Outbreak of Cutaneous *Rhizopus arrhizus* Infection Associated with Karaya Ostomy Bags

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**Background.** We investigated an outbreak involving 2 patients hospitalized at hospital A with cutaneous *Rhizopus arrhizus* (oryzae) infections of surgically created stomas.

**Methods.** A cohort study involving all patients having ileostomy or colostomy surgery during the outbreak period (January–April 2005) was performed. Environmental samples, including samples obtained from nonsterile karaya (a plant-derived adhesive) ostomy bags and from select hospital areas, were collected. A point prevalence survey was conducted at 5 unrelated hospitals to assess stoma care practices and mold contamination of karaya ostomy bags outside of hospital A. Zygomycete isolates were identified by standard methods.

**Results.** Infections occurred 7 and 10 days after operations for the 2 patients; 1 patient died. In a 21-patient cohort, receiving the equivalent of \(\geq 0.5\) mg/kg per day of prednisone during the week prior to the index date was associated with infection (infection rate, 33% for patients receiving \(\geq 0.5\) mg/kg per day of prednisone vs. 0% for patients receiving <0.5 mg/kg per day of prednisone; \(P = .07\)). The time to first ostomy bag change was longer for patients with infection (median duration, 8.5 days; range, 7–10 days) than for the 19 patients without infection (median duration, 1.5 days; range, 1–17 days; \(P = .08\)). At unrelated hospitals, the median time to first ostomy bag change was 2 days (range, 1–6 days) for 18 patients after ostomy. *R. arrhizus* was recovered from 10 of 18 karaya ostomy bags from hospital A and from karaya ostomy bags donated from 3 of 5 other hospitals, but it was not recovered from the hospital A environment.

**Conclusions.** The initial karaya ostomy bag was likely to be the source of *Rhizopus* infection, and prolonged exposure before the first ostomy bag change might have precipitated infection in these susceptible individuals. Karaya might contain opportunistic molds that can pose an infectious risk among susceptible persons.

*Rhizopus arrhizus* (oryzae), a mold in the class Zygomycetes and order Mucorales, can cause life-threatening infections, typically in immunocompromised patients or those with poorly controlled diabetes mellitus [1]. The most common manifestation is pulmonary or rhinocerebral infection; yet, cutaneous infection may also occur. Epidemics of cutaneous *Rhizopus* infection have been associated with contaminated wooden tongue depressors [2] and elasticized adhesive bandages [3–6]. There have also been 3 reports of cutaneous *Rhizopus* infection at stomas, although the source of the infections was not determined [7, 8].

During February–April 2005, 2 patients at hospital A, both of whom had recently undergone surgery to create stomas, developed infection due to *R. arrhizus* at the stoma site. The adhesive of the ostomy bag, used to affix the pouch to the abdominal surface, contained karaya gum, a product derived from the sap of the *Sterculia urens* tree (a native species of India) [9]. Karaya is nonsterile and is commonly used as a skin barrier in ostomy supplies. We describe these infections and the epidemiologic investigation, and we discuss the clinical significance and public health implications of the findings.

