Non-healing wound from disseminated blastomycosis

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Blastomycosis is a relatively rare fungal infection. Yearly incidence rates are reported to be 1 to 2 cases per 100,000 population in certain states where it's reported. It is a potentially fatal infection that often occurs as a primary pulmonary infection and after lymphohematogenous spread presents with cutaneous ulcerations. The authors report a case of disseminated blastomycosis that originally manifested as a cutaneous lesion rapidly turning into a chronic wound.

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Blastomycosis is a relatively rare fungal infection. Yearly incidence rates are reported to be one to two cases per 100,000 population in states in the US where it is notifiable (Centers for Disease Control and Prevention [CDC], 2019). It is a potentially fatal infection resulting in 2.9 hospitalisations per 100,000 person-years and was the cause of 1,216 deaths in the US between1990 and 2010 (Khuu et al, 2014; Seitz et al, 2014).

Evidence suggests that *Blastomyces (B.) dermatitidis* exists in wet earth that has been enriched with animal droppings, rotting wood and other decaying vegetable matter. Disruption of wet soil or organic matter releases the infectious conidia and airborne inhalation by a susceptible host is by far the most common route of transmission (Saccente and Woods, 2010). Active pulmonary defenses in alveolar macrophages inhibit the transformation of conidia to yeast form. When they fail, lymphohematogenous dissemination triggers a suppurative response followed by non-caseating granuloma formation (Saccente and Woods, 2010; Brick et al, 2013). Skin lesions are almost always a primary site of clinical manifestation of disseminated infection. However, it can involve organs other than the skin, such as bone, genitourinary tract, and central nervous system in descending frequency (Bradesher, 1997). It has the potential to affect nearly every organ system during chronic disease (Mercurio and Elewski, 1992; Chapman and Sullivan, 2010). Primary cutaneous blastomycosis is quite rare, but has been reported to occur after direct inoculation from an outdoor injury or an animal bite in endemic areas (Gray and Baddour, 2002; Saccente and Woods, 2010). A total of 22 cases were reported in a major literature review by Gray and Baddour of reported cases from 1903 to 2002 (Gray and Baddour, 2002). Rare incidences of direct contact or intrauterine transmission have been documented. *B. dermatitidis* is not transmitted from person to person, and thus, blastomycosis is generally not contagious (Saccente and Woods, 2010).

The differential diagnosis of cutaneous blastomycosis is wide and includes scrofuloderma, lupus vulgaris, squamous cell carcinoma, keratoacanthoma, cutaneous tuberculosis, nocardiosis, syphilis, bromoderma, iododerma, granuloma inguinale, pyoderma granulosum, venous ulceration and other deep fungal infections and hence may not be discovered until extensive testing and biopsy performed (Mason et al, 2008; Kuzel et al, 2018). Fungal cultures provide a firm diagnosis of blastomycosis, but require a 2–4 week incubation period for growth. Although microscopic broad-based budding is often diagnostic, cultures of cutaneous biopsies for *B. dermatitidis* should always be done, especially when microscopy is inconclusive or even negative (Mason et al, 2008).

A case of a cutaneous lesion is presented in this article that has rapidly turned into a chronic wound, which was at first erroneously identified as *Pyoderma Gangrenosum* (PG). However, after laborious diagnostic workup was eventually diagnosed and treated as disseminated blastomycosis, leading to complete healing of the wound. The patient developed only one cutaneous lesion, as compared to published cases from a literature review where most of the disseminated

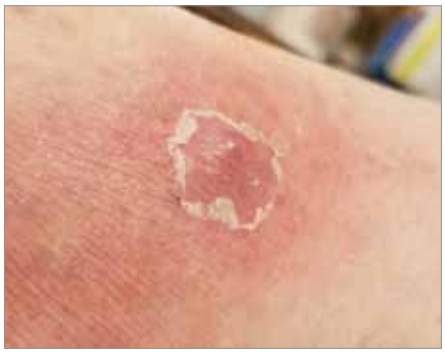

Figure 1. 12/26/2018 — within 48 hours after a claimed "spider bite".

