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Fungal Infections of the Gastrointestinal Tract in the Immunocompromised Host-An Update

Laura W. Lamps, M.D.,
Dept. of Pathology, University of Arkansas for Medical Sciences, 4301 W. Markham Street, Slot 517, Little Rock, AR, 72205, 501-296-1458, Fax: 501-603-1479

Keith K.T. Lai, M.D., and
Dept. of Pathology, University of Arkansas for Medical Sciences, 4301 W. Markham Street, Slot 517, Little Rock, AR, 72205, 501-686-5182, Fax: 501-603-1479

Dr. Danny A. Milner Jr., M.D., MSc
Dept. of Pathology, Brigham and Women's, Harvard Medical School, 75 Francis Street, MR-7, Boston, MA 02115, 617 -525- 7761

Abstract

Fungal infections are one of the most significant causes of morbidity and mortality in immunocompromised patients. The incidence of invasive fungal infections, including those of the gastrointestinal tract, has increased significantly as numbers of immunocompromised patients have increased. The diagnosis of fungal infections in immunocompromised patients may be particularly problematic as these patients may present with atypical clinical features. Although *Candida* and *Aspergillus* species represent the majority of fungi diagnosed in the immunocompromised patient population, other fungi are emerging as increasingly common pathogens, and this review will focus on several important emerging fungal infections in immunocompromised patients.

Infections are one of the most common complications in immunocompromised patients, and the endemic mycoses are one of the most significant infectious causes of morbidity and mortality in this population (1-3). The incidence of invasive fungal infections, including those of the gastrointestinal tract, has increased significantly over the past 20 years as numbers of immunocompromised patients have increased. Despite advances in laboratory technology, particularly in the areas of serologic and molecular testing, the recognition, diagnosis, and classification of fungal infections in this patient population remains challenging.

Although primary transmural invasion by fungi cause some gastrointestinal infections, disseminated fungal disease (and recognition therof) is equally important. Signs and symptoms of gastrointestinal fungal infections include diarrhea, vomiting, melena, hemorrhage, abdominal pain, and fever, and are often similar regardless of the type of

Correspondence to: Laura W. Lamps.
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fungus involved. The diagnosis of fungal infections in immunocompromised patients may be particularly problematic as these patients may present with atypical clinical features, and it is important to remember that GI signs and symptoms may be the initial and only presenting features of a disseminated illness.

The term “immunocompromised” is primarily associated with underlying disorders such as AIDS, chemotherapy, and solid organ and bone marrow transplantation. However, many other forms of immunocompromise also result in susceptibility to fungal infections, including primary immunodeficiencies (e.g. common variable immunodeficiency), patients on chronic immunomodulatory therapy or steroids, very young or very elderly patients, diabetics, patients who are status-post splenectomy, and those with chronic alcoholism, malnutrition, or any chronic debilitating disease (4-7).

Although *Candida* and *Aspergillus* species represent the majority of fungi diagnosed in the immunocompromised patient population (5-6), other fungi are emerging as increasingly common serious pathogens. The organism to which any individual patient is susceptible varies with a number of factors, including the underlying disease, the degree of immunocompromise, and environmental factors such as where the patient lives and types and magnitude of exposure. Furthermore, the host is the sole source of the inflammatory response to the organism, and the specific deficits in the host immune system along with the patient's environment and exposure history create the differential diagnosis for any given mycosis. This review will focus on several important emerging fungal infections in immunocompromised patients.

Filamentous Fungi

Mucormycosis is a life-threatening infection caused by fungi of the order *Mucorales* (8-12). As noted above, *Aspergillus* species have long been recognized as the most commonly encountered filamentous fungus in the immunocompromised patient population. For reasons that remain poorly understood, however, the incidence of mucormycosis is increasing, particularly in patients with diabetes, hematologic malignancies, and bone marrow transplants (8). Recent reclassification abolished the order known as the *Zygomycetes*, and placed the order *Mucorales* in the subphylum *Mucormycotina* (13). Therefore, infection by these organisms is now referred to as “mucormycosis” rather than “zygomycosis.” Mucormycosis is associated with diabetes and other causes of metabolic acidosis, deferoxamine therapy, organ or bone marrow transplant, neutropenia, skin and soft tissue breakdown, intravenous drug use, neonatal prematurity, and malnourishment. Interestingly, HIV/AIDS does not appear to be a risk factor for this infection. The incidence appears to be increasing, especially in cancer patients. The mortality rate is quite high (over 40% in general, and even higher in patients with hematologic malignancies and those status post bone marrow transplant (9-12).

The major categories of disease caused by the *Mucorales* are sinonasal/rhinocerebral, pulmonary, cutaneous/subcutaneous, gastrointestinal, and disseminated infection (9-12). Sinonasal/rhinocerebral disease represents one-third to one-half of all cases, and is most often associated with diabetic ketoacidosis. Pulmonary disease is also common.

Gastrointestinal zygomycosis (14-16) is relatively uncommon, but often fatal, with mortality reportedly approaching 40-50%. Although any portion of the alimentary tract can be affected, gastric and colonic involvement are the most frequent. Ulcers are the most common gross manifestation, often large, with rolled, irregular edges that may mimic malignancy. These fungi may also superinfect previously ulcerated tissues, and disseminated disease may arise from primary gastrointestinal infection.

The lesions caused by *Mucor* and related species are histologically very similar to those seen in aspergillosis (Figure 1) (17-18). Both *Mucor* and *Aspergillus* are angioinvasive (Figure 2), leading to thrombosis and areas of infarction and necrosis. The inflammatory response is variable, but neutrophils are usually prominent (Figure 3). *Mucor* produces broad, ribbon-like pauciseptate hyphae with irregular walls, which branch randomly at any angle (Figure 4). When cut at cross-section, they may appear optically clear. They do not produce spores. Segmented atypical forms can rarely be seen, which have a variable large, round to oval appearance and bear internal structures (Figure 3C).

Differential Diagnosis

The differential diagnosis of mucormycosis primarily includes other fungal infections (see Table 1). As above, aspergillosis and mucormycosis can closely mimic each other both clinically and morphologically (Figure 5) (17-18). In contrast to *Mucor*, however, *Aspergillus* has septate hyphae of uniform width that branch at acute angles. *Fusarium*, an emerging filamentous fungal pathogen that is also associated with neutropenia, closely mimics aspergillosis both clinically and radiographically, and is indistinguishable from *Aspergillus* on morphologic grounds alone (19).

Basidiobolomycosis—Basidiobolomycosis is another fungus in the differential diagnosis of mucormycosis that has recently gained attention as a gastrointestinal pathogen (20-27). The causative organism, *Basidiobolus ranarum*, is a zygomycete of the order *Entomophthorales*, and a worldwide soil saprophyte. This infection was originally described in Africa, Saudi Arabia, and Southeast Asia, but has recently gained attention in the United States, primarily in Arizona (24,26). Risk factors include pediatric age group, peptic ulcer disease, diabetes, pica, ranitidine use, and living in an endemic area. Of note, unlike many of the other filamentous fungi, typical causes of immunocompromise such as neutropenia, HIV/AIDS, and organ transplantation are not risk factors for this infection. Gastrointestinal infections may mimic malignancy or chronic idiopathic inflammatory bowel disease clinically, and pericolonic masses that are worrisome for colon cancer are common in this disease (27).

Although the fungi themselves are morphologically similar to *Mucor*, there are typically fewer of them on a given tissue section, and the fungi may have a “cellophane-ball” or crumpled appearance (Figure 6). In addition, *Basidiobolus* is not angioinvasive. The inflammatory response is also quite different from that of mucormycosis, featuring prominent eosinophilia, granulomas, and a Splendore-Hoeppli reaction to organisms (Figure 7).

