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# Hospital-Acquired Gangrenous Mucormycosis

JAN EVANS PATTERSON, M.D., GERTRUDE E. BARDEN, M.H.S., AND FRANK J. BIA, M.D., M.P.H.

*Infectious Disease Section, Department of Internal Medicine, West Haven Veterans Administration Medical Center, West Haven, and Yale University School of Medicine, New Haven, Connecticut*

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A post-operative diabetic patient who had been treated for *Serratia marcescens* bacterial sepsis developed recurrent thrombosis of the left femoral artery following intra-arterial instrumentation. Pathological examination of arterial thrombus ultimately demonstrated invasive mucormycosis of the femoral artery and cultures of this material grew *Rhizopus oryzae*. The occurrence of cutaneous and subcutaneous mucormycosis is reviewed, as well as recently recognized nosocomial risk factors for mucormycosis, such as elasticized bandages and wound dressings.

## CASE PRESENTATION

DR. JAN EVANS PATTERSON *(Infectious Disease Fellow:)* A 64-year-old diabetic white man was admitted to the West Haven Veterans Administration Medical Center in July 1985 for coronary artery bypass graft surgery. The patient had a history of chronic atrial fibrillation for at least three years. He received antimicrobial prophylaxis with cephapirin during his surgery. An intra-aortic balloon pump (IABP) was inserted as he was removed from extracorporeal circulation. The IABP was placed into his left femoral artery via an extension of the incision which had been required to harvest his left saphenous vein graft. It was removed on the first post-operative day. On that day, he developed sternal wound drainage and routine povidone-iodine (Betadine) irrigation of the wound was initiated. Elasticized bandages were used to cover the femoral artery wound dressing. Cephapirin was continued. Five days post-operatively, he developed a fever of 101° F. The cephapirin was discontinued, and his blood, sputum, urine, and sternal wound were cultured. At that time, he was started on parenteral ampicillin, gentamicin, and clindamycin. Later that day he underwent mediastinal debridement. Necrotic material was removed and purulent drainage from the sternal wound became evident. Cultures of this material grew *Serratia marcescens* sensitive to cefoxitin, mezlocillin, trimethoprim-sulfamethoxazole, and the aminoglycosides. Two blood cultures grew the same organism, as did cultures obtained from his chest tube.

The Infectious Disease Service was called to see him regarding antibiotic therapy. His physical examination at that time was remarkable for a rectal temperature of 101° F, obesity, drainage from the sternal wound, clear lung fields, and atrial fibrillation without a murmur. His abdominal exam was benign and his extremities were edematous, the left lower extremity slightly more so than the right. The Infectious Disease Service recommended therapy with mezlocillin, and he defervesced.



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Address reprint requests to: Jan Evans Patterson, M.D., Dept. of Internal Medicine, Section of Infectious Disease, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510

Eight days post-operatively, his left leg was noted to be increasingly edematous and slightly cyanotic. Both the edema and cyanosis were thought due to chronic arterial insufficiency when evaluated by his vascular surgeons. He was already on intravenous heparin, which had been started post-operatively because of atrial fibrillation. Two days later he became hypotensive, requiring pressors to maintain blood pressure; he developed a metabolic acidemia with an arterial pH in the range of 7.28 to 7.35. He was intermittently hyperglycemic with serum glucoses measured in the range of 200–300 mg/dl. His white blood count rose from a baseline of 20,000 to 29,000 cells/$\mu$l and he was noted to have some drainage from his left inguinal wound incision. The serum creatinine had risen to 6 mg/dl; the blood urea nitrogen was 112 mg/dl, and the urine sediment was unremarkable. Peritoneal dialysis was started and tobramycin was added to his antibiotic regimen. He underwent local debridement of the left groin wound which contained necrotic material. Culture of this material grew *Serratia marcescens* with the same antibiotic susceptibility pattern as the blood and mediastinal isolates. The left lower extremity had become cold and cyanotic. On post-operative day 11, he had extensive debridement of the left groin wound. A large amount of dead tissue, including muscle, was noted. Two days after this debridement, his left lower extremity was noted to be even colder and more cyanotic. There were no distal pulses present. The vascular surgeons saw him and further debridement of his left groin wound was performed.

