Blastomycosis

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Blastomycosis is caused by the dimorphic fungus *Blastomyces dermatitidis*. The organism exists in nature in the mould or mycelial phase and converts to the parasitic or yeast phase at body temperature. Epidemics of blastomycosis after a point-source exposure have been described, but most cases occur sporadically in the endemic areas. *B. dermatitidis* can cause an infection with a subclinical illness and subsequent protection against infection afforded by cellular immune mechanisms. Patients infected with *B. dermatitidis* can present with pneumonia or with extrapulmonary disease, or both. Lung involvement often mimics acute bacterial pneumonia, lung cancer, or tuberculosis. Skin lesions, presenting as either verrucous or ulcerative lesions, are the most common extrapulmonary manifestation, followed by bone, prostate, and central nervous system (CNS) disease. Diagnosis is usually confirmed by visualization of the yeast in smears or in tissue specimens, or by culture. Itraconazole has been shown to be the drug of choice for both pulmonary and extrapulmonary infection, except in cases of life-threatening infection, in which case, amphotericin B is recommended.

Organism

Gilchrist first described blastomycosis in Baltimore in the 1890s as a skin infection caused by what he thought was a protozoan organism [1], and the illness was known for a time as Gilchrist's disease. There were some errors in the initial description. Infection of the skin occurs secondarily rather than as a primary infection, and the organism is not a protozoan but a fungus. Gilchrist was the first to refute portions of his own description when he isolated and named the fungus *Blastomyces dermatitidis* [2]. Because skin manifestations of blastomycosis are often very striking, the initial cases were perceived to be a dermatologic condition. The concept of primary pulmonary blastomycosis was not recognized until pathologic descriptions allowed the pathophysiologic mechanisms to be delineated [3, 4]. There are rare cases of cutaneous inoculation of the fungus in laboratory workers and veterinarians, but almost all cases of blastomycosis are considered to originate from a pulmonary portal of entry [3].

B. dermatitidis is dimorphic, in that it exists as a mycelial form or mould in nature and as a yeast form in tissue. The mould is the infectious form, producing conidia that can be dispersed and subsequently inhaled. The perfect or sexual stage of the fungus is named *Ajellomyces dermatitidis*, with the imperfect or conidial stage named the familiar *B. dermatitidis*. In culture, *B. dermatitidis* grows at 25–28°C as a mould and at 37°C as a yeast. The physiologic mechanism for the dimorphism has been shown to be from hybrid histidine kinase sensing of host signals stimulating the conversion from mycelia to yeast [5].

This imperfect stage grows as a fluffy white mould on Sabouraud's agar at room temperature and as a brown, wrinkled, folded yeast at 37°C. In the yeast phase, the organism appears as a round, budding, thick-walled yeast cell with a daughter cell forming a single bud that has a broad base (Figs. 1 and 2). The yeast varies in size from 5 to 15 μm. Most are round and have a double cell wall appearance, which consists of the interior and exterior components of the thick cell surface. The yeast may be found inside or outside of macrophages in the pyogranulomatous tissue response.

Epidemiology

The endemic areas in North America for *B. dermatitidis* include the states bordering the Mississippi and Ohio Rivers, the Midwestern and Canadian provinces that border the Great Lakes, and a small area in New York and Canada along the St. Lawrence River [3]. The vast majority of patients with blastomycosis who were reported prior to the mid-1980s were from a fairly well defined geographic area of the South Central United States, comprising predominantly Mississippi,

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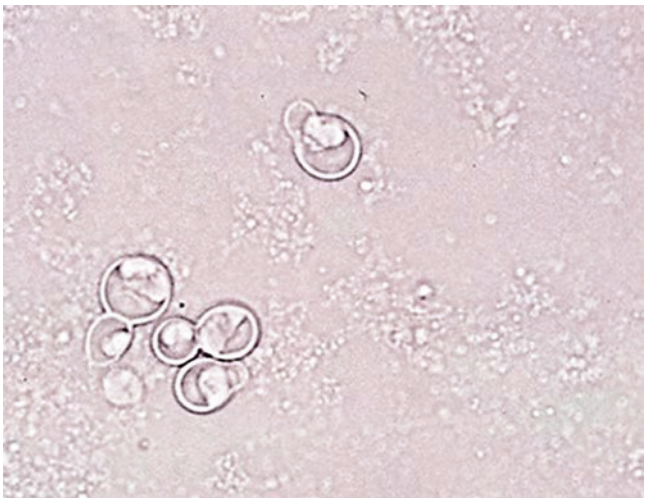

Fig. 1 Sputum sample showing the refractile thick walls and broad-based budding typical of *Blastomyces dermatitidis* (potassium hydroxide preparation, 40×)

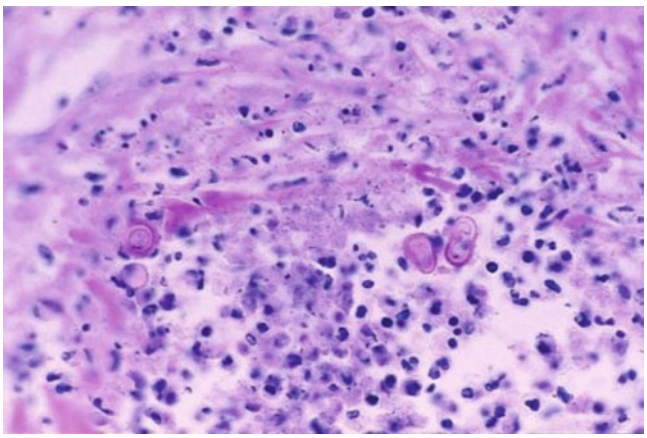

Fig. 2 Tissue obtained at lung biopsy showing broad-based budding yeast. Culture yielded *Blastomyces dermatitidis* (periodic acid – Schiff stain, 40×)

Arkansas, Kentucky, and Tennessee [6]. In the last 2 decades, there have been more cases reported from Illinois, Wisconsin, Ontario, and Manitoba [7–10]. There have been reports of cases of blastomycosis from Colorado, Hawaii, Israel, several areas of Africa, and South America. For the most part, the incidence of blastomycosis depends on the reporting of clinically diagnosed cases of infection because there are no simple and reliable markers of previous mild infection. Mandatory public health reporting of blastomycosis is required in only a few states or provinces, namely Illinois, Wisconsin, Mississippi, Manitoba, and Ontario, and thus cases are likely underreported.

