Opportunistic Fungal Infection of the Burn Wound With Phycomycetes and Aspergillus

A Clinical-Pathologic Review

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Thirty cases of invasive infection of the burn wound with opportunistic fungi of the Phycomycetes and Aspergillus species occurred. Mycotic invasion of the burn wound has a wide clinical spectrum including focal and multifocal infection, deep invasion with extensive tissue destruction, and systemic dissemination. Nine patients (30%) died from fungal invasion. Of 15 survivors, seven (46.7%) required amputation to eradicate disease. Prompt, adequate biopsy of any suspicious area of the burn wound must be processed immediately. The observation of hyphae invading viable tissue associated with an acute inflammatory response establishes the diagnosis. Immediate wide surgical excision, which may include amputation, is necessary to eradicate this potentially lethal infection.

Opportunistic fungal infection is a well-known complication of uncontrolled diabetes mellitus, malignant neoplasms, and other debilitating diseases associated with impaired immunologic defense mechanisms.1,2 Mycotic infections of the burn wound have been rare. Until 1967, only five cases of fungal burn wound infection were reported. Since then, an increase in fungal burn wound infections, recognized and treated during life or present at autopsy, has been observed at the US Army Institute of Surgical Research. In many cases amputation of a part has been necessary as treatment and eight cases with wide-spread dissemination have been fatal.

A variety of fungi may be cultured from burn wounds, but deep invasion of the burn wound with tissue necrosis, vascular invasion, and systemic dissemination is caused predominantly by Phycomycetes or Aspergillus species. The clinical and pathologic features of these opportunistic infections of the burn wound form the basis of this report.

Case Material

The clinical diagnosis of invasive fungal infection of the burn wound with Phycomycetes or Aspergillus was established in 30 burn patients between Jan 1, 1954, and June 30, 1970, at the US Army Institute of Surgical Research. This group includes three cases previously reported.3,4 During that time, over 3,000 patients were treated for thermal injury at this institute. Our patient population consists largely of military personnel and their dependents referred from military bases by air evacuation. Of the 30 cases reported in this communication, 11 were injured in the continental United States, one in Puerto Rico, one in El Salvador, and 17 in Vietnam, a distribution which closely parallels that of all admissions. Among these 30 patients there were 26 men, aged 18 to 35 years; two women, aged 20 and 27 years; and two children, aged 2 and 9 years. Each patient's record was reviewed for predisposing causes and for common clinical or laboratory abnormalities. The diagnosis was supported in each case by histologic study of biopsy material or by necropsy. Specimens from 19 patients were also submitted for mycologic culture.

Onset, Location, and Clinical Spectrum of Disease

Mycotic invasion of the burn wound was noted most frequently between the ninth and 15th postburn days, but infection occurred as early as the fifth day and as late as the 64th day postinjury. The average area of burn injury in this group was 53% of the total body surface, with a range of 22% to 73%. Only two patients had burns under 30%. Lesions occurred in second- and third-degree burns with approximately equal frequency. Mycotic invasion of the burn wound was variable in location (Table 1) and in its clinical presentation and course. The early clinical signs were those of infection and are listed in Table 2. Fever was the most common clinical sign. Temperature elevation of 101 F (38.3 C) to 103 F (39.4 C), observed in this group, was higher than that generally seen in an uncomplicated burn. Persistent swelling in an involved part with or without induration or edema was frequently noted; and a change in the appearance of the...
Fig 1.—Large areas of fungal infection on chest wall and upper arm have "converted" from partial-thickness to full-thickness injury. Note fat necrosis in biopsy wound at superior margin of chest burn and violaceous discoloration and edema of unburned skin in that area.

Fig 2.—Ulceration of partial-thickness burn has occurred with heaped up margins and characteristic fat necrosis as described in text. Wide excision was curative.
burn wound, often noted as “conversion” from partial to full thickness injury, occurred in high frequency.

In nine patients, invasive fungal infection was either the cause of death or a major contributing factor, a mortality of 30%. In five additional patients, death was caused by bacterial sepsis which was well established for several days before the appearance of fungal infection, and in one patient death occurred well after successful excision, making the overall mortality 15 (50%) (Table 3).