DR. VINCENT T. ANDRIOLE *(Chief, Infectious Disease Section):* After the thrombectomy was there any improvement in the left lower extremity?

DR. PATTERSON: No. There was no detectable pulse in his left lower extremity. After thrombectomy it remained both cyanotic and cold. The vascular surgeons recommended amputation, but the family declined.

DR. ANDRIOLE: In thinking about a differential diagnosis for the problems this patient presented, several possibilities arise. This could have been a local post-operative infection following the insertion of an IABP. The arterial occlusion could represent a local inflammatory process. If this were the case, when thrombectomy was done there should have been immediate improvement. If there were a more serious problem, such as invasion of the vessel in addition to vascular thrombosis, then improvement after the thrombectomy would be unlikely. We have to think about other organisms that are known vascular invaders. That limits the etiology somewhat to *Pseudomonas* species and certain fungi that are likely to invade the vessel wall itself.

DR. PATTERSON: What particular fungi would you be concerned about in such a case?

DR. ANDRIOLE: The most notorious vascular invaders are the *Mucor* species, which are found in the order *Mucorales*. In a diabetic, those and *Aspergillus* species would be my first considerations.

DR. PATTERSON: At this point, a pathology report on the thrombectomy specimen was received. The specimen shown under low power is diagnostic (Fig. 1).

DR. ANDRIOLE: There are hyphae present throughout the specimen; we need to know whether there are any septae, i.e., cross-walls within the hyphae, to distinguish *Aspergillus* species from the non-septate *Mucor* species.

DR. PATTERSON: No septae are visible. A methenamine silver stain (Fig. 2) confirms what was seen on the hematoxylin and eosin stains. These are non-septate hyphae which branch at wide angles.

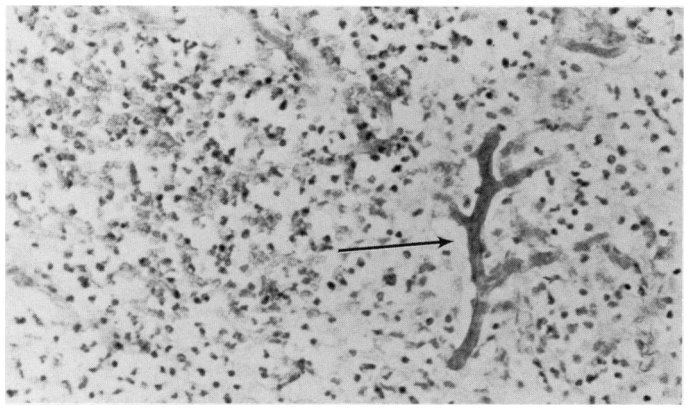

FIG. 1. A low-power view of the patient's infected thrombectomy specimen in which many hyphae (*arrow*) were present throughout the infected thrombus.

A culture of the thrombectomy material grew *Candida tropicalis* and *Rhizopus oryzae,* of the order *Mucorales.* A wet preparation of the *Rhizopus* obtained directly from culture shows the sporangium and rhizoid structures (Fig. 3). In *Rhizopus* species these root-like structures, or rhizoids, are directly below the sporangium. In culture the organism has a loose woolly mycelium with black pinpoints, which are the spore-filled sporangia. It fills the test tube within a few days. This is characteristic of *Rhizopus* and other members of the order *Mucorales.*