Phaeohyphomycosis—Phaeohyphomycosis refers to infections caused by various (over 70 recognized species) dematiaceous or naturally pigmented fungi that develop as black molds in culture, and are visible as pigmented brown organisms in tissue sections. These fungi are worldwide saphrophytes present in soil, wood, and compost. Infections typically occur in immunocompromised hosts, and risk factors include neutropenia, bone marrow or solid organ transplantation, and exposure to dirt/soil through farming, gardening, or other outdoor work (28-34). Infections are most often subcutaneous, but gastrointestinal infections rarely occur, probably through colonization of pre-existing ulcers (35). The inflammatory reaction is mixed, and may consist of neutrophils, granulomas, or both. The organisms appear as variable sized, often branched fungi that are pigmented (Figure 8), although the pigment may be difficult to detect on H&E in some cases (17). Fontana Masson stains may be useful in accentuating the melanin pigment. (Table 1)

Ancillary Tests

Accurate speciation of fungal infections is critical, because it significantly affects antifungal therapy. Culture remains the gold standard of diagnosis and speciation for fungal infections but it may require a substantial amount of time for cultures to grow and to achieve speciation. More importantly, because of the clinical setting, culture material is not always available. The use of 18S rRNA sequence to identify fungus directly by polymerase chain reaction and sequencing is increasingly available as well, and can be performed directly from either culture material or the paraffin tissue block. The phaeohyphomycoses cannot be speciated with certainty morphologically, and culture or molecular studies are required for definite classification. If no material is available for culture, then molecular assays should be attempted, or the patient should be re-biopsied so that cultures can be performed.

In addition to molecular testing, there are two serological laboratory tests (36) that are helpful for distinguishing between the various filamentous fungi that may be encountered on a slide. Galactomannan is a component of the *Aspergillus* cell wall that is released during growth. The galactomannan assay is a serologic test that is helpful in diagnosing invasive aspergillosis, as it is positive in invasive aspergillosis but negative in other invasive fungal infections. Thegalactomannan assay will cross-react with *Penicillium marneffei*, however(see below). The beta (1.3) D glucan assay is also helpful, as it is positive in virtually all disseminated fungal infections including *Pneumocystis* infection, but is negative inmucormycosis.

The Differential Diagnosis of Yeast

Candida species are what most often comes to mind when considering gastrointestinal infections with yeast forms, and *Cryptococcus* remains the most common cause of mortality due to fungal infection in the HIV population (37). However, many other less common but important yeasts are emerging as important pathogens in the immunocompromised patient population.

Penicillium marneffei is a dimorphic fungus that is endemic in Thailand, China, Hong Kong, Vietnam, and Indonesia. Patients with this infection who are encountered in the USA have almost always either traveled in these areas or lived there (38-42). Penicilliosisis emerging

as one of the most common opportunistic infections in Asian patients with AIDS (39, 42). Patients with this infection who are HIV-negative often have other immunocompromising conditions such as hematologic malignancies, autoimmune diseases, malnutrition or other debilitating infections, and this infection has rarely been described in immunocompetent persons. *P. marneffei* most commonly involves the lungs and liver, followed by the GI tract. Dissemination can occur in a matter of a few weeks and be quickly fatal, especially in immunocompromised patients.

The organism infects the mononuclear phagocyte system, and multiplies within histiocytes that enlarge to accommodate increasing numbers of organisms. The inflammatory response may be granulomatous, suppurative, or mixed (Figure 9). The organisms themselves are spherical to ovoid, and pack and distend the involved macrophages. As the lesions expand, necrosis predominates, and the macrophages may lyse and release free organisms. The fungi are typically small (2-5 microns) and resemble histoplasma; however, occasional elongated and/or curved forms with a central septum and rounded ends ("pill capsule" form) may be present (Figure 10), and these may measure up to 20 microns. In addition, *P. marneffei* do not bud, as they divide at their central septum by fission.

Differential Diagnosis

Histoplasmosis—The major organism in the morphological differential diagnosis is *Histoplasma capsulatum*, as both may be intracellular and are of similar size (43-44). *Histoplasma capsulatum* is endemic to the central United States but has been described in many nonendemic areas as well. GI involvement occurs in more than 80% of patients with disseminated infection. Histologic findings include diffuse lymphohistiocytic infiltrates and nodules, usually involving the mucosa and submucosa, with associated ulceration (Figure 11). These lesions are often located over lymphoid aggregates. Discrete granulomas and giant cells are present in only a minority of cases. In immunocompromised patients, large numbers of organisms may be seen with virtually no tissue reaction. Whereas *Histoplasma* have easily identified buds at their pointed pole (Figure 12) *P. marneffei* does not bud and has a transverse septum. On H&E staining, *Histoplasma* with in macrophages also have a surrounding small "halo," reflecting the thin, poorly stained cell wall in contrast to the basophilic cytoplasm. In addition, the areas in which these two yeasts are endemic are very distinct.

Cryptococcosis—*Cryptococcus neoformans* is a very commonly encountered yeast in the immunocompromised patient population that is an unusual but important cause of GI infection (45-46). Virtually all patients with GI cryptococcosis have hematogenously disseminated disease with multisystem organ involvement, and most have associated pulmonary and meningeal disease. The inflammatory reaction is variable and depends on the immune status of the host, ranging from a suppurative, necrotizing inflammatory reaction, often with granulomatous features, to virtually no reaction such as in anergic hosts. *Cryptococcus* (measuring 4-7 microns) is larger than *P. marneffei*, typically shows considerable variation in size (Figure 13). *Cryptococcus* is round to oval and often has a "soap-bubble" area of clearing around the organism representing the poorly stained capsule on H&E sections. It also has frequent budding, and lacks the transverse septum of *P.*

marneffei. Cryptococcus stains with Fontana-Masson and often with mucicarmine. Of note, capsule-deficient *Cryptococcus neoformans* and *Cryptococcus gattii* (an emerging variant of *Cryptococcus* that is particularly prominent in the Pacific Northwest [47-48]) will often be negative with mucicarmine staining, and require Fontana-Masson or other diagnostic methods for diagnosis (Figure 14).

Pneumocystosis—*Pneumocystis jiroveci* (formerly *carinii*) is also an important entity in this patient population. Although the life cycle of this organism more closely resembles that of a protozoan, there is convincing molecular evidence indicating that *P. jiroveci* has greater homology with fungi. Extrapulmonary (including GI) involvement is not uncommon in the immuncompromised population (49-50), and in addition to patients with AIDS, *Pneumocystis* infection rarely has been reported in the context of organ transplant, hematologic malignancy, other immunodeficiency states, and steroid therapy. *Pneumocystis* infection has also been reported in association with infliximab therapy, an immunosuppressive treatment for Crohn's disease and rheumatoid arthritis (50). Microscopically, granular, foamy eosinophilic casts similar to those seen in pulmonary *Pneumocystis* infection may be seen in mucosal vessels or in the lamina propria, which helps differentiate this from other types of infection (Figure 15). As in the lung, a wide variety of inflammatory responses may occur, including granulomatous inflammation, prominent macrophage infiltrates, and necrosis. The organisms are 5-7 micron spherules that have cup or crescent shapes when collapsed (Figure 16), but lack the transverse septum of *P. marneffei*, and do not pack and distend macrophages. Many contain characteristic single or paired comma-shaped internal structures. Organisms stain with GMS and Toluidine blue. *Pneumocystis* does not bud, as well, which helps differentiate them from other similarly sized yeast.

Other entities in the differential diagnosis include *Candida glabrata*, which features tiny budding yeast forms of similar size to *Histoplasma* and *P. marneffei*, but does not produce hyphae or pseudohyphae (Figure 17) (17). *C. glabrata* also have more frequent buds than *Histoplasma*, are often extracellular, and lack the “halo” that *Histoplasma* have in tissue sections. *C. glabrata* does not typically pack and distend macrophages, and lacks the transverse septum of *P. marneffei. Candida* species yeast forms will also stain Gram positive on Gram stain.

