RHIZOPUS NECROTIZING CELLULITIS IN A PRETERM INFANT: A CASE REPORT AND REVIEW OF THE LITERATURE

The term zygomycosis or mucormycosis applies to fungal infection by members of the order Mucorales in the class Zygomycetes. Although these fungi are ubiquitous plant pathogens and have little intrinsic pathogenicity for the normal human host, under certain clinical conditions invasive and fatal infection can occur. The rhinoencephalitis and gastrointestinal forms of mucormycosis are the most frequently recognized.

Rhizopus species are placed in the family Mucoraceae of the order Mucorales which also includes Absidia, Apophysomyces, Mucor, and Rhizomucor species. Nosocomial outbreaks of primary skin infection by Rhizopus species related to contaminated elastic bandages have been reported. A few other cases of Rhizopus skin infection have been described in newborns and older children. We present a case of Rhizopus necrotizing cellulitis in a preterm infant and review the literature of documented cases of Rhizopus skin infection in children.

Case report. A 33-day-old baby girl was transferred to Texas Children’s Hospital in February, 1993. She was born at 23 weeks of gestation by vaginal delivery and had a birth weight of 560 g with poor Apgar scores. She had multiple postnatal complications including respiratory distress syndrome, pulmonary interstitial emphysema, severe bronchopulmonary dysplasia, intraventricular hemorrhage and Staphylococcus epidermidis bacteremia.

On admission the infant was awake and intubated with a temperature of 36.3°C, heart rate of 150/minute, respiratory rate of 25/minute on mechanical ventilation and blood pressure of 87/55 mm Hg. Skin, mucous membranes and sclera were icteric. The remainder of the examination was unremarkable. Initial laboratory studies included a hemoglobin of 7.1 g/dl; a hematocrit of 21%; a white blood cell count of 8810 cells/mm³ with 45% neutrophils, 6% band forms, 32% lymphocytes, 11% monocytes and 1% eosinophils; platelet count of 109,000/mm³; conjugated bilirubin of 8.2 mg/dl; and unconjugated bilirubin of 0.8 mg/dl.

She underwent ligation of a patent ductus arteriosus and therapy was started with dexamethasone for respiratory decompensation and hypotension. She also developed metabolic acidosis and azotemia. On the 45th day of life a deep infiltration at an intravenous insertion site and a chemical burn on the dorsum of the right hand and wrist developed. The following day she was given vancomycin for S. epidermidis bacteremia. The lesion of the dorsum of the hand progressed with skin and subcutaneous tissue ulceration and necrosis. The area was incised and drained, and cultures from the wound grew Rhizopus sp. and Candida parapsilosis. Therapy was started with intravenous amphotericin B in a dose of 0.25 mg/kg/day that was gradually increased to the full dose of 1.0 mg/kg/day. The necrotic area continued to worsen and went on to develop total necrosis of the four fingers, dorsum of the hand and dorsal surface of the forearm. At the proximal edge of the necrotic area there was deep necrosis of skin, subcutaneous tissue and muscles which involved more than 50% of the circumference of the arm. The area of deep necrosis was extensively debrided (the family did not agree to amputation of the arm). Candida albicans and Rhizopus sp. were isolated from the culture of debridement tissue. During the course chest radiographs
were not suggestive of pulmonary infection. Her clinical condition continued to deteriorate and she died on the 56th day of life from severe renal failure. Approval for autopsy was not obtained.

Discussion. Zygomycosis is a fulminant fungal infectious disease that affects individuals immunosuppressed by age, drug therapy or underlying disease. Mucomycosis caused by the order Mucorales is a rare infection in childhood; only 16 cases were documented during a 30-year period at Texas Children's Hospital. This disease may present in several distinct clinical forms, including rhinocerebral, pulmonary, gastrointestinal, cutaneous or disseminated. Although Rhizopus spp. are potentially pathogenic members of this order a review of the literature has shown it to be a rare cause of necrotizing cellulitis in children (Table 1). Of the nine reported cases eight patients had predisposing conditions. Three patients had acute lymphoblastic leukemia; one patient had diabetes insipidus and renal transplantation. Four patients were premature infants with several complicated prematurity-related problems. Four patients had exposure to a contaminated elastic bandage. One of these patients was a previously healthy individual who underwent surgery for idiopathic scoliosis.

In seven of the patients associated organisms were isolated from the wound; S. epidermidis was found in three patients, Pseudomonas aeruginosa, C. albicans and C. parapsilosis were isolated in two patients each, and one each had Klebsiella species, Enterobacter cloacae, Bacillus spp. and Aspergillus spp. Eight patients were treated with amphotericin B, either as a single antifungal drug or in combination with potassium iodide in one patient or flucytosine and intravenous immunoglobulin in another. One immunosuppressed patient recovered after local transection therapy was applied over an extended period of time. It is likely that the response was related to an intact immunologic status and the relatively superficial nature of the infection in this patient because antifungal therapy was not administered. Of the nine patients seven recovered. Two patients with prematurity and related problems died, including the one in this report. Surgical debridement was carried out in six of the seven survivors.

