

## Disseminated Zygomycosis Due to *Rhizopus schipperae* after Heatstroke

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**A 21-year-old woman suffered heatstroke and developed diarrhea while trekking across south Texas. The heatstroke was complicated by seizures, rhabdomyolysis, pneumonia, renal failure, and disseminated intravascular coagulation. The patient's stool and blood cultures grew *Campylobacter jejuni*. The patient subsequently developed paranasal and gastrointestinal zygomycosis and required surgical debridement and a prolonged course of amphotericin B. The zygomycete cultured was *Rhizopus schipperae*. This is only the second isolate of *R. schipperae* that has been described. *R. schipperae* is characterized by the production of clusters of up to 10 sporangiophores arising from simple but well-developed rhizoids. These asexual reproductive propagules are produced on Czapek Dox agar but are absent on routine mycology media, where only chlamydospores are observed. Despite multiorgan failure, bacteremia, and disseminated zygomycosis, the patient survived and had a good neurological outcome. Heatstroke has not been previously described as a risk factor for the development of disseminated zygomycosis.**

Campylobacters are small, curved, motile, microaerophilic gram-negative rods. *Campylobacter jejuni* is the most common cause of bacterial diarrhea in the United States. However, *C. jejuni* bacteremia is uncommon; only about 0.4% of reported *C. jejuni* isolates originate from blood (1), and the bacteremia usually occurs in patients with underlying medical conditions or at the extremes of age (3). Likewise, disseminated infection by fungi of the order Mucorales, known as zygomycosis, is a rare infection and typically occurs in those immunocompromised by malignancy or renal disease (16). Here we report a case in which exertional heatstroke provided the setting for both disseminated zygomycosis and *Campylobacter* bacteremia. The zygomycete cultured was *Rhizopus schipperae*. This is only the second isolate of *R. schipperae* that has been described.

### CASE REPORT

In June 1998, a 21-year-old Mexican woman crossed the United States border without documentation. She had a sore throat and cough prior to departure. She left San Luis Potosi, México, and rode a bus to Nuevo Laredo. With a group of men, she crossed the Rio Grande by boat and hiked into Dimmit County, Tex. In the morning, the woman had chills and diaphoresis. The immigrants drank from stock ponds and walked for several hours. The high temperature on this day was 105°F, and the woman became delirious and collapsed. She had convulsions and was taken to a local hospital. Initial vital signs were a rectal temperature of 107.1°F, a blood pressure of 71/44 mm Hg, a heart rate of 123 beats per minute, and a respiration rate of 30 breaths per minute. The patient was intubated and transferred to University Hospital in San Antonio, Tex. The assessment was exertional heatstroke with circu-

latory collapse, severe brain injury, shock liver, rhabdomyolysis, renal insufficiency, pancreatitis, and disseminated intravascular coagulation (DIC). Due to the probable exposure to enteric pathogens, levofloxacin was initiated on admission after blood and stool samples for cultures were obtained. The patient developed a lung infiltrate on day 3, and *Enterobacter cloacae* and a single colony of a *Rhizopus* species grew from tracheal aspirates. Blood and stool cultures grew *C. jejuni*. The antibiotic was changed to meropenem. On day 3, *E. cloacae* was also isolated from a blood culture.

On day 9, a 5-mm dark eschar was noted on her right nasal ala (Fig. 1A). Resection of the ala, lower lateral cartilage, and a portion of the nasal septum was performed until bleeding tissue was obtained (Fig. 1B). The nasal tissue showed non-septate fungal hyphae (Fig. 1C). Amphotericin B (AMB) was started at 1 mg/kg/day on day 9. On day 21, the patient passed bright red blood per rectum, and her hematocrit dropped to 10%. An angiogram revealed bleeding from the superior mesenteric artery. A resection of the terminal ileum and ascending colon was performed. An ulcerating lesion, 5.5 by 2.5 by 1.5 cm, was found on the mucosal surface at the ileocecal valve. Histopathological examination showed transmural necrotizing granulomatous inflammation and vascular invasion by nonseptate hyphae (Fig. 1D).

The patient received AMB at 1 mg/kg/day for a total of 40 days and AMB-lipid complex (ABLC) at 5 mg/kg/day intermittently for 12 days during periods of renal insufficiency. Two months after the heatstroke, she has had significant neurological recovery but suffers from dysarthria and ataxia.