Observations in this group of patients describe a broad clinical spectrum of invasive mycotic infection ranging from well-localized infection of skin and subcutaneous tissue to rapidly invasive infection and death, with dissemination of fungi to other organs. Various forms of the disease bear further description.

Invasive fungal infection that occurs in the hand may be chronic and indolent, recurs commonly, and often requires amputation for cure. In one illustrative case, a 23-year-old man with 39% total body surface burns developed an ulcerated lesion at the base of his right thumb on the 12th postburn day (Fig 1). A diagnosis of fungal invasion of subcutaneous fat and thenar musculature was made by biopsy; and metacarpal-carpal disarticulation of the thumb was performed. Infection recurred, first in the greater multangular bone and subsequently in other carpal bones. X-ray changes of osteomyelitis in the second and third metacarpals with suggestive changes in several carpal bones were evident four weeks following the original infection (Fig 2). Biopsy confirmed fungal osteomyelitis in the wrist and following radiocarpal disarticulation, microscopic examination revealed marrow invasion of all carpal and metacarpal bones of the hand. The organism was identified histologically as *Aspergillus*. Amputation was necessary for cure in all five patients with hand infections in this series. Four amputations were performed at the wrist and one at the thumb.

Invasive fungal infection has the potential for rapid invasion and death, and the surface appearance of the lesion often does not convey the extent or the depth of tissue necrosis. One patient, with predominantly partial thickness burns “converted” two small patches of “third degree” burn on his right anterior pectoral region into a large area of gangrene with a surrounding zone of violaceous discoloration (color Fig 1). On both upper extremities, there were blackened lesions consistent in appearance with third degree burn. Following biopsy confirmation of invasive fungal infection in the chest lesion, exploration revealed necrosis of tissue deep to the pectoralis involving the intercostal muscles. Subsequent autopsy in this patient revealed fungal invasion with avascular necrosis of the triceps bilaterally and direct extension of fungal infection into the parietal pleura with dissemination of fungi to lungs, heart, and spleen. The organism was identified histologically as a Phycomycetes.

In another patient, a 5 x 8-cm area of hemorrhagic discoloration in burn of the upper arm which developed over a 12-hour period was associated with deep destruction of muscle adjacent to the humerus and extensive necrosis of subcutaneous tissue and muscle in the forearm and wrist. Immediate glenohumeral disarticulation was performed in this case with ultimate survival.

Multifocal infection of the burn wound with fungi occurred in one third of the patients in this group (Table 1) and infection can occur...
Fig 4.—Advancing infection on scalp has spread laterally, undermining wound margins and causing necrosis of overlying unburned skin.

Fig 5.—Gross specimen of case in Fig 4. Note extension of infection beneath ulcer margin and, at left, characteristic appearance of involved fat.

Fig 6.—Necrotic subcutaneous fat beneath burn wound invaded by broad hyphae characteristic of phycomycotic infection (hematoxylin-eosin, ×200).

in several sites simultaneously or serially. One patient had fungal invasion documented in seven separate locations.

Recurrence of fungal infection following what appears to be adequate excision is not infrequent and occurred in ten patients (33.3%) in this series. Recurrence is evident within 24 to 48 hours of excision and has the same clinical appearance as the original lesion (Fig 3).

Pathology

Burn wound infections with Phycomycetes and Aspergillus have a characteristic gross appearance. The subcutaneous fat is necrotic, yellow-brown, or yellow-grey (color

Fig 2) and lobules of involved fat frequently separate from underlying viable tissue. Infected muscle becomes ischemic and has a dull grey-tan appearance. The wound edges are frequently heaped up and undermined (Fig 4 and 5) and necrotic fat can be expressed from beneath the wound edges.

Microscopic examination of biopsy and autopsy material demonstrates invasive mycotic infection of the burn wound with an inflammatory response in the underlying viable tissue (Fig 6 and 7). Although the eschar or wound surface may exhibit colonization with a variety of fungi, broad rarely septate hyphae of Phycomycetes or branching septate hyphae of Asper-

gillus extend through the wound into subcutaneous fat or deeper tissue frequently resulting in extensive necrosis. Hyphal invasion of viable tissue with an inflammatory response is considered diagnostic of fungal burn wound infection. Fungi also may extend laterally in subcutaneous tissue and involve areas beneath unburned intact skin. Fungal invasion often extends into fascia and skeletal muscle, and in two patients Phycomycetes invaded intercostal muscles and endothoracic fascia to involve the parietal pleura. In another case, hyphae penetrated the cortex of metacarpal and carpal bones and invaded the marrow space. These fungi also tend to invade the walls and lumens of blood vessels causing thrombosis and local avascular necrosis (Fig 7). Vascular invasion is responsible for the dissemination of infection to lungs, heart, kidney, or other organs which occurred in eight patients.