The majority of reported cases of blastomycosis are sporadic and not related to outbreaks. Many patients with blastomycosis have a history of recreational or occupational exposure to wooded areas and often to bodies of water such as lakes or rivers. The stereotypical patient is a young to middle-aged man who either works in or visits outdoor areas in the endemic area. In sporadic cases, the male-to-female ratio has been reported to range from 4:1 to 15:1 in various series [11]. Some of these studies, however, were conducted in Veterans Affairs Medical Centers, which obviously adds bias to the ratio. However, in an outbreak, women and children are as likely as men to be infected. Aside from outbreaks, only rarely are children diagnosed with blastomycosis [12, 13].

Dogs in the same environment as humans also can become infected with *B. dermatitidis*. A clinical clue to the diagnosis of blastomycosis is a history of a pet dog having been found to have blastomycosis [14]. Blastomycosis is not transmitted from dogs to humans, but rather, both are infected as a result of similar exposure in the environment. However, there are very rare reports of a dog with oral lesions transmitting infection via a bite [15].

Outbreaks of blastomycosis have been well described [16–19]. Most have been associated with waterways [17–19]. It has yet to be determined whether water is the primary factor or simply an explanation for greater exposure potential because of recreational activities in areas with wildlife or water [20]. Investigation of these outbreaks has increased our knowledge of the spectrum of disease manifestations of infection with *B. dermatitidis* and allowed the recognition of subclinical infection due to this organism. The majority of cases associated with point-source outbreaks at Big Fork, Minnesota, and Eagle River, Wisconsin, recovered without antifungal therapy [16, 19]. In the Eagle River outbreak, only nine of the 44 patients with infection were treated with an antifungal agent, and none of the 35 untreated patients had relapse or progressive infection [16]. In the latter outbreak, further study revealed that not all of those who had immune markers of infection, such as positive serology or specific antigen-induced lymphocyte transformation, had signs and symptoms characteristic of blastomycosis [16].

In a study of specific immunity to *Blastomyces* antigens using cells from treated blastomycosis patients, two control persons who had no history of blastomycosis had evidence of immunity [21, 22]. Cells from these two control subjects displayed lymphocyte responses to a *Blastomyces* antigen and macrophage inhibition of intracellular growth of the fungus similar to those seen in patients who had culture-proven blastomycosis. Both of these control persons had potential exposure as long-term avid hunters in an endemic region for blastomycosis [22]. This observation prompted studies of other persons who had comparable environmental exposures to patients with clinical blastomycosis, specifically, forestry workers in areas endemic for blastomycosis, but not histoplasmosis, in northern Minnesota and Wisconsin [23]. Thirty percent of the workers had in vitro markers of immunity as evidence of subclinical infection with no question of cross-reactions due to prior infection with *Histoplasma capsulatum*.

Thus, it appears that blastomycosis has comparable patterns of subclinical infection with development of cellular immunity as the more extensively studied endemic mycoses, histoplasmosis and coccidioidomycosis.

It is thought that the ecologic niche for *B. dermatitidis* is the soil. However, the organism has been very difficult to isolate from soil. *B. dermatitidis* was recovered from soil and rotted wood in Georgia on three occasions [24]. The organism has been isolated from bird droppings on one occasion and from a dirt floor in Canada on another [25, 26]. The organism was recovered without animal inoculation from a woodpile from a hyperendemic region in Wisconsin in which several dogs in a nearby kennel had been found to have blastomycosis [27]**.** *B. dermatitidis* was isolated from soil in association with outbreaks in two separate reports [16, 17]. The isolations were from wet earth that was taken from near bodies of water and that contained animal droppings, showing that the fungus exists in microfoci in soil. However, many other investigators have been unsuccessful in recovering the organism from soil, including areas linked by epidemiologic information to a point-source exposure.

It has become clear that certain areas are hyperendemic for *B. dermatitidis* with unusually high rates of blastomycosis. In one report from Wisconsin, as many as 41.9 cases per 100,000 persons were reported with blastomycosis [28]. Factors that promote this hyperendemicity are being elucidated [29]. During a recent investigation of an outbreak in dogs, a polymerase chain reaction (PCR)–based technique successfully identified *B. dermatitidis* from environmental samples [30]. Additionally, molecular techniques are being used to look at genetic differences detected by PCR of components of the organisms recovered from patients and from the environment [31].

Pathogenesis

Infection with *B. dermatitidis* begins with inhalation of conidia into the alveoli, followed by clearing of the organism by bronchopulmonary phagocytes. Alveolar macrophages have been shown to kill conidia [32], which may explain why some persons are not infected even though they have the same exposure as an infected individual in an epidemic. As the fungus undergoes transition to the yeast phase, growth occurs in the lung, and the organisms can also spread hematogenously to other organs, especially the skin. With the development of immunity, inflammatory reactions occur, initially as a suppurative response with polymorphonuclear phagocytes and then with subsequent influx of monocyte-derived macrophages. This pyogranulomatous response is typical for blastomycosis, although necrosis or fibrosis can also be found. Typically, the granulomas of blastomycosis do not develop caseation necrosis, as found in tuberculosis. The host response leads to resolution of the initial infection. However, it is likely that foci of viable organisms remain, which can later reactivate and cause disease at either pulmonary or extrapulmonary sites [33]. Endogenous reactivation is the logical reason for patients with AIDS developing blastomycosis after leaving their initial residence in the endemic area many years before [34].