**METHODS**

**Case definition and ascertainment.** A case patient was defined as a patient who had undergone ileostomy or colostomy surgery that created a new stoma at hospital A during the period 1 January–25 April 2005 who had confirmation of a skin or soft-tissue infection due
Table 1. Selected exposures and associated attack rates for infection due to *Rhizopus arrhizus*, hospital A, 1 January–25 April 2005.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of case patients/no. of patients exposed</th>
<th>Attack rate, %</th>
<th>Relative risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1/14</td>
<td>7.1</td>
<td>2.0 (0.03–6.86)</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>1/7</td>
<td>14.3</td>
<td>2.0 (0.03–6.86)</td>
<td>1.00</td>
</tr>
<tr>
<td>Initial admitting service</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>0/15</td>
<td>0</td>
<td>ND (0.62–208.44)</td>
<td>0.07</td>
</tr>
<tr>
<td>Medicine</td>
<td>2/6</td>
<td>33.3</td>
<td>ND (0.62–208.44)</td>
<td>0.07</td>
</tr>
<tr>
<td>Type of ostomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colostomy</td>
<td>0/12</td>
<td>0</td>
<td>ND (0.62–208.44)</td>
<td>0.07</td>
</tr>
<tr>
<td>Ileostomy</td>
<td>2/9</td>
<td>22.2</td>
<td>ND (0.34–120.79)</td>
<td>0.17</td>
</tr>
<tr>
<td>Timing of surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>0/9</td>
<td>0</td>
<td>ND (0.62–208.44)</td>
<td>0.07</td>
</tr>
<tr>
<td>Emergent</td>
<td>2/12</td>
<td>16.6</td>
<td>ND (0.01–4.83)</td>
<td>0.48</td>
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<tr>
<td>Steroid use (equivalent of ≥0.5 mg/kg prednisone per day)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0/15</td>
<td>0</td>
<td>ND (0.62–208.44)</td>
<td>0.07</td>
</tr>
<tr>
<td>Yes</td>
<td>2/6</td>
<td>33.3</td>
<td>ND (0.62–208.44)</td>
<td>0.07</td>
</tr>
<tr>
<td>Total parental nutrition after operation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0/9</td>
<td>0</td>
<td>ND (0.62–208.44)</td>
<td>0.07</td>
</tr>
<tr>
<td>Yes</td>
<td>2/12</td>
<td>16.6</td>
<td>ND (0.20–71.47)</td>
<td>0.48</td>
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<td>Any intensive care unit stay</td>
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<td></td>
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</tr>
<tr>
<td>No</td>
<td>0/10</td>
<td>0</td>
<td>ND (0.24–85.32)</td>
<td>0.47</td>
</tr>
<tr>
<td>Yes</td>
<td>2/11</td>
<td>18.2</td>
<td>ND (0.24–85.32)</td>
<td>0.47</td>
</tr>
<tr>
<td>Period from hospital admission to surgery ≥5 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0/15</td>
<td>0</td>
<td>ND (0.62–208.4)</td>
<td>0.07</td>
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<tr>
<td>Yes</td>
<td>2/6</td>
<td>33.3</td>
<td>ND (0.62–208.44)</td>
<td>0.07</td>
</tr>
<tr>
<td>Period from surgery to first enterostomal nurse visit ≥7 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0/15</td>
<td>0</td>
<td>ND (0.62–208.44)</td>
<td>0.07</td>
</tr>
<tr>
<td>Yes</td>
<td>2/6</td>
<td>33.3</td>
<td>ND (0.62–208.44)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

**NOTE.** ND, not defined.

Microbiologic investigation. Lot numbers of stoma care products, including ostomy bags, were not routinely recorded. Samples from available unused stoma care products at hospital A were cultured. Samples included a karaya ostomy bag and nonkaraya containing supplies, such as powder, from patient A’s room. Stoma care products from the enterostomal nurses’ supply and from the central distribution supply were also cultured. A convenience sample of 5 hospitals unrelated to this outbreak also donated karaya ostomy bags, and they were cultured at the Centers for Disease Control and Prevention (Atlanta, GA).

Karaya adhesive was removed from ostomy bags, cut into pieces, and placed on Rose Bengal agar chloramphenicol plates for culture. Plates were incubated at 25°C for a minimum of 7 days.

Confirmatory identification of the mold species associated

to a mold in the class Zygomycetes (i.e., histopathological findings consistent with zygomycosis or a positive culture result in a symptomatic patient). Case patients were identified by a review of surgical procedures and laboratory data. In addition, queries were posted on the Centers for Diseases Control and Prevention Epidemic Information Exchange (Epi-X) and on the Infectious Diseases Society of America Emerging Infections Network to inquire about additional possible cases of postostomy zygomycosis in the United States.