Occasionally other types of organisms such as *Leishmania* or *Toxoplasma* may enter the differential diagnosis of the smaller yeasts. *Leishmania* have a characteristic kinetoplast, are GMS negative, and stain with Giemsa stain (Figure 18). Toxoplasma is also GMS negative and stains with Giemsa (Figure 19).

Ancillary Tests

As with the filamentous fungi, accurate speciation of these invasive yeasts is critical, because it significantly affects therapy. When material is available, cultures are extremely helpful, although diagnostic features may be present on tissue sections that allow institution of therapy without waiting for mycological culture results. Molecular assays for many of these yeasts are increasingly widely available as well, and can often be performed directly

from the paraffin block. Immunohistochemistry and in-situ hybridization assays are available for some of these entities, but are not widely available.

As mentioned above, serologic tests (36) may be helpful in this category of fungal infections as well. The galactomannan assay for detection of *Aspergillus* infection will cross-react with *P. marneffei* (51), which may have utility as the organisms appear quite different in tissue. The beta (1.3) D glucan assay is also helpful, as it is positive in *Pneumocystis* infection. (Table 2)

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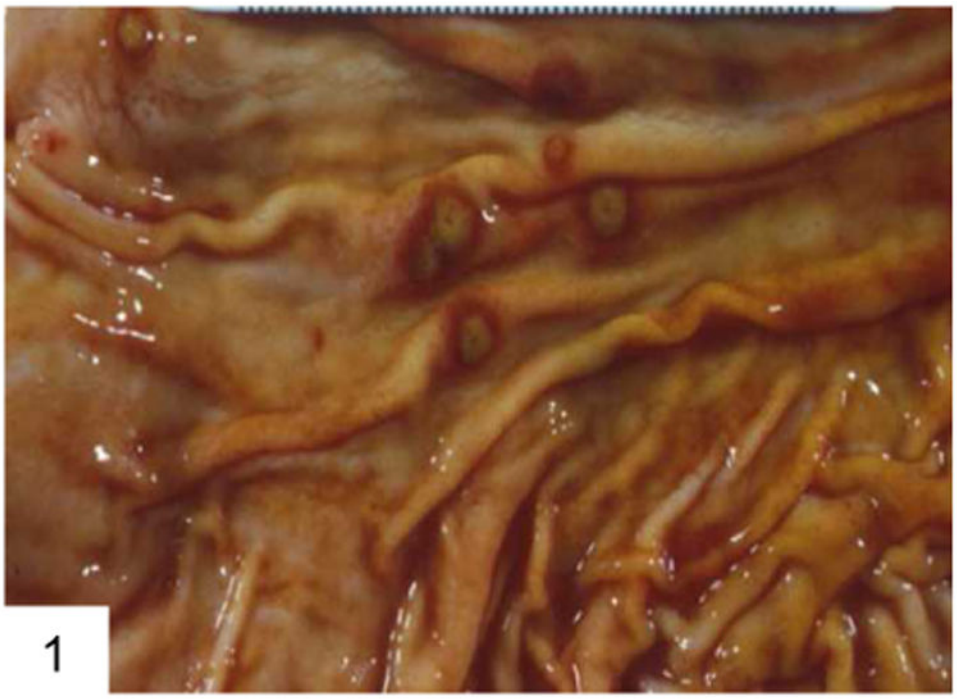

Figure 1.
This case of gastric aspergillosis illustrates the classic “target lesions” produced by angioinvasive fungi, which occlude vessels and lead to surrounding infarction and necrosis (courtesy Dr. George F. Gray Jr.).

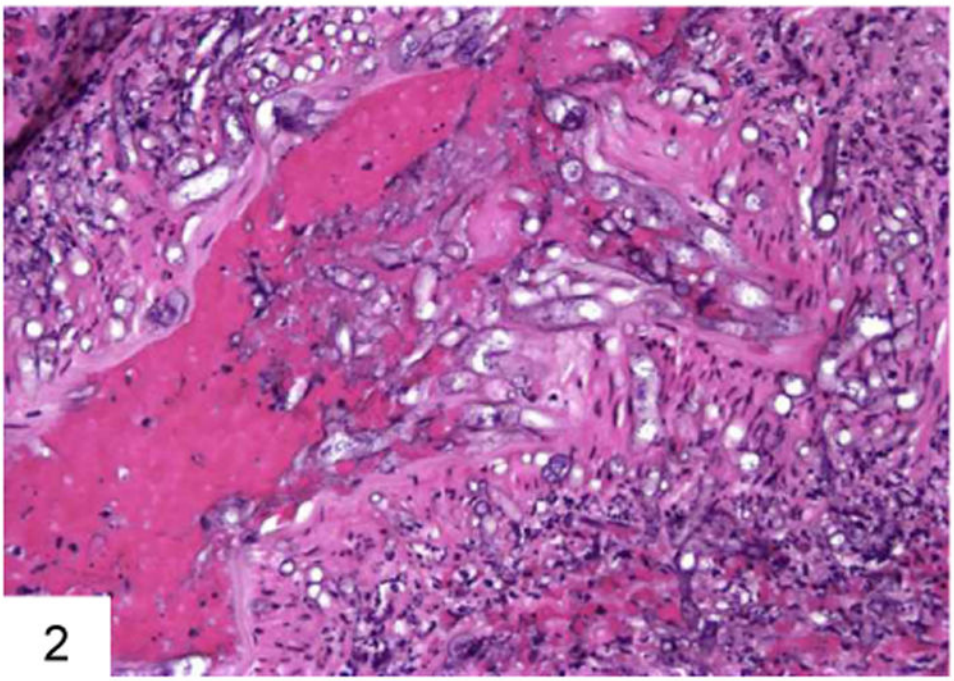

Figure 2.
This blood vessel wall has been invaded by *Mucor*, with associated inflammation and necrosis. Note the large pauciseptate hyphae with optically clear centers on cross section.

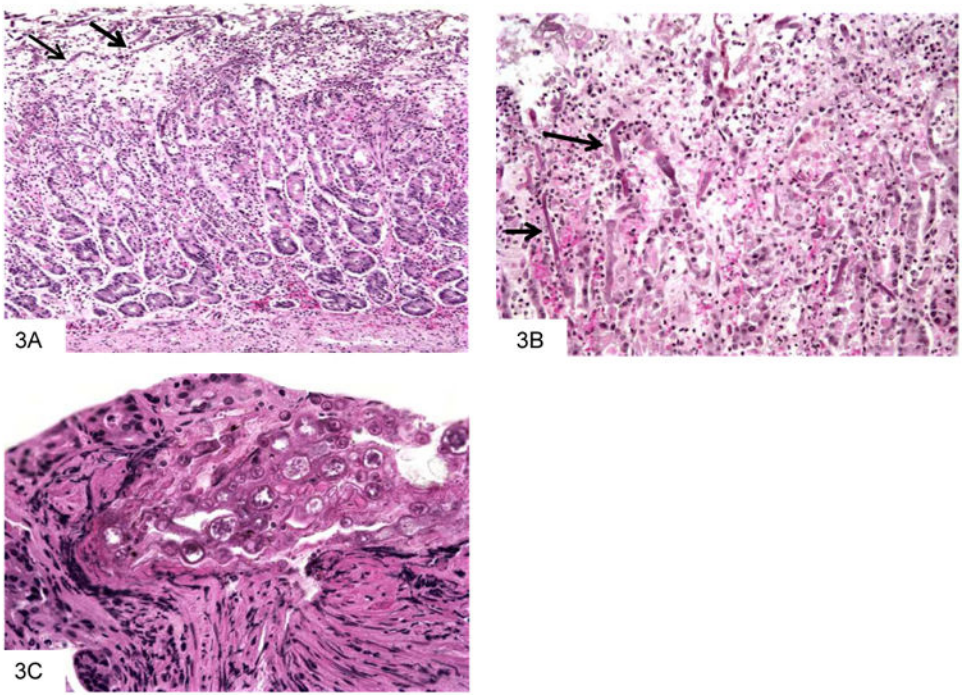

Figure 3.