Clinical Manifestations

Blastomycosis is not a common diagnosis in most clinical practices, which often leads to a delay in diagnosis. The clinical presentations are protean and are similar to other more common conditions. Weight loss, fever, malaise, fatigue, and other nonspecific complaints are common but not helpful diagnostically. The stereotypical patient is a young to middle-aged man who either works in or visits outdoor areas in the endemic area, but in an outbreak, women and children are as likely as men to be infected. In an observational review of referrals of 135 patients over a 13-year period in Arkansas, 78 were male and 57 female [35]. Extrapulmonary manifestations were found in 47%, and 53% had only lung involvement. Women accounted for only 30% of the extrapulmonary cases, but 47% of the pneumonia cases were in women [35].

Pulmonary

The presentation of blastomycosis for most patients is pneumonia; radiography reveals an alveolar or mass-like infiltrate (Fig. 3). This was noted in 16 of 17 patients in one report [36]. In another series of 46 patients, 26 of whom had had only pulmonary disease, 8 had acute pneumonia and 16 had a chronic pneumonia picture; 32% of the radiographs revealed a mass-like lesion and 48% an alveolar infiltrate [21].

Acute pneumonia due to blastomycosis often presents the same as acute bacterial pneumonia, with fever, chills, and a productive cough with purulent sputum, with or without hemoptysis. Patients who have chronic pneumonia due to blastomycosis usually have weight loss, night sweats, fever, cough with sputum production, and chest pain. They are initially thought to have tuberculosis or lung cancer (Fig. 4). Although cavitary disease may occur, this pattern is not found as commonly as it is in chronic pulmonary histoplasmosis or tuberculosis. Miliary or reticulonodular types infiltrates can also be seen in patients with symptoms of pneumonia.

Patients may have no pulmonary symptoms, and the diagnosis is made following the discovery of pulmonary abnormalities on a chest radiograph obtained for another reason.

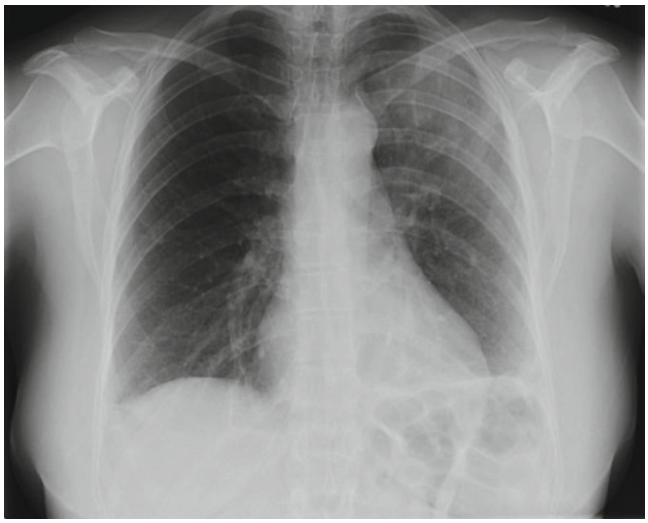

Fig. 3 Left upper and left lower lobe infiltrates in a 36-year-old woman with pulmonary blastomycosis (Courtesy of Dr. William Muth)

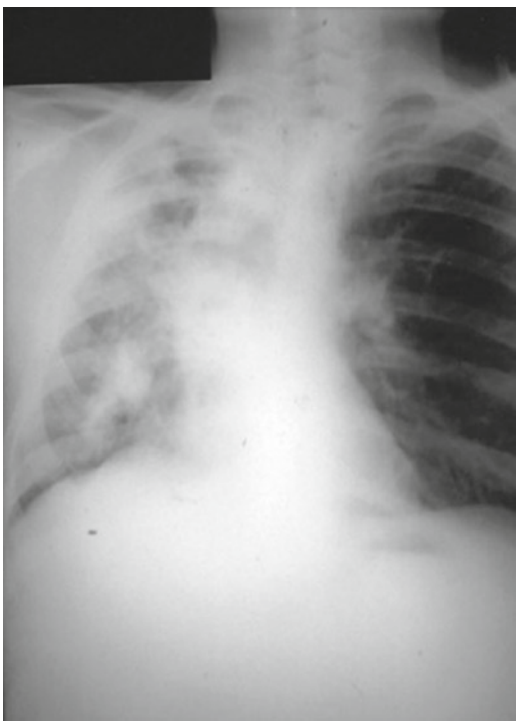

Fig. 4 Chronic destructive pneumonia due to *Blastomyces dermatitidis*

In a series of 46 patients, 26 of whom had had only pulmonary blastomycosis, two patients were found who were asymptomatic [21].

Uncommonly, patients with pulmonary blastomycosis develop the acute respiratory distress syndrome (ARDS) [37–40] (Fig. 5). These patients have diffuse pulmonary infiltrates and hypoxemia, and require ventilatory support. The mortality rate remains high, and often death ensues within a few days of the development of ARDS. For most patients it is unclear whether they have been infected with a huge burden of organisms or whether the host inflammatory response is responsible for the development of ARDS. One patient with this syndrome had a tracheal ulcer at the carina found on bronchoscopy, prompting speculation that a subcarinal lymph node ruptured into the trachea and spilled enough organisms into the lungs to precipitate this syndrome [37]. Early therapy may improve survival rates, and reports of the use of corticosteroids in patients who develop this complication need further study [40].

