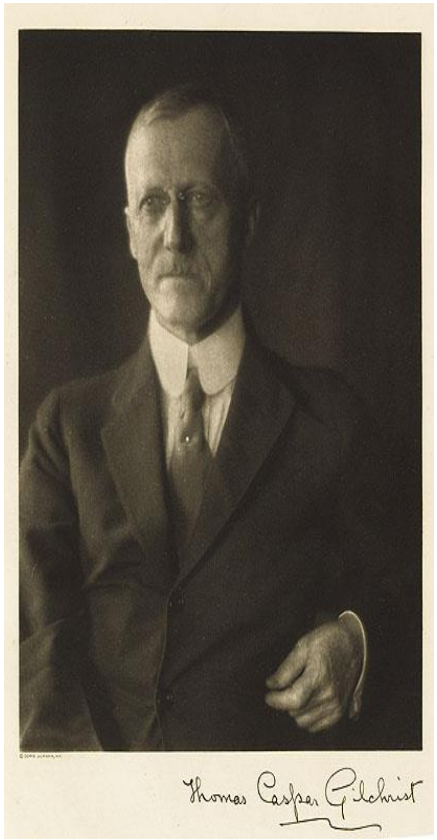
Blastomycosis

Prepared by
Ass. Prof. Dr. Thekra Ahmed

What is Blastomycosis?



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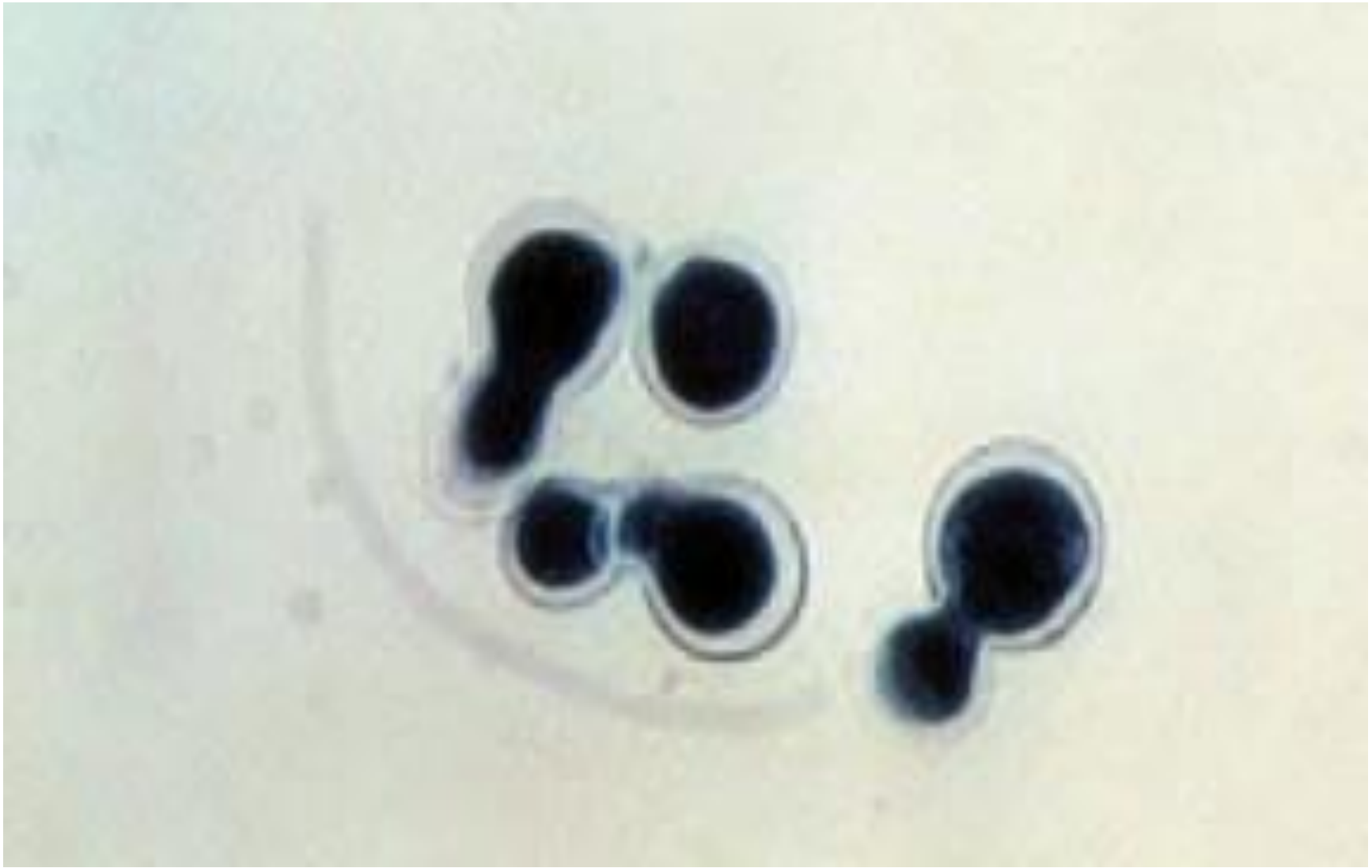
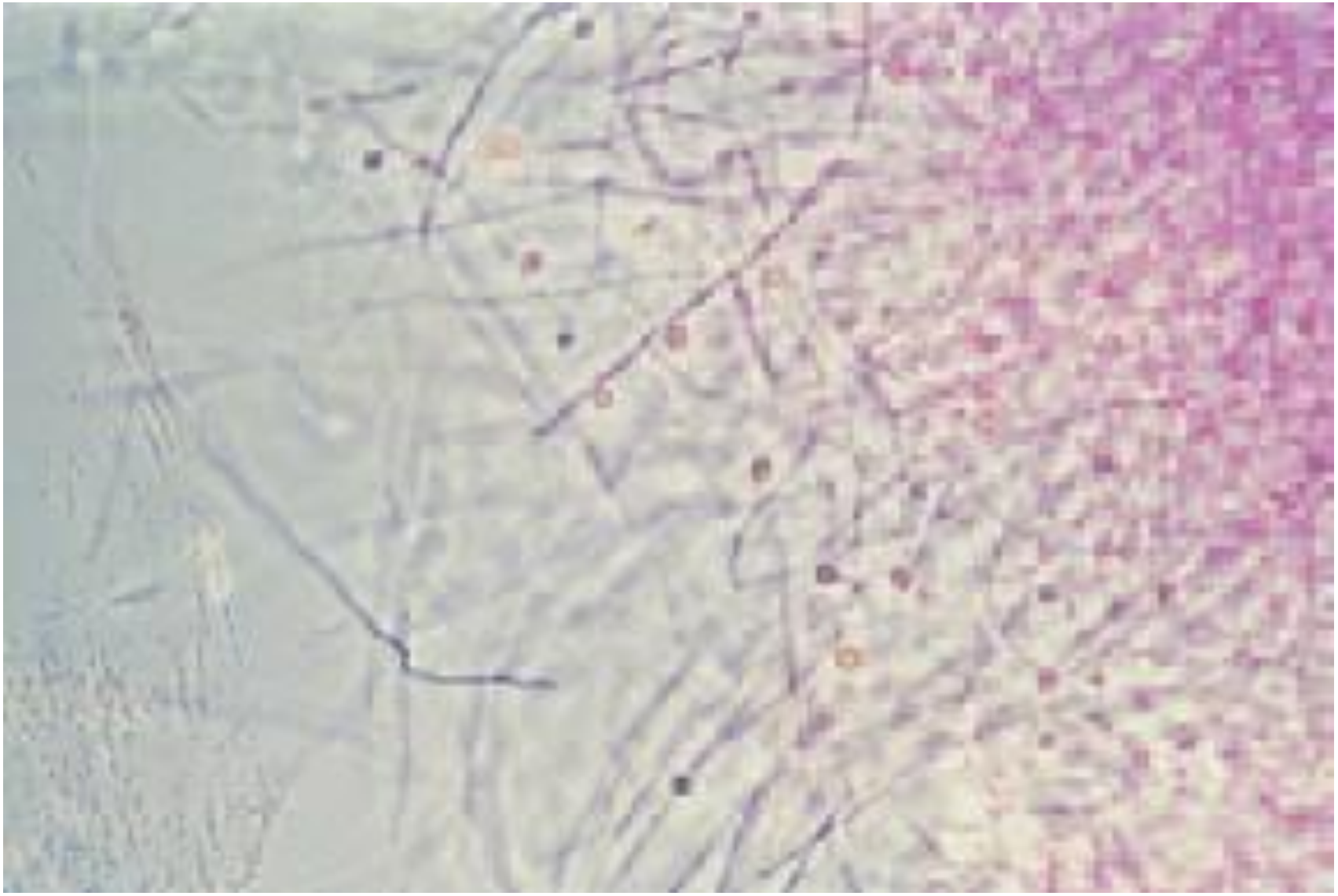
- A systemic pyogranulomatous infection endemic to regions of mid-western and eastern North America
- Caused by *Blastomyces spp.*
- First identified by Dr. T. Caspar Gilchrist, a dermatologist in Baltimore