This gastric biopsy shows a predominantly neutrophilic infiltrate, with admixed fungal forms that are most easily seen near the mucosal surface (A). A higher power view shows the irregular, ribbon-like appearance of the hyphae (B). Segmented atypical forms are rarely seen, which have a variable large, round to oval appearance and bear internal structures (C).

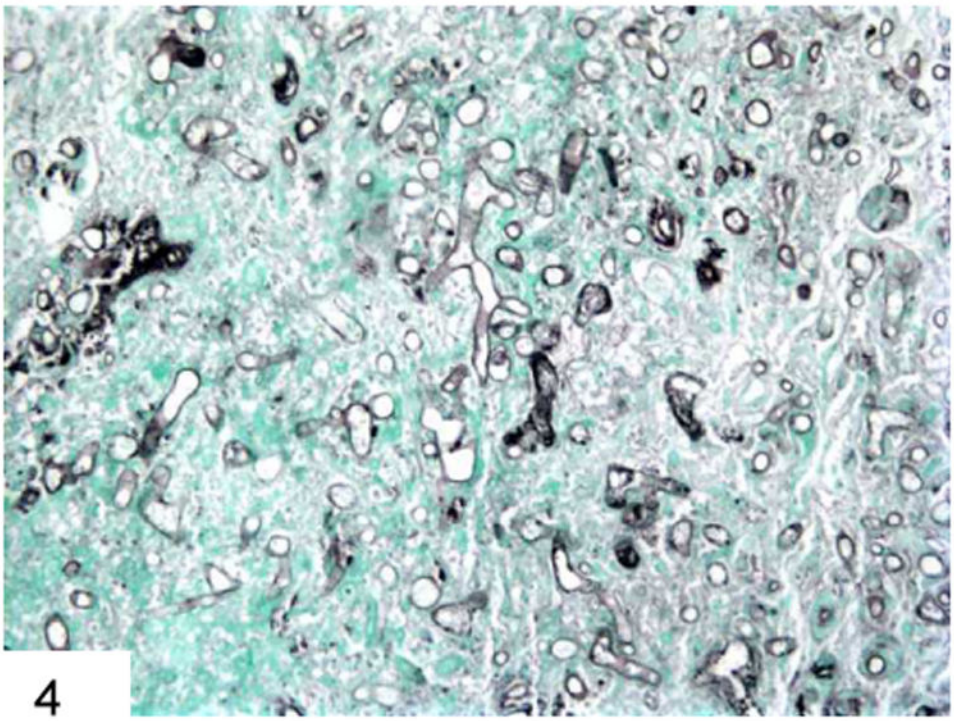

Figure 4.
GMS stain shows the broad, pauciseptate ribbon-like hyphae of *Mucor* with irregular branches and optically clear centers, especially on cross-section.

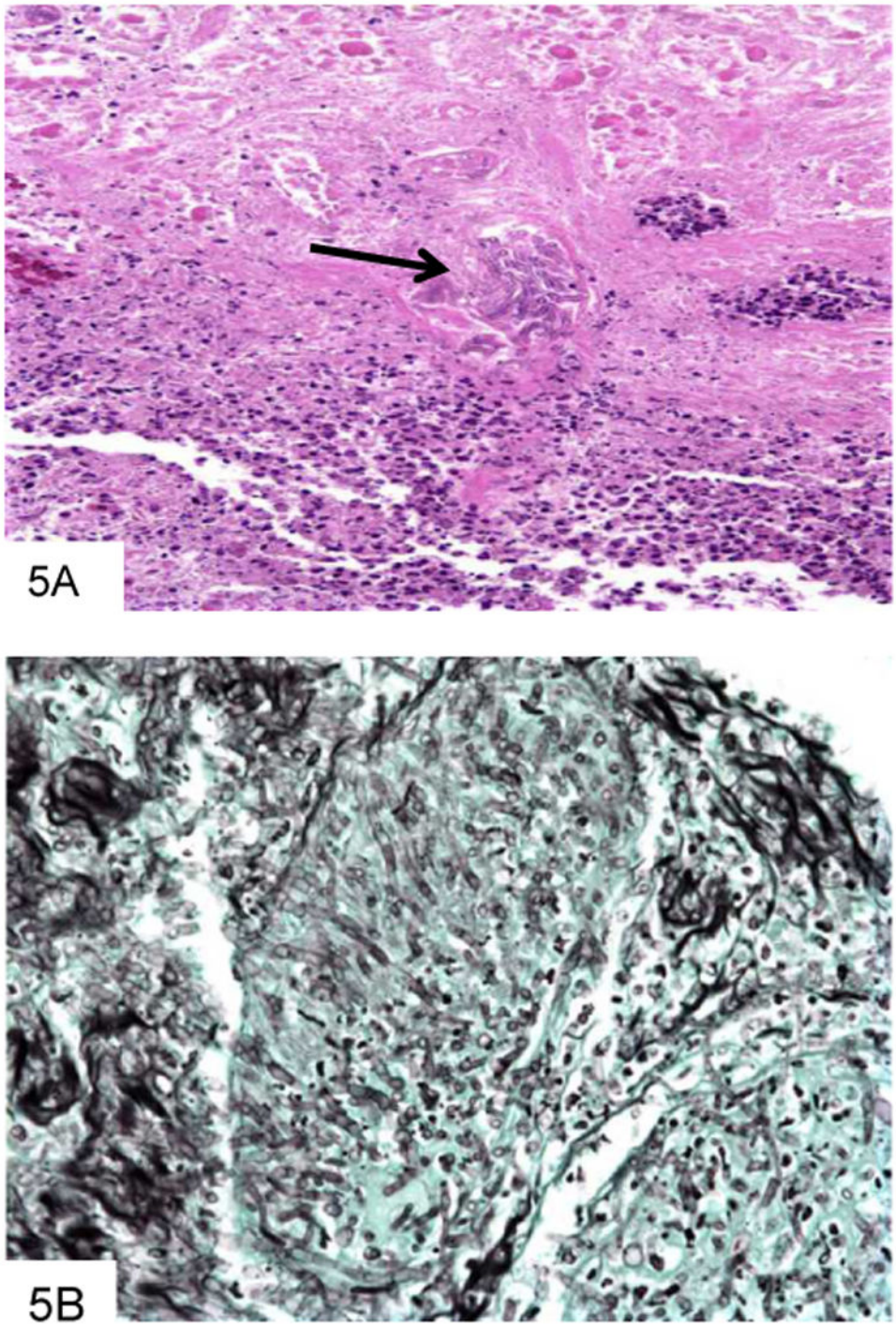

Figure 5.

This gastric biopsy shows a vessel occluded with *Aspergillus*, with surrounding necrosis and infarction (A). The septate hyphae of *Aspergillus* are narrower than *Mucor*, as seen on this GMS stain, and branch at acute angles (B). Note the vessel occluded by fungi in the middle of the field.

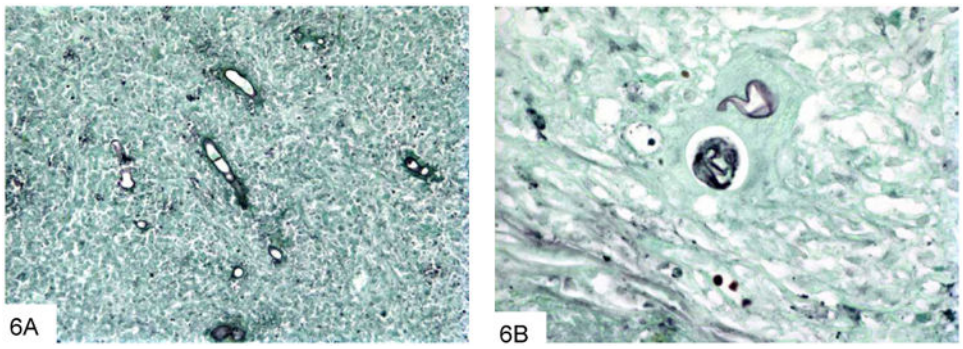

Figure 6.

