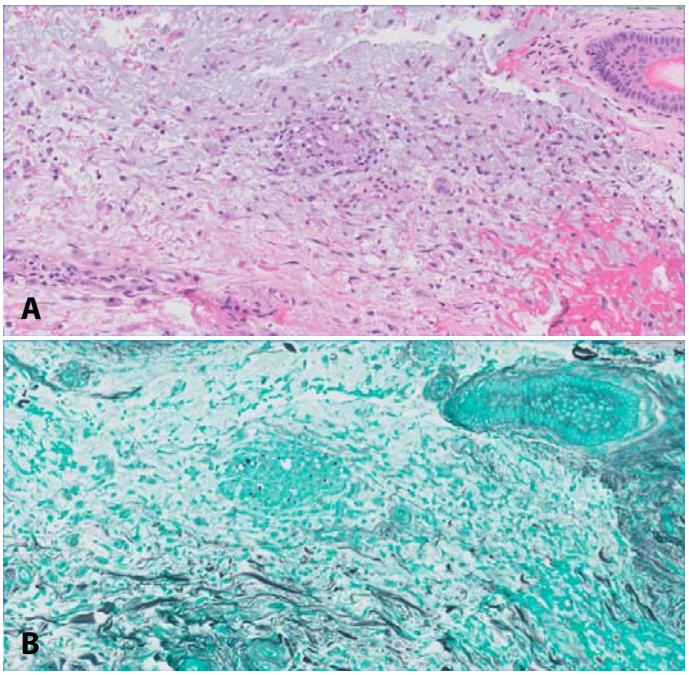

Figure 2. ***A)*** *Histopathology demonstrating a neutrophil and lymphocyte rich infiltrate. H&E, 400×.* ***B)*** *Histopathology revealing pleomorphic yeasts in the area of granuloma formation. Grocott methenamine silver, 400×.*

who presented with primary cryptococcosis of the lower legs but lacked systemic involvement and improved with oral fluconazole [3].

Cryptococcosis can present with myriad cutaneous manifestations including pustules, ulcers, granulomas, abscesses, nodules, draining sinuses, and cellulitis [4]. However, in our patient the umbilicated papulonodules suggested a distinct etiology from her existing intertrigo. Punch biopsy was important for pathological correlation by identification of findings consistent with an infectious process.

Umbilicated papules represent the most common clinical presentation for cryptococcosis. The differential diagnosis for such lesions also includes molluscum contagiosum, which is significantly more common. Cryptococcosis shares many features with molluscum contagiosum including a preponderance for immunocompromised individuals such as HIV-seropositive patients [5]. However, the distribution of lesions, specifically perioral umbilicated papules, can be pathognomonic for cryptococcosis [6]. In addition, patients with cryptococcosis often report exposure to contaminated environments that patients with molluscum contagiosum may not. Case reports have also identified cases of cryptococcosis clinically mimicking other dermatologic diseases including necrotizing fasciitis [7], keloid [8], and basal cell carcinoma [9]. Thus, a broad differential diagnosis is essential for patient evaluation and management to avoid missed diagnosis.

Rapid touch preparation, “touch prep” or "crush prep," analysis of skin punch biopsy specimen may be helpful in differentiating between cryptococcosis and other dermatologic conditions, namely molluscum contagiosum [10, 11]. Touch preparation has been used extensively for hematologic and solid malignancies but has more recently been applied to the diagnosis of invasive cutaneous infections [12]. Touch preparation is significantly faster than tissue culture and pathology interpretation and may therefore enhance speed of diagnosis. Early intervention is important in opportunistic infections, which may cause significant morbidity and mortality for immunocompromised patients. Although the gold standard for diagnosis of opportunistic infection remains tissue biopsy specimen and species confirmation by culture, touch preparation is a valuable bedside diagnostic tool when cryptococcosis is a diagnostic possibility.

Meningoencephalitis is the most frequent clinical manifestation of cryptococcosis and cerebral spinal fluid analysis is indicated for patients with central nervous system symptoms such as headache, tremor, seizures, paralysis, hyperreflexia, or slurred speech.

This case reveals that cutaneous features, specifically diffuse, umbilicated papulonodules, may suggest a diagnosis of disseminated *Cryptococcus* when characteristic neurological features are absent. Our patient ultimately developed acute encephalopathy after diagnosis of disseminated cryptococcosis, although her underlying hepatic dysfunction likely contributed to neurologic disease progression. Although patients may lack classic risk factors, prompt recognition of skin signs can mitigate systemic organ involvement and expedite treatment.

Conclusion

This case highlights cryptococcosis as a rare, but potentially life-threatening opportunistic infection. Fungal culture demonstrating the classic encapsulated yeast is often necessary for diagnosis given its myriad of cutaneous presentations. Patient comorbidities can complicate successful treatment of disseminated cryptococcosis.

Potential conflicts of interest

The authors declare no conflicts of interests.

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