Mycologic Identification

While the diagnosis of fungal invasion is based on firm histologic criteria, identification of the organism is difficult. Tissue cultures on Sabouraud's agar frequently yield a number of saprophytes, including Cephalosporium, Cladosporium, Penicillium, Geotrichum, Trichophyton, and Candida. A variety of hyphae and spores frequently are seen microscopically on the wound surface or within the eschar but wound invasion is almost invariably due to fungi of the Phycomycetes or Aspergillus. These pathogens were recovered in culture in only (9) (30%) of the cases. This difficulty in isolating opportunistic fungal pathogens has been shared by others. Considering the limitations of mycologic cultures, identification must rest on histologic observations. Fungi of the Phycomycetes class were identified histologically as the offending organisms in 22 cases and an Aspergillus was recognized in eight cases. Of the 22 cases of invasive phycomycosis, two were further identified as Rhizopus and the remaining 19 were probably Mucor.

Diagnosis and Treatment

The rapidly invasive nature of
this disease and its proclivity for vascular invasion with the potential of systemic dissemination, which occurred in eight patients in our series, makes prompt diagnosis and aggressive surgical treatment mandatory for a successful outcome. Clinical symptoms and signs are those of infection but are often difficult to assess in the burned patient (Table 2). A change in the appearance of the burn wound, particularly the development of purpuric or black "spots," ulceration of the burn wound, early separation of eschar, unexplained fever, swelling, and tenderness should prompt suspicion of invasive fungal infection.

The entire burn wound must be carefully examined on at least a daily basis to search for multifocal sites of disease which occurred in one third of our cases. Biopsy should be done immediately and an emergency histologic reading obtained. Suspicious tissues should be placed on Sabouraud’s agar and sent for culture at the time biopsy is carried out. One must not wait for culture reports since only 30% of histologically proved fungal infections are confirmed by culture, and a time lapse of two to five days may occur prior to growth of the organism in culture media.

Treatment must be instituted promptly and varies with depth and location of disease. For lesions confined to the subcutaneous tissues, wide local debridement is generally adequate. When infection extends beneath the fascial plane and involves skeletal muscle, facial and truncal lesions must be excised wide, and amputation may be required for lesions on the extremity. Amputation was performed in 11 patients or slightly more than one third of the cases in this series (Table 4). On a burned extremity, amputation should be performed proximal to the greatest extent of infection to ensure adequate excision. Ideally, this is carried out as a disarticulation to avoid the danger of bone marrow infection and generalized sepsis.

Local recurrence is common (38.8% of cases in our series) within 24 to 48 hours following excision. Close observation with frequent, careful reevaluation and repeated biopsy of wound margins in suspicious cases are necessary to confirm the presence of residual or recurrent fungal infection. Our best results have been obtained when initial surgery has been "radical."

Although systemic chemotherapy with amphotericin B has been efficacious in treating a number of diabetics with the rhinocerebral form of pyomyositis, we do not recommend its use when initial surgical debridement eradicates disease. We have reserved the use of amphotericin B to those cases where there is evidence or strong suspicion of dissemination, beginning with a dose level of 0.1 mg/kg/day and gradually building up to 1 mg/kg/day. Treatment is continued for a minimum of two weeks and longer if indicated.