This GMS stain of basidiobolomycosis shows fewer organisms than typically seen with *Mucor*, rare septae, and optically clear centers on cross-section. There is very little branching (A). *Basidiobolus* may show a “crumpled cellophane ball” appearance as well.

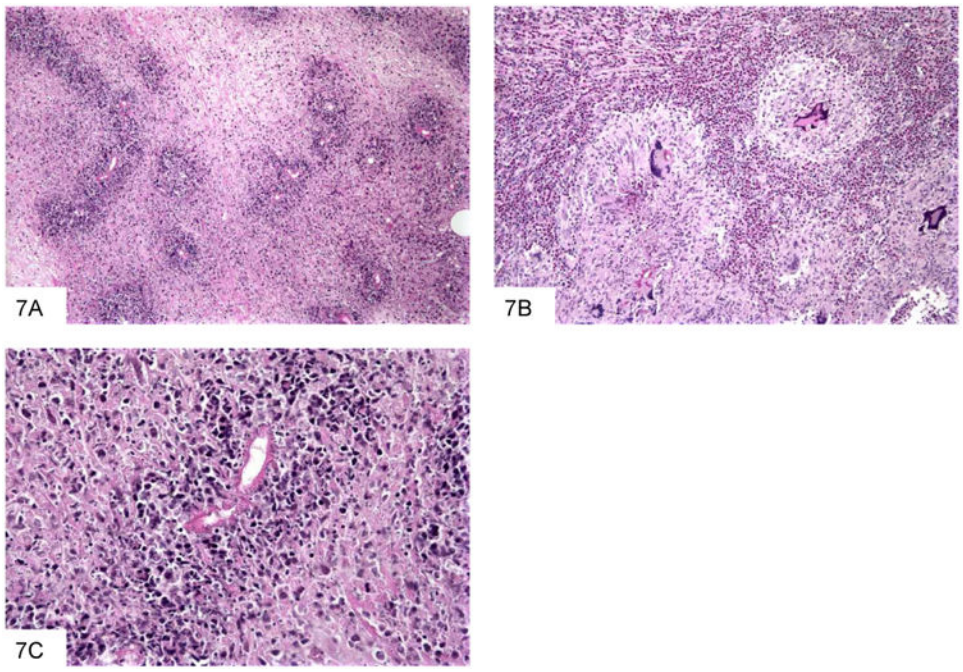

Figure 7.

This section of a paracolonic mass due to *B. ranarum* shows extensive necrosis and scattered organisms highlighted by the bright pink protein deposition known as Splendore-Hoeppli phenomenon (A). Basidiobolomycosis often features granulomas with giant cells, and abundant eosinophils (B). This high power view shows a fungus outlined by bright pink proteinaceousmaterial (C).

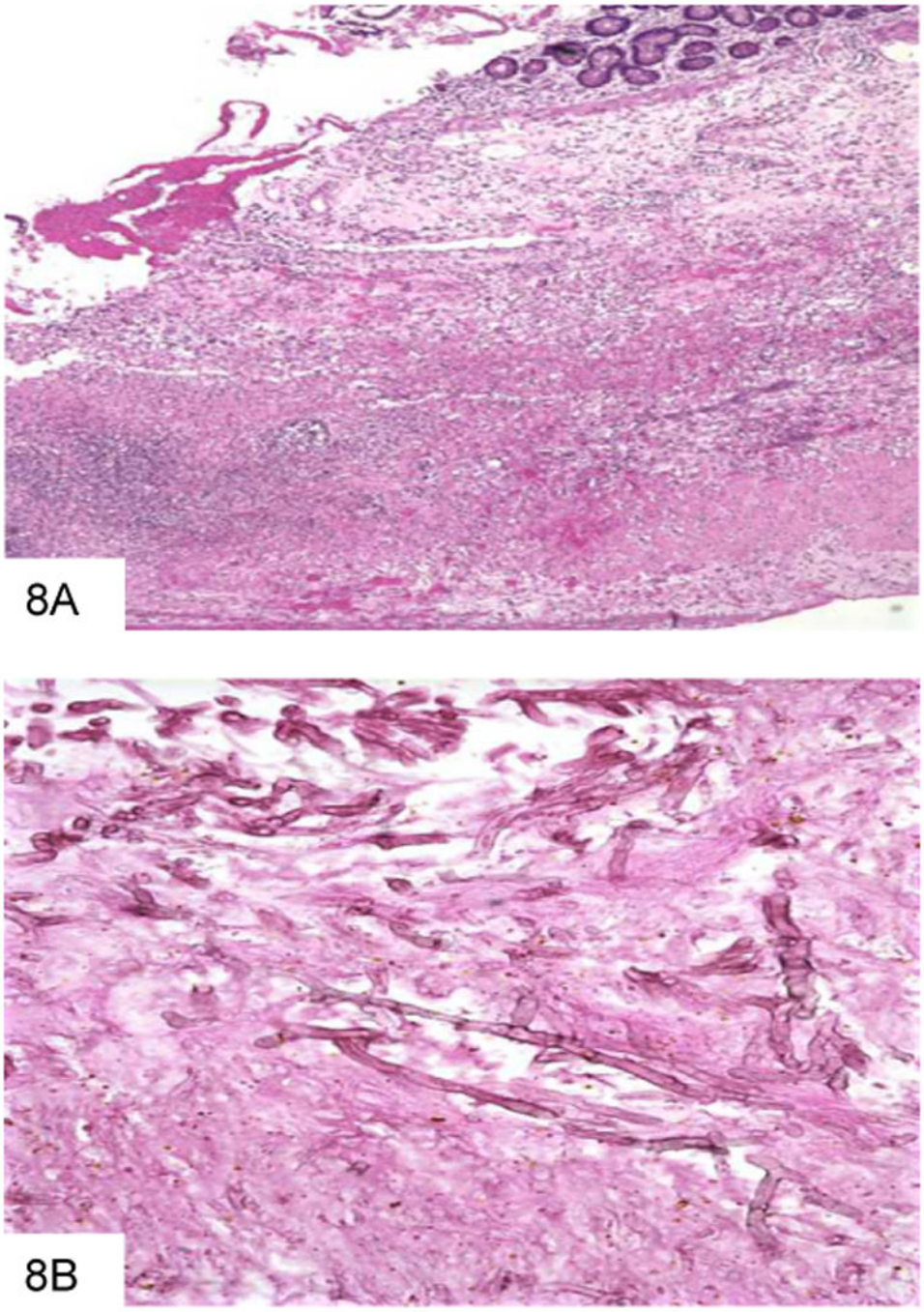

Figure 8.
This duodenal ulcer with transmural inflammation and necrosis is from a plasma cell myeloma patient who presented with an acute abdomen (A). The necrotic ulcer debris contains numerous pigmented filamentous fungi, indicating an infection by phaeohyphomycosis (B).

