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Disseminated blastomycosis with cutaneous involvement in a 57-year-old woman: a case report and review of management

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Abstract

Blastomycosis is an infectious disease produced by the fungal organisms, *Blastomyces dermatiditis* and *Blastomyces gilchristi.* We present a 57-year-old woman with pulmonary blastomycosis and secondary cutaneous involvement. Her diagnosis was facilitated by dermatology consultation after approximately one year of delay. In endemic areas including Canada and the USA, individuals are at risk for blastomycosis when non-motile fungal spores are inhaled, thus producing pulmonary disease. The organism may disseminate over time, affecting a variety of extrapulmonary organ systems including the skin. In endemic regions of blastomycosis, this important cutaneous manifestation of disease should be considered with a high index of suspicion as to avoid delayed resolution and adverse outcomes.

Keywords: B. dermatiditis, B. gilchristi, blastomyces, cutaneous blastomycosis, fungal infection

Introduction

Blastomycosis is an invasive fungal disease which classically produces pneumonia; the responsible fungal pathogens include *Blastomyces dermatitidis, and B. gilchristi*. Mimicking other infections and malignancy, misdiagnosis is not uncommon. In endemic regions of Canada and the USA, it is important to consider this disease along with other infections in the differential diagnosis. Herein, we describe a case of misdiagnosis for this systemic fungal infection in an endemic region, despite classical presentation. We aim to bring more awareness to health care providers about disease.

Case Synopsis

In the summer of 2019, a 57-year-old woman from rural Northern Ontario, Canada, developed symptoms of an upper respiratory tract infection, involving shortness of breath, night sweats, and fevers. She was initially diagnosed with bacterial pneumonia, which led to two separate hospital admissions within three months. With each admission, she received antibiotic treatment and her respiratory symptoms reportedly improved. Shortly thereafter, cutaneous lesions developed over her elbow, leg, and abdomen. Of note, the lesions at the leg and elbow resolved spontaneously, whereas her abdominal plaque became chronic and increased in size over a 7-month period. Her family physician performed a punch biopsy of the lesion and the histology report showed pseudoepitheliomatous hyperplasia, with no fungal or bacterial organisms seen on special stains.

Due to the chronicity, continuous expansion of the cutaneous plaque, central superficial ulceration, and absence of malignant or infectious changes on biopsy, a diagnosis of pyoderma gangrenosum was considered. She was treated with oral prednisone at 50mg daily, with a taper over four weeks. This provided minor symptomatic relief, though systemic

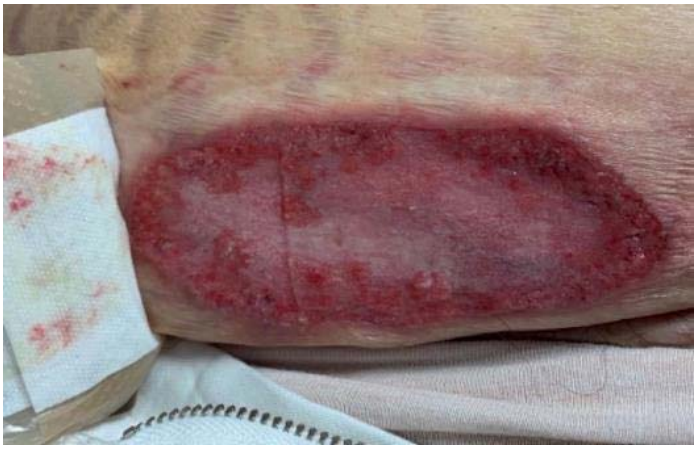

Figure 1. *A photo of the patient's lower right abdomen, showing a large, well demarcated, chronic plaque with a deep red, verrucous, undermined border.*

corticosteroids were halted in March of 2020 due to her history of longstanding pneumonia and continuous occasional cough. As a result, she was prescribed clobetasol wraps in place of systemic glucocorticoids. Despite continuation of topical corticosteroid treatment, her ulcerated plaque did not resolve and continued to enlarge, thus, she was referred to the dermatology department in the summer of 2020.

Considering the COVID-19 pandemic, the initial dermatology consultation was performed via telephone in July 2020 and the patient was offered an urgent in-person assessment the following day.