### MATERIALS AND METHODS

**Histopathology.** Fragments of skin, soft tissue, and cartilage from the right nasal vault and segments of the terminal ileum and ascending colon were submitted for hematoxylin-eosin and Gomori methenamine-silver staining.

**Mycology.** Samples from the tracheal aspirates, nasal tissue, and small intestine were initially incubated on Sabouraud dextrose agar (SDA) (BBL Microbiology Systems, Cockeysville, Md.) at 25°C. Since the cultures did not sporulate, a small portion of SDA containing fungal growth was excised and incubated in a

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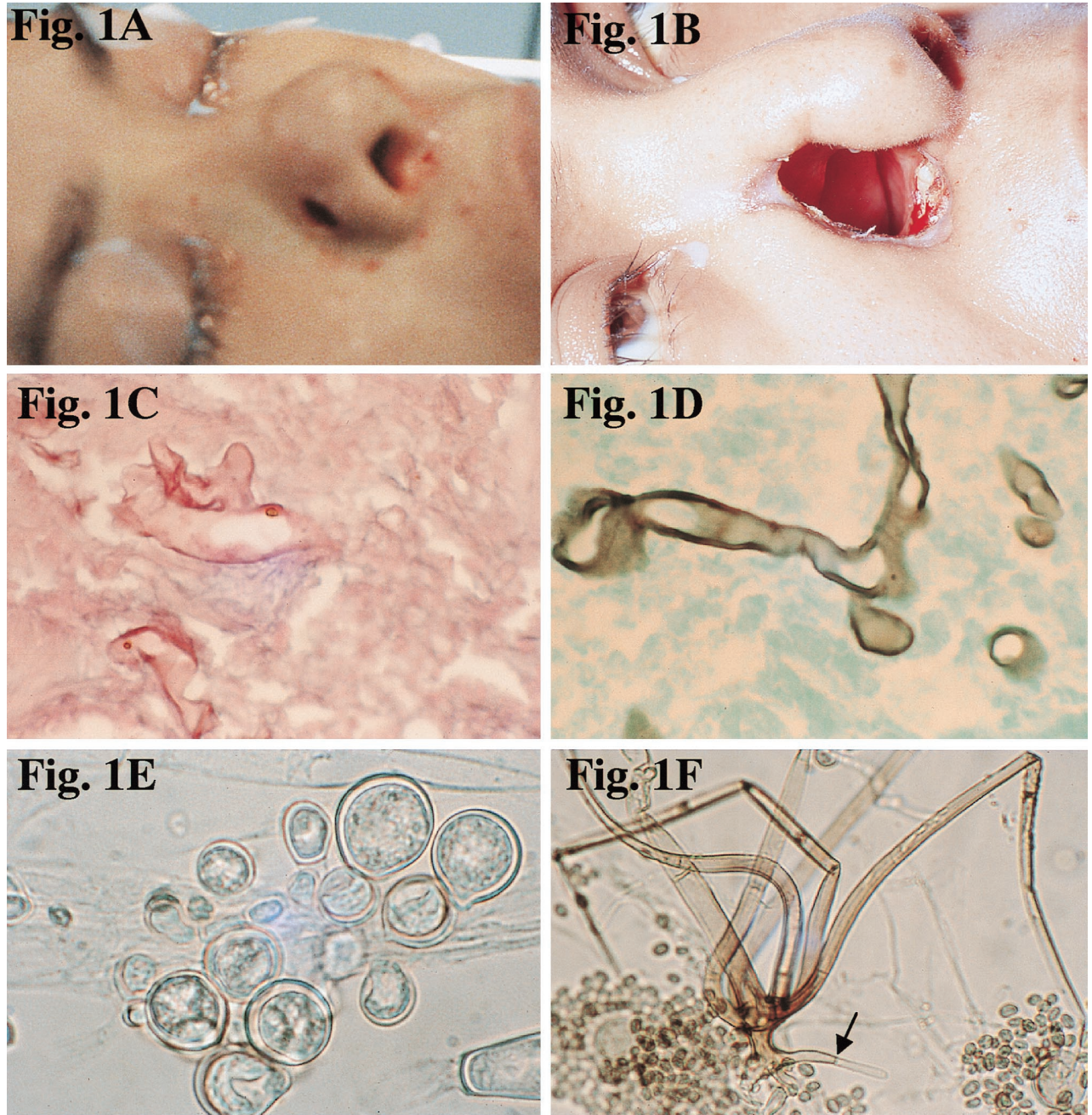