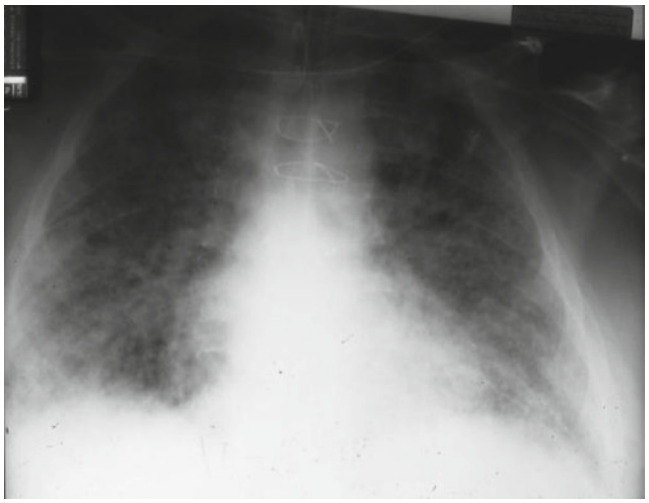

Fig. 5 Acute respiratory distress syndrome (*ARDS*) due to blastomycosis in a 60-year-old man who was previously healthy

Cutaneous

Skin lesions are the most common manifestation of extrapulmonary blastomycosis [3, 4]; these lesions may be present with or without concomitant pulmonary lesions. Cutaneous lesions are either verrucous or ulcerative [11, 41]. The verrucous, or fungating, form has an irregular raised border, often with crusting and exudate above an abscess in the subcutaneous tissue (Figs. 6–8). Histologically, papillomatosis, downward proliferation of the epidermis with intraepidermal abscesses, and inflammatory cells in the dermis are features of the lesions [3, 41]. The cutaneous ulcerative form occurs when a subcutaneous abscess spontaneously drains; these demonstrate the same histologic changes as the verrucous form. The borders of the ulcer are usually raised and distinct (Fig. 9), and the base of the ulcer usually contains exudate. Polymorphonuclear leukocytes are typically present on the biopsy, even in those patients with little inflammation clinically apparent in the ulcer (Fig. 10). Subcutaneous lesions lacking either ulceration or the verrucous appearance also can be found (Fig. 11). These lesions are typically tender and may be confused with panniculitis or Weber-Christian disease [42]. The cutaneous lesions of

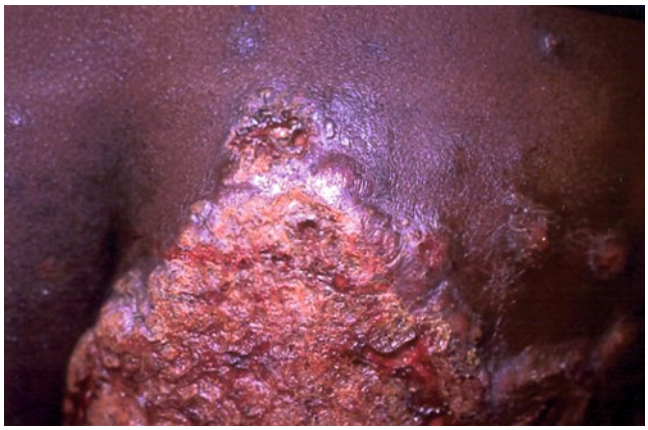

Fig. 6 Verrucous lesion with subcutaneous abscesses on the buttock caused by *Blastomyces dermatitidis*

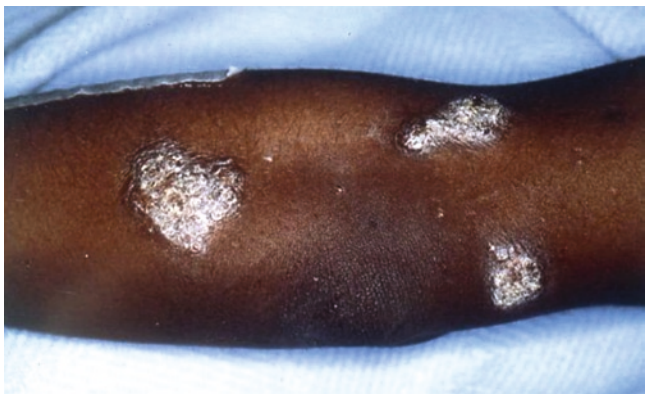

Fig. 7 Multiple verrrucous lesions on the forearm of a 20-year-old man with blastomycosis (Courtesy of Dr. Hector Bonilla)

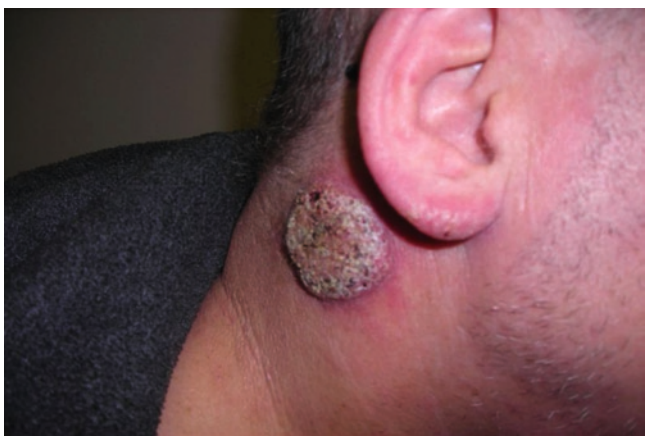

Fig. 8 Non-painful, heaped-up lesion due to *Blastomyces dermatitidis* behind the ear of a 35-year-old man