Blastomycosis (also known as "North American blastomycosis," "Blastomycetic dermatitis," and "Gilchrist's disease”) is a fungal infection caused by the organism Blastomyces dermatitidis. It is endemic to portions of North America. Blastomycosis is a dimorphic fungus that causes clinical symptoms similar to histoplasmosis.



Yeast cells of *Blastomyces dermatitidis* in pus.



Microscopic appearance of *Blastomyces dermatitidis*

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 pointsource

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.

- On Sabouraud's dextrose agar at 25C, colonies are variable in both morphology and rate of growth. They may grow rapidly, producing a fluffy white mycelium, or slowly as glabrous, tan, non-sporulating colonies. Growth and sporulation are enhanced by nitrogenous substances found in starling dung and yeast extract. Most strains become pleomorphic with age. Microscopically, hyaline, ovoid to pyriform, one-celled, smooth-walled conidia (2-10 um in diameter) of the *Chrysosporium* type, are borne on short lateral or terminal hyphal branches.
- On blood agar at 37C, colonies are wrinkled and folded, glabrous and yeast-like. Microscopically, the organism produces the characteristic yeast phase as seen in tissue pathology. *B. dermatitidis* can be described as a dimorphic fungus because it has both a mould and yeast phase.

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].*

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].

Epidemiology

The endemic areas in North America for *B. dermatitidis*

include the states bordering the Mississippi and Ohio Rivers,

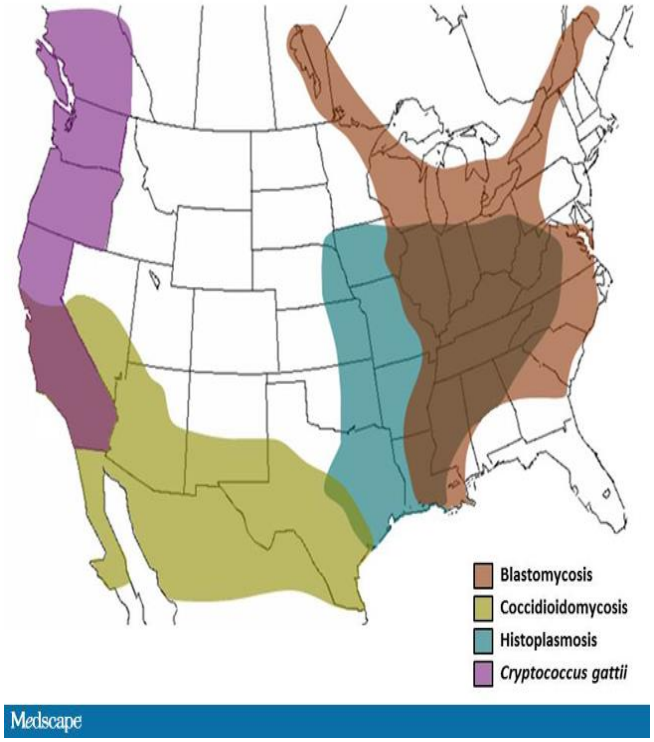
the Midwestern and Canadian provinces that border the

Great Lakes, and a small area in New York and Canada along

the St. Lawrence River [3].

Geographic Distribution

- **Eastern United States**
- **Central Canada**
- **Globally**
  - Southeast Asia
  - Africa
  - Europe
  - Middle East



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Environmental Factors

- Typically exist in mycelial form in environment

Spores bound tightly to filaments and become unbound in presence of high humidity

Transmission typically associated with humid environments (Rivers, streams etc)