FIG. 1. (A) Necrotic lesion on nasal ala prior to surgery. (B) Appearance of patient 1 month after surgery. (C) Branching, nonseptate hyphae of *R. schipperae* in nasal mucosa. Hematoxylin-eosin stain. Magnification,  $\times 613$ . (D) Hyphae of *R. schipperae* in intestinal mucosa. Gomori methenamine-silver stain. Magnification  $\times 613$ . (E) Thick- and thin-walled chlamydozoospores of *R. schipperae* on PDA. Magnification,  $\times 613$ . Lactophenol cotton blue mount. (F) Cluster of sporangiophores of *R. schipperae* on CDA. The arrow shows a septate rhizoid. Magnification,  $\times 213$ . Lactophenol cotton blue mount.

10% yeast extract-water culture at 35°C for 10 days in an attempt to promote sporulation (26). Cultures remained sterile, producing only large, thick-walled, globose to somewhat irregularly shaped chlamydozoospores (Fig. 1E). The nasal isolate was plated on Mycosel agar (BBL), potato dextrose agar (PDA) (Remel, Lenexa, Kans.) (32), and SDA plates for temperature studies at 25, 30, 45, and 50°C. Subcultures of the nasal isolate (UH F 1746) were sent to the Fungal Testing Laboratory, Department of Pathology, University of Texas Health Science Center at San Antonio, for further characterization and designated UTHSC R-3053. There, the isolate was subcultured on Czapek Dox agar (CDA) (Remel) at 30°C, and temperature studies were repeated, but with the addition of 35°C testing.

**Antifungal susceptibility testing.** The nasal isolate was tested to determine its susceptibilities to AMB, fluconazole (FLU), 5-fluorocytosine (5-FC), and itra-

conazole (ITRA). Tests were performed by previously described macrodilution methods (22, 33, 43). The minimum lethal concentrations (MLCs) were determined by plating 100-ml samples from the drug-free control tube, the MIC tube, and a tube containing each concentration above the MIC on an SDA plate incubated at 35°C. The MLC was defined as the lowest concentration of antifungal compound resulting in five or fewer colonies on the SDA plate (33).

## RESULTS

**Mycology.** Initial cultures on SDA at 25°C produced white, sterile, floccose colonies after 4 days of incubation; the colonies became buff colored at day 6. Temperature studies re-



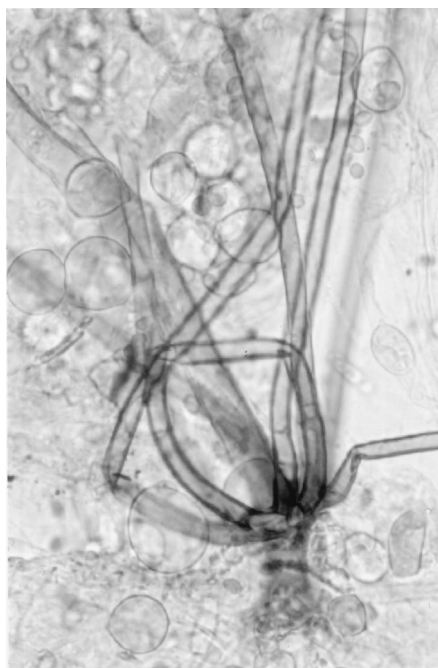


FIG. 2. Cluster of sporangiophores of *R. schipperae* on CDA. Magnification,  $\times 306$ . Lactophenol cotton blue mount.

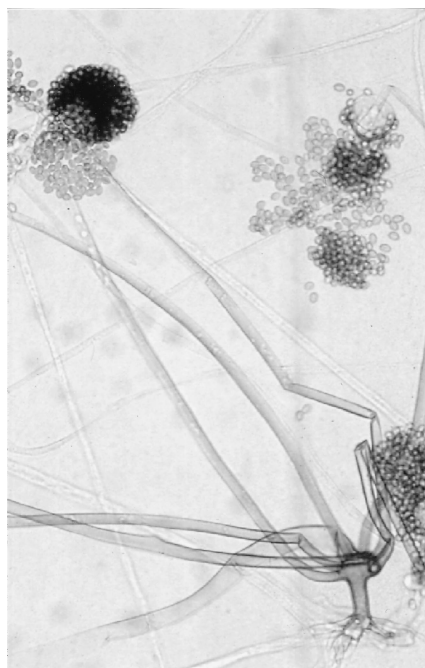


FIG. 3. Rhizoids and sporangiospores of *R. schipperae* on CDA. Magnification,  $\times 306$ . Lactophenol cotton blue mount.

