PRIMARY CUTANEOUS ASPERGILLOSIS ASSOCIATED WITH HICKMAN INTRAVENOUS CATHETERS

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Abstract We describe nine patients with underlying hematologic cancer in whom primary cutaneous aspergillosis developed at the sites of Hickman intravenous catheters. Our patients, 17 to 74 years of age, were all immunocompromised either from their primary disease or from chemotherapy, and the Hickman catheters had been placed to provide venous access for chemotherapy or hyperalimentation or both. Clinical signs of infection included erythema, induration, and cutaneous or subcutaneous necrosis at the point of entry into the subclavian vein, in the subcutaneous tunnel, or at the exit site from the skin. Diagnosis was confirmed by positive wound culture for Aspergillus flavus in all but one patient. Treatment consisted of intravenous amphotericin B, oral fluconazole, and local wound care. Three patients recovered completely without operative débridement; three others recovered after operative débridement and delayed grafting. Two patients died of disseminated aspergillosis, and one died of unrelated causes while recovering from primary cutaneous aspergillosis. Successful treatment required resolution of apleasia or leukopenia, catheter removal, systemic treatment with amphotericin B, and local wound care.

We conclude that primary cutaneous aspergillosis, a rare infection, may occur at the sites of Hickman catheters in immunocompromised patients, and that it is a serious complication requiring prompt diagnosis and treatment. (N Engl J Med 1987; 317:1105-8.)

Methods

Patients

Nine patients 17 to 74 years of age were treated for primary cutaneous aspergillosis associated with Hickman catheters between September 1985 and January 1986. All were immunosuppressed, eight had hematologic cancer, and the ninth had aplastic anemia. Three patients underwent bone marrow transplantation immediately after placement of the Hickman catheter, in the remaining six patients, catheters were inserted before initiation of chemotherapy for acute leukemia. All patients had leukopenia (white-cell count <1000 per cubic millimeter) at the time of onset of infection, and all had received broad-spectrum antibiotics. Four patients had received amphotericin B immediately before the onset of infection.

The characteristics of the patients are summarized in Table 1.

Epidemiologic Background

Aspergillus infections and colonizations among the patients at our hospital have been routinely tabulated by the epidemiology unit since the early 1970s. Since 1983, a distinct seasonal pattern with peaks in late fall has been noted. Most isolates were from immunocompromised patients in the Oncology Center. In December 1985, 15 patients who had had 29 operative procedures, including 9 Hickman catheter insertions, were colonized or infected at the operative wound site. Patients other than those with Hickman catheters were not immunocompromised. The operations had occurred from mid-September to mid-November. Attack rates specific to the operating rooms revealed a significant association between infection or colonization and undergoing an operation in 1 of 4 rooms that shared a common air supply separate from that of 14 other operating rooms during the period from July 1 to November 24, 1985 (21 of 1305 operations [1.61 percent] in the 4 rooms, as compared with 8 of 3878 operations [0.21 percent] in the remaining 14 operating rooms and 6 additional operating rooms (A through F) in an adjacent building \((x^2 = 32.06; \text{two-tailed } P < 0.001)\). No other environmental or patient variable investigated was significantly associated with infection or colonization.

Operations in the four implicated rooms were suspended, and a slit-air sampler was used to examine 45 liters of air in the four rooms and compare these rooms with the remaining rooms. The number of viable fungal particles averaged 0.24 (range, 0.02 to 0.64) per liter in the four rooms and 0.01 (range, 0 to 0.04) per liter in the other rooms. The number of viable particles of Aspergillus flavus averaged 0.2 (0.04 to 0.4) per liter in rooms 1 to 4, and the organism was not recovered from the air in rooms 5 to 9. The air-supply system into rooms 1 to 4 was renovated, and all air-supply ducts into all operating rooms were vacuumed; samples from the four implicated operating rooms revealed no viable fungal particles. Con-
Table 1. Characteristics of Nine Patients with Primary Cutaneous Aspergillosis.