Comment

A variety of factors that may enhance the growth of opportunistic fungi have been noted by many investigators and include the following: (1) decreased host resistance particularly in patients with antecedent diseases such as disorders of the reticuloendothelial system and patients with terminal cancer; (2) metabolic disturbances such as diabetes mellitus which led to acidosis; (3) impaired or decreased phagocytosis (4) ecologic disturbances which may occur following the use of antibiotics, corticosteroids, and antimetabolites that may suppress the growth of bacteria or promote the growth of fungi; and (5) local tissue defects which may serve as portals of entry. Experimental work has emphasized the relationship between acute stress and the development of pyomyositis and aspergillosis in acute alloxan diabetes in which impaired or decreased phagocytosis is known to occur. Each of these factors may be present to some degree in patients with thermal injury. Marked decreases in IgG have been documented in burn patients. A marked increase in IgM in response to fungal infection in the burned patient has also been reported but its significance is unclear. Rappaport and Converse have shown a depression of tuberculin type skin sensitivity in thermal injury, thereby demonstrating alterations in cellular immunity in burns. Abnormalities of polymorphonuclear leukocytes and neutrophil dysfunction have also been described in burns. Alexander and Wixson have reported a decreased ability of the neutrophils of burn patients to kill ingested bacteria and Balch et al have shown a delayed migration of leukocytes to occur following thermal injury.

Ecologic disturbance in bacterial population in the burn wound may play an important role in the evolution of this disease in burns. In 1964, mafenide acetate cream was instituted as topical chemotherapy in all burn patients treated at the US Army Institute of Surgical Research and the effective control of bacterial wound sepsis by this topical agent has been documented. An increase in fungal infection of the burn wound was noted at autopsy in 1964 through 1965. A review of that data by Nash et al has revealed a marked increase in the postmortem incidence of fungal
infection of the burn wound since the institution of topical antibacterial therapy. Fungal infection was found in 24.7% of patients autopsied from 1960 through 1963 as compared with 64.2% of autopsied cases from 1964 through 1969. Clinically significant fungal burn wound infections have remained infrequent. In 1968, six cases of fungal infection (1.5%) of admissions were documented on our service. Twenty additional cases, excluding those with incidental focal lesions discovered at autopsy, occurred in 1969 and 1970 with the current clinical infection rate approximately 3%.

A prospective study of burn wounds by serial biopsy in 70 consecutive patients treated at this institution in 1969 showed an incidence of fungal colonization in 64.7% of third-degree burn wounds (unpublished data). It must be emphasized that these figures represent colonization of the burn wound which refers to growth of organisms on or within the eschar in contrast to invasion through the eschar into viable tissue.

In that study the predominant organism by histologic and cultural criteria was Candida, but Phycocytetes, Aspergillus, and Geotrichum also occurred. Although Candida is usually confined to the wound surface, it has been responsible for rare cases of invasion.23

Acidosis and systemic antibiotics have been cited as playing important roles in the development of opportunistic fungal infections.1 17 24

Except for three patients who were in septicemic shock, none of our patients were acidic at the time the disease was first noted. All of our patients are initially treated with penicillin for five days and antibiotics are administered subsequently only on specific bacteriologic indication. While 17 of our patients were injured in Southeast Asia, 13 received their injuries within the continental United States, confirming the ubiquitous nature of these fungi.

The treatment of infection caused by these opportunistic organisms in nonburn patients has been directed at control of the underlying disease when possible, as in diabetes mellitus, and eradication of the disease by systemic chemotherapy. A variety of chemotherapeutic agents has been tried including iodides, nystatin, propionate sodium, and mixtures of systemic antibiotics. Among these amphotericin B appears to be the best antifungal agent presently available. In the burn patient, however, the spread of disease can be so rapid that radical surgical excision is currently the best available mode of therapy and the use of amphotericin B appears to be limited to patients with multifocal lesions which appear serially, or those in whom there is a high suspicion of disseminated disease.

Nonproprietary and Trade Names of Drugs

Amphotericin B—Fungizone.
Mafenide acetate—Sulfamylon Cream.

References

13. Munster AM, Hoagland HC: Serum immunoglobulin patterns after infection caused by these opportunistic organisms in nonburn patients has been directed at control of the underlying disease when possible, as in diabetes mellitus, and eradication of the disease by systemic chemotherapy. A variety of chemotherapeutic agents has been tried including iodides, nystatin, propionate sodium, and mixtures of systemic antibiotics. Among these amphotericin B appears to be the best antifungal agent presently available. In the burn patient, however, the spread of disease can be so rapid that radical surgical excision is currently the best available mode of therapy and the use of amphotericin B appears to be limited to patients with multifocal lesions which appear serially, or those in whom there is a high suspicion of disseminated disease.

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