vealed good growth at 25, 30, 35, and 45°C and no growth at 50°C. The isolate also failed to grow on media containing cycloheximide. Subcultured colonies at 25°C on PDA and SDA were white, floccose in the central portion, and thin and effuse near the periphery. Rapid growth resulting in numerous chlamydospores occurred on both media, but sporangia were lacking. Chlamydospores were thin or thick walled (0.5 to 1 or 3.9  $\mu\text{m}$  wide), globose to subglobose, oval to irregularly shaped, and 10 to 40  $\mu\text{m}$  in diameter (Fig. 1E). A culture in 10% yeast extract–water at 35°C was sterile after 10 days of incubation. Colonies on CDA at 30°C were white, thin, diffuse, and floccose, produced fewer numbers of chlamydospores than at 25°C, but promoted the production of the fruiting structures of *R. schipperae* Weitzman, McGough, Rinaldi, et Della-Latta (1996). These consisted of up to 10 (usually 4 to 8) sporangiophores arising from a cluster of rhizoids (Fig. 1F, 2, and 3). Mature sporangiophores were brown, being darker at the base, occasionally septate, 150 to 400  $\mu\text{m}$  in length, and 3 to 13  $\mu\text{m}$  in diameter. Sporangia were globose, greyish black, and up to 65  $\mu\text{m}$  in diameter; columellae were subglobose and hyaline (Fig. 4). Sporangiospores were subglobose to oval and faintly striated in water, measuring 4.8 to 6.8  $\mu\text{m}$  long by 3.9 to 5.8  $\mu\text{m}$  wide (Fig. 5). Rhizoids were pale to darker brown, mostly simple (seldom branched), and occasionally septate (Fig. 1F). Some hyphal strands on all media were covered by crystals (Fig. 6). The case isolate was compared with the type isolate (UTHSC 94-538, ATCC 96514, CBS 138.95) obtained from a human lung in San Antonio, Tex., in 1996 (46). On the basis of the above features, the isolate was identified as *R. schipperae*.

**Antifungal susceptibility testing.** The results of in vitro antifungal susceptibility testing are displayed in Table 1. Based upon drug concentrations normally achievable in patients receiving recommended dosages, the isolate appeared resistant to all antifungal agents tested (AMB, 5-FC, FLU, and ITRA). On the basis of an observed MIC of 4  $\mu\text{g}/\text{ml}$ , *R. schipperae* appears to be somewhat more resistant to AMB than *R. arrhi-*

*zus*, the most commonly isolated *Rhizopus* species, for which AMB MICs are typically 0.125 to 2.0  $\mu\text{g}/\text{ml}$  (42). The MICs obtained for the azoles corroborated in vitro data for the type isolate; the MICs of FLU and ITRA were  $>64$  and  $>8$   $\mu\text{g}/\text{ml}$ , respectively. The patterns of resistance to azoles observed for this fungus are similar to those seen for other *Rhizopus* species and zygomycetous genera (25).



FIG. 4. Columella of *R. schipperae* on CDA. Magnification,  $\times 213$ . Lactophenol cotton blue mount.

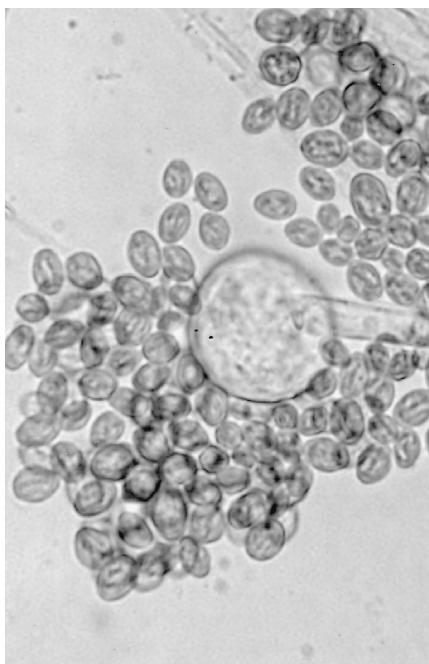


FIG. 5. Columella and striated sporangiospores of *R. schipperae* on CDA. Magnification,  $\times 613$ . Lactophenol cotton blue mount.