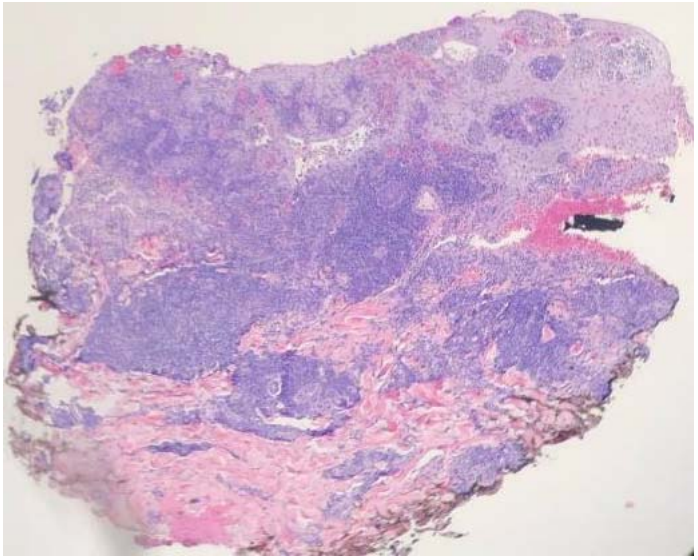

Figure 2. *Punch biopsy under low magnification H&E staining, showing ulceration, pseudoepitheliomatous hyperplasia, and severe acute and chronic inflammation. Neutrophils and epithelioid histiocytes are also noted.*

Physical examination revealed an 8.5cm×3.2cm plaque on the right lower abdomen with an undermined, red-purple, granulomatous border. The center of the lesion appeared to be healed, but atrophic (**Figure 1**). Although fungal staining on the initial punch biopsy was negative the year prior, two additional biopsies were performed for tissue culture and sensitivity, as well as cultures for fungus and acid-fast bacillus. Intralesional triamcinalone was injected for interim symptomatic relief and the patient underwent computed tomography (CT) of her chest the following day to rule out any lung pathology.

Fresh tissue potassium hydroxide (KOH) preparation revealed classic broad-based budding yeast forms under microscopy. Interestingly, the final report for fungal culture on skin tissue was negative at 7 weeks of incubation. On routine H&E staining of cultured tissue, low power magnification showed ulceration, pseudoepitheliomatous hyperplasia, and severe acute and chronic inflammation including neutrophils and epithelioid histiocytes (**Figure 2**). Under higher power magnification (40×), uniformly-sized, round, yeast cells with double refractory cell walls and broad-based budding were observed, both with H&E stain (**Figure 3**) and Grocott methenamine silver stain (**Figure 4**). Ziehl-Nieelsen stain for acid-

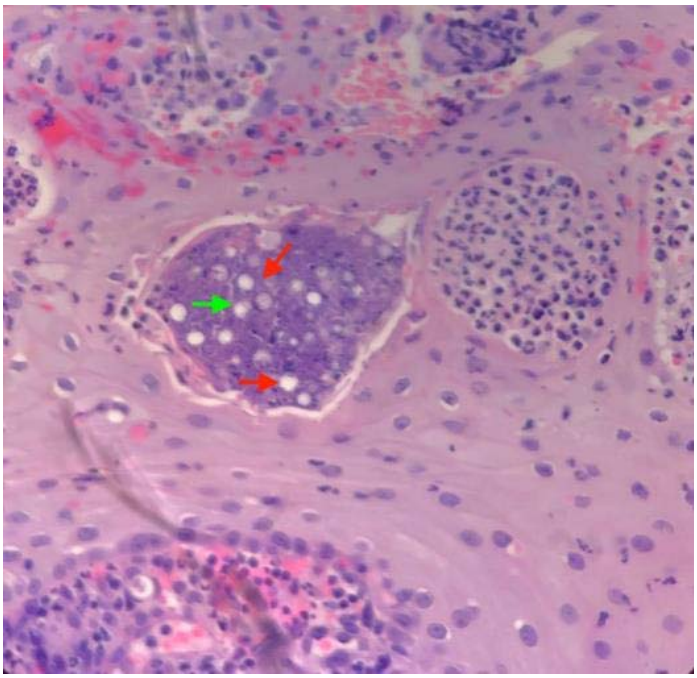

Figure 3. *H&E staining highlighting many round yeast cells (red arrows) and broad-based budding (green arrow), 40×.*