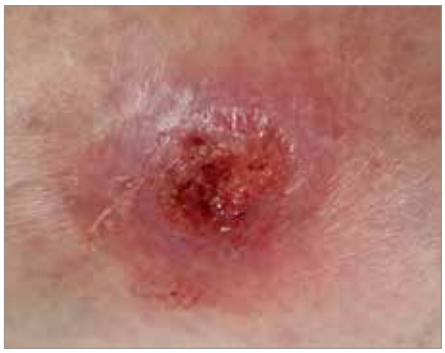

Figure 2. Week 7 — The lesion is larger and more erythematous.

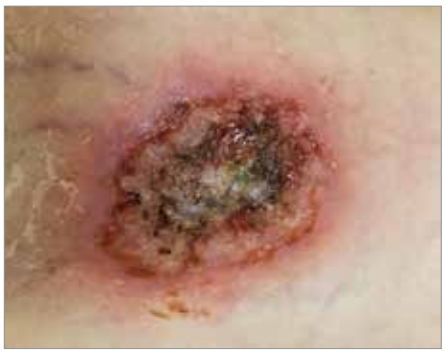

Figure 3. Week 12.

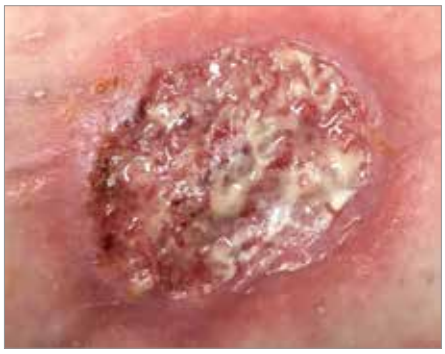

Figure 4. Week 14.

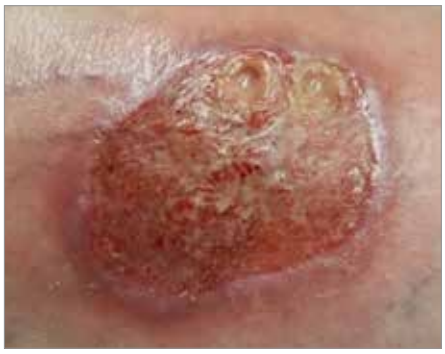

Figure 5. Week 17, at the first visit at wound care clinic.

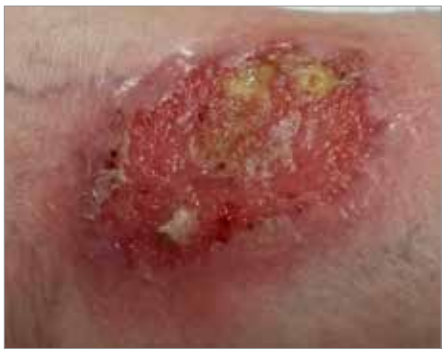

Figure 6. Week 20.

blastomycosis cases described involve multiple cutaneous sites.

Case Report

A 68 year-old woman presented to our Wound Care Center (WCC) with the chief complaint of a chronic ulcer on the right lower leg of 4 months' duration. Her past medical history is significant for advanced Parkinson's disease, supraventricular tachycardia, Reiter's Syndrome, endometriosis, lower back pain with walking instability, headaches, sleep disturbance and anxiety. She resides in Princeton, West Virginia, and not in close proximity to any wooded areas, water, lakes or rivers. She denied working or spending time outside. The patient had approximately 20 indoor rescue cats with up-to-date vaccinations. She denied any cat scratches to the area of the ulcer, chronic steroid use and she is not a transplant recipient. Her medications were acetaminophen, aspirin, atenolol, carbidopa-levodopa, duloxetine, furosemide, gabapentin, hydrochlorothiazide, ibuprofen, lorazepam, transdermal rotigotine patch and trihexyphenidyl. The patient reported that she had been bitten by a spider, causing a painful red area on her leg that has subsequently turned into an open draining ulcer *[Figure 1]*.

She was evaluated by numerous healthcare providers and based on clinical presentation was diagnosed as having PG. She was treated with prednisone (20 mg orally daily), and a variety of topical wound care products, including various collagen dressings, absorbent foam dressing, lidocaine and prednisone gels, without displaying any improvement. Her symptoms continued to worsen. Her friend meticulously documented the skin lesions progress by taking photographs on a regular basis *[Figures 1–6]*.