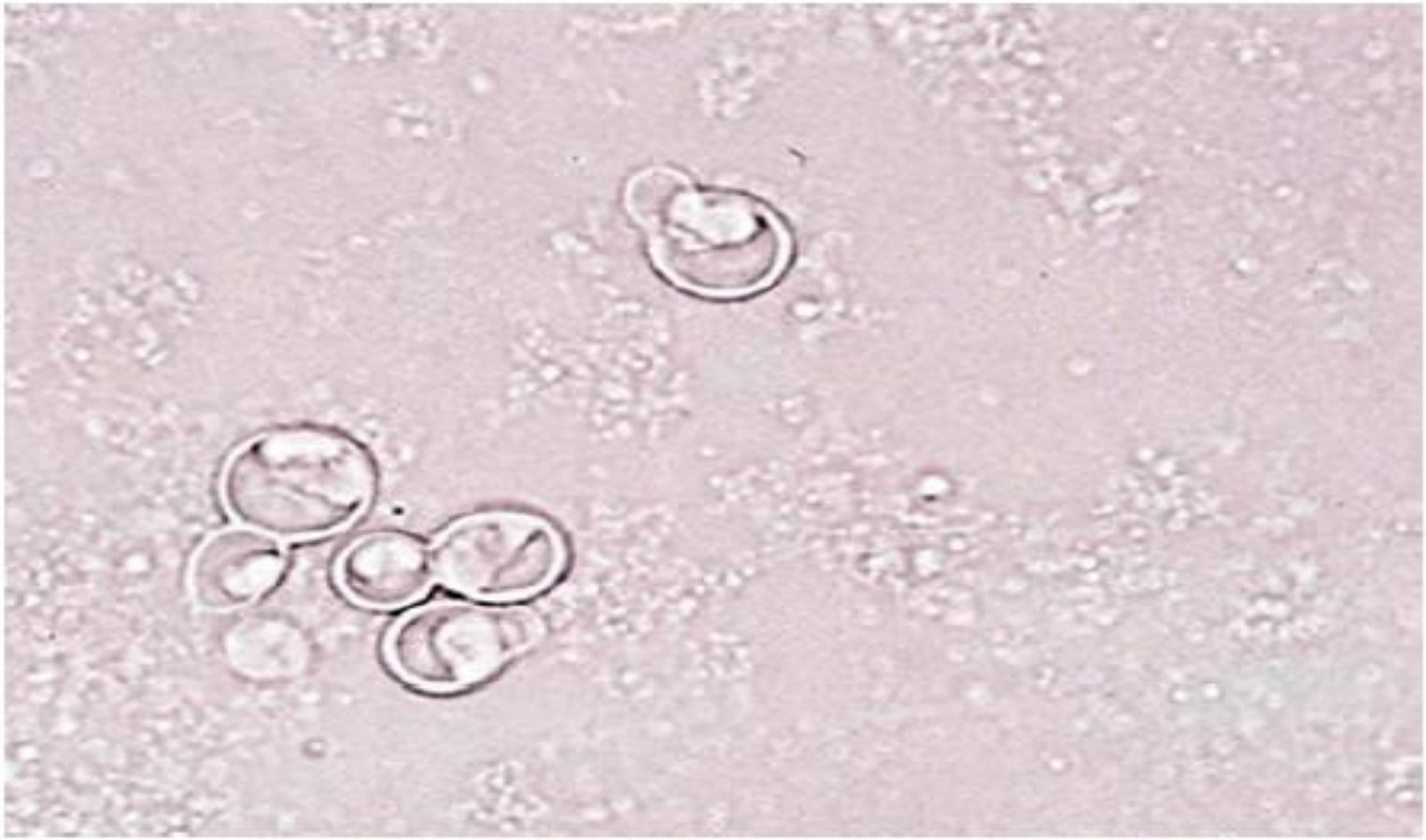


Fig. 1 Sputum sample showing the refractile thick walls and broad-based budding typical of *Blastomyces dermatitidis* (potassium hydroxide preparation, 40×)

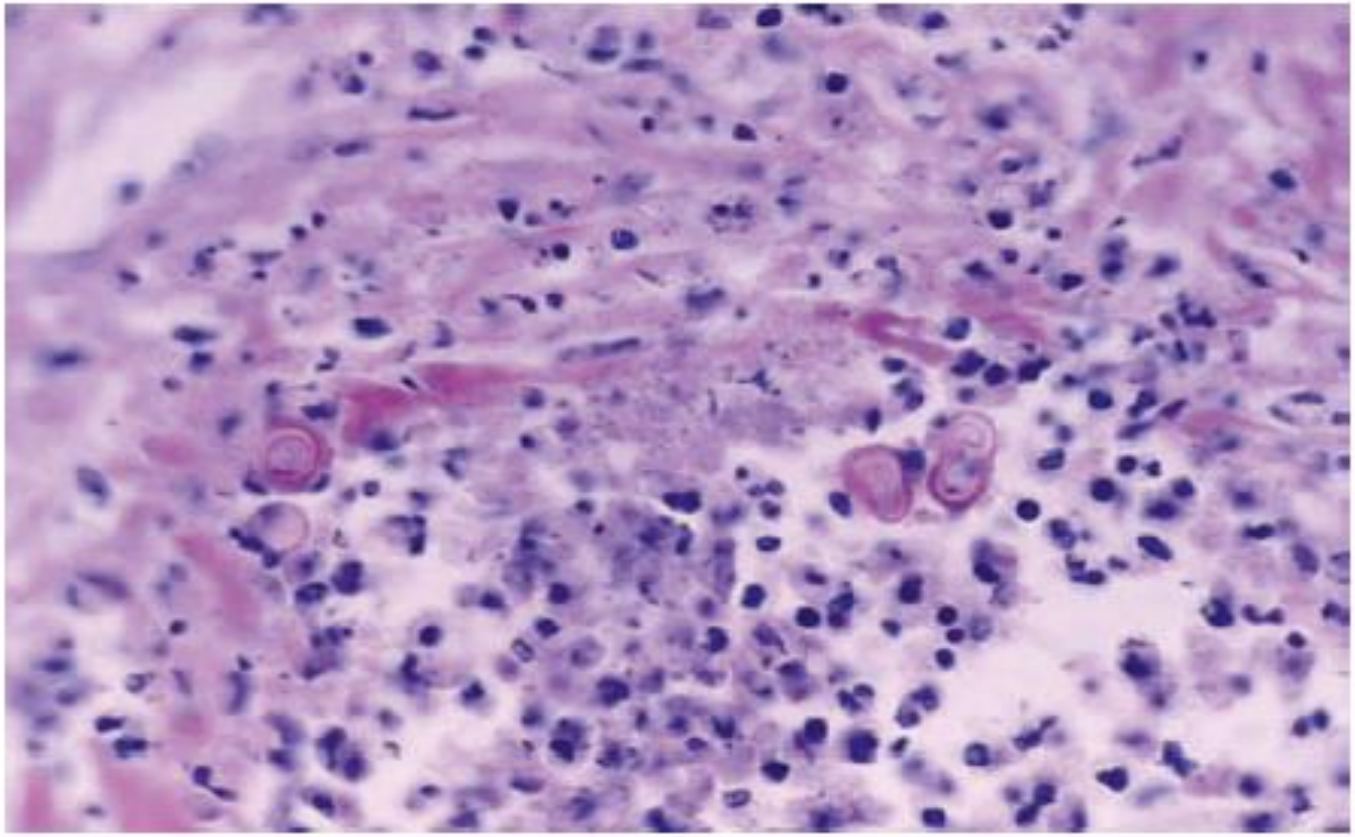


Fig. 2 Tissue obtained at lung biopsy showing broad-based budding yeast. Culture yielded *Blastomyces dermatitidis* (periodic acid – Schiff stain, 40×)

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, 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.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

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].

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 crossreactions
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 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 monocytederived 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 middleaged 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.