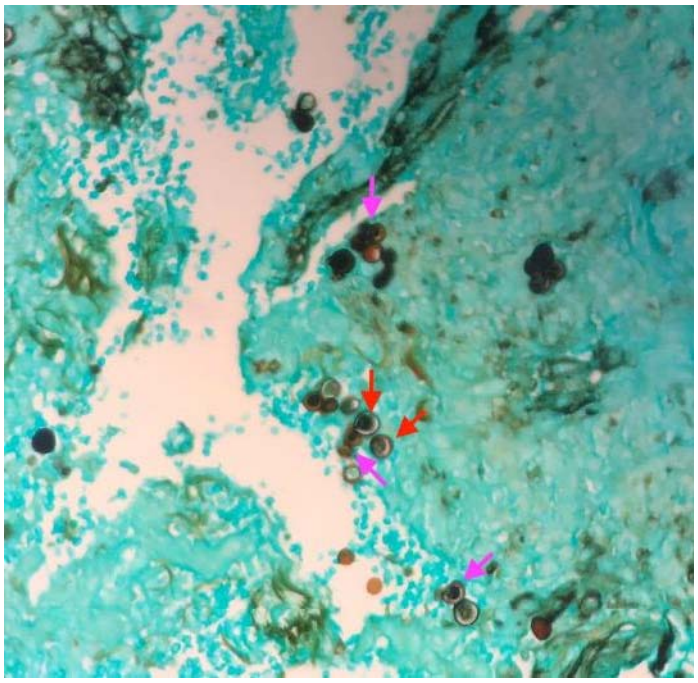

Figure 4. *Grocott methenamine silver staining, showing uniformly sized yeast cells, with double refractile cell walls (red arrows), and broad-based budding (pink arrows).*

fast bacilli was negative, as was Gram staining. Her CT scan results were also compatible with pulmonary blastomycosis. No further investigations were performed from a respiratory perspective, including bronchoscopy, bronchoalveolar lavage, or biopsy from lung tissue.

At the time of diagnosis, an infectious diseases specialist was consulted and a focused social history was gathered surrounding activities involving exposure to soil, wood, and other decay. A passion for gardening and crafting involving driftwood was revealed. The initiated treatment regimen consisted of oral itraconazole 200mg three times daily for two days, then 200mg twice daily thereafter for a total of 6 months. At the 3-month follow-up, the patient had complete resolution of the skin plaque.

Case Discussion

Blastomycosis may affect any mammalian host, including humans and dogs. Also called Gilchrist disease, blastomycosis may present as sporadic cases or as clusters within a population [1-3]. From reports of the disease, inferences about the geographical distribution of *Blastomyces* spp. in North America have been made. Involved regions include central and midwestern USA and central Canada [3-4]. However, environmental isolation of these organisms themselves is rare, suggesting endemicity data is incomplete [3].

In the USA, mandatory reporting is not necessary among many states, but those with highest incidence include midwestern, south-central, and southeastern states encompassing the Ohio and Mississippi River valleys, the Great Lakes, and the Saint Lawrence River [5]. Wisconsin has the highest reported incidence of blastomycosis, at 2.9 hospitalizations per 100,000 people, though certain counties have reported rates of 10-40 per 100,000 [5-7]. In Canada, four centrally located provinces report on this disease (Ontario, Manitoba, Saskatchewan, and Quebec), with an estimated incidence rate of 0.62 cases per 100,000 people [8]. However, in select areas of northern Ontario, hospitalizations are reported as nearly 100-fold this value, at 57.9 per 100,000 [7].