The patient had a progressive downhill course, while the family continued to resist allowing an amputation. He was started on parenteral amphotericin B at a dose of 50 mg per day. Approximately three days after the leg was found to be gangrenous, the family finally agreed to an operation. A high above-the-knee amputation was done. At exploration, his femoral artery was again thrombosed and thrombus had extended into his iliac artery. Dissection into the retroperitoneal area was required in order to remove the entire thrombus. At surgery tissues were described as brown and necrotic. Pathological examination of thrombus material again demonstrated mucormycosis. A KOH preparation of the material (ground) demonstrated numerous very large hyphal elements suggestive of *Rhizopus* or *Mucor,* as well as smaller hyphal elements with yeast forms suggestive of *Candida.* The patient was persistently acidemic, and expired four days after his leg amputation. Cultures of the material obtained at amputation grew both *Rhizopus oryzae* and *Candida tropicalis.*

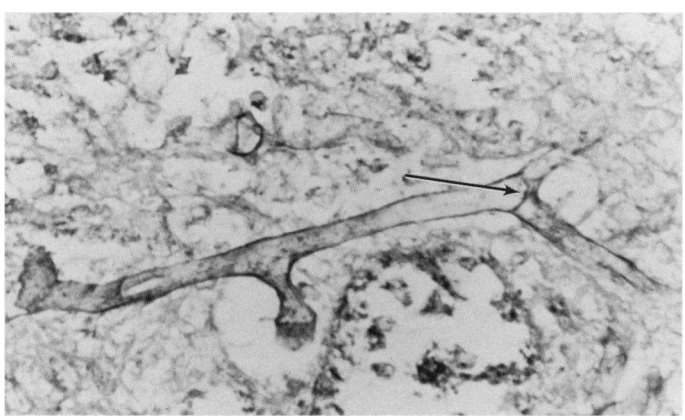

FIG. 2. A higher power view of the same material stained with silver shows large-diameter hyphae branching at wide angles. Note that an occasional structure resembling a septum (*arrow*) may be seen in some *Mucor* or *Rhizopus* species. This may be a hyphal fold or rarely a true septum.

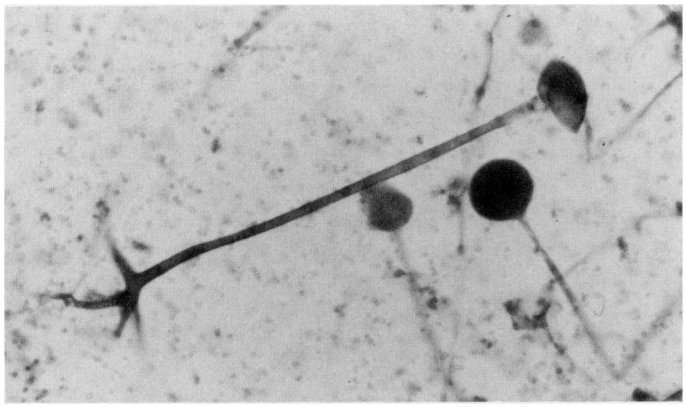

FIG. 3. A slide preparation of cultured *Rhizopus oryzae* demonstrates sporangia (spherical spore-containing structures) and rhizoids (root-like structures) at the opposite end.

A PHYSICIAN: How did *Serratia* fit in the picture? Was it a predisposing infection?

DR. JOHN RYAN *(Chief, Infectious Diseases, West Haven Veterans Administration Medical Center):* I would like to comment on that. When we first saw him two days after his mediastinal debridement, he was clinically toxic and both his toes were blue. He was still on high doses of vasopressors and his course was suggestive of sepsis. He had positive blood cultures for *Serratia,* and there was heavy drainage of material from the sternal wound. It seems more likely that the fungal pathogen was a superinfection.

DR. PATTERSON: I agree. He had been on broad-spectrum antibiotics before and after the *Serratia* infection. These factors may well have predisposed him to fungal superinfection, along with several other risk factors, which we shall discuss further.