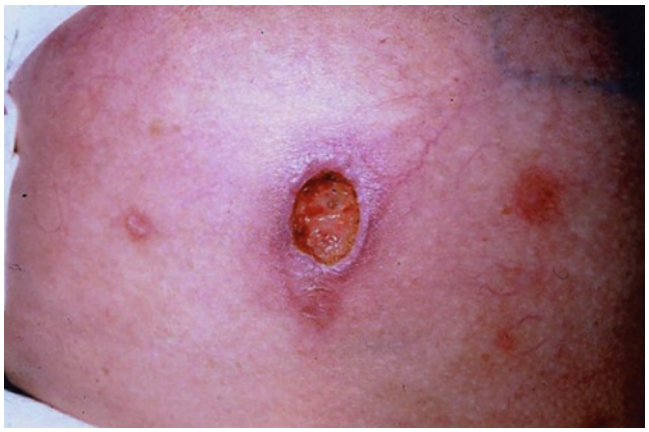

Fig. 9 Ulcerative lesion on the breast caused by *Blastomyces dermatitidis*. Note the distinct and raised borders

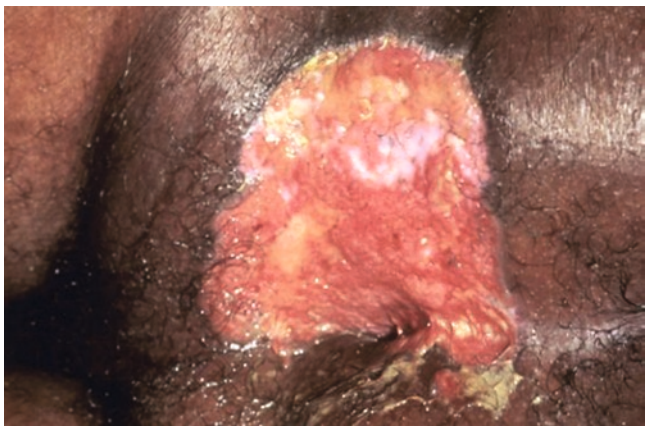

Fig. 10 Extensive perirectal ulcerative lesion with overlying exudate in a patient who had disseminated blastomycosis

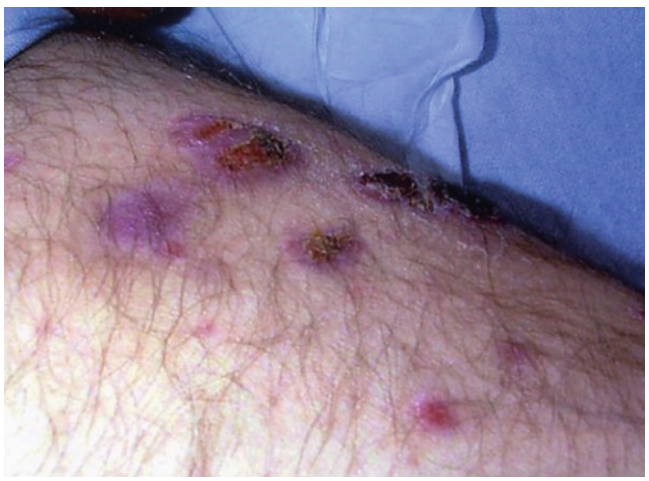

Fig. 11 Subcutaneous nodules with superficial crusts due to blastomycosis on the thigh of a young man

blastomycosis can be confused with a number of alternative diagnoses, including basal cell carcinoma, squamous cell carcinoma, pyoderma gangrenosum, or keratoacanthoma. One patient was reported with what appeared to be condyloma acuminatum surrounding the anus [43]. Only after postoperative suppurative drainage occurred was the histology re-reviewed, and *B. dermatitidis* found. Another similar case has been more recently reported [44].

Osteoarticular

Osteoarticular infection due to *B. dermatitidis* infection is reported in as many as one-fourth of extrapulmonary cases and may be the reason the patient seeks medical attention [45]. The symptoms of involvement of long bones are pain and swelling, with erythema, tenderness, and warmth noted on examination. Vertebral involvement manifests primarily as pain, but with epidural extension, neurologic signs can be seen. Granulomas, suppuration, or necrosis can be found in the bone biopsy. The vertebrae, pelvis, sacrum, skull, ribs, and long bones are the most frequently reported sites of infection, but essentially any bone may be involved [4]. The radiographic appearance of blastomycosis is not specific and cannot be discriminated from that of other fungal, bacterial, or neoplastic diseases. Debridement may be required for cure, but most blastomycosis bone lesions resolve with antimicrobial therapy alone.

Genitourinary

The genitourinary (GU) system follows lung, skin, and bone in frequency of involvement. Prostatitis and epididymo-orchitis have been the more commonly reported forms of genitourinary involvement [3, 4, 46]. Patients present with symptoms of prostatism or with a firm, nontender scrotal mass. In some patients, GU involvement is found incidentally on digital rectal examination. In most circumstances it is thought that the patient has cancer. Patients can have isolated GU disease or, as occurs more frequently, they have GU tract lesions concomitant with pulmonary disease. Chest radiographs should be performed in every case of GU tract blastomycosis, even in the patient without pulmonary complaints. GU infection can be detected when urine collected after prostatic massage yields the organism [46]. Endometrial infection acquired by sexual contact with a man who has blastomycosis on the penis and tubo-ovarian abscess following hematogenous disseminaton are examples of female genital tract infection, an uncommon manifestation of blastomycosis [47, 48]. Massive endometrial infection that caused uterine hemorrhage has been described in one patient [49].