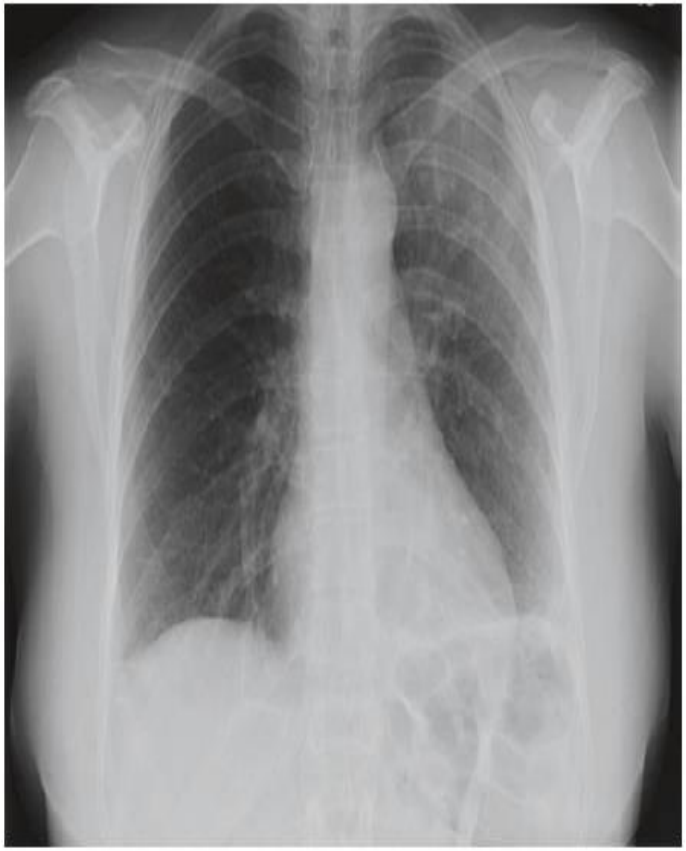


Fig. 3 Left upper and left lower lobe infiltrates in a 36-year-old woman with pulmonary blastomycosis (Courtesy of Dr. William Muth)

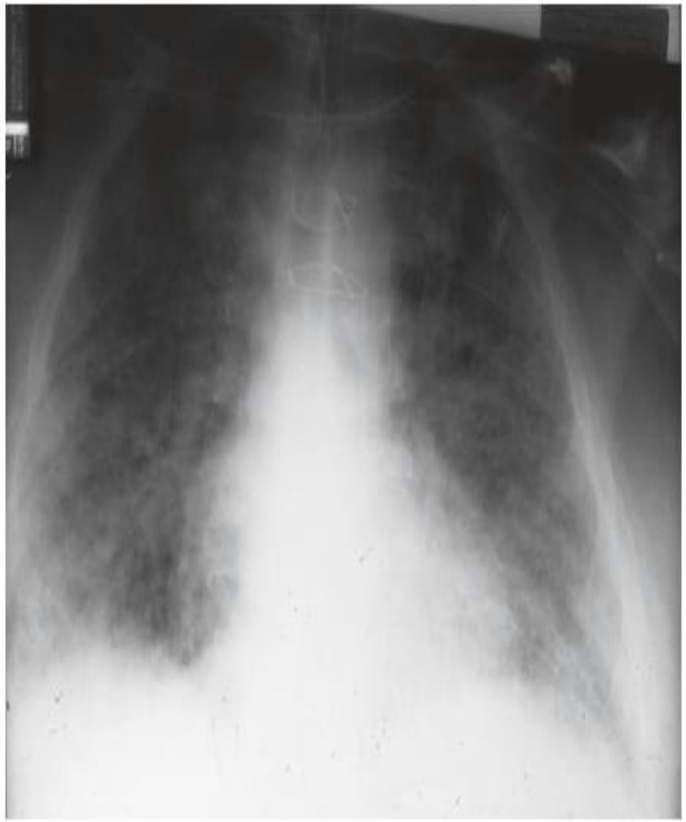


Fig. 5 Acute respiratory distress syndrome (*ARDS*) due to blastomycosis in a 60-year-old man who was previously healthy

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 verrucousappearance also can be found (Fig. 11).

These lesions are typically tender and may be confused with panniculitis or Weber-Christian disease [42].

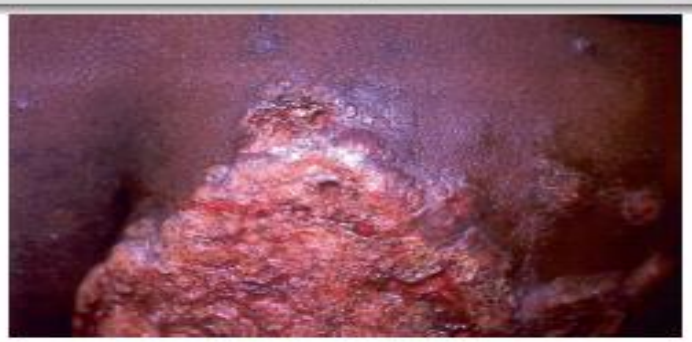


Fig. 6 Verrucous lesion with subcutaneous abscesses on the buttock caused by *Blastomyces dermatitidis*

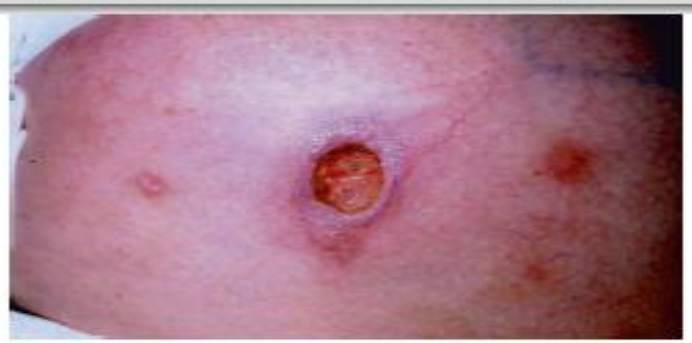


Fig. 9 Ulcerative lesion on the breast caused by *Blastomyces dermatitidis*. Note the distinct and raised borders

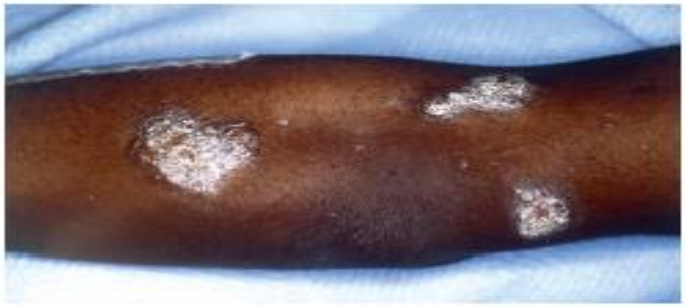


Fig. 7 Multiple verrrucous lesions on the forearm of a 20-year-old man with blastomycosis (Courtesy of Dr. Hector Bonilla)

