Cutaneous blastomycosis masquerading as pyoderma gangrenosum

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Abbreviations: ARDS=acute respiratory distress syndrome; BAL=bronchoalveolar lavage; PG=pyoderma gangrenosum;
Abstract

Cutaneous blastomycosis (CB) is associated with a variety of skin manifestations. Among other entities, CB may be mistaken for pyoderma gangrenosum due to overlap of findings on histopathologic examination. We report a case of CB, initially diagnosed as pyoderma gangrenosum and treated with steroids, leading to disseminated blastomycosis and ARDS.
Case report

A 30-year-old male with a history of presumed pyoderma gangrenosum of the left foot treated with high-dose prednisone was transferred from an outside hospital to our intensive care unit with respiratory distress. Exposure history included working outdoors and landscaping. He was initially treated with non-invasive mechanical ventilation, but developed worsening hypoxemia requiring endotracheal intubation for mechanical ventilation. Chest x-ray demonstrated diffuse bilateral mixed alveolar and interstitial opacities with increased confluence in the left lung consistent with acute respiratory distress syndrome (ARDS). An urgent bronchoscopy was performed. Cytologic examination of the bronchoalveolar lavage (BAL) fluid demonstrated abundant broad-based budding yeast, consistent with *Blastomyces dermatitidis* (Fig 1A & B). *Blastomyces* urine antigen was measured at >14.7 ng/ml. Intravenous amphotericin B deoxycholate [1 mg/kg/day] was started in addition to methylprednisolone (125 mg IV every 6 h) for severe disseminated blastomycosis and ARDS[1, 2]. The patient was placed on RotoProne bed therapy for refractory hypoxic respiratory failure. The hypoxemia improved gradually.

He was ultimately extubated, transitioned to oral itraconazole (400mg twice daily), and discharged home 53 days after admission. Culture of BAL fluid eventually grew *B. dermatitidis*, which was confirmed by DNA probe [Gen-Probe, Inc., San Diego, CA]

Four months prior to this admission, the patient had noted a painful blister on the medial aspect of his left mid-foot, which progressed to an ulcer. A punch biopsy of the lesion revealed acute and chronic inflammation with necrosis, possibly representing PG. This biopsy specimen was not submitted for
The patient was treated with 100 mg prednisone, orally, with some improvement of the lesion. Later, the slides from this biopsy were retrieved and reviewed by our pathologists, who identified yeast consistent with *Blastomyces dermatitidis* (Fig 1 A, B, C, & D).

Cutaneous blastomycosis usually occurs after hematogenous dissemination from a primary pulmonary infection, even in the absence of overt pneumonia [3]. Much less commonly, *Blastomyces dermatitidis* can be directly inoculated into the skin, resulting in cutaneous inoculation blastomycosis [4]. These skin lesions are most often described as verrucous or ulcerative, however, a broad variety of presenting lesions have been described, including, nodules, pustules, papules, and abscesses [4, 5]. The variety of skin manifestations combined with the presence of suppurating granulomas on histopathological examination has led to multiple reports of initially misdiagnosed cutaneous blastomycosis [3, 4, 6]. Most often implicated are granulomatous skin processes, such as scrofuloderma, lupus vulgaris, and granuloma inguinale. Other misdiagnoses include nocardiosis, syphilis, tuberculosis, and endemic mycoses, as well as squamous cell carcinoma and arthropod bite reactions [3, 4, 7]. Our patient was initially diagnosed with PG.

*Pyoderma gangrenosum* is a non-infectious neutrophilic dermatosis that presents as an inflammatory skin lesion progressing to a hemorrhagic pustular ulcer. It is most often associated with underlying systemic disorders, including inflammatory bowel disease, malignancies, arthritides, and hematologic
dyscrasias [8]. Though there are no pathognomonic clinical or histopathologic
features of PG, pathology specimens often exhibit a sterile dermal neutrophilia,
with accompanying chronic inflammation, and at times, intradermal abscess and
granuloma formation. The clinical and histopathologic overlap with cutaneous
blastomycosis, may lead to misdiagnosis, particularly in cases where the
characteristic yeast forms are not identified. Of note, a condition called
blastomycosis-like pyoderma can present as vegetating skin lesions similar to
blastomycosis and pseudoepitheliomatous hyperplasia with abscesses on tissue
biopsy specimen. It occurs most commonly in the immunocompromised host and
is related to infection with common bacterial skin pathogens not fungi [9]. We
found two other reported cases of cutaneous blastomycosis misdiagnosed as PG
(Table 1). In both cases, a work-up for systemic diseases associated with PG
yielded negative results and corticosteroids were initiated, by subcutaneous
injection into the ulcer and/or systemic delivery. In all three cases, inadvertent
iatrogenic immunosuppression likely led to clinical worsening, with an especially
devastating effect in our patient. Though our patient first presented with a skin
lesion, it is much more likely that this was due to secondary dissemination from
an asymptomatic lung infection rather than a primary cutaneous inoculation
event, since the latter is a much rarer occurrence. We cannot ascertain this
because no chest imaging was performed at the time of evaluation for the skin
lesion.