The wound continued to increase in size and started to become progressively more ulcerative with superficial slough formation. By week 14, (April 5, 2019; *Figure 4*), the patient was seen in dermatology clinic. At this time, the wound was described as being a "painful ulcer with purulent base and erythematous undermined border of the right medial lower leg above the ankle". Work up included a swab culture that was positive for 4+ MRSA, and a punch biopsy (2 samples, 4 mm each). The plan of care after dermatology evaluation was oral antibiotic (doxycycline), oral prednisone and referral to wound care clinic. Prednisone was stopped soon after, because of elevated intraocular pressure.

Around mid-April, the patient was evaluated in the neurology clinic as a regular follow-up for her Parkinson's disease and was noticed to exhibit an array of neurological symptoms that did not appear related to this condition, such as leg tremors, dyskinesia's, cramping, increased frequency of falls, dizziness, gait freezing, speech and vision changes.

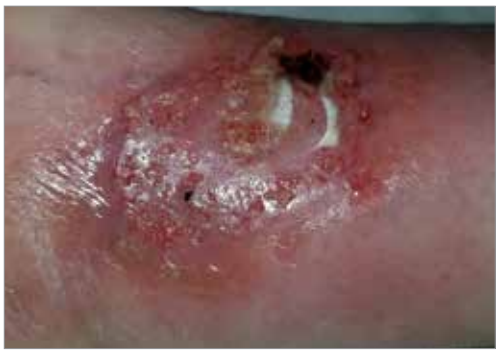

Figure 7. Mid-22nd week.

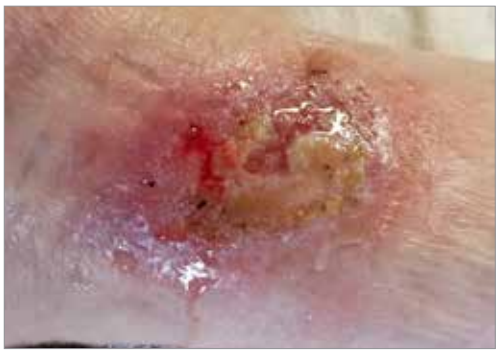

Figure 8. End of week 22 (while hospitalised).

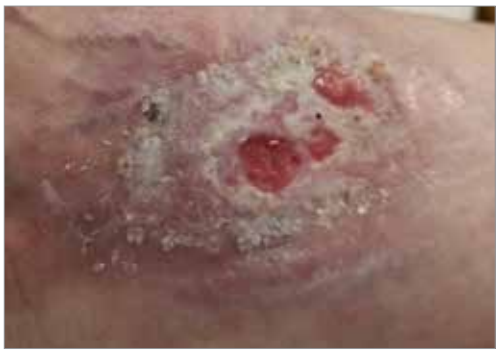

Figure 9. End of week 26.

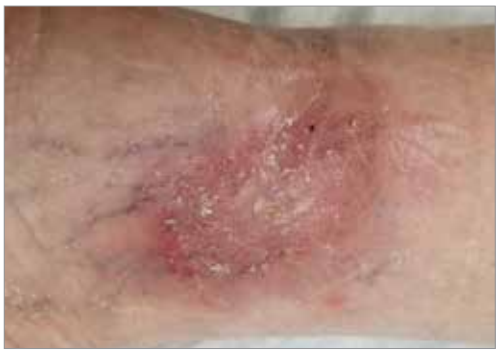

Figure 10. Beginning of week 30.

These symptoms were attributed to anxiety/depression and she was referred to psychiatry.

At the initial visit in the wound care centre at the end of week 17 (on 04/29/19; *Figure 5*), the wound on the right lower extremity, medial malleolus with ulceration and exposed fat, measured 4.0 x 3.0 x 0.2 cm. There was slough and fibrotic tissue in the wound bed and an erythematous ring in the periwound with no streaking. Two sites of previous biopsy were noticeable. There was no maceration. There was no significant undermining or tunneling. Wound was extremely painful. 1+ lower extremity oedema bilaterally was present. A resting tremor of the right upper extremity was also noted. The rest of the physical exam was unremarkable. The initial main working diagnosis was venous leg ulceration and work up initiated included arterial, venous studies and metabolic labs.