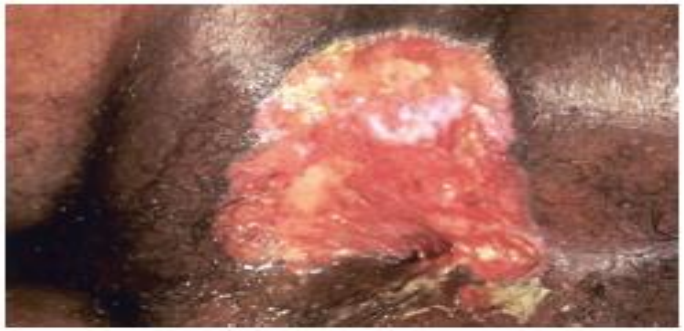


Fig. 10 Extensive perirectal ulcerative lesion with overlying exudate in a patient who had disseminated blastomycosis

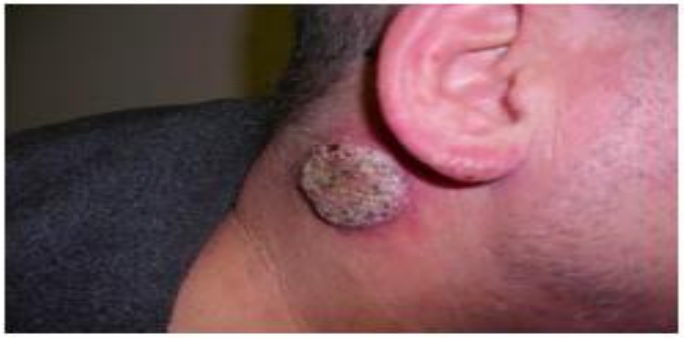


Fig. 8 Non-painful, heaped-up lesion due to *Blastomyces dermatitidis* behind the ear of a 35-year-old man

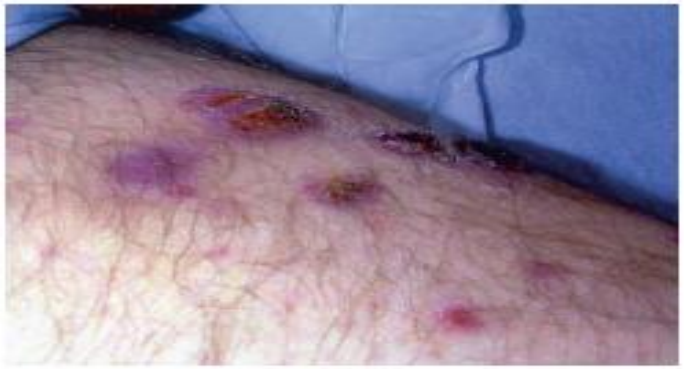
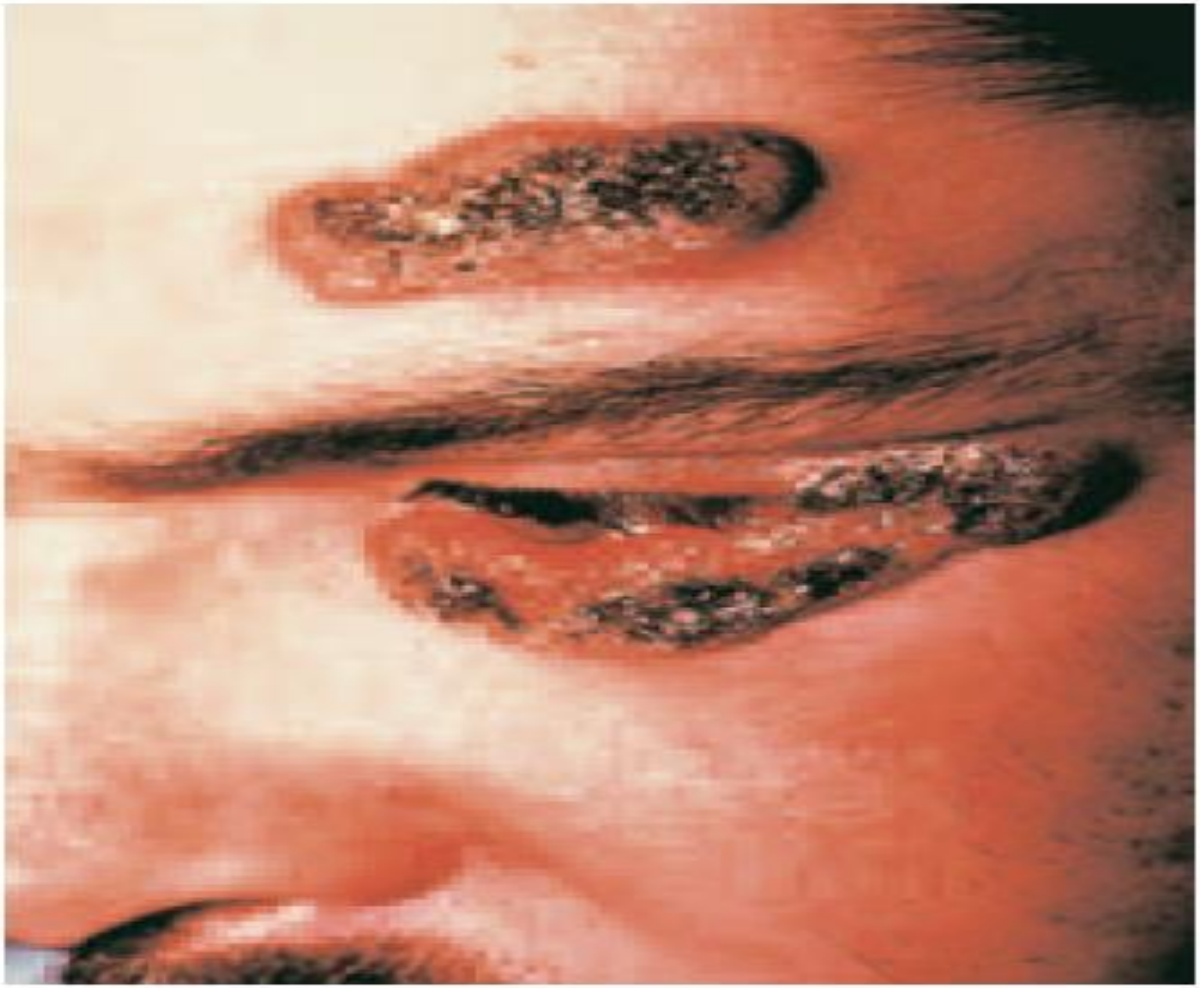


Fig. 11 Subcutaneous nodules with superficial crusts due to blastomycosis on the thigh of a young man

blastomycosis can be confused with a number of alternative



Cutaneous blastomycosis.