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Site of Lesion</th>
<th>Duration of Leukopenia*</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>M</td>
<td>Acute myelogenous monocytic leukemia (in remission)</td>
<td>Exit</td>
<td>21 days; WBC 1.2</td>
<td>Pulmonary infiltrate; healed cutaneous lesion and normalized chest film</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>M</td>
<td>Undifferentiated lymphoblastic lymphoma (in remission)</td>
<td>Exit</td>
<td>22 days; WBC 2.8</td>
<td>Healed totally; never had other sites of aspergillosis</td>
</tr>
<tr>
<td>3</td>
<td>74</td>
<td>F</td>
<td>Acute erythoblastic leukemia (active)</td>
<td>Exit, entrance, tunnel</td>
<td>20 days; WBC 6.9</td>
<td>Wound began granulating and was healing when patient died of unrelated causes; no other site of aspergillosis</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>M</td>
<td>Acute myelogenous leukemia (active)</td>
<td>Exit, entrance, tunnel</td>
<td>24 days; WBC 10.4</td>
<td>Cavitary lung lesion; both skin and lung lesions healed; skin grafting was required</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>M</td>
<td>Acute lymphoblastic leukemia (active)</td>
<td>Exit</td>
<td>25 days; WBC 4.4</td>
<td>Pulmonary infiltrates; both skin and lung lesions healed</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>F</td>
<td>Acute nonlymphoblastic leukemia (active)</td>
<td>Entrance</td>
<td>46 days; aplectic until death</td>
<td>Cavitary lung lesion; died of pulmonary aspergillosis; unhealed chest-wall lesions; no autopsy</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>F</td>
<td>Acute myelogenous leukemia (active)</td>
<td>Exit, entrance, tunnel, catheter tip</td>
<td>29 days; WBC 6.2</td>
<td>Cavitary lung lesion; skin lesion healed after skin grafting; pulmonary infiltrates resolved</td>
</tr>
<tr>
<td>8</td>
<td>53</td>
<td>M</td>
<td>Acute myelogenous monocytic leukemia</td>
<td>Tunnel</td>
<td>23 days; WBC 6.1</td>
<td>Nodular lung infiltrate; skin lesions healed after grafting; pulmonary infiltrates resolved</td>
</tr>
<tr>
<td>9</td>
<td>53</td>
<td>M</td>
<td>Aplastic anemia</td>
<td>Exit, catheter tip</td>
<td>35 days; aplectic until death</td>
<td>Bronchoscopic washings grew A. flavus; lung and skin lesions healed; patient died after respiratory arrest; autopsy determined aspergillosis to be the cause of death</td>
</tr>
</tbody>
</table>

*WBC denotes white-cell count (x 10^9 per liter).

continued surveillance revealed no viable fungal particles and no additional colonizations or infections of operative wounds in patients undergoing surgery after these rooms were reopened in January 1986.

Hickman Catheter Procedure

All patients had double-lumen catheters placed for parenteral hyperalimentation and chemotherapy. With the patient in the supine position, the chest and neck were painted with povidone-iodine and draped in standard fashion. The area beneath the clavicle was anesthetized with 1 percent lidocaine without epinephrine, and a needle was placed in the subclavian vein. A guide wire was passed through the needle, and a subcutaneous tunnel was made from the mid-anterior chest to the subclavicular region. The catheter was passed through the tunnel with a silk tie and positioned so that the Teflon cuff was approximately 1 cm above the exit site from the skin. A 13-French introducer with a peel-away sheath was placed viaian vein through the sheath.

The position of the catheter tip in the superior vena cava was confirmed by fluoroscopy. The subcutaneous incision was closed with a running 4-0 polyglycolic acid (Dexon) subcuticular stitch, and the catheter was secured in place with two 3-0 nylon sutures at the exit site. Sterile dressings were applied.

Characteristics of Infection

Erythema with induration developed at the catheter site in all nine patients and progressed to necrosis extending radially from the initial focus. No infected site had a purulent discharge. Figure 1 shows a typical lesion. The exit site was involved in seven patients, and in three of these seven, the tunnel and entrance sites were also involved. In one patient, the entrance site alone was involved, and in another, the tunnel alone was involved. Once infection was suspected, the catheters were removed. Tissue from wounds was excised for culture; eight of nine specimens grew A. flavus; one patient had a negative culture but a clinical picture that matched that of the others. Only two of the nine patients had cultures from the catheter tip that grew A. flavus.

All patients were treated with intravenous amphotericin B (0.75 to 1.25 mg per kilogram of body weight per day) and flucytosine (3 to 8 g per day). Wound care was individualized among the patients in the group and included wet-to-dry dressings with normal saline or povidone-iodine, topical amphotericin cream, hydrogen peroxide irrigations, and silver sulfadiazine (Silvadene) cream. There were no appreciable differences in outcome with the different regimens. Sharp debridement was deferred until bone marrow recovery began. Healing of lesions correlated with resolution of leukopenia. The two patients who did not recover from leukopenia had progression of their cutaneous lesions and eventually died of disseminated aspergillosis.

Dissemination of primary cutaneous aspergillosis to the lungs occurred in five patients and was manifested by new infiltrates on the chest roentgenogram and cavitary chest infiltrates on the chest CT scan. Two of these patients had direct positive cultures for pulmonary aspergillus (specimens were obtained by CT-guided needle aspiration in Patient 8 and bronchoscopy in Patient 9) before skin lesions appeared. Only two patients with disseminated aspergillosis died.