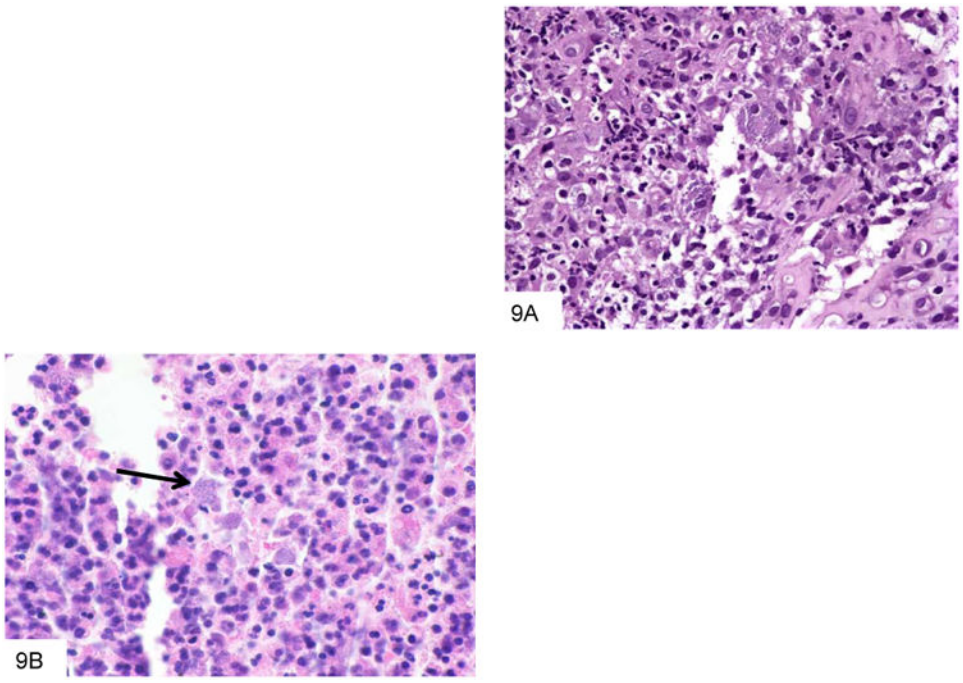

Figure 9.

This colon biopsy is from a Vietnam veteran who developed diarrhea after undergoing chemotherapy. The mixed inflammatory infiltrate contains numerous macrophages that are distended by *P. marneffei* (A). This smear from a liver abscess in a Chinese patient shows numerous macrophages distended by *P. marneffei*, and surrounded by a mixed inflammatory infiltrate (B).

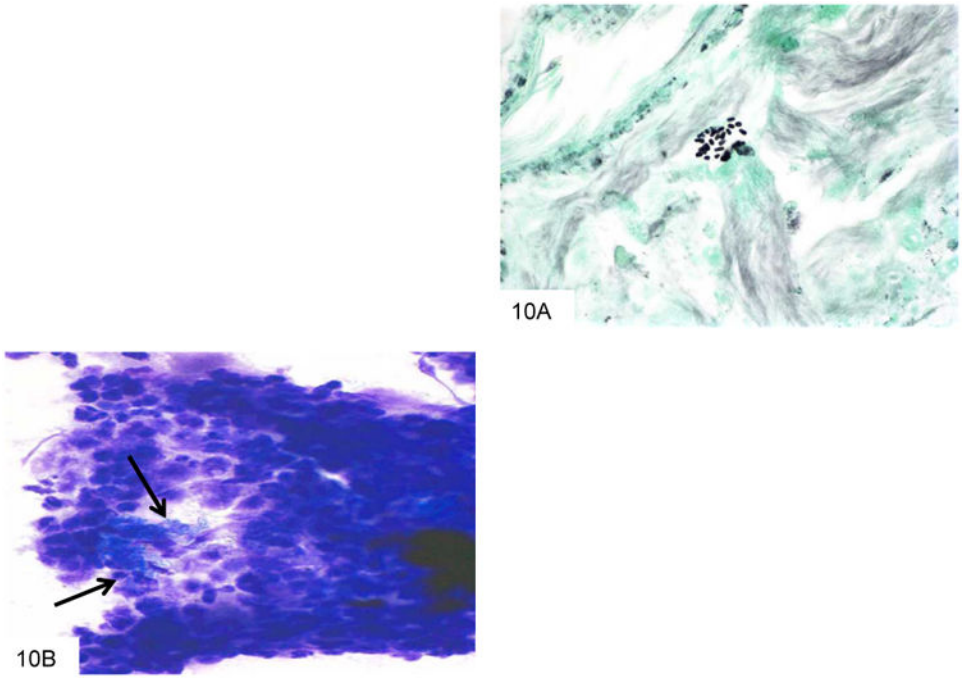

Figure 10.

This GMS stain from the colon biopsy above shows *P. marneffei* that have been released from a lysed macrophage. The larger fungi have rounded ends, and some have a transverse septum at the point at which the fungus appears “pinched” in the middle (A). This Wright-Giemsa smear from a liver abscess shows a macrophage that has burst, and is releasing the numerous fungi that it contained (B).

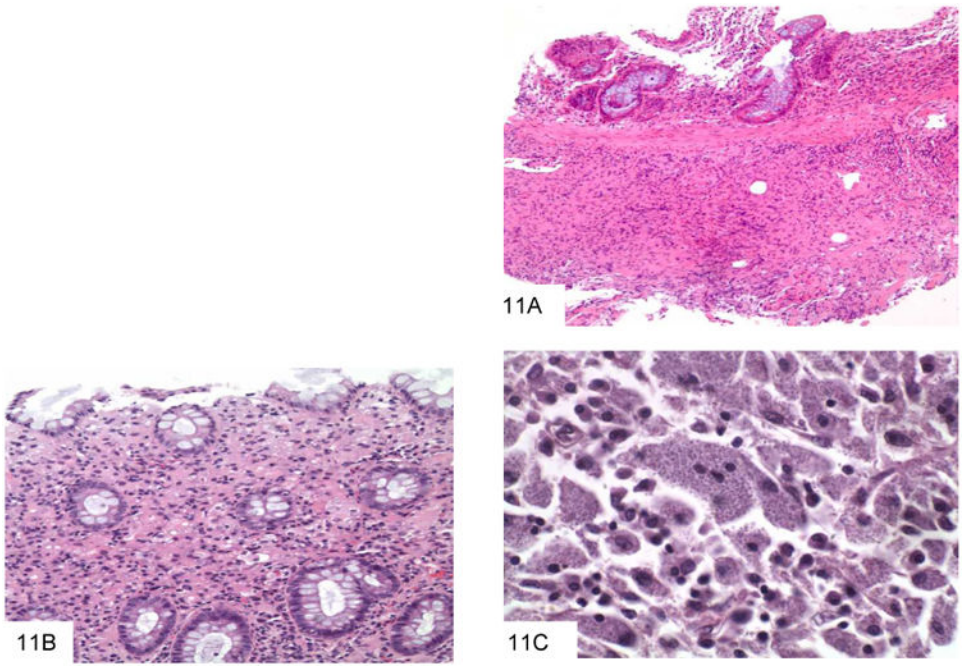

Figure 11.

This colon biopsy shows a submucosal lymphohistiocytic infiltrate, typical of gastrointestinal histoplasmosis (A). A second colon biopsy shows a lymphohistiocytic infiltrate expanding the lamina propria. Small dot-like organisms with a surrounding halo can be appreciated within histiocytes (B). This high power view shows macrophages distended by *Histoplasm capsulatum*, which have a white halo surrounding each fungus (C).

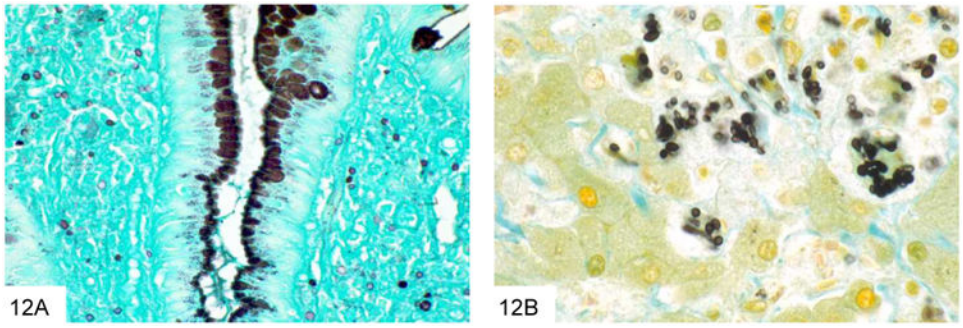

Figure 12.