The treatment plan included topical silver collagen dressings (cellulose/collagen matrix wound dressing) and silver alginate, compression therapy with stockinette (8–15 mmHg compression). In addition, she received celecoxib and gabapentin for pain. Blood workup with CBC (complete blood count), CMP (comprehensive metabolic panel), C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), prealbumin, as well as arterial and venous vascular studies were ordered. Preliminary biopsy results were inconclusive, but raised suspicion and concern for blastomycosis from mycotic subcutaneous species seen.

The patient was referred to and then evaluated in the infectious disease clinic on week 20 on 5/17/19 *[Figure 6]*. Wound progression stalled by this time, but did not improve; pain was better controlled with medications. At that time biopsy results revealed no acid-fast bacteria growth in 21 days, no yeast or fungal growth in 14 days, and 4+ *Staphylococcus aureus* growth with sensitivities. The pathology report showed: "An ulceration with mixed inflammatory infiltrate, within which there are numerous spores with refractile walls and broad-based budding. Special stains were performed with PAS, GMS and AFB. PAS and GMS highlight the spores within the epidermis and dermis. The morphology of the spores are most consistent with blastomycosis, cryptococcosis is within the differential." Additional laboratory work-up was significant for a CRP of 11.7 mg/L with ESR similarly elevated at 31 mm/hour.

The patient reported to experience a myriad of different symptoms, some of which were chronic but had been exacerbated since the development of the wound. Her symptoms included subjective fever, chills, drenching night sweats, blood pressure lability (90–200 systolic), anxiety, leg cramps and pain, paresthesia and dysesthesia of the right toes, nonproductive cough, dyspnea, and orthopnea, requiring elevation at 30 degrees recumbency. Pertinent negatives included loss of consciousness,

falls, worsening vision, diplopia, nausea, vomiting, diarrhea, constipation, dysuria, haematuria, dysphagia, odynophagia or other skin lesions.

Based on chronicity of the single cutaneous lesion of 4–5 months' duration, clinically consistent with cutaneous blastomycosis and additional symptoms of generalised malaise, right lower-quadrant pain, nonproductive cough, subjective fever and chills, worsening headaches over the past few months, together with supporting histopathological findings, disseminated blastomycosis was high in the differential diagnosis. Differentiation between the involvement or lack of involvement of the CNS was essential to the decision between itraconazole or amphotericin therapy. The infectious disease team ordered further imaging with MRI of the brain to evaluate for brain abscess versus meningitis, as well as CT of the chest, abdomen and pelvis, Blastomyces urinary antigen and HIV assay to evaluate for further extent of disease.

The patient was subsequently followed in the wound care clinic. Work up previously initiated showed normal perfusion studies and negative venous insufficiency studies (no DVT and no reflux) The wound was extremely tender, and the patient did not tolerate debridement. At week 20, it increased in size to 4.3 x 3.2 cm; at week 22, it measured 4.5 x 4.0 cm *[Figure 7]*.

Investigation with CT Chest/Abdomen/Pelvis showed findings of "bilateral consolidative nodular airspace opacities with peripheral groundglass suggesting multifocal infection/septic emboli. Atypical agents are high on the differential including angioinvasive fungal disease. Multiple wedge-shaped hypodensities within the liver which may represent embolic phenomenon". Urinary enzyme immunoassay (EIA) returned as positive, combined with cutaneous biopsy/culture findings and aforementioned involvement of liver and lung based on imaging, it was concluded that patient had disseminated blastomycosis by the infectious disease team.

The patient was admitted to the hospital (corresponding to mid-22nd week). She was started on IV amphotericin B complex with supportive IV fluids, diphenhydramine, and acetaminophen. Lumbar puncture was performed resulting in: WBC 0, protein 46, lactate 1.7. Pulmonology consult felt bronchoscopy would unlikely change the wound management regimen given low respiratory tract cultures, and they recommended a repeat of the CT of the chest in 6–12 weeks after resolution of symptoms.