Cohort study. A cohort study involving patients who had undergone new ileostomy or colostomy surgery at hospital A during the period 1 January–25 April 2005 was performed. Abstracted data included demographic characteristics, underlying illnesses, and perioperative exposures. The index date was defined as the date of infection for cases patients and the date of discharge for noncase patients.
with the cases was performed at the Ohio Department of Health (Columbus) and Centers for Disease Control and Prevention laboratories by using standard methods [10]. For PCR, DNA was isolated using a modification of the procedure of Gardes and Bruns [11] and was performed using species-specific amplification of large subunit rDNA as described by Voigt et al. [12]. Isolates were scored as either R. arrhizus or Rhizopus microsporus on the basis of the predominant band found after amplification; all experiments were repeated at least twice.

Environmental and product evaluation. We sampled horizontal surfaces and ceiling tiles in central distribution where ostomy supplies were stored. For comparison, samples from a supply closet not used for ostomy supply storage were also collected. Air sampling was performed in central distribution and the adjacent machine room using an SAS 90 air sampler (PBI International), collecting volumes of 10 L and 200 L onto Rose Bengal agar plates. Manufacturing practices were reviewed with the company that produces karaya ostomy bags.

Ostomy care assessment. Ostomy care practices were reviewed with the enterostomal nursing team and surgeons. In addition, a point prevalence survey was performed on a convenience sample of 5 hospitals unrelated to the outbreak that had contributed karaya ostomy bags for culture. The survey was designed to determine whether the ostomy care practices at hospital A were different from the practices at other institutions. The prevalence of all surgically created new stomas and time from patients’ surgeries to first enterostomal nurse visit were determined.

Statistical analysis. Data were entered into a Microsoft Access database (Microsoft) and analyzed in SAS, version 9.0 (SAS Institute). Univariate analysis was performed using Fisher’s exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. Reported P values are 2-tailed.

RESULTS

Case Reports

Patient A. A 47-year-old man was admitted to hospital A in January 2005 with chest pain and had elective coronary artery bypass graft surgery on hospital day 7. Postoperative complications included severe ischemia of his lower extremities, hepatic necrosis, and acute renal failure. He received broad-spectrum antibiotics postoperatively.

On hospital day 24, the patient developed ischemic bowel that required resection and ileostomy. In the operating room, an ostomy bag with karaya adhesive was affixed to the skin surrounding the stoma. One day after ileostomy, intravenous hydrocortisone therapy was started for adrenal insufficiency (prednisone equivalent, 0.56 mg/kg per day). Caspofungin was also initiated for suspected fungal infection of the gangrenous lower extremities.

The first enterostomal nurse visit and ostomy bag change occurred 10 days after ileostomy. On postileostomy day 15, the stoma site appeared to be necrotic, and the patient underwent emergent laparotomy for debridement and stoma revision. A mold in the order Mucorales was identified from debrided tissue; caspofungin therapy was discontinued, and amphotericin B therapy was initiated. The patient died 1 week later of vasomotor shock and resultant multiorgan system failure. The autopsy revealed mucormycosis involving the adipose tissue around the colon and small bowel. Of note, the patient had received 23 U of packed RBCs for bleeding and disseminated intravascular coagulation from the time of his initial ileostomy to the time of his death.

Patient B. A 76-year-old woman was admitted to hospital A in March 2005 with mucoid diarrhea and abdominal pain. A colonoscopy performed on hospital day 2 revealed focal colitis. On hospital day 5, the patient developed severe hypoxia and dyspnea, and treatment with 40 mg of methylprednisolone per day was started (average prednisone equivalent, 0.96 mg/kg per day).

An abdominal CT scan revealed intraperitoneal free air. An emergent laparotomy revealed a perforated cecum, and a total abdominal colectomy with ileostomy was performed; an ostomy bag with karaya adhesive was affixed to the skin. At the time of surgery, the patient had received ≤2 days each of broad-spectrum antibiotics and methylprednisolone.