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 esions 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.

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].

Other Patient Groups

Blastomycosis has been reported to occur with other infections

or other illnesses, including tuberculosis, histoplasmosis,

and coccidioidomycosis [78].

Blastomycosis has beenbreported in two patients, one of whom presented with idiopathic

hrombocytopenic 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.

Colonies on blood agar at 37ºC are wrinkled, waxy and soft, the cells are morphologically similar to the tissue stage, although short hyphal segments may also be present.

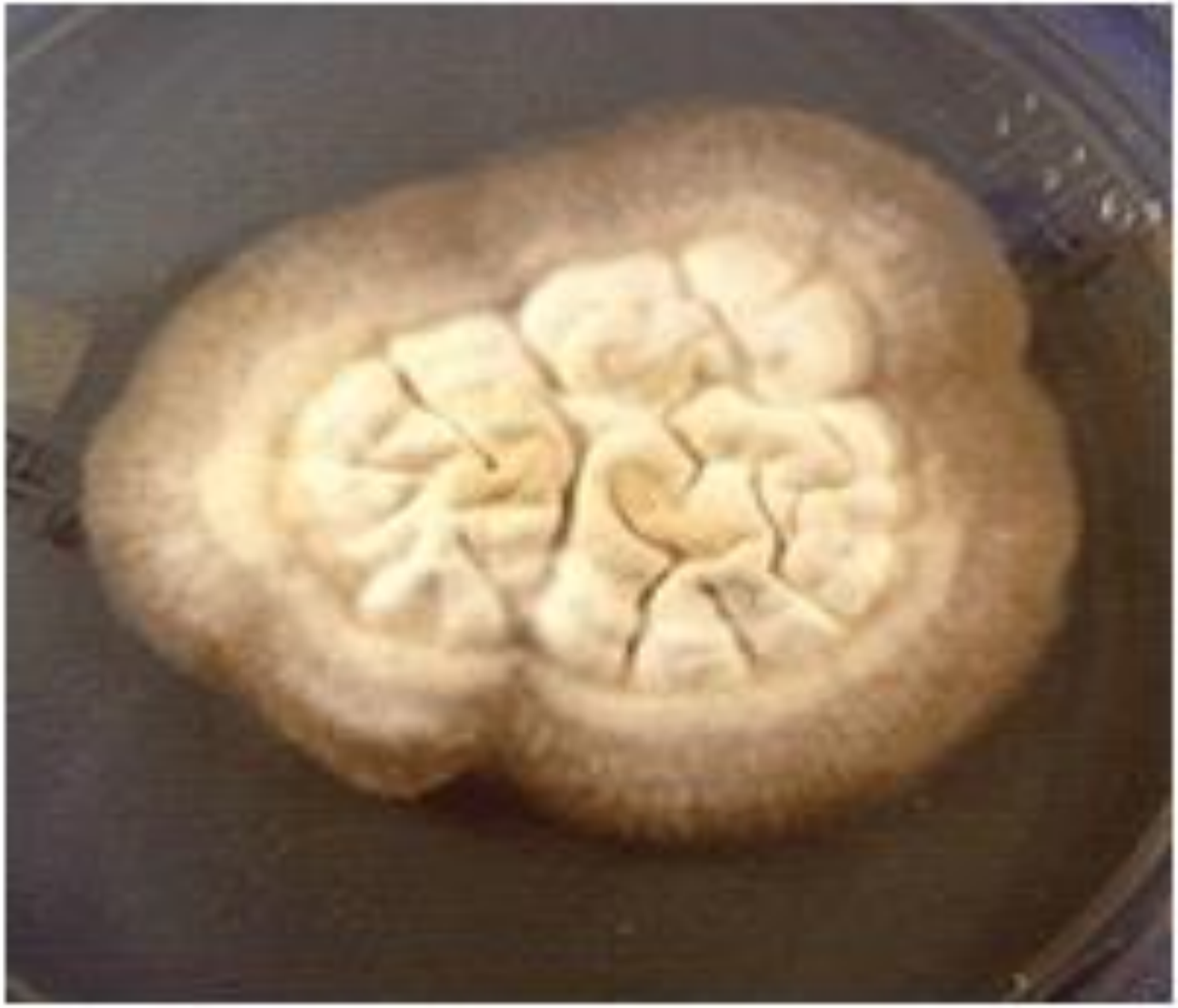
On sabouroad agar at room temperature, a white or brownish colony develops.

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.*

Colonies (SDA) at 25OC are variable in morphology and rate of growth. They may grow rapidly, producing a fluffy white mycelium or slowly as glabrous, tan, nonsporulating colonies (Fig. a).

Growth and sporulation may be enhanced by yeast extract.

Moststrains become pleomorphic with age. Microscopically, hyaline, ovoid to pyriform, onecelled, smooth-walled conidia (2-10 µm in diameter) of the *Chrysosporium type, are* borne on short lateral or terminal hyphal branches.

