ORIGINAL ARTICLE

Necrotizing Cutaneous Mucormycosis after a Tornado in Joplin, Missouri, in 2011

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ABSTRACT

BACKGROUND

Mucormycosis is a fungal infection caused by environmentally acquired molds. We investigated a cluster of cases of cutaneous mucormycosis among persons injured during the May 22, 2011, tornado in Joplin, Missouri.

METHODS

We defined a case as a soft-tissue infection in a person injured during the tornado, with evidence of a mucormycete on culture or immunohistochemical testing plus DNA sequencing. We conducted a case–control study by reviewing medical records and conducting interviews with case patients and hospitalized controls. DNA sequencing and whole-genome sequencing were performed on clinical specimens to identify species and assess strain-level differences, respectively.

RESULTS

A total of 13 case patients were identified, 5 of whom (38%) died. The patients had a median of 5 wounds (range, 1 to 7); 11 patients (85%) had at least one fracture, 9 (69%) had blunt trauma, and 5 (38%) had penetrating trauma. All case patients had been located in the zone that sustained the most severe damage during the tornado. On multivariate analysis, infection was associated with penetrating trauma (adjusted odds ratio for case patients vs. controls, 8.8; 95% confidence interval [CI], 1.1 to 69.2) and an increased number of wounds (adjusted odds ratio, 2.0 for each additional wound; 95% CI, 1.2 to 3.2). Sequencing of the D1–D2 region of the 28S ribosomal DNA yielded *Apophysomyces trapeziformis* in all 13 case patients. Whole-genome sequencing showed that the apophysomyces isolates were four separate strains.

CONCLUSIONS

We report a cluster of cases of cutaneous mucormycosis among Joplin tornado survivors that were associated with substantial morbidity and mortality. Increased awareness of fungi as a cause of necrotizing soft-tissue infections after a natural disaster is warranted.

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Mucormycosis (formerly known as zygomycosis) is a rare infection caused by molds belonging to the subphylum Mucoromycotina in the order Mucorales.[1] These fungi are ubiquitous in nature, particularly in soil, decaying wood, and other organic matter.[2] Mucormycetes have an affinity for iron-rich, acidic environments; iron-overload states and acidemia are risk factors for infection.[3] A classic feature of mucormycosis is tissue necrosis as a result of vascular invasion and subsequent thrombosis.[3,4] Although mucormycosis predominantly affects immunocompromised persons, cutaneous mucormycosis may also occur after trauma in immunocompetent persons.[4-6]

On May 22, 2011, a tornado rated EF-5 (the highest category on the Enhanced Fujita Scale) with wind speeds exceeding 322 km (200 mi) per hour struck Joplin, Missouri, resulting in more than 1000 injured persons and approximately 160 deaths.[7] On June 3, a local physician notified the Springfield–Greene County Health Department and the Missouri Department of Health and Senior Services that two patients who were hospitalized with injuries sustained during the tornado had suspected necrotizing fungal soft-tissue infections.[8] By June 10, eight patients with suspected mucormycosis had been identified. We conducted an investigation into these cases; the objectives were to identify the causative agent (or agents) of infection, determine the clinical characteristics of the patients, and identify risk factors for infection.

METHODS

DESCRIPTIVE EPIDEMIOLOGY

Active surveillance for fungal infections among tornado survivors was conducted at local and regional hospitals and reference laboratories by local and state health departments in Missouri, Kansas, Oklahoma, and Arkansas (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Any fungal infection in a person injured in the tornado was investigated for possible mucormycosis. A health advisory notice was released to inform health care providers throughout Missouri about the cluster of infections and to promote the reporting of possible cases.

A case was defined as a necrotizing soft-tissue infection in a person injured during the tornado, with an organism consistent with a mucormycete identified either by culture or by histopathological testing plus genetic sequencing. Wounds were defined as punctures, lacerations, or abrasions, and the mechanism of injury was categorized as penetrating or blunt; the incident wound was defined as the wound yielding mucormycetes. Using a standardized medical-record review form, we collected information about the patients' demographic characteristics, tornado-related injuries, post-traumatic wound management, underlying medical conditions, medical treatment received, and outcomes. We conducted in-person and telephone interviews with case patients (or a surrogate if the patient was incapacitated or deceased). Interviews consisted of questions adapted from a tornado-related mortality questionnaire.[9,10] All participants provided oral informed consent. Because this investigation involved a public health emergency, it was deemed to be nonresearch by the Centers for Disease Control and Prevention (CDC), and the requirements for written informed consent and approval by an institutional review board were therefore waived.