DISCUSSION

**Heatstroke.** Heatstroke occurs when exposure to high ambient temperatures produces hyperthermia and neurological dysfunction. Heatstroke produces damage in multiple organs, causing shock, DIC, renal failure, lung injury, lactic acidosis, and electrolyte abnormalities. The mortality rate in heatstroke

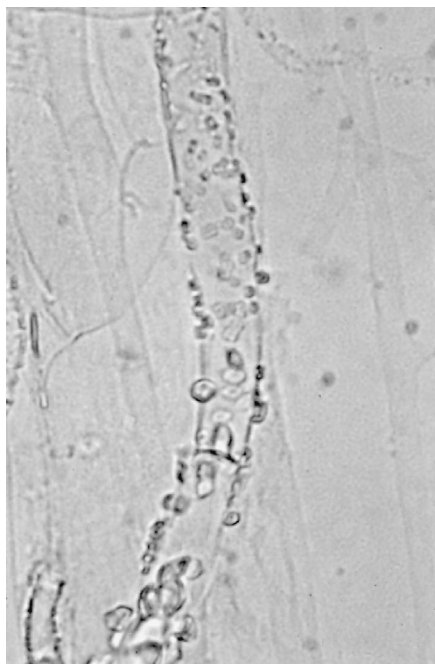


FIG. 6. Crystals on hyphae of *R. schipperae* on PDA. Magnification,  $\times 613$ . Lactophenol cotton blue mount.

TABLE 1. In vitro susceptibility data for *R. schipperae*

Antifungal agent	MIC ( $\mu\text{g/ml}$ ) at:		MLC ( $\mu\text{g/ml}$ ) at:	
	24 h	48 h	24 h	48 h
AMB <sup>a</sup>	1	4	8	16
5-FC <sup>b</sup>	>64	>64	>64	>64
FLU <sup>b</sup>	>64	>64	>64	>64
ITRA <sup>b</sup>	>8	>8	>8	>8

<sup>a</sup> Tested in antibiotic medium 3 (Difco, Detroit, Mich.).

<sup>b</sup> Tested in RPMI 1640 (American Biorganics, Inc., Niagara Falls, N.Y.).

is 10 to 50%, with 7 to 14% of the survivors suffering permanent neurological impairment (4).

Intestinal ischemia plays a central role in the pathophysiology of heatstroke (15). During exertion under heat stress, blood is shunted to exercising muscle and to the skin to dissipate heat. Blood flow is also maintained to the liver in order to access glucose and to remove lactate. However, the kidneys and intestines suffer a decrease in blood flow, with resultant ischemia and gut wall damage. If the ischemia is sufficiently prolonged, there is increased gut wall permeability, with leakage of endotoxin and bacteria into the circulation. Several cases of gram-negative sepsis have been described in exertional heatstroke (17).

**Pathophysiology.** The following scenario attempts to explain why this woman experienced heatstroke while her male companions did not and why the uncommon conditions of *C. jejuni* bacteremia and zygomycosis arose in this patient. The patient's home, San Luis Potosi, lies at an altitude of 1,877 m, and thus, despite its tropical latitude, has a moderate climate (44). Therefore, the patient was not acclimatized prior to departure, increasing the risk of heatstroke (15, 40). Half of her 12-h bus ride was in a non-air-conditioned vehicle; this situation may have also had a detrimental effect on her heat tolerance, because heat stress is cumulative (15).

Based on the patient's symptoms of sore throat and cough, she may have had an antecedent upper-respiratory-tract viral infection. Viral infections may affect thermoregulation (18) and alter heat shock protein levels (15), thereby increasing susceptibility to heatstroke. The episode of diaphoresis experienced early in the journey indicates that a preexisting fever may have been another predisposing factor for heatstroke. Infection has previously been suggested as a risk factor for the development of heatstroke (19). In a study of 58 heatstroke survivors, 57% were noted to have had infections on admission (8).

*C. jejuni* infection can be food-borne or waterborne (12), and this organism has been found in cow feces (45); thus, the stock ponds from which this traveller drank were the probable source of exposure. *C. jejuni* is thermophilic, with an optimal growth temperature of 42°C, and it is also microaerophilic (12). Thus, it may have an increased rate of replication at higher body temperatures, especially in a situation of decreased oxygen tension in an ischemic bowel. As bowel ischemia progressed, bowel wall integrity was compromised, and the organism rapidly gained egress into the blood. Loss of intestinal mucosal integrity has been cited as a risk factor for *C. jejuni* bacteremia (30). The *Enterobacter* bacteremia that occurred only 3 days into the patient's hospital course further suggests a loss of bowel wall integrity.