Central Nervous System

Blastomycosis is reported to involve the CNS in 5–10% of cases of disseminated disease. Meningitis and/or cerebral or cerebellar abscesses are the most common manifestations of CNS blastomycosis [50–54]. Either can occur as isolated manifestations of blastomycosis, but more frequently CNS symptoms and signs occur in patients who have manifestations of widespread disease. MRI imaging is helpful in the diagnosis of mass lesions. For patients with meningitis, cerebrospinal fluid (CSF) analysis reveals high protein, slightly low glucose, and the presence of increased numbers of lymphocytes, but the organism is rarely grown from the fluid obtained by lumbar puncture. In one series of 22 patients with chronic meningitis, CSF from lumbar puncture provided the diagnosis in only two patients, whereas ventricular CSF was positive when cultured in six of seven cases [51]. A recent series noted that CSF obtained at lumbar puncture yielded the organism in a larger proportion of cases [54].

Other Organ Involvement

Lesions of blastomycosis can occur in virtually any organ. Abscesses are most common in the subcutaneous tissue, but they can be found in the brain, skeletal system, prostate, or any other organ, including the myocardium, pericardium, spleen, liver, lymph nodes, orbit, sinuses, pituitary, adrenal gland, and other organs [3, 4, 43, 55]. Blastomycosis can involve the mouth, oropharynx, and especially the larynx, where it mimics sqauamous cell carcinoma [56]. Laryngeal biopsy reveals histologic features similar to those seen in the skin and may initially be mistaken for carcinoma. In some cases, fixation of the vocal cords secondary to fibrosis has led to radiation therapy or total laryngectomy because of an incorrect diagnosis of cancer.

Ocular involvement may assume several forms. A patient with a mass on the iris prompted a review of the literature by Lopez and colleagues. A total of 11 cases of ocular blastomycosis, including cases with iritis, uveitis, endophthalmitis, and choroidal lesions, were found [57]. More cases of choroidal involvement have been reported [58, 59]. Eyelid involvement has been reported to occur in as many as 25% of patients with disseminated blastomycosis [60, 61], but this frequency appears to be higher than that noted in most experts' experiences. Ocular disease, endophthalmitis in particular, is very common in canine blastomycosis, but this type of involvement is rare in humans [62]. The reason for this discrepancy is not understood but may be due to later diagnosis in dogs, allowing more dissemination of the infection.

Two cases of otitis media with cranial extension due to *B. dermatitidis* have been reported [63]. One patient was described with infection in a presumed branchial cleft cyst [43]. Surgical removal demonstrated lymphadenopathy and suppurative and granulomatous inflammation with *B. dermatitidis* organisms. Peripheral lymphadenopathy is found in systemic blastomycosis; amyloid deposition in the node has rarely been reported [43].

Cases of blastomycosis involving the breast have been reported [64–66]. An abnormal mammogram may be the first sign, and the diagnosis is almost always thought to be carcinoma. In one patient, a CT scan which revealed partial destruction of a vertebral body consistent with metastatic disease almost led to treatment with cancer chemotherapy until a breast biopsy revealed *B. dermatitidis* on microscopy and subsequent culture [64].

Endocrine abnormalities have been reported in patients with blastomycosis [4]. Adrenal insufficiency from destruction of both adrenal glands is the most common. Thyroid involvement has been recently reported [67, 68]. Rarely, hypercalcemia, as seen with other granulomatous diseases, has been reported with blastomycosis. A single case of diabetes insipidus and another of hyperprolactinemia with galactorrhea and amenorrhea have been reported [69, 70].

Immunocompromised Patients

Blastomycosis causes infection in immunocompromised patients, including patients with AIDS, recipients of solid organ transplants, patients treated with tumor necrosis factor antagonists, and patients on corticosteroid therapy [71–77]. However, blastomycosis is seen much less commonly than infection with *Histoplasma capsulatum* or *Cryptococcus neoformans* in these groups. Immunosuppressed patients can develop infection following exposure in the environment or from reactivation of a latent focus of infection.

Pappas et al. reviewed the cases of immunosuppressed patients with blastomycosis who were seen in several tertiary care medical centers from 1956 to 1991. They found an increased proportion of cases from 1978 to 1991, as compared with 1956–1977 [76]. Although this could have been from a bias in referral patterns of patients, they speculated that this more likely reflected the continually enlarging population of patients who have complicated immune compromising illnesses and who have lived in the endemic area for this fungus. Tumor necrosis factor antagonist therapy is increasingly associated with disseminated infection with fungi and mycobacteria. A total of seven cases of blastomycosis had been reported to the FDA registry by the summer of 2008 [77].

Although not common in the immunosuppressed population, when blastomycosis is seen in a patient who is immunosuppresssed, it is usually widely disseminated and particularly severe. ARDS has developed in a number of cases, and CNS involvement is common [71, 74, 76]. The mortality rate in patients with AIDS who developed blastomycosis was 40% and most died within a few weeks [71]. With the use of current antiretroviral therapy, the occurrence of severe manifestations is less frequent, and the mortality rates are lower.

Other Patient Groups

Blastomycosis has been reported to occur with other infections or other illnesses, including tuberculosis, histoplasmosis, and coccidioidomycosis [78]. Blastomycosis has been reported in two patients, one of whom presented with idiopathic thrombocytopenic purpura and the other with hemolytic anemia [35]. Both patients were treated with corticosteroids for the hematologic conditions, and blastomycosis was treated with antifungal agents. Steroids were rapidly tapered, and the hematologic conditions did not recur after the blastomycosis was cured. Another patient with both sarcoidosis and blastomycosis was treated with both corticosteroids and itraconazole with cure of the fungal infection [43]. As long as effective antifungal chemotherapy is being given, steroid therapy may not have the deleterious result that has been described in untreated blastomycosis.