On postoperative day 7, the first enterostomal nurse visit and ostomy bag change occurred. On postoperative day 14, the patient was discharged with a prescription for antibiotics and a prednisone taper.
Figure 2. PCR amplification of species-specific fragments. Lanes 1 and 20, molecular weight (M.W.) size standards; lanes 2 and 3, ATCC control strain B3689 (Rhizopus arrhizus); lanes 4 and 5, ATCC control strain B6600 (Rhizopus microsporus); lanes 6 and 7, patient A isolate 505392; lanes 8 and 9, patient B isolate 505393; lanes 10 and 11, karaya from unused patient A ostomy bag isolate 50503; lanes 12 and 13, karaya from ostomy bag stored in central distribution at hospital A (isolate 29-42); lanes 14–19, karaya from ostomy bags from 3 outside hospitals (isolates 29-61, 29-70, and 29-71). PCR fragment sizes, measured in base pairs (bp), are shown on the right and are the expected sizes for the specific species. RH, primers specific for R. microsporus; RO, primers specific for R. arrhizus.

The patient returned to hospital A 5 days after discharge from the hospital, because the stoma was necrotic. Ostomy revision and wide-debridement were performed. The pathology report confirmed the presence of a mold in the order Mucorales; the patient was treated with 43 days of amphotericin B therapy and additional debridements.

Cohort Study

Review of laboratory data and national queries did not identify additional cases of postostomy zygomycete infections. Twenty-one ileostomy or colostomy surgeries performed at hospital A during the period 1 January–25 April 2005 involved the creation of a new stoma. Exposures predictive of infection included admission to the medicine service, receipt of the equivalent of $0.5\text{ mg/kg}$ of prednisone daily in the week before the index date, hospitalization at least 5 days before ostomy surgery, and change of the initial ostomy bag $\geq 7$ days after surgery (table 1), but these associations were not statistically significant. Case patients did have significantly fewer enterostomal nurse visits during the exposure period (median number of visits, 0.5; range, 0–1), compared with noncase patients (median number of visits, 3; range, 2–10; $P = .03$). The time to first ostomy bag change was longer for case patients (median duration, 8.5 days; range 7–10 days), compared with noncase patients (median duration, 1.5 days; range, 1–17 days; $P = .08$) (figure 1).

Environmental Evaluation

Case patients’ surgeries and postoperative care were in areas supplied by different air-handling systems; the only common environmental exposure was the central distribution area, where ostomy supplies were stored. No fungi were isolated from cultures of the surfaces or ceiling tiles in central distribution. One swab sample of the wall in the control area grew an Aspergillus species and a Penicillium species. Air sampling in central distribution and in the adjacent machine room yielded no fungal growth.

Laboratory Investigation

The isolates from the case patients were identified as R. arrhizus. Culture of an unused karaya ostomy bag from patient A’s room grew a zygomycete and a Scopulariopsis species, but molds were not available for confirmatory identification. The remaining patient A stoma care products (i.e., wafer and powder) did not grow any fungus. R. arrhizus was isolated from a total of 10 (56%) of 18 unopened karaya ostomy bags from central distribution at hospital A. R. arrhizus was also recovered from...
cultures of 3 of 29 karaya ostomy bags donated from 5 other hospitals (figure 2). These 3 karaya ostomy bags were from 3 different hospitals.

Ostomy Care Assessment
At hospital A, upon completion of ileostomy or colostomy surgery, the initial karaya ostomy bag is placed directly on the peristomal skin without the use of a skin barrier, such as a pectin ring, wafer, powder, or paste. Postoperatively, the enterostomal team is notified about patients with new stomas by a nurse’s or physician’s order. The enterostomal nurses change patients’ ostomy bags while they are hospitalized and provide patients with education on stoma care.

For patients A and B, the first ostomy bag changes were 10 and 7 days after the operation, respectively (figure 2). Of the 18 patients surveyed at the 5 unrelated hospitals, the median time to first ostomy bag change was 2 days (range, 1–6 days). None of these 18 patients were using karaya ostomy bags; all were using ostomy bags with synthetic adhesive.

Manufacturing Practices
The manufacturer had not received prior reports of infections related to the karaya ostomy bags. The manufacturer tests for the absence of the 4 key marker pathogens (Salmonella species, Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa), in accordance with US Pharmacopeia guidelines, and has established microbial limits for bacteria and molds. According to the manufacturer’s report, all recent test results were within normal acceptable limits.