CASE–CONTROL STUDY

An unmatched 1:3 case–control study was performed to identify factors associated with cutaneous mucormycosis. A control was defined as a person 14 years of age or older who had been hospitalized after injuries sustained during the tornado with a break in skin integrity, who had a culture of the wound performed between May 22 and June 15, and who had no clinical or laboratory evidence of mucormycosis. Infection-control staff at two of the hospitals where most of the case patients were treated identified potential controls by reviewing electronic medical records on the basis of the date of wound culture; a random-number generator was used to create a randomly ordered list of controls for inclusion in the study. For controls, the incident wound was defined as the wound that yielded nonmucormycete fungi or bacteria or, if no organism was recovered, the wound deemed to be most substantial by the reviewer. The physical locations of case patients and controls at the time of the tornado were plotted with the use of ArcMAP Desktop software, version 10.0 (Esri), with addresses of the case patients geocoded with the use of the North America Geocode Service, version 10.0 (ArcGIS Online). Results were overlaid on a map showing the tornado path and the resulting structural damage.[11]

LABORATORY ANALYSIS

Fungal isolates and tissue blocks were sent to the CDC for species identification, which was performed with the use of microscopy, immunohistochemical assays, and DNA sequencing. Histopathological examination, assessment with special stains, and immunohistochemical testing with the use of an indirect immunoalkaline phosphatase technique were conducted on tissue blocks. The primary antibodies used in immunohistochemical testing included a mouse polyclonal anti-

Table 1. Characteristics of the Case Patients with Mucormycosis.*

Characteristic	Case Patients
Age — yr	
Median	48
Range	13–76
Male sex — no. (%)	6 (46)
White race — no. (%)†	13 (100)
Tornado-related injury	
Soft-tissue injury	
No. of wounds	
Median	5
Range	1–7
Laceration — no. (%)	12 (92)
Puncture — no. (%)	6 (46)
Abrasion — no. (%)	8 (62)
Crush injury with rhabdomyolysis — no. (%)	5 (38)
Fracture — no. (%)	11 (85)
Traumatic brain injury — no. (%)	3 (23)
Intraabdominal trauma — no. (%)	3 (23)
Mechanism of injury — no. (%)	
Blunt trauma	9 (69)
Penetrating trauma	5 (38)
Anatomical site of incident wound — no. (%)	
Head or neck	4 (31)
Leg	4 (31)
Back or spine	2 (15)
Groin or pelvis	2 (15)
Chest	1 (8)
Wound management — no. (%)	
Irrigation	13 (100)
Surgical débridement	13 (100)
Suturing or stapling	8 (62)
Removal of foreign matter	6 (46)
Microbiologic assessment of wound — no. (%)‡	
Bacteria recovered§	10 (77)
Nonmucormycete fungi recovered	7 (54)
Testing for fungal growth — no. (%)	
Culture	13 (100)
Histopathological testing	10 (77)
Visual inspection¶	8 (62)

Table 1. (Continued.)

Characteristic	Case Patients
Medical history — no. (%)	
Immunocompromise‖	0
Chronic renal insufficiency	1 (8)
Heart disease	0
Chronic obstructive pulmonary disease	1 (8)
Thyroid disease	3 (23)
Diabetes	2 (15)
Hypertension	7 (54)
Obesity**	5 (38)
Medication within 14 days before fungal growth — no. (%)	
Systemic glucocorticoids	2 (15)
Total parenteral nutrition	3 (23)
Systemic antibacterial agents	13 (100)
Features of hospitalization — no. (%)	
ICU admission	10 (77)
Death ≤14 days after incident fungal culture	5 (38)
Receipt of systemic antibacterial therapy	13 (100)
Receipt of systemic antifungal therapy	13 (100)
Sepsis	7 (54)
Ventilator-associated pneumonia	2 (15)
Renal failure	1 (8)
Disseminated mucormycosis	0
Multiple primary cutaneous mucormycosis infections	2 (15)
Location at time of injury — no. (%)	
Zone of most severe tornado damage	13 (100)
Type of structure or shelter at time of injury	
Home	9 (69)
Motor vehicle	2 (15)
Public or commercial building	1 (8)
Unknown	1 (8)