## DISCUSSION

Mucormycosis is a general term referring to mycotic infections caused by fungi in the order *Mucorales.* The three genera that we most commonly encounter clinically are *Rhizopus, Absidia,* and *Mucor. Rhizopus oryzae* is a prominent member of this group and *Rhizopus* species are the usual pathogens in man. Typically, the risk factors for serious infection include diabetes mellitus and systemic acidosis. Hematologic malignancies, uremia, sepsis, and burns also predispose to infections with these organisms [1,2]. It has been suggested that acidosis may be the important factor in these disease states.

Rhinocerebral mucormycosis is probably the most common manifestation of such infections, typically occurring in diabetics with systemic metabolic acidosis. The initial infection is usually nasal, advancing through the retroorbital regions and into the brain, where it causes parenchymal infarction by thrombus formation. The diagnosis requires tissue biopsy to demonstrate tissue invasion and cannot be made by culture alone. Pulmonary mucormycosis is most common in patients with hematologic malignancies, but can also be seen in patients with the other risk factors. Again, the diagnosis is usually obtained by examining tissue biopsy specimens, or made presumptively by demonstrating positive sputum cultures in the presence of suggestive lung lesions.

Cutaneous mucormycosis is uncommon, but it certainly does occur. Possibly the first histologically proven case was reported in 1958; it was found in a diabetic ulcer of the

lower extremity and resolved after several months of potassium iodide therapy [3]. Subsequent case reports have emphasized the importance of mucormycosis in diabetics with leg ulcers [4,5]. Marchevsky et al. reviewed fifteen cases which were seen at Mount Sinai Hospital in New York from 1958–1978 [6]. Four of these cases were skin or subcutaneous infections. The authors noted that although cerebral and pulmonary mucormycosis were still the most common forms of this infection, skin and subcutaneous infections were emerging as important new sites for mucormycosis. Cutaneous mucormycosis can be superficial or gangrenous; usually the gangrenous cases occur in patients who are immunocompromised.

In 1976 two post-operative immunocompromised patients were reported with *Rhizopus arrhizus* abdominal wall infections, and nine other cases of gangrenous cellulitis were reviewed [4]. By 1978–1979 there were several reports in the literature of *Rhizopus* infections in association with Elastoplast (Beiersdorf, Inc., Norwalk, CT) bandages [8,9,10]. In 1978, the Mayo Clinic Associated Hospitals reported six patients who had *Rhizopus* infections and all these patients had been exposed to Elastoplast dressings [8]. Three of these patients were not immunocompromised; they were treated successfully with topical therapy alone. Two other children, with acute lymphocytic leukemia, developed buttock abscesses where dressings were covered with Elastoplast bandages following bone marrow biopsy procedures.

*Rhizopus* was found in bandages that were obtained from four different sites within the hospital. At that point, investigators from the Centers for Disease Control (CDC) became involved. They found that the manufacturing plant produced bandages which were culture-positive for the same *Rhizopus* species. A follow-up from CDC six months later reported 17 more cases from ten different hospitals. All implicated the use of Elastoplast bandages to cover sterile wound dressings [9]. The lesions were described as vesiculopustular, ulcerative, or necrotic. Only four of these patients were immunocompromised. Two additional patients had sternal wound infections with *Rhizopus*. Their wounds had been dressed with sterile gauze covered by elasticized bandage [10]. One was diagnosed early by pathological examination of a skin biopsy and he was successfully treated with local applications of amphotericin B. The other patient was not diagnosed until autopsy, which demonstrated pulmonary vessels and carotid arteries thrombosed by mucormycosis. The respiratory care unit in which these patients were cared for had Elastoplast bandages which were culture-positive for *Rhizopus*. However, this situation was found in only four of ten hospitals so investigated.

Diabetes appears to be an independent risk factor for development of mucormycosis. Diabetics have developed similar infections under wound dressings which did not include Elastoplast [15,16]. A spontaneous inguinal abscess caused by *Rhizopus rhizopodiformis* was reported in 1983 [17]. It occurred in a diabetic renal transplant patient and was not associated with instrumentation. The patient was cured by surgical drainage and systemic administration of amphotericin B.