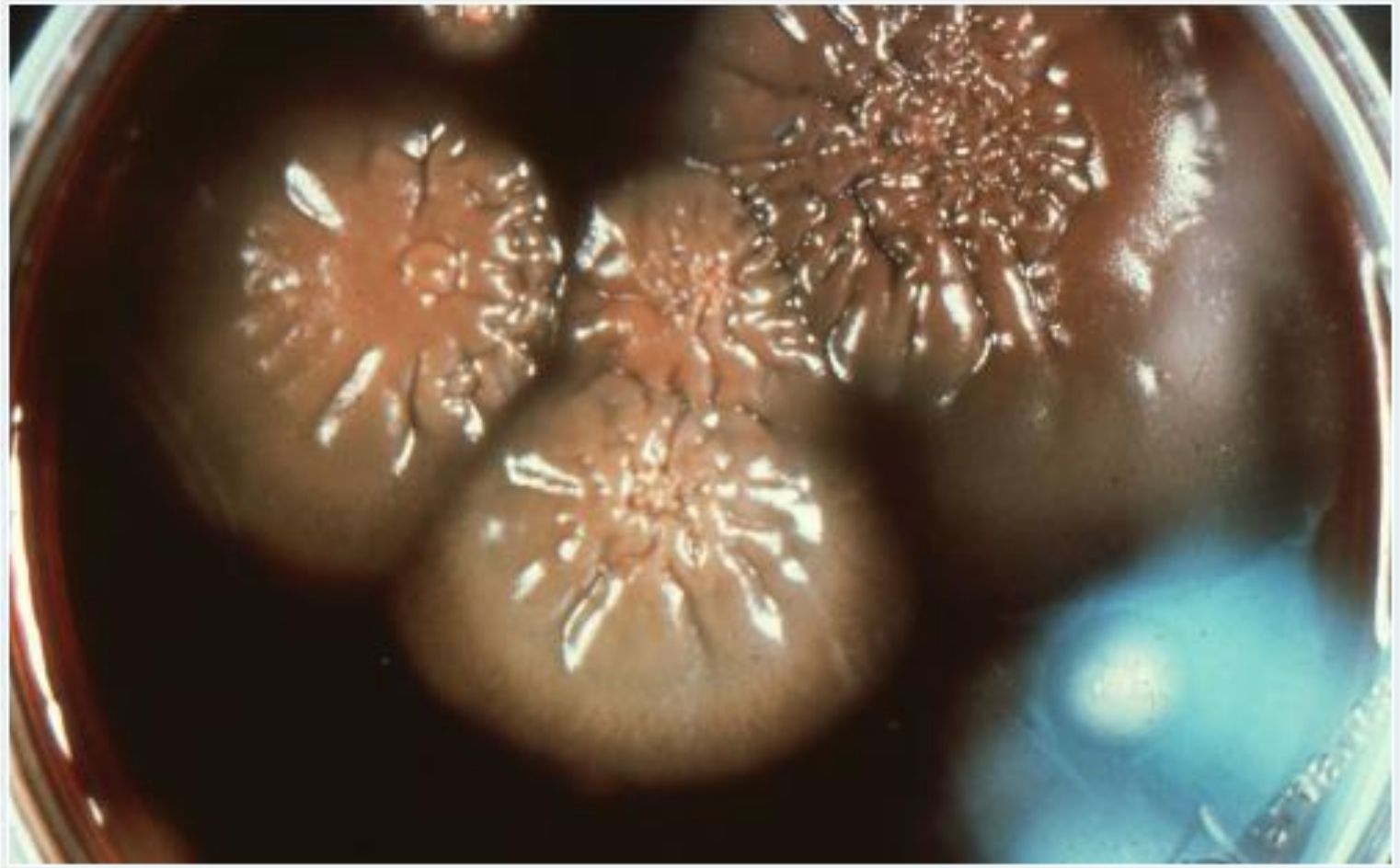


Colonies on blood agar at 37OC are wrinkled and folded, glabrous and yeast-like. Microscopically,

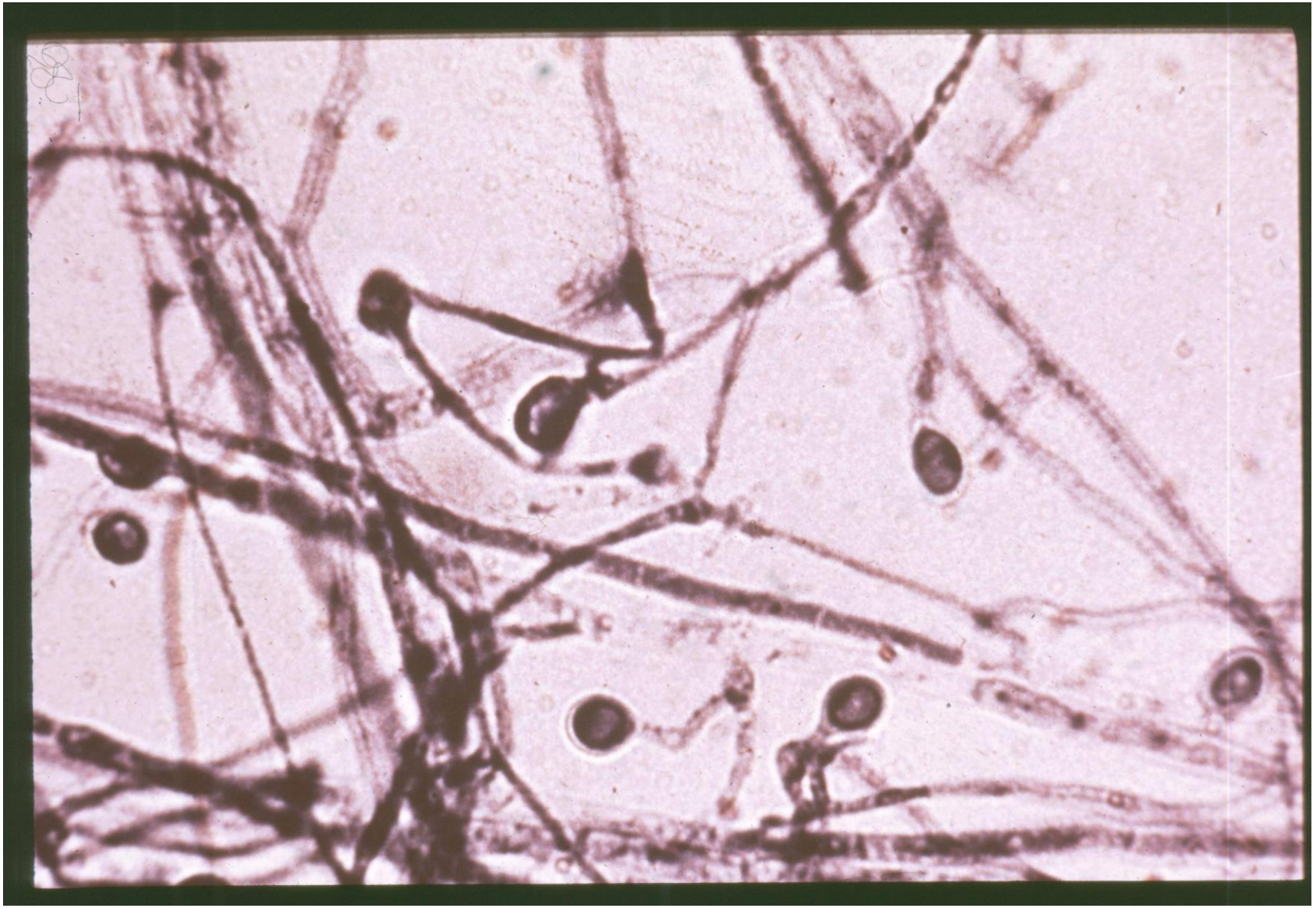
the organism produces the characteristic yeast phase as seen in tissue

pathology; ie. *B. dermatitidis is a dimorphic fungus.*

Colonies B. dermatitidis on blood agar at 37ºC



Colonies of Blastomyces dermatitidis on blood agar plates incubated at 30 C



Microscopic appearance of *Blastomyces dermatitidis*

WARNING: RG-3 organism. Cultures of *Blastomyces dermatitidis may represent a*

biohazard to laboratory personnel and should be handled in an appropriate pathogen

handling cabinet. In the past, conversion from the mould form to the yeast form was

necessary to positively identify this dimorphic pathogen from species of *Chrysosporium*

or *Sepedonium; however, culture identification by exoantigen test is now the method*

of choice.