* ICU denotes intensive care unit.
† Race was determined by review of hospital medical-record documentation.
‡ Organisms were recovered from the incident wound 5 days before or after the initial mucormycete fungal culture.
§ The following bacteria were recovered: pseudomonas (four patients [31%]), enterococcus (four [31%]), staphylococcus (three [23%]), enterobacter (two [15%]), klebsiella (two [15%]), streptococcus (one [8%]), and proteus (one [8%]).
¶ White, fluffy macroscopical growth of fungus associated with necrotic borders was noted on visual inspection.
‖ Immunocompromise was defined as a history of infection with the human immunodeficiency virus, the acquired immunodeficiency syndrome, hematologic cancer, history of solid-organ or stem-cell transplantation, or neutropenia.
** Obesity was defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or higher.

mucormycete antibody known to react with other Mucorales and Entomophthorales but not with aspergillus species (M3565, Dako), a mouse polyclonal antiaspergillus species antibody known to react with *Aspergillus fumigatus*, *A. flavus*, and *A. niger* but not with mucormycetes (M3564, Dako), and a rabbit polyclonal anti–*Candida albicans* antibody that reacts with other candida species but not with mucormycetes or aspergillus species (B65411R, Biodesign International). Positive and negative control tissue samples were evaluated in parallel.

Genomic DNA was extracted from culture isolates and formalin-fixed, paraffin-embedded tissue samples.[12,13] Polymerase-chain-reaction (PCR) amplification and sequencing of the D1 and D2 regions of the 28S ribosomal DNA were performed with the use of primers NL-1 and NL-4.[14] From formalin-fixed, paraffin-embedded blocks, the ITS-2 region was amplified with the use of primers ITS-3 and ITS-4.[15] Sequences were aligned with the use of Sequencher software, version 4.8 (Gene Codes) and subjected to species identification with the use of the Basic Local Alignment Search Tool algorithm in the GenBank database.[16]

To understand the genetic grouping of the isolates, we conducted whole-genome sequencing.[17] DNA from 18 culture isolates (11 isolates from case patients and 7 additional, unrelated, clinical isolates) was extracted and prepared in fragment libraries for whole-genome sequencing on the Genome Analyzer IIx (Illumina). Assembly, alignment, and single-nucleotide-polymorphism (SNP) phylogenetic analysis of sequence data were performed with the use of multiple bioinformatics tools. SNP phylogenies were then used for whole-genome sequencing analysis to identify genotypes and clustering.

STATISTICAL ANALYSIS

Fisher's exact test and bivariate logistic regression were used for categorical variables, and Student's t-test was used for continuous variables; two-sided P values of 0.05 or less were considered to indicate statistical significance. Variables that were significant at a P value of 0.20 or less were included in a stepwise multivariate logistic-regression model, and the Hosmer–Lemeshow test was used to assess the goodness of fit of the model. Statistical analyses were conducted with the use of SAS software, version 9.2 (SAS Institute).

RESULTS

EPIDEMIOLOGIC FEATURES

We identified 13 case patients; the date of the culture of the incident wound ranged from May 28 to June 15, 2011 (median interval after the injury, 14 days). The median age of the case patients was 48 years (range, 13 to 76); 6 patients (46%) were male (Table 1). All case patients were brought initially to triage at a single hospital in Joplin, but 3 were transferred immediately to other facilities without receiving any care at this site. The case patients were hospitalized at any of six hospitals, and 10 (77%) required admission to the intensive care unit (ICU). The median number of tornado-related wounds was 5 (range, 1 to 7); 11 patients (85%) had one or more fractures, 9 (69%) had blunt trauma, and 5 (38%) had penetrating trauma. Five patients (38%) had rhabdomyolysis at hospital admission. Five patients (38%) had underlying medical conditions (history of chronic renal insufficiency, chronic liver disease, cardiovascular disease, chronic obstructive pulmonary disease, thyroid disease, or diabetes); none were immunocompromised. All cases occurred among persons injured during the tornado; none were among first responders or relief workers.