By the end of week 22, the wound size increased to 5.0 x 5.5 x 0.1 cm and was treated with barrier cream to the wound border, collagen wound dressing to wound bed, covered with Vaseline Gauze, absorbent foam dressing with ABD-pad, gauze and low-grade 8-12 mmHg compression stockinette for compressions.

Despite reported neurological symptoms, the patient did not have evidence for CNS involvement. She was treated with 7 days of amphotericin B. She was transitioned to oral itraconazole for a recommended 1 year of treatment duration. After initiation of antifungal treatment, the wound started to improve *[Figure 8]*. While it was larger, it was much less erythematous and less exudative. At week 26, after 3.5 weeks of antifungal treatment, the wound epithelialised by 80%, was not painful, had minimal drainage and no erythema *[Figure 9]*. She was completely healed after 6 weeks of antifungal treatment *[Figure 10]*. She remains on itraconazole with close follow up in the infectious disease clinic.

Discussion

Blastomycosis was first described by Johns Hopkins pathologist T. Caspar Gilchrist in 1894 (Gilchrist, 1894). In 1898, Gilchrist gave the organism the name *Blastomyces dermatitidis*, by which it is still recognised (Starrs and Klotz, 1948). It is the thermally dimorphic fungus, which commonly involves the lungs and skin. Later in 1939, Martin and Smith categorised blastomycosis into cutaneous and systemic types (Martin and Smith, 1939). However, in 1951 an in-depth data review by Schwarz and Baum proclaimed that most cases of cutaneous blastomycosis occur after lymphohematogenous spread from a primary pulmonary infection. In some cases, patients did not demonstrate the symptoms of overt pulmonary disease (Schwarz and Baum, 1951).

Although point source outbreaks have been described, most blastomycosis cases are sporadic. Endemic areas include the southeastern states, the Mississippi and Ohio River basins, and the Midwestern states and Canadian provinces bordering the Great Lakes (Owen et al, 2012) with annual incidence rate as high as 12–40 cases per 100,000 (CDC, 2019; Miceli and Krishnamurthy, 2019). Other commonly affected states include Mississippi, Kentucky, Arkansas, Wisconsin, North Carolina, Tennessee, Louisiana and Illinois, where the annual incidence reports vary from less than one case to one to two cases per 100,000 (CDC, 2019; Miceli and Krishnamurthy, 2019).

Historically, it was erroneously referred to as North American blastomycosis, as it was thought to be geographically localised to North America only. However, it has a worldwide distribution and has been documented in at least 15 African countries, as well as in Europe, South America, the Middle

East and South Asia (Mason et al, 2008), with a recently published rare fatal case of disseminated cutaneous blastomycosis in a 12-year-old child in India (Shekhar et al, 2016).

Five categories of blastomycosis have been defined: primary pulmonary disease, single organ system disease, generalised multiorgan disease, chronic cutaneous disease and inoculation blastomycosis. Cutaneous blastomycosis most often presents in two forms: verrucous and ulcerative (Mason et al, 2008; Saccente and Woods, 2010).

The patient lives in Princeton, West Virginia that is equidistant between the Ohio River and North Carolina. Although cases of blastomycosis are sporadically seen in West Virginia and not mandatory to report (CDC, 2021), there were two case reported recently of very rare cutaneous intranasal blastomycosis infection seen in two patients from Southern West Virginia (Kuzel et al, 2018).

The patient discussed here presented with an ulcerative skin lesion that she thought was caused by a spider bite. From case description above it is notable that she was erroneously diagnosed with PG and was treated with steroids for several months with no improvement. It was identified as cutaneous blastomycosis after biopsy, however, upon exhibiting systemic symptoms and further diagnostic workup, it was concluded that fungal infection was not isolated to skin, but was indeed disseminated blastomycosis. The wound demonstrated some features of venous stasis ulcer, but different wound care modalities were not successful in healing the wound or reducing pain.