In areas where Blastomyces dermatitidis is endemic, the differential diagnosis of
PG should include cutaneous blastomycosis and should prompt a thorough
investigation, including specific fungal stains such as the Gomori methenamine
silver and the Periodic acid-Schiff stains and cultures of the skin biopsy, in
addition to work-up of concomitant pulmonary infection. Detection of Blastomyces antigen in urine or serum can also be useful in such a scenario [10-12]. The inquiry should be completed prior to initiation of steroids, in order to prevent iatrogenic worsening of cutaneous fungal infection, and/or systemic dissemination.
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<tr>
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<tbody>
<tr>
<td>Age, Sex, Site</td>
<td>26, F, Right palm</td>
<td>63, M, Right thigh</td>
<td>30, M, Left mid-foot</td>
</tr>
<tr>
<td>Exposure history</td>
<td>Lesion appeared after a splinter implantation</td>
<td>Forestry worker and recreational boatsman</td>
<td>Working outdoors, landscaping, effluent from a broken sewage pipe in the home</td>
</tr>
<tr>
<td>Location endemic for blastomycosis</td>
<td>Yes (Rural South Carolina)</td>
<td>Yes (New Brunswick, Canada)</td>
<td>Yes (Indiana)</td>
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<tr>
<td>Immunocompromising condition</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Gross description of skin lesion</td>
<td>Multiple vegetative plaques with a friable verrucous surface</td>
<td>Purplish, multifocal, boggy dermal plaque with overlying crusted scale</td>
<td>Deep ulcer with pale irregular borders, some granulation tissue at margins</td>
</tr>
<tr>
<td>Features on histopathologic examination</td>
<td>Pseudoepitheliomatous hyperplasia without evidence of vasculitis</td>
<td>Necrotizing granulomas</td>
<td>Necrotizing granulomas with acute and chronic inflammation</td>
</tr>
<tr>
<td>Fungus noted on initial histopathological examination</td>
<td>No Special stains for fungi and acid-fast bacilli were reported to be negative</td>
<td>No Special stains did not reveal fungi</td>
<td>No No special stains were performed</td>
</tr>
<tr>
<td>Fungus noted on subsequent histopathological examination</td>
<td>Yes Review of initial skin</td>
<td>Unear Repeat skin biopsy</td>
<td>Yes Review of initial skin</td>
</tr>
<tr>
<td>Examination</td>
<td>Biopsy Specimen revealed multiple budding organisms suggestive of blastomycosis</td>
<td>was done but it is not reported if fungus was directly visualized.</td>
<td>Biopsy Specimen revealed multiple budding organisms suggestive of <em>Blastomyces dermatitidis</em>.</td>
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<tr>
<td>Positive Culture</td>
<td>Yes (on repeat culture)</td>
<td>Yes (on repeat culture)</td>
<td>Yes</td>
</tr>
<tr>
<td>Initially Treated with Steroids</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Worsening of Skin Lesions after Steroids</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Dissemination after Steroids</td>
<td>Likely</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Pulmonary Illness</td>
<td></td>
<td></td>
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<tr>
<td>Antifungal Treatment</td>
<td>Itraconazole 200mg daily</td>
<td>Itraconazole 200mg daily</td>
<td>Amphotericin B for disseminated blastomycosis followed by Itraconazole 400mg twice daily</td>
</tr>
<tr>
<td>Outcome</td>
<td>Resolution</td>
<td>Resolution</td>
<td>Ongoing improvement</td>
</tr>
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References:


A, Diff-Quik stain of the BAL specimen demonstrating the broad-based budding yeast of *Blastomyces dermatitidis*. B, The same specimen stained by the Gomori methenamine silver stain method. The double walls of the yeast-form of this dimorphic pathogen are clearly demonstrable in both stains (bar for A & B, 20 \( \mu m \)). C, Low-power (original magnification, X100) examination of a hematoxylin and eosin-stained skin biopsy demonstrates pseudoepitheliomatous hyperplasia and a predominately neutrophilic inflammatory infiltrate. D, High-power magnification (original magnification, X400) of the skin biopsy reveals a broad-based budding yeast cell and adjacent yeast with thick, double refractile walls within a multinucleate giant cell (bar, 10 \( \mu m \)).