All case patients underwent irrigation and extensive surgical débridement (Table 2). In 11 patients (85%), initial débridement was performed before the diagnosis of mucormycosis, owing to trauma and the need to remove foreign bodies (wood, soil, and gravel were the most common). After the diagnosis of mucormycosis, all case patients underwent wide surgical débridement, and as the infection progressed (shown by necrotic borders or macroscopical fungal growth), additional surgical débridement was performed. Case patients underwent an average of 4 surgical débridements (range, 1 to 14). In 10 patients (77%), bacteria were recovered from the incident wound (Table 1).

All 13 case patients received systemic antifungal therapy for treatment of the incident wound (Fig. 1). Three case patients were already receiving antifungal treatment, either as empirical therapy or for treatment of another fungal infection, at the time of the incident mucormycete culture (Table 2). Among the remaining 10 case patients, the median number of days from the incident mucormycete culture to the start of antifungal treatment was 0.5 (range, 0 to 7). Initial antifungal therapies included liposomal amphotericin B (at a dose of 5 mg per kilogram of body weight per day) for 7 patients (54%), fluconazole for 4 (31%), an echinocandin for 3 (23%), and voriconazole for 2 (15%). Of the 6 case patients who initially received antifungal therapy that was not active against mucormycetes (fluconazole, voriconazole, or an echinocandin), 2 (33%) were switched to amphotericin B after cultures showed a mucormycete, and 3 (50%) died before mucormycetes were definitively identified (1 case patient had insufficient data available). In 7 of the 8 surviving case patients, a transition was made from amphotericin B to posaconazole. Five case patients (38%) died within 14 days after the incident culture; all 5 patients had infections that

Table 2. Timing of Antifungal Treatment, Surgical Débridement, and Death among the 13 Case Patients.*

Patient No.	Admission to ICU	Clinical Description of Incident Wound†	No. of Days from Injury to First Positive Culture	No. of Days from Injury to First Surgical Débridement	Initial Antifungal Treatment	No. of Days to Treatment‡	Other Fungi Isolated from Incident Wound	Subsequent Antifungal Treatment	Death	No. of Days to Death§
1	Yes	4-cm curved laceration on flank	11	3	Amphotericin B	0		Posaconazole	No	—
2	Yes	Foreign body on scalp, according to CT	10	10	Amphotericin B	1	*Candida glabrata* and geotrichum	None	Yes	5
3	Yes	Avulsion of skin and muscle on legs	16	16	Amphotericin B	7		Posaconazole	No	—
4	Yes	6-cm wound on cheek	9	6	Echinocandin	0	Candida species	None	Yes	0
5	Yes	Wound on right side of chest	6	1	Amphotericin B	3	*C. tropicalis* and aspergillus	Posaconazole	No	—
6	Yes	Extensive, penetrating trauma on legs	9	1	Fluconazole and voriconazole	0	*C. albicans* and *C. tropicalis*	None	Yes	4
7	Yes	Lacerations on scalp and face with underlying fractures	12	4	Fluconazole	1	*C. albicans*, *C. tropicalis*, and fusarium	None	Yes	5
8	No	15-cm laceration on hip	14	12	Amphotericin B and fluconazole	0		Posaconazole	No	—
9	Yes	10-cm laceration on thigh	16	2	Fluconazole and voriconazole	−5	*C. albicans* and candida species	Amphotericin B and then posaconazole	No	—
10	No	Lacerations on leg with purulent discharge	19	3	Amphotericin B	0		Posaconazole	No	—
11	No	5-cm laceration on scalp	22	14	Amphotericin B	4		Posaconazole	No	—
12	Yes	18-cm laceration on flank	15	3	Echinocandin	−3	*C. tropicalis*	None	Yes	1
13	Yes	Wound on sacrum and buttock	24	2	Echinocandin	−16		Amphotericin B	No	—

* CT denotes computed tomography.
† Information on the clinical description of the wound was obtained from a hospital-chart review.
‡ The number of days to treatment was defined as the number of days before the initial antifungal treatment began and after the first positive mucormycete culture was sent. Negative numbers indicate that the case patient was receiving antifungal treatment before the first positive mucormycete specimen was documented.
§ The number of days to death was defined as the number of days from the date that the first positive mucormycete culture was documented.

