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Case Presentation

A case report of primary cutaneous histoplasmosis requiring deep tissue sampling for diagnosis

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Abstract

Importance: This is a case of primary cutaneous histoplasmosis, without any systemic involvement, that occurred without a history of trauma. Due to its rarity and varied clinical presentation, there is much difficulty in diagnosis of this disease entity, especially in differentiating it from pyoderma gangreosum. This patient required deep tissue sampling and a DNA probe for Histoplasma to establish a time-sensitive diagnosis as multiple superficial biopsies are nondiagnostic.

Background

Cutaneous histoplasmosis lesions are rare but when present are divided into primary and secondary lesions [1]. Secondary cutaneous lesions occur in cases of disseminated infection. Disseminated infections usually occur in immunosuppressed patients with human immunodeficiency virus, cancer, leukemia, lymphoma, diabetes, collagen vascular disease, renal transplants or patients on anti-TNF alpha therapy [2]. Primary cutaneous histoplasmosis without evidence of systemic infection is extremely rare and has been reported in only a few cases [2-10]. We present a case of 34-year-old Caucasian male who presented with extensive necrosis and ulceration of his right thigh and required a deep tissue biopsy with a histoplasmosis DNA probe assay (after several nondiagnostic punch biopsies) to render a diagnosis of primary cutaneous histoplasmosis.

Case synopsis

A 34-year-old Caucasian male was admitted to the hospital with new onset, worsening edema, pain and erythema of his right thigh. The patient had a past medical history of osteoarthritis, hypertension, gastroesophageal reflux disease, depression, restless leg syndrome and systemic lupus erythematosus. Past medications included cimetidine, hydroxychloroquine, mycophenolate, ropinirole, escitalopram, lisinopril, and prednisone. On examination, the patient had an erythematous, indurated area covering most of his right upper thigh with a six-centimeter necrotic black area at the inferior edge of the induration. Subcutaneous tissue, including fat, was exposed in the necrotic area (Figure 1). Right inguinal lymphadenopathy was also noted.

A computed tomography scan of the right thigh showed dermal and soft tissue damage without pyomyositis or myonecrosis. Punch biopsy revealed ulceration with extensive necrosis and neutrophilic infiltrate. There was no evidence of vasculitis. Periodic acid-schiff, acid-fast bacillus, sulfated Alcian blue and Congo red stains were negative. Aerobic, anaerobic, and fungal cultures were also negative. HSV I-II immunohistochemical stain and direct immunofluorescence were negative as well. Repeat punch biopsy showed superficial and deep lymphoplasmocytic inflammation with giant cells and underlying necrosis. The patient’s prednisone was increased to 80mg for ten days, and the patient received azathioprine 50 milligrams twice daily and intralesional
and intramuscular Kenalog for presumed pyoderma gangrenosum. Resolution of the necrotic area occurred, but the erythematous induration did not resolve.

**Figure 1.** Erythematous and indurated area evident with a six-centimeter necrotic area.

**Figures 2-3.** H&E stain showing dermal and panniculic necrosis

**Figure 4-5.** Methenamine silver stain showing 2-6 μm narrow based yeast compatible with Histoplasma capsulatum.
Due to the spread of induration to the groin and return of necrosis, a deep tissue biopsy extending through the fat to fascia was performed. This biopsy showed dermal and pannicular necrosis (Figures 2-3) associated with multiple small narrow-based budding yeasts on methenamine silver and periodic acid-Schiff stains (Figures 4-5). The morphology of the yeast was suggestive of *Histoplasma capsulatum*. Most importantly, *Histoplasma capsulatum* was confirmed by the DNA probe method. *Histoplasma* was further confirmed by positive culture two weeks later. Urine antigen and serologic assays for histoplasmosis were performed to rule out systemic infection, and both were negative. The patient did not report any current or historical systemic symptoms and did not have any clinical signs suggestive of systemic infection.

Using the results of the DNA probe (as the culture results had not come back yet), the patient was treated with oral Itraconazole 200 milligrams twice daily for a total of eight weeks with regression of thigh induration and necrosis. His wound has completely healed with severe scarring (Figure 6) and no systemic or local recurrence of histoplasmosis for over one year.

**Discussion**

This case highlights the fact that in some cases repeat biopsy with deeper tissue sampling extending into the fat may be necessary for definitive diagnosis. The patient was repeatedly mistreated for pyoderma gangreosum as numerous superficial punch biopsies did not yield evidence of the deep mycosis. Furthermore, a DNA probe for *Histoplasma capsulatum* was also done to render a diagnosis in a time sensitive manner as fungal culture results can take multiple weeks to come back. It was due to rapid diagnosis via DNA probe that antifungal therapy was started in a timelier manner in this patient.

*Histoplasma capsulatum* is a saphrophyte found in the soil in the central, southeast and mid-Atlantic regions of the United States[11]. Infection is commonly acquired via airborne transmission of aerosolized microconida, leading to the first four disease patterns [12]. Cutaneous lesions occur in the chronic disseminated subtype via hematogenous spread but are extremely rare [11]. On rare occasions, cutaneous lesions can occur after direct percutaneous inoculation [12].

Typically, a history of a puncture wound or injury to the skin helps aid in the diagnosis of primary cutaneous histoplasmosis and differentiates it from disseminated histoplasmosis [13]. Papules, plaques, punched-out ulcers, purpuric lesions, abscesses, impetigo, local dermatitis, or generalized dermatitis at the site of inoculation may be the presenting sign [1, 14]. The diagnosis of primary cutaneous histoplasmosis should not be made until disseminated infection has been ruled out. Measurement of the histoplasmosis antigen in urine and blood can be considered to rule out disseminated histoplasmosis infection. In order to establish a diagnosis, diagnostic procedures such as a skin biopsy, histoplasmin skin test, serologic tests, complement fixation test, fungal and bacterial cultures, and smears of the exudate stained with special stains are important [1].
The histopathology is an especially important component of establishing the correct diagnosis. A diagnosis of histoplasmosis is likely if 2-4 μm, oval, narrow-based budding yeasts are present on with methenamine silver or periodic acid-Schiff stains. The organism can be found both in the macrophages and freely within the tissue. Cutaneous deep mycosis can also result in granuloma formation [15].

Prior reports have established criteria for diagnosis of primary cutaneous histoplasmosis: 1) history of traumatic inoculation, with development of a chancriform lesion within three to four weeks at area of trauma, 2) cultural evidence of fungus in wound, 3) development of lymphangitis and regional lymphadenopathy, and 4) no history or clinical or laboratory evidence of previous pulmonary or systemic mycosis [2]. The patient met all of the criteria outlined above except for the history of traumatic inoculation.

Therapeutic options for cutaneous histoplasmosis depend on the extent and severity of the disease. For localized treatment, topical antifungal therapy with nystatin and amphotericin B has been reported to be effective [3]. For wide spread areas, oral and intravenous therapy has been beneficial [4,11,13]. Itraconazole and fluconazole have also been used to treat primary cutaneous histoplasmosis [14]. Spontaneous remission has been reported in limited disease [7].

Primary cutaneous histoplasmosis can be difficult to diagnose due to its rarity as well as its varied clinical presentation. It can easily be misdiagnosed and mistreated as pyoderma gangrenosum when superficial biopsies are not diagnostic. Thus, deep tissue biopsies with DNA probe assays for *Histoplasma capsulatum* should be considered if superficial biopsies are unyielding and a deep mycosis is suspected.

**References**