When the bandage problem became evident, the manufacturer took preventive measures and began irradiation of their Elastoplast bandages before distribution. There were additional case reports [11,12,13,14], but the association of infection with Elastoplast decreased markedly after 1979. Since 1979 the manufacturer has added antifungal preservatives and anti-oxidants to their adhesives [personal communication]. Their industrial microbiologist does routine stability testing on bandages and checks their lots at three, six, nine, twenty-four, and thirty-six months to determine if

they contain any viable fungi. Test bandages are also inoculated with *Rhizopus, Aspergillus,* and *Candida* species. No significant growth of fungus should occur after inoculation.

The Elastoplast package insert now clearly indicates that the bandages are neither sterile nor are they to be used on open wounds. Unfortunately, after opening, bandages are often kept unwrapped in ward refrigerators. At our institution cultures of one such Elastoplast bandage kept open in a refrigerator grew 13 colonies of *Penicillium spp.,* three colonies of *Paecilomyces,* two colonies of *Candida parapsilosis,* and two colonies of *Aspergillus spp.* A cultured Elastoplast bandage from a previously unopened package was sterile except for one colony of *Rhodotorula rubra,* quite possibly a culture contaminant.

There have been two reports of cutaneous mucormycosis related to intravenous catheter sites. One infection occurred in a child with acute lymphocytic leukemia and resolved with local debridement and amphotericin B [7]. Another infection occurred in a diabetic, necessitating amputation; the outcome was fatal nevertheless [17]. Intra-aortic balloom pump infections do occur, but they are probably underreported. The incidence noted in previous reviews ranges from 1–12 percent [18,19]. They may occur when the IABP is in place or after removal in the form of a subsequent wound abscess. The organisms that have been involved are usually Gram-negative rods and staphylococci. We could not find a single report of IABP-related fungal infection, although *Candida* species are known causes of intra-arterial catheter infections [20].

Therapy of patients with gangrenous cutaneous mucormycosis is difficult. It involves debridement and sometimes amputation of the involved area, as well as high-dose (0.7–1.0 mg/kg/day) systemic amphotericin B [1,5].

DR. RYAN: I am concerned about the use of the elasticized bandages in our hospital.

DR. FRANK BIA *(Associate Professor of Medicine):* One of the problems is that Elastoplast bandages are left open in refrigerators on the wards; mold is easily picked up that way. The manufacturer cannot be implicated in such a case since they do extensive quality control testing, and an unprotected roll can lie around for weeks.

A PHYSICIAN: Has any work been done to try to determine what it is in the Elastoplast that supports the growth of these fungi?

DR. PATTERSON: It is simply not known. It would be interesting because fungi have been noted in other wound dressings as well. The roll which grew the multiple fungi has been discarded. We suggest that bandages be kept in their packages, rather than uncovered in the ward refrigerators.

## COMMENT

A patient with a history of diabetes mellitus and intermittent acidemia developed post-operative *Serratia marcescens* sepsis from infection of his sternal and inguinal wounds. Recurrent thrombosis of his left femoral artery followed, and ultimately a pathologic specimen was diagnostic for mucormycosis. Cultures grew *Rhizopus oryzae* and, although he was treated with both high-dose amphotericin B and underwent amputation, he was persistently acidemic and expired.

In the clinical setting of recurrent thrombosis, especially following arterial instrumentation, such fungi are suspect since they are notorious vascular invaders. Diagnosis is usually made by histopathological examination of tissue specimens rather than by

culture. Tissue samples, and thrombus material in particular, should be examined early if these organisms are suspected.

The well-known risk factors for mucormycosis, including diabetes mellitus, acidosis, and uremia, were present in this patient. He had two additional risk factors, arterial instrumentation and Elastoplast wound dressings, both of which have been recognized more recently in the literature as nosocomial risk factors for fungal infection. The association of bandages and wound dressings with mucormycosis infections is immunocompromised patients has been particularly striking.

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