DISCUSSION
This report describes 2 cases of cutaneous R. arrhizus infection of new stomas at hospital A that occurred within a 2-month period. The epidemiologic and microbiologic investigations suggest that exposure to a karaya ostomy bag was the source of R. arrhizus infection in these 2 susceptible hosts. The most likely factors that contributed to the infections were prolonged exposure of cutaneous tissue to the initial karaya ostomy bag and acute immunosuppression during the week preceding the infection. Although immunosuppression is a well-described risk factor for zygomycosis, patient A also had received multiple RBC transfusions, which might have caused iron overload, another risk factor for zygomycosis. In a study of 5 allogeneic transplant recipients who developed zygomycosis, mean levels of serum ferritin and transferritin saturation were significantly higher among infected patients than among noncase patients because of transfusional iron overload [13].

The initial karaya ostomy bag was applied directly to the peristomal skin at the conclusion of the ileostomy surgery. It likely served as the inoculum of Rhizopus species, because the ostomy bag was not changed for at least 1 week. Contamination of karaya is likely intrinsic, because the product is plant-based, and the final product is not sterile. In 1976, an information letter was sent by the US Food and Drug Administration to manufacturers of karaya-based ostomy products to advise of proposed labeling changes, because karaya-based products were found to contain opportunistic pathogens. Subsequently, this labeling became voluntary, because there was no evidence of infection associated with the use of karaya-based ostomy products, and there were few alternative stoma care products available at that time [14]. Low concentration of Rhizopus species might be sufficient to cause disease when karaya is directly in contact with nonintact skin for prolonged periods and when patients are at risk for zygomycosis because of immunosuppression, as was observed in these cases. Based on the results of our survey, it is unusual to change the first ostomy bag >6 days after surgery. It is likely that prolonged exposure and immunosuppression contributed to the pathophysiology of the infection. Of note, 1 patient who was immunosuppressed did not have the initial ostomy bag changed until 17 days after surgery and did not develop infection.

Similar to our findings, primary cutaneous disease due to infection with R. arrhizus and R. microsporus var. rhizopodiiformis has been reported in association with use of nonsterile adhesive bandages and with use of tongue depressors as splints [2–6], when spores were introduced directly into the surgical wound or introduced into traumatized skin at the time of bandage removal. However, to our knowledge, this is the first report that describes isolation of R. arrhizus from ostomy bag adhesive.

As a result of these findings, hospital A has implemented procedures to avoid delays in providing initial stoma evaluation, and the ostomy bag product has been changed to one that uses synthetic adhesive material. The wide distribution of these karaya-based products and the lack of similar infections suggest that contamination might be infrequent and intermittent or has stopped. Perhaps more importantly, the prolonged exposure time that these patients had to the initial karaya ostomy bag might not occur at other hospitals, as suggested by the point prevalence survey. Prolonged exposure to nonsterile karaya ostomy supplies in patients with compromised immune systems should be avoided.

Persons providing stoma care might consider recording lot numbers and the expiration dates of products used to treat patients to assist with trace back if the product is subsequently associated with an infection. Clinicians suspicious of skin or soft-tissue infection should submit tissue samples for both histopathological examination and culture. If a zygomycete is identified in the tissue specimen, then antifungal treatment should be initiated promptly; culture results may be delayed. It is important for clinicians to have a high level of suspicion for fungal
skin and soft-tissue infections in patients using karaya-based products. These products should be added to established lists of products that have been associated with the development of zygomycosis in areas of skin breakdown [2–6, 15].

Acknowledgments

We are grateful for the assistance of Diane Kuehnlenz, Cook County Hospital, Chicago, IL; Linda Roof, University of California Los Angeles Medical Center, Los Angeles; Linda Stamm, Barnes-Jewish Hospital, St. Louis, MO; Sally Thompson, Akron City Hospital, Akron, Ohio; Usha Patel, Oak Forest Hospital, Oak Forest, IL; and Shirley Zeigler, Office of Surveillance and Biometrics, US Food and Drug Administration, Rockville, MD.

Potential conflicts of interest. All authors: no conflicts.

References