Only at the arrival of correct aetiology and diagnosis, the treatment rendered to be successful in treating the fatal infection and start of the wound improvement. The wound completely resolved within 6 weeks after initiation of systemic antifungal therapy. Upon discussions with several physicians, many inquired about the immunocompetency state of our patient. However, unlike many opportunistic fungal pathogens, *B. dermatitidis* appears no more likely to cause disease in a person with compromised cellular immunity than to cause disease in a normal host (Saccente and Woods, 2010).

Conclusion

Clinical diagnosis for disseminated blastomycosis requires a high index of suspicion, correlation of clinical suspicion, subjective and clinical findings, and confirmation with surgical pathology. Biopsy of a wound should always be considered if it has an 'unusual' clinical aspect and is refractory to typical and advanced wound care measures. Consequently, a multidisciplinary approach is indicated with guidance from infectious disease, dermatology and wound care teams. Without treatment, the prognosis is grave in disseminating blastomycosis with case fatality rate of 78% prior to the availability of specific fungal therapy (Saccente and Woods, 2010). WINT

Acknowledgement

The authors thank Dr. William Wei-Ting Huang, MD, MPH, Department of Dermatology for providing clinical information used in this case report.

References

Bradsher RW (1997) Clinical features of blastomycosis. *Semin Respir Infect* 12(3): 229–34

Brick KE, Drolet BA, Lyon VB, Galbraith SS (2013) Cutaneous and disseminated blastomycosis: a pediatric case series. *Pediatr Dermatol* 30(1): 23–8

Centers for Disease Control and Prevention (2019) *Blastomycosis*. Atlanta, GA: CDC, Available at: https://bit.ly/37Ctttx (accessed 24.02.2021)

Centers for Disease Control and Prevention (2021) *Reportable Fungal Diseases by State*. Atlanta, GA: CDC. Available at: https://bit.ly/3kivH6q (accessed 24.02.2021)

Chapman SW, Sullivan DC (2010) Blastomyces dermatitidis. Mandell GL, Bennett JE, Dolin R (eds.) *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases* (7th ed.) London: Churchill Livingstone pp3319–32

Gilchrist T (1894) Protozoan dermatitis. *J Cutaneous General* 12: 496–9

Gray NA, Baddour LM (2002) Cutaneous inoculation blastomycosis. *Clin Infect Dis* 34(10): e44–9

Khuu D, Shafir S, Bristow B, Sorvillo F (2014) Blastomycosis mortality rates, United States, 1990–2010. *Emerg Infect Dis* 20(11): 1789–94

Kuzel AR, Lodhi M, Syed I et al (2018) Cutaneous, intranasal blastomycosis infection in two patients from Southern West Virginia: diagnostic dilemma. *Cureus* 10(1): e2095

Martin D, Smith D (1939) Blastomycosis (American blastomycosis, Gilchrist's disease): II. A report of 13 new cases. *Am Rev Tuberc* 39(4): 488–515

Mason AR, Cortes GY, Cook J et al (2008) Cutaneous blastomycosis: a diagnostic challenge. *Int J Dermatol* 47(8): 824–30

Mercurio MG, Elewski BE (1992) Cutaneous blastomycosis. *Cutis* 50(6): 422–4

Miceli A, Krishnamurthy K (2019) Blastomycosis. *StatPearls [Internet]*

Owen WR, Thurs K, Kim DSL (2012) Blastomycosis presenting as a nonhealing wound. *Adv Skin Wound Care* 25(7): 321–3

Saccente M, Woods GL (2010) Clinical and laboratory update on blastomycosis. *Clin Microbiol Rev* 23(2): 367–81

Schwarz J, Baum GL (1951) Blastomycosis. *Am J Clin Pathol* 21(11): 999–1029

Seitz AE, Younes N, Steiner CA, Prevots DR (2014) Incidence and trends of blastomycosis-associated hospitalizations in the United States. *PLoS One* 9(8): e105466

Shekhar A, Gupta PK, Gahalaut P, Mishra N (2016) A rare fatal case of disseminated cutaneous blastomycosis in a child. *Indian Journal of Paediatric Dermatology* 17(4): 300–2

Starrs RA, Klotz MO (1948) North American blastomycosis (Gilchrist's disease) a study of the disease from a review of the literature. *Arch Intern Med (Chic)* 82(1): 1–28