*C. jejuni* is typically susceptible to the nonspecific bactericidal activity of the complement in human serum; thus, *C. jejuni* bacteremia is uncommon (1). However, complement consumption has been reported in heatstroke, as a conse-

TABLE 2. Features of *R. schipperae* and similar species<sup>a</sup>

Organism	Colony color on PDA	Chlamydo-spores	Sporangiophores		Description of sporangiospores in water (length $\mu\text{m}$ )	Sporangia		Rhizoids	Zygospor-es	Growth at the following temp ( $^{\circ}\text{C}$ ) <sup>b</sup>				
			Grouping	Length		Formation	Morphology			35	40	45	50	
<i>Rhizopus schipperae</i>	Ivory to buff	Numerous on all media	Clusters, up to 10	Short, up to 460 $\mu\text{m}$	Striated, angular, oval (up to 6.8)	On special media: best on CDA	Normal, globose	Simple, abundant, and well developed	None with positive and negative mating strains of <i>R. microsporus</i> var. <i>microsporus</i>	+	+	+	-	
<i>Rhizopus microsporus</i> var. <i>microsporus</i>	Pale brownish gray	Varying with isolate, rare to numerous	Usually single, up to 3	Short, up to 400 $\mu\text{m}$	Striated, angular (up to 6.5)	On routine media	Normal, globose	Simple	Easily obtained, present in crosses between positive and negative mating strains of <i>R. microsporus</i> var. <i>microsporus</i>	+	+	+	-	
<i>Rhizopus caespitosus</i>	White to gray	In aerial mycelium	Clusters, up to 9	Short, 200–500 $\mu\text{m}$	Smooth, angular (up to 8)	On routine media	Long, ellipsoidal	Simple	Unknown, none with positive and negative mating strains of <i>R. microsporus</i> var. <i>microsporus</i>	+	+	+	+	
<i>Amylomyces rouxii</i> ( <i>Rhizopus chlamydo-sporus</i> )	White to brownish gray	Numerous on all media	Usually single	Long, up to 2.5 mm	Abortive, spore-like bodies	Fair on CDA but abortive	Abortive, globose to oval	Rare	Unknown	+	+	-	-	

<sup>a</sup> Adapted from references 11, 37, 38, and 39.

<sup>b</sup> +, growth; -, no growth.

quence of DIC (6, 11). Hypocomplementemia is therefore a risk factor for *C. jejuni* bacteremia (3). This patient also developed pancreatitis. Although multiorgan system failure is common in heatstroke, pancreatitis is uncommon (19). Pancreatitis has been reported to occur in 6% of patients hospitalized for *Campylobacter* enteritis (29). Thus, the *Campylobacter* infection may have been the inciting factor for pancreatitis.

The zygomycotic fungi are ubiquitous saprobes of the air and soil and cause spoilage of fruits and vegetables. Rhinocerebral and paranasal zygomycosis results from the inhalation of spores, the deposition of these spores on the nasal turbinates, germination on the nasal mucosa, and subsequent penetration by the hyphae either directly or via the vasculature into the sinuses, orbits, and brain (20, 41). Diabetic ketoacidosis (DKA) is the most common risk factor cited for paranasal and rhinocerebral zygomycosis (28, 41). Frequent blood gas analyses indicated that this patient had metabolic acidosis with compensatory respiratory alkalosis, as observed previously in heatstroke (4). She also had mild hyperglycemia; the highest blood glucose level recorded prior to the paranasal zygomycosis was 205 mg/dl. Nevertheless, these abnormalities are mild compared to the extreme metabolic derangements that occur in DKA. Thus, other factors may have contributed to the development of paranasal zygomycosis. Degeneration of the nasal mucosa, with capillary proliferation, occurs in heatstroke (2). Because the zygomycetes are angioinvasive (41), morphological changes of the nasal mucosa may have facilitated the spread of the fungus. Complement depletion was probably not important in the pathogenesis of the zygomycosis, because complement does not have a significant inhibitory effect on zygomycetes (10).