Several cases of blastomycosis have been reported during pregnancy [79–85]. In several well-documented cases, blastomycosis has been transmitted to the fetus via intrauterine transfer of the organisms [79, 82, 85].

Diagnosis

Culture

Growth of *B. dermatitidis* in culture is the definitive test to prove a diagnosis of blastomycosis. The organism is not particularly difficult to culture, but it may take 2–4 weeks for the organism to grow as a mould at 25–28°C. The appearance of the mould phase is not distinctive, and a confirmatory test must be performed. An exoantigen assay was developed to discriminate early cultures of *H. capsulatum* and *B. dermatitidis* [86], but currently, most laboratories use a rapid DNA probe test that is specific for *B. dermatitidis* [87]. With these rapid specific tests, it is no longer necessary to convert the mould phase to the yeast phase to confirm the organism as *B. dermatitidis*.

Histopathology

If suspected, a diagnosis of blastomycosis can be established quickly by seeing the characteristic yeasts in tissue, exudates, or body fluids. Exudates or sputum can be treated with potassium hydroxide or calcofluor white, which is more sensitive because the fluorescent dye allows easy visualization of the 8–15 μm thick-walled, broad-based, budding yeast cells [34]. Cytological preparations stained with Papanicolau stain

also can be used for a dependable diagnosis [88]. Tissues stained with hematoxylin and eosin do not allow visualization of the yeasts in most circumstances; staining with periodic acid–Schiff or methenamine silver stains are preferred for visualization of the yeasts in tissues.

Serology

Serodiagnostic tests for blastomycosis started with complement fixation (CF) with yeast-phase antigens (blastomycin) to detect antibodies to *B. dermatitidis* and then proceeded to the use of an immunodiffusion (ID) assay and an enzyme immunoassay (EIA) [89–93]. The CF test had a low sensitivity (57%) and specificity (30%). In a large outbreak, only 9% of patients were found to have CF antibodies to blastomycin [90]. In another series, patients were as likely to have CF antibodies to *H. capsulatum* antigens as they were to *B. dermatitidis* antigens [3]. Given the overlapping endemic regions of these two fungi, this was obviously problematic.

Better results were obtained with the ID assay and with the EIA using a more specific antigen for *B. dermatitidis,* the A antigen. The ID assay resulted in reported sensitivity rates of 65–80% with 100% specificity. However, when applied to sera obtained from the previously mentioned outbreak in Wisconsin, antibodies were detected in only 28% of documented cases with the ID assay. The EIA using the A antigen proved more sensitive, detecting antibody in 77% of cases [91]. While better than CF antibody tests, ID and EIA tests were still plagued with cross-reactivity problems with other endemic mycoses, especially histoplasmosis, and the low sensitivity led to an unacceptable number of false-negative results, hindering its use as a diagnostic test, especially given the low prevalence in most areas.

Klein et al. described a 120 kD surface protein termed WI-1 and later renamed BAD-1 [92]. This protein was purer than A antigen and lacked the carbohydrate moieties that caused the majority of cross-reactions with *H. capsulatum* [92]. A radioimmunoassay (RIA) using this protein showed promise, identifying antibodies in 85% of patients with known blastomycosis. Only 3% of patients with other mycoses, and no healthy volunteers, tested positive using this assay [93]. This RIA, however, has not been adapted for clinical use.

Antigen Detection

There is now a commercially available assay for the detection of *B. dermatitidis* antigen in humans [94]. It has mostly been used in urine specimens and has a reported overall sensitivity in the urine of 92.9% and a reported specificity of 79.3%. Antigen was detected at levels considered positive in patients with both disseminated blastomycosis and isolated pulmonary blastomycosis. Cross-reactions were seen in subjects with other fungal infections, especially histoplasmosis, paracoccidioidomycosis, and penicilliosis. The cross-reactivity between *B. dermatitidis* and *H. capsulatum* is felt to be due to a shared polysaccharide [95]. The clinical pictures for these two infections can sometimes be similar, especially with isolated pulmonary disease, and the endemic areas for these fungi overlap. On the other hand, patients with either disseminated or pulmonary blastomycosis have had negative assays for *B. dermatitidis* antigen at the time of initial diagnosis. Thus, in the right clinical setting, a negative antigen should not be used to eliminate blastomycosis from the differential diagnosis.

The antigen assay has been shown to revert to a level considered negative in patients successfully treated for blastomycosis [96–98]. The time to resolution, however, remains undetermined, and there have been no large studies to evaluate the usefulness of repeated antigen testing during therapy to monitor for response. Antigen detection might prove helpful in less common presentations of blastomycosis, but this has not been studied. In clinical practice, the *Blastomyces* antigen assay can be a helpful tool, but should not supplant clinical evaluation and judgment.

Treatment

Spontaneous resolution of chronic blastomycosis is very uncommon, and untreated blastomycosis is associated with mortality rates approaching 60% [3, 4]. Thus, all patients with chronic pulmonary and extrapulmonary blastomycosis should receive antifungal therapy.

Controversy once existed concerning the need for antifungal therapy in all recognized cases of acute pulmonary blastomycosis. Experts agree that some of the cases of acute blastomycosis are self-limited [99, 100], but most advocate specific antifungal therapy for all cases of pulmonary blastomycosis, whether acute or chronic. Careful follow-up for several years is mandatory in patients with acute pneumonia who do not receive antifungal therapy to ensure that there is no recrudescence of infection.