Blastomycosis can be difficult to diagnose, with about 40% of patients experiencing an average delay of one month or more [9-11], whereas only about 18% of cases may be correctly diagnosed on first presentation [11]. Presenting complaints are non-specific, including fever, night sweats, and malaise, thus imitating a numerous other conditions. Common misdiagnoses include bacterial pneumonia, tuberculosis, and malignant neoplasms [4,9,11]. Coupled with a relatively high mortality rate of 5-10% even in treated individuals, these factors contribute to adverse outcomes, unnecessary antibiotic regimes, and increased healthcare costs. Unfortunately, blastomycosis is not often considered within the differential diagnosis, unless other clues are revealed, such as persistent symptoms despite antibiotic treatment, new or evolving skin lesions, or historical clues with risk factors for exposure [9].

Originally, the portal of entry into the host was thought to be via the skin, though in 1951, Baum and Schwarz argued that the respiratory system was indeed the conduit into the human body [12]. This realization was pivotal in understanding the pathologic mechanism of blastomycosis. Once inhaled into the warm pulmonary system of any

mammal, the fungal pathogen undergoes reversible morphological transition into a thick-walled yeast. A thickened cell wall serves many advantageous functions including additional defence against phagocytosis, while also facilitating the ability to form non-caseating granulomas. These properties confer rapid growth, while an exaggerated inflammatory reaction allows for hematogenous spread [4,9]. Subsequently, other bodily sites may become involved, including the musculoskeletal, central nervous, genitourinary, and integumentary systems, in which case the diagnosis is termed *disseminated blastomycosis* [4,9].

With respect to respiratory symptoms, the disease mimics tuberculosis and a spectrum of presentations have been described, ranging from a lack of symptoms to acute respiratory distress syndrome (ARDS) with high mortality rate [9]. Radiography may reveal interstitial infiltrates bilaterally, which may be difficult to differentiate from pulmonary edema or community acquired pneumonia. There may also be nodules, cavitation, or masses, contributing to the non-descript diagnostic picture [9,11]. Due to the nonspecific pulmonary manifestations and radiographic findings, this condition has been dubbed the *great pretender* in the literature [1,11,13].

Cutaneous manifestations of disseminated blastomycosis are common and present a great opportunity for the correct diagnosis since they are easily accessible for biopsy. Cutaneous lesions may be single or numerous. In early stages they present as papulo-pustules and verrucous plaques with scale-crust, with or without pustules at the border [2,7]. In more advanced disease central ulceration occurs and, coupled with spontaneous healing with cribriform scar, this appearance mimics pyoderma gangrenosum [13].

Other entities in the differential diagnosis include various infectious diseases such as tuberculosis, folliculitis, nocardiosis, anthrax, and other dimorphic fungal infections, along with inflammatory dermatoses such as sarcoidosis. Finally, it is imperative to consider squamous cell carcinoma.

Primary cutaneous involvement of blastomycosis is quite rare and occurs after some trauma to the skin, with inoculation of the pathogen [14] This type of infection results in an indurated area with chancre and appears 1-2 weeks after the fungus is introduced [4].

Obtaining a diagnosis from cutaneous disease requires skin tissue or pus sampling to perform a culture of the material at either 25°C, or 37°C. When cultured at 25°C, microscopy will reveal coremia (white spikes), representing the colonial morphology. Conversely, when cultured at 37°C, broad-based, budding yeast become apparent, with thickened, double-refractile walls with size ranging from 8-20μM [9,13].

In North America, general treatment recommendations for mild to moderate blastomycosis begin with the antifungal itraconazole for six to twelve months. Second-line therapy voriconazole can also be used in the event of itraconazole failure. Other azole medications have also been used with varied success rates. More severe cases of blastomycosis can be treated with lipid formulation amphotericin B or extracorporeal membrane oxygenation [15].

Conclusion

In summary, as northern Ontario and the central midwestern USA are endemic areas for *B. dermatitidis*, patients within the catchment area who experience lung disease and skin manifestations may require specific investigations for blastomycosis, along with subsequent treatment. Investigations may include skin biopsy with KOH staining, tissue for fungal culture from skin and/or lung, and CT scans of the chest; treatment may involve long term antifungals, for example, itraconazole. As blastomycosis is sometimes referred to as the *great pretender* [1], it is an important disease to consider.

Potential conflicts of interest

The authors declare no conflicts of interest.

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