Discussion

In immunosuppressed patients with aspergillosis, the lung is almost exclusively the portal of entry. Hematogenous dissemination occurs in 20 to 30 percent of patients and most commonly involves the central nervous system and gastrointestinal tract. Metastatic foci of aspergillus are characterized by microscopic fungal vasculitis with a minimal host response because of the underlying immunosuppression.
Figure 1. A Typical Lesion in a Patient with Primary Cutaneous Aspergillosis Associated with a Hickman Intravenous Catheter.

In reports on immunocompromised and immunocompetent patients with secondary metastatic cutaneous aspergillosis,3,24-29 the lung was always the primary focus of invasion. All age groups were represented. The pathologic lesion was usually a diffuse maculopapular erythematous eruption followed by pustule formation, a pattern consistent with hematogenous spread. A. fumigatus was the particular species involved in these cases. Findlay et al. have estimated that dermal involvement occurs with an incidence of less than 5 percent in disseminated aspergillosis.25 Skin involvement has also been attributed to direct extension from a paranasal-sinus focus of infection.24

The skin and subcutaneous tissue are only rarely involved as either the primary or secondary focus of invasive aspergillosis in immunocompromised hosts. In otherwise healthy patients, skin involvement is rarer.26-35 Only one nonlocalized invasive infection was reported among six cases in the literature.30-35 In all cases, complete healing without systemic dissemination occurred. Nonspecific chronic urticarial skin lesions attributed to hypersensitivity following ingestion or inhalation of fungal spores is another dermatologic manifestation of aspergillosis in the normal host.26

Preceding reports of primary cutaneous aspergillosis have been rare.36-42 Between 1970 and 1984, only 10 such cases were reported in the English-language literature. These involved three adults, six children, and one premature neonate. Most patients were immunocompromised as a result of hematologic cancers or their treatment. As in our series, the infections were characterized by necrotizing ulcerations, usually near an area of local skin trauma resulting from intravenous access, arm boards, or tape.

In 1985, Grossman et al.43 described a cluster of primary cutaneous aspergillosis in six children with neutropenia and leukemia who were receiving broad-spectrum antibiotics. The lesions were characterized by hemorrhagic bullae at sites of intravenous access. Rapid diagnosis was aided by direct examination of the blister roof with potassium hydroxide before progression to a necrotic ulcer occurred. Prompt treatment with intravenous amphotericin B was begun when aspergillus was identified. In one patient, whose treatment with amphotericin B was delayed, systemic aspergillosis developed, but no patient died as a result of dissemination. The 17th patient was a 15-year-old girl with chronic hepatitis treated with steroids. Her infection began as skin necrosis with pustule formation near the site of an intravenous catheter. Treatment was not described in the report.24 The patient died of disseminated disease.

Despite the seasonal occurrence of pulmonary aspergillosis among patients with neutropenia and leukemia, cutaneous lesions had not been observed previously at our institution. Before this outbreak, more than 200 catheters had been inserted by the same surgical team in a comparable patient population, and no similar infections had occurred. The absence of previous aspergillus colonization or infection in the majority of the nine patients in the outbreak raised the question of whether the source might be outside the Oncology Center. This prompted a review of cultures from all surgical patients to detect aspergillus in the period of the outbreak. Aspergillus colonization in several general surgical patients without neutropenia directed attention to the operating rooms.

The patients described here had an unusually low mortality as compared with previously reported series. We attribute this to early recognition of the nature of the infection, to aggressive antifungal chemotherapy, and to deferral of wide débridement of the eschar until the aplasia had resolved. Removal of the eschar does not promote healing in the absence of white cells, and it leads to increased blood loss and enlargement of the chest-wall lesion. Control of the size of the eschar appears to be related to the adequacy of antifungal chemotherapy. In this series, once patients received amphotericin B, the lesion size stabilized, and it diminished once the white-cell count became normal. Conversely, one patient had a 2-mm increase in eschar size after amphotericin B had been withheld for 48 hours.

Successful management requires a high index of suspicion, prompt treatment with amphotericin B, and carefully individualized wound care until aplasia resolves. The presence of nonpurulent erythema pro-
gressing to a radial necrotic lesion in a patient with aplasia or leukeopenia, particularly one treated with broad-spectrum antibiotics, should prompt an aggressive search for aspergillosis or other opportunistic fungal organisms, such as mucor or rhizopus, which can cause similar cutaneous lesions.

**References**