The treatment of blastomycosis has evolved with the development of the azoles, ketoconazole, itraconazole and fluconazole. However, no randomized, blinded studies comparing different regimens have been performed, and there are only a few comparative trials for therapy of blastomycosis. Thus, the recently published treatment recommendations for blastomycosis are based on relatively small, open-label, controlled trials, case series, and anecdotal experience [101].

Ketoconazole was the first oral azole to be studied for the treatment of non-life-threatening, non-CNS blastomycosis. A single daily dose of 400 mg of ketoconazole for at least 6 months was recommended for patients with uncomplicated blastomycosis. Of note, there were multiple reports of CNS relapses following "successful" therapy of pulmonary blastomycosis with an appropriate course of ketoconazole [21, 102, 103], underscoring the poor penetration of this agent into the CNS and the need for careful monitoring during therapy and long-term follow-up after completion of therapy.

Itraconazole, an oral triazole with broad-spectrum antifungal activity, is now considered to be the drug of choice for patients with non-life-threatening, non-CNS blastomycosis. In a prospective, open-label, noncomparative multicenter study, 43 of 48 (90%) patients with mild-to-moderate disease were cured with itraconazole at doses ranging from 200 to 400 mg daily [104]. Of 40 patients who received at least 2 months of therapy, 39 (95%) were cured. Most patients responded to the lower dosage of itraconazole (200 mg), and the drug was better tolerated than ketoconazole based upon historic comparison. Another report suggested similar success among an additional 42 patients who received itraconazole at a daily dosage of 200 mg [105]. Based on these studies, the current recommendation for patients with non-life-threatening, non-CNS blastomycosis is to treat with itraconazole at an initial dosage of 200 mg daily for 6–12 months. For patients not responding to therapy, the dose should be increased to 200 mg twice daily [101]. Because absorption of the itraconazole capsule formulation is not reliable, measurement of drug levels is recommended, particularly if the infection does not respond quickly [101]. A minimum of 12 months of therapy is recommended for osteoarticular infection.

Fluconazole, another oral and parenteral triazole with broad-spectrum activity and superior pharmacokinetics compared with either itraconazole or ketoconazole, has also been studied for the treatment of non-life-threatening, non-CNS blastomycosis. To date, two multicenter trials have been conducted using fluconazole [106, 107]. In the pilot study comparing 200 and 400 mg of fluconazole daily, success was seen in only 65% of 23 patients who received therapy for at least 6 months [106]. The follow-up study using 400 and 800 mg daily showed improved efficacy with 34 (87%) of 39 patients successfully treated [107]. Average duration of therapy in this study was almost 9 months, and patients tolerated this therapy with few significant adverse events. The results of these studies suggest that fluconazole is comparable in efficacy to ketoconazole at similar doses, but it does not appear to be as efficacious as itraconazole. Therefore the role of fluconazole in the treatment of blastomycosis is limited and should be reserved for patients who are unable to tolerate itraconazole or ketoconazole because of adverse effects or specific drug-drug interactions. However, given the favorable pharmacokinetics of fluconazole, including its good penetration into the CNS, fluconazole could be considered in the treatment of patients with CNS blastomycosis who have had a favorable response to initial therapy with amphotericin B. Clinical experience with fluconazole in this setting is limited to a few patients [54].

Voriconazole has been used to treat patients with blastomycosis. Most have had CNS infection, and the response rate in this group of patients with severe disease has been excellent [54, 108, 109]. In additon, voriconazole has been used in solid organ transplant recipients with blastomycosis but the results have been mixed [74]. Posaconazole has potent activity against *B. dermatitidis* in vitro, but there are very limited anecdotal reports of patients with blastomycosis who have been treated with this agent.

For patients with severe, life-threatening blastomycosis, amphotericin B remains the drug of choice. Traditionally, a cumulative dose of 1.5–2.5 g of amphotericin B deoxycholate was advocated [110, 111], but this approach has been supplanted by current recommendations to treat with amphotericin B until the patient has improved and can take oral medications and then to step down to therapy with oral itraconazole, 200 mg twice daily [101]. Many institutions have eliminated amphotericin B deoxycholate in favor of lipid formulations of amphotericin because of the toxicity of the older agent. For CNS blastomycosis, the Infectious Diseases Society of America (IDSA) Guidelines recommend a lipid formulation of amphotericin B at a dosage of 5 mg/kg daily for the initial 4–6 weeks of therapy. These patients should then be treated with high doses of an oral azole (voriconazole, fluconazole, or itraconazole) for a minimum of a year [101].

Patients with blastomycosis who have AIDS, transplant recipients, those receiving chronic corticosteroids or tumor necrosis factor antagonists, and other significantly immunocompromised patients should receive initial therapy with amphotericin B. Blastomycosis among these patients is associated with significant complications, including ARDS, CNS, and multiorgan involvement, and with substantially higher mortality. Thus, early and aggressive therapy is essential in this population. Long-term suppressive therapy with oral itraconazole is generally advised in patients with significant ongoing immune dysfunction [101].

Pregnant women with blastomycosis constitute a special population in regards to therapy. Only a few cases of blastomycosis in pregnancy have been reported, and none have failed therapy with amphotericin B; lipid formulations are recommended [101]. There has been no evidence of adverse effects on the fetus from amphotericin B; thus it appears to be safe and effective in pregnant women. Azoles should specifically be avoided in this population due to potential teratogenicity.

Blastomycosis is uncommon in children, and therapeutic studies in this group are lacking. Current recommendations

are based solely on anecdotal data. Some investigators suggest that children with blastomycosis have a less favorable response to initial therapy with an azole than do their adult counterparts and have advocated initial therapy with amphotericin B [12]. However, the IDSA Guidelines recommend therapy similar to that noted above for adults, with itraconazole as the agent of choice for mild-to-moderate infection and amphotericin B reserved for severely ill children [101].

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