This GMS stain of the colon biopsy from Figure 11 shows small, similarly sized yeast within the lamina propria, characteristic of *Histoplasma* (A). A high power GMS stain shows that the yeast are pointed at one pole, which may give rise to narrow-based buds (B, courtesy Dr. A. Brian West).

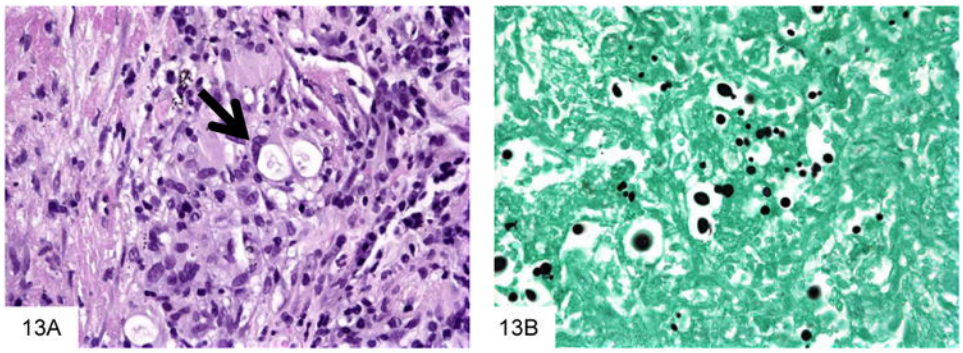

Figure 13.

Cryptococcus neoformans are surrounded by a “soap bubble,” indicating the capsule, and then by a granulomatous reaction (A, courtesy Dr. Matthew Lindberg). This GMS stain shows that *Cryptococcus* are very pleomorphic in size, and have occasional narrow-based buds (B).

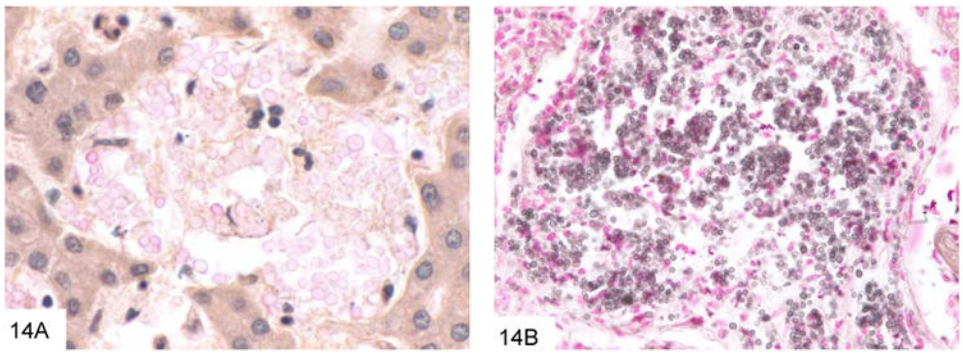

Figure 14.

This example of capsule-deficient *Cryptococcus neoformans* in an AIDS patient shows that only rare fungi show significant mucin positivity (A). The Fontana-Masson stain (B) can be very useful in staining cryptococci, especially those that are capsule-deficient. Note the variation in size as well.

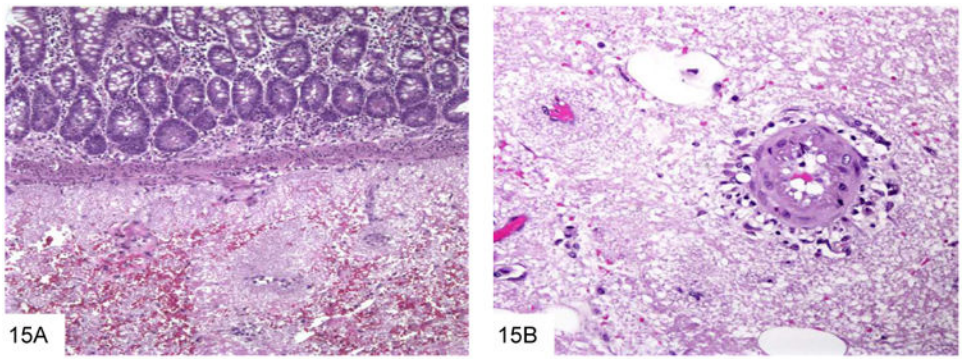

Figure 15.

The foamy casts typical of *Pneumocystis* are seen in the submucosa of the small bowel in this AIDS patient with disseminated *Pneumocystis* infection (A, courtesy Dr. Henry Appelman). The foamy casts extend to surround vessels in the submucosa and mesentery (B).

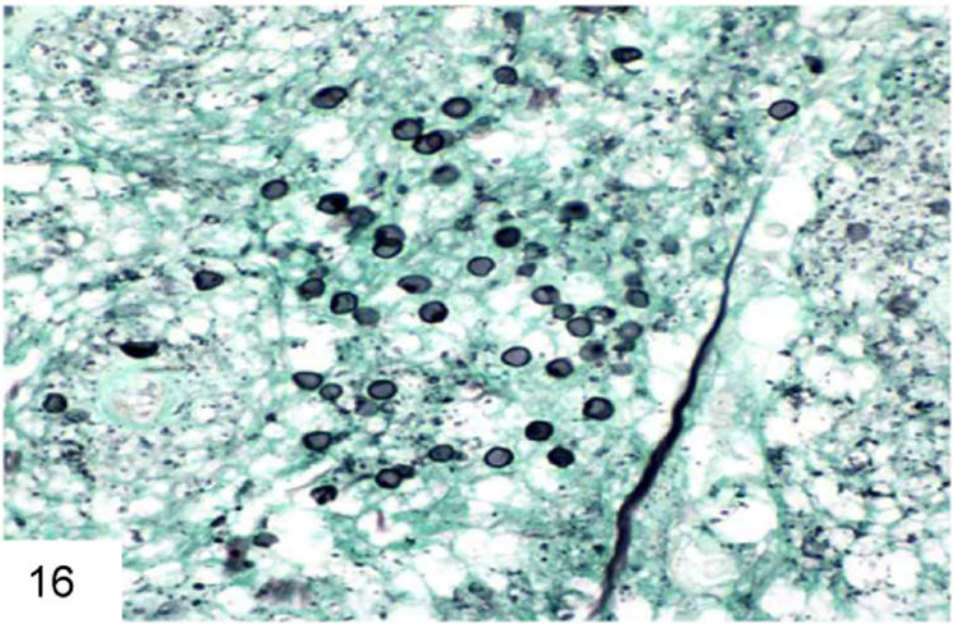

Figure 16.
Pneumocystis has a cup-shaped or “deflated football” appearance when collapsed. Some of them contain a delicate internal dot structure (GMS). Note the lack of buds or a transverse septum.