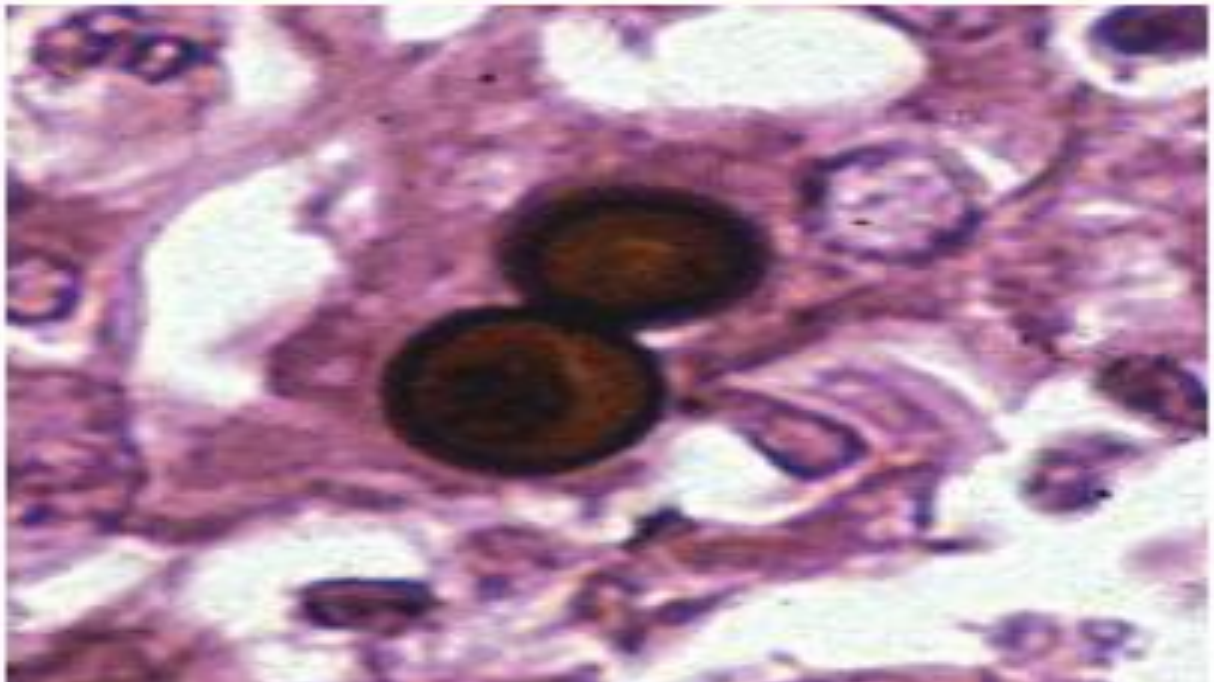
Histopathology

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 mm thick-walled, broad-based, budding yeast cells
[34].

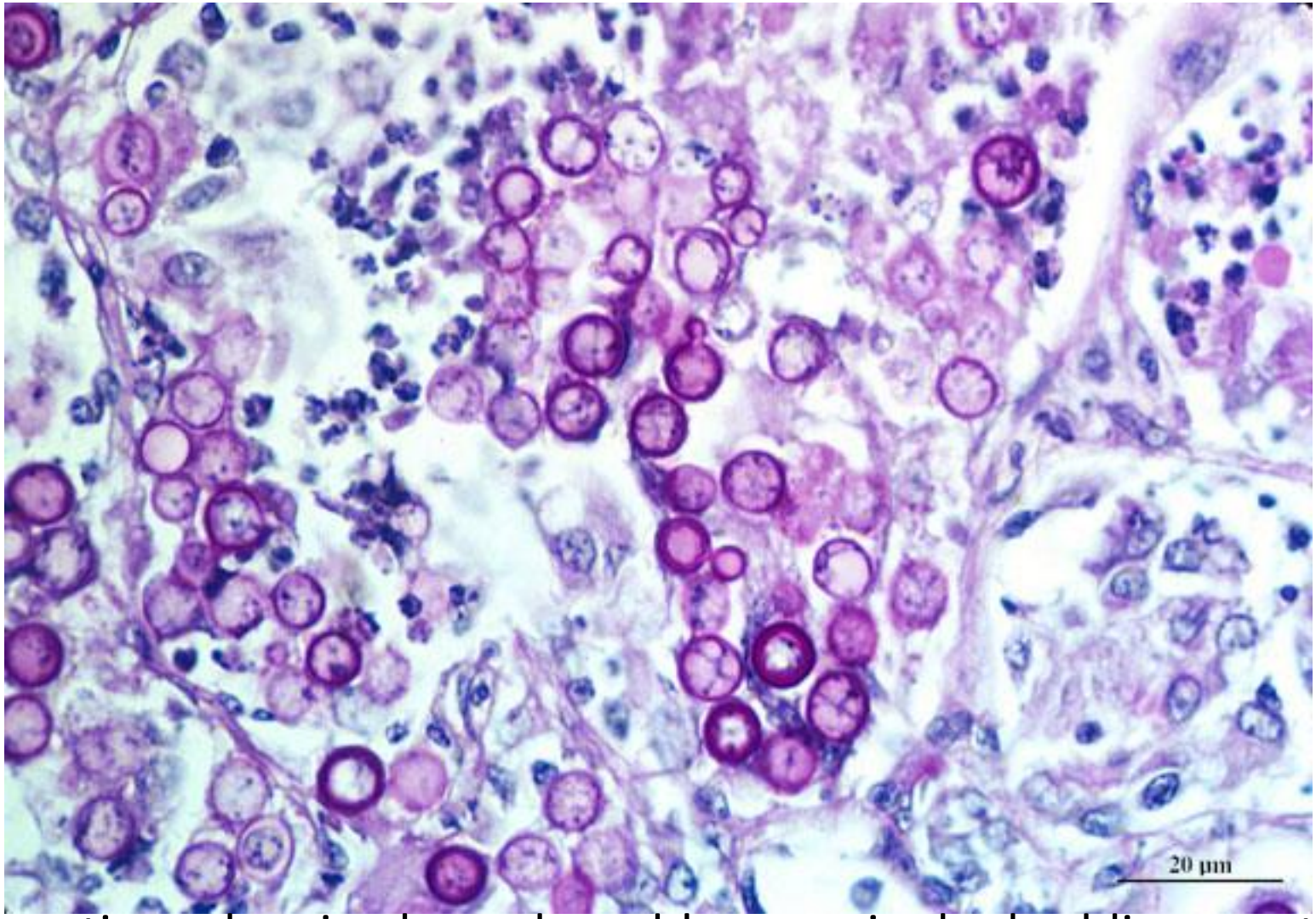
Cytological preparations stained with Papanicolau stain

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.



Tissue section showing large, broad-base, unipolar budding yeast-like cells and culture of *Blastomyces dermatitidis*.



Tissue sections showing large, broad-base, unipolar budding yeast-like cells, 8-15 um in diameter. Note: tissue sections need to be stained by Grocott's methenamine silver (GMS) method to clearly see the yeast-like cells.

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.

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.