Cutaneous infection caused by these fungi appears to begin at the site of prior tissue injury, such as trauma, burns or invasive procedures. The pathology in mucomycosis is characterized by vascular invasion with resultant thrombosis and tissue necrosis and accompanying acute and chronic inflammation, which may lead to septic embolization. Broad spectrum antibiotics and corticosteroids encourage colonization with opportunistic pathogens and intravenous catheters may provide portals of entry. The clinical presentation may vary from a relatively indolent vesicle or pustule with ulceration to a gangrenous cellulitis with necrotic plaque. Ryan and Ochs suggested two distinct clinical expressions of cutaneous mucomycosis: a superficial type, characterized by a subacute course; and a rapidly progressive gangrenous type with tendency to disseminate and high mortality.

The diagnosis can be established by tissue biopsy showing the characteristic hyphal forms invading tissue or by isolating the organism from a tissue specimen. Because of the fulminant nature of the infection therapy must be started promptly. The management of necrotizing cellulitis caused by Rhizopus also depends on the patient's underlying and/or current clinical condition. The standard medical therapy for Rhizopus necrotizing cellulitis is intravenous amphotericin B and aggressive surgical debridement where possible. In vitro synergism of amphotericin B with rifampin against Rhizopus has been suggested.

Despite the overall poor prognosis for all other forms of mucomycosis, it appears that necrotizing cellulitis caused by Rhizopus species carries a better prognosis in pediatric patients than in adults, with seven of the nine described cases recovering from this disease. Although this is a rare infection, it must be strongly considered in a patient with necrotizing cellulitis. Early diagnosis and treatment with surgical debridement and systemic antifungal drugs are essential if the patient is to survive.

A. Engin Arisoy, M.D.
K. Sami Arisoy, M.D.
Armando Correa-Calderon, M.D.
Sheldon L. Kaplan, M.D.
Department of Pediatrics
Baylor College of Medicine and Texas Children's Hospital
Houston, TX

TABLE 1. Summary of documented cases of necrotizing cellulitis caused by Rhizopus species in children

<table>
<thead>
<tr>
<th>Case</th>
<th>Reference</th>
<th>Sex</th>
<th>Age</th>
<th>Predisposition</th>
<th>Associated Organisms</th>
<th>Antifungal Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>M</td>
<td>7 years</td>
<td>ALL, chemotherapy, neutropenia, elastic bandage</td>
<td>Staphylococcus epidermidis Bacillus sp.</td>
<td>Amphotericin B</td>
<td>Recovered</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>F</td>
<td>6 years</td>
<td>ALL, sepsis, neutropenia, elastic bandage</td>
<td></td>
<td>Amphotericin B</td>
<td>Recovered</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>M</td>
<td>Newborn</td>
<td>Prematurity, RDS, possible septic, elastic bandage</td>
<td>Staphylococcus epidermidis Aspergillus sp.</td>
<td>Amphotericin B</td>
<td>Recovered</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>F</td>
<td>13 years</td>
<td>Orthopedic surgery, elastic bandage</td>
<td>Staphylococcus epidermidis Aspergillus sp.</td>
<td>Tramcinolone octoxide (local)</td>
<td>Recovered</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>F</td>
<td>9 years</td>
<td>Diabetes mellitus, renal transplantation</td>
<td>Candida albicans</td>
<td>Amphotericin B</td>
<td>Recovered</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>M</td>
<td>14 years</td>
<td>ALL, chemotherapy</td>
<td></td>
<td></td>
<td>Recovered</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>M</td>
<td>6 days</td>
<td>Prematurity, NRC, perforation of ileum, surgery, DIC, dexamethasone</td>
<td>Pseudomonas aeruginosa</td>
<td></td>
<td>Recovered</td>
</tr>
<tr>
<td>8</td>
<td>17</td>
<td>M</td>
<td>Newborn</td>
<td>Prematurity, RDS, diaphragm, perforation, Right subluxation in the internal agenesis</td>
<td>Candida parapsilosis</td>
<td>Amphotericin B, potassium iodide</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>This report</td>
<td>F</td>
<td>33 days</td>
<td>Prematurity, RDS, PDA, PDA surgery, lacteum, renal failure</td>
<td>Staphylococcus epidermidis Candida parapsilosis Candida albicans</td>
<td></td>
<td>Died</td>
</tr>
</tbody>
</table>

ALL, acute lymphoblastic leukemia; RDS, respiratory distress syndrome; NRC, necrotizing retrolenticulitis; DIC, disseminated intravascular coagulation; PDA, patent ductus arteriosus; IVIG, intravenous immunoglobulin.
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Address for reprints: Sheldon L. Kaplan, M.D., Mail Code: 3-
2571, Texas Children's Hospital, 6621 Fannin Street, Houston, TX
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