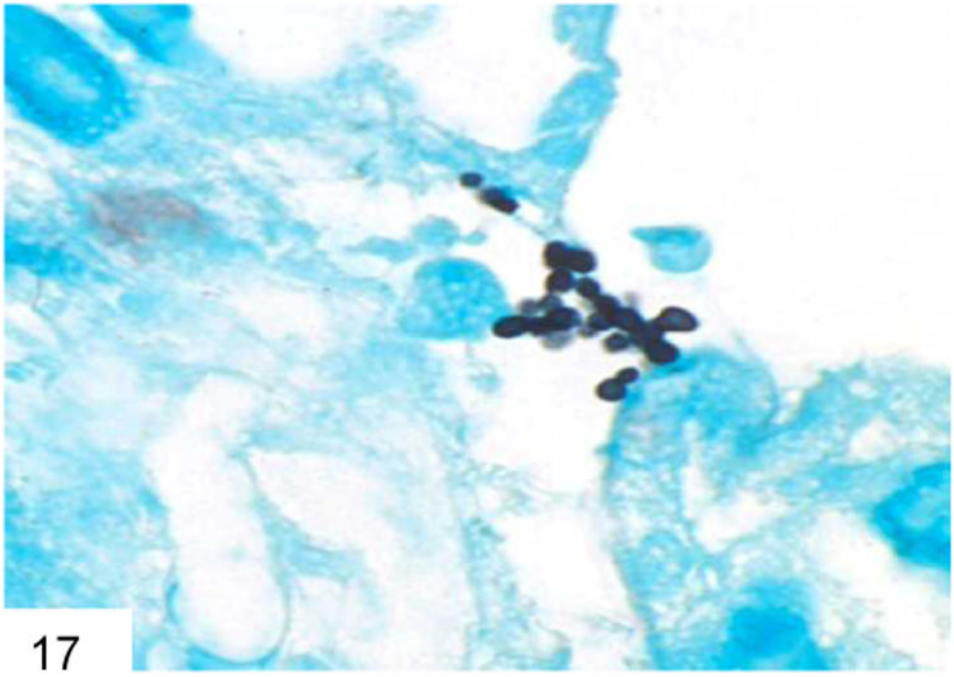

Figure 17.
Candida glabrata does not form hyphae, only buds, and is often extracellular rather than within a macrophage (GMS).

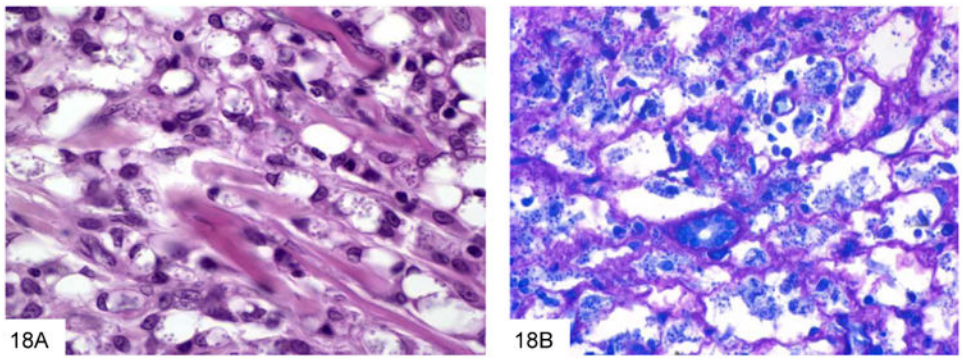

Figure 18.

Leishmania have a characteristic kinetoplast, as seen here in this case of visceral leishmaniasis with numerous organisms within macrophages (A, courtesy Dr. Rhonda Yantiss). These parasitesare GMS negative, and stain with Giemsa stain (B).

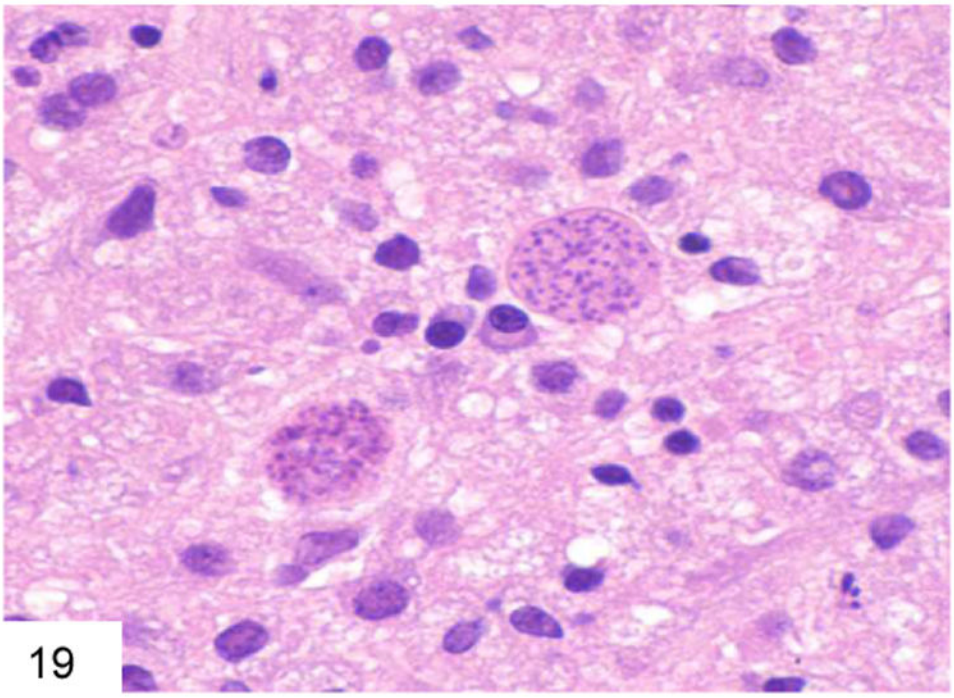

Figure 19.

The cyst forms of *Toxoplasma* may mimic organisms within a macrophage as well. *Toxoplasma* is also GMS negative and Giemsa positive (courtesy Dr. Becky Wheeler).

Table 1
Morphologic Features of Filamentous Fungi in the GI Tract

Organism	Primary Geographic Distribution	Morphologic Features	Host Reaction	Major Differential Diagnoses
Aspergillus species (e.g. *fumigatus*, *flavus*, and *niger*)	Worldwide	Hyphae- Septate Uniform width Branching-Regular Acute angles Conidial head formation in cavitary lesions	Ischemic necrosis with angioinvasion Acute inflammation Occasionally granulomatous	Mucormycosis *Fusarium*
Candida albicans; Candida tropicalis	Worldwide	Mixture of budding yeast and pseudohyphae; occasional septate hyphae Yeast forms are Gram positive	Usually suppurative, with variable necrosis and ulceration Occasionally granulomatous Occasional angioinvasion	*Trichosporon (*produces arthrocondia; disseminated disease in iron overload with immunosuppression especially AML; causes positive Cryptococcal latex agglutination test)
Candida (Torulopsis) glabrata	Worldwide	Budding yeast No hyphae No “halo” effect Yeast forms are Gram positive	Similar to other Candida species	*Histoplasma Cryptococcus*
Mucormycosis	Worldwide, associated with diabetics more than any other mycosis	Hyphae-Pauciseptate Ribbon-like Thin walls Branching-Haphazard	Similar to *Aspergillus*	Similar to *Aspergillus*
Basidiobolomycosis	Saudi Arabia, Africa, Parts of Asia; Arizona	Similar to mucor; fewer organisms, “cellophane ball” appearance	Eosinophilia, necrosis, granulomas, Splendore-Hoeppli reaction to organisms Produces mass	Mucor
Fusarium	Worldwide	Similar to *Aspergillus;* hyphae constricted at sites of origin	Similar to *Aspergillus*	*Aspergillus Mucor*
Phaeo-hyphomycosis (Dematiaceous Fungi)	Worldwide; associated with immuno-suppression	Pigmented; hyphae are closely septate and constructed at septations. Budding and vesicular swellings may be present.	Granulomatous inflammation with associated giant cells, necrosis, and dense fibrosis	Chromo-blastomycosis

Table 2
Characteristics of Morphologically Distinct Yeast In Human Tissue

Organism	Exposure	Histology
Histoplasma capsulatum; Histoplasma duboisii	Ohio River Valley/Lower Mississippi River (NA); East Southern Cone (SA); Central Africa	Small, round to oval yeast (2 to 6 uM) with narrow based budding; “halo” effect
Penicillium marneffei	Southeast or Far East Asia	Small, round to oval yeast (2-5) with occasional large septated forms “pill form”
Cryptococcus neoformans (plus 36 additional species)	Worldwide distribution	Small, round to oval yeast (5 to 10 uM) with narrow based budding; pleomorphic in size; “soap bubble” Fontana-Masson positive
C. glabrata	Worldwide distribution	Budding yeast without hyphae; may be extracellular Gram positive