Gastrointestinal zygomycosis is rare (23, 39, 47); only five cases were observed in a series of 32 patients with zygomycosis over 20 years (20). Conditions that predispose to gastrointestinal zygomycosis are malnutrition, dehydration, DKA, aplastic anemia, leukemia, and gastroenteritis (21). In animal models of zygomycosis, damage to the gastrointestinal mucosa leads to fungal invasion (7). There is one previous example of *Enterobacter* bacteremia preceding gastrointestinal zygomycosis (31). There are two other factors that may have contributed to the development of disseminated zygomycosis: uremia, which produces defects in neutrophil and macrophage function (47), and the use of broad-spectrum antibiotics, which alters the usual bowel flora (16, 21, 23).

In disseminated zygomycosis with gastrointestinal involvement, the gastrointestinal tract is usually the primary site, with disease spreading hematogenously from this focus (16); however, there was no evidence for this process occurring in this case. For this patient, we propose that the nose and sinuses were the primary site of involvement, as indicated by the *Rhizopus* found in the sputum culture early in the hospital course and the observation of the paranasal process about 10 days before the recognition of the gastrointestinal disease. Apparently, postnasal secretions containing fungi were swallowed, and these organisms invaded the colonic mucosa previously damaged by heatstroke and *C. jejuni*.

**In vitro antifungal susceptibility.** Currently, AMB is the only antifungal agent with clinical utility in the treatment of zygomycosis (25). Although the in vitro data for AMB suggested resistance, the incidence of infections with mold pathogens is sufficiently low that strict correlation of antifungal MICs with clinical results of antifungal treatment has not yet been established (24).

With early diagnosis, metabolic stabilization, aggressive debridement, and administration of AMB, survival for zygomycosis

restricted to a single site has increased to 73 to 80% (27, 41). However, disseminated zygomycosis, defined as infection occurring in two or more noncontiguous organ systems, has a grim prognosis. In a series of 185 cases reviewed by Ingram et al. (16), only five patients survived. This patient received prolonged therapy with conventional AMB at 1 mg/kg/day before susceptibility results were available. The patient also received ABLC at 5 mg/kg/day for 12 days; such lipid preparations permit higher doses to be tolerated (14). Administration of ABLC, prolonged treatment with conventional AMB, aggressive surgical debridement, and resolution of metabolic abnormalities all provided sufficient conditions for eradication of the fungus.

**Taxonomy and identifying features.** *R. schipperae* was first described in 1996 after the organism was obtained from bronchial washings and lung specimens from a patient with multiple myeloma in San Antonio, Tex. (46). This case represents only the second isolate of *R. schipperae* ever described. However, we suspect that the organism may be more common but is not often identified due to the requirement of CDA for sporulation. The organism belongs to the *R. microsporus* complex, being closely related morphologically to *R. microsporus* var. *microsporus* Schipper (1984) Schipper et Sampson (1994) and sharing characteristics with *R. caespitosus* Schipper et Sampson (1994) in the same complex (35–37) and with *Amylomyces rouxii* Ellis, Rhodes, et Hasseltine (1976) (9). Characteristics which differentiate these species are displayed in Table 2. Distinguishing features for *R. schipperae* include its ivory to buff color on PDA, the production of numerous intercalary and terminal chlamydospores on a variety of media, clusters of up to 10 short sporangiophores arising from simple, well-developed rhizoids, the limited range of media for the development of sporangia (especially CDA), and striated sporangiospores. The species is named in honor of M. A. A. Schipper for her work with the Mucorales.

**Conclusions.** This case exemplifies the severe pathophysiological disturbances that occur in heatstroke with accompanying infectious complications. Heatstroke may alter immune status and predispose to infection by a number of mechanisms: increased translocation of organisms across an ischemic bowel wall, acidosis, complement depletion secondary to DIC, and altered lymphocyte function (5, 8, 11, 13). Heatstroke has previously been recognized as a risk factor for gram-negative bacteremia (11, 17). However, this is the first report of heatstroke as a setting for disseminated zygomycosis. There is one previous example of disseminated infection with the fungus *Fusarium oxysporum* in a patient with heatstroke (40).

This case also illustrates the larger problem of severe heatstroke in undocumented Mexican immigrants. During the 1998 Texas heat wave, from 1 May to 2 August, at least 47 undocumented immigrants died from heatstroke (34). This patient survived six-organ dysfunction (lungs, brain, coagulation system, liver, intestines, and pancreas) and four invasive infections and achieved a good neurological outcome, but only with intensive application of health-care resources.

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