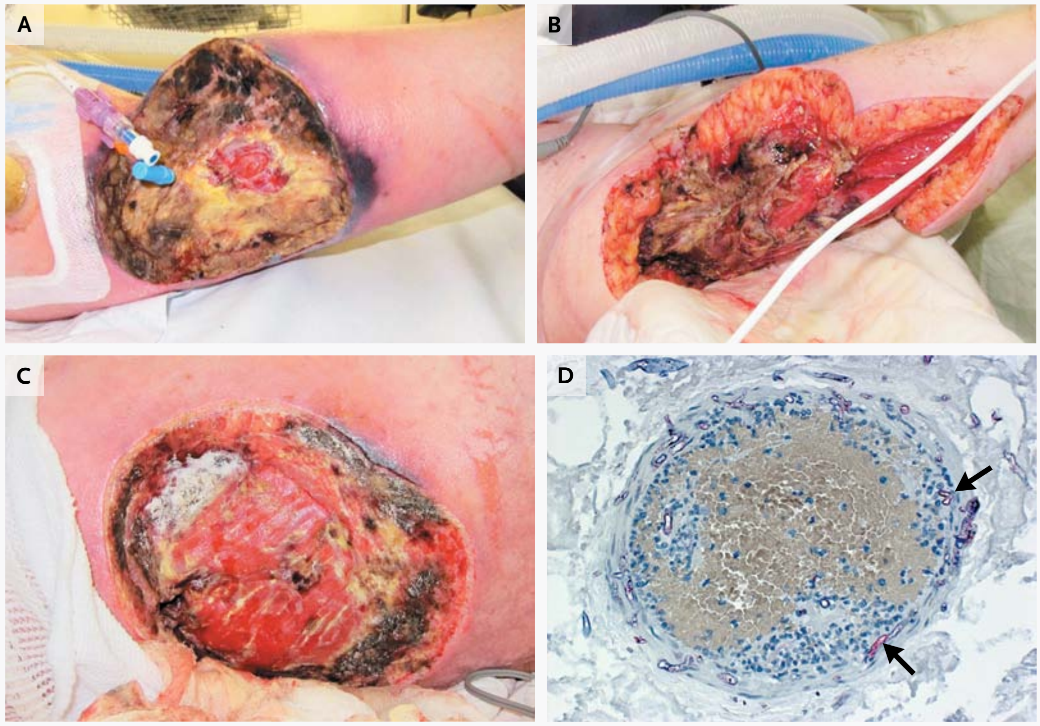

Figure 1. Necrotizing Cutaneous Mucormycosis.

Panel A shows a left-arm wound with areas of tissue necrosis visible in subcutaneous tissue, with some extension to the muscle layer. Panel B shows the same wound the next day, after surgical débridement, with visible tissue necrosis and soft-tissue extension into muscle layers. Panel C shows a left-flank wound in another case patient, with macroscopical fungal growth (a white, fluffy appearance) and necrotic borders before repeated surgical débridement. Immunohistochemical staining in Panel D shows mucormycetes (arrows) in the vascular wall and lumen of a necrotic vessel with inflammatory microthrombi (immunoalkaline phosphatase staining with naphthol–fast red substrate and a light hematoxylin counterstain).

were active at the time of death, and for 3 of the 5, fungal infection was listed as a primary or contributing cause of death on the death certificate. Autopsy was not performed in any of the case patients who died, which made it difficult to determine conclusively whether these deaths were primarily due to mucormycosis.

The tornado initially touched down just west of Joplin and moved eastward through the more densely populated section of the city. We interviewed 12 case patients (92%) or their surrogates, who were able to provide data on their precise locations during the tornado. All case patients had been located in the most severely damaged zone (Fig. 2). The case patient who had been closest to the start of the tornado path was approximately 3 km (2 mi) east of the touchdown site of the tornado. The remaining case patients had been distributed along the next 5 km (3 mi) of the tornado path. A total of 9 case patients (69%) had been in single-family homes during the tornado; none of these homes had a basement, safe room (above-ground, hardened structure designed to provide near-absolute protection during an extreme weather event), or predesignated storm shelter (above-ground or below-ground structure near the home or a public site). Two case patients (15%) had been in a vehicle, and 1 (8%) had been in a public building.

CASE–CONTROL STUDY

The 13 case patients and 35 controls did not differ significantly in terms of age, sex, race, or status with respect to underlying medical conditions (Table 3). Case patients were more likely to be admitted to the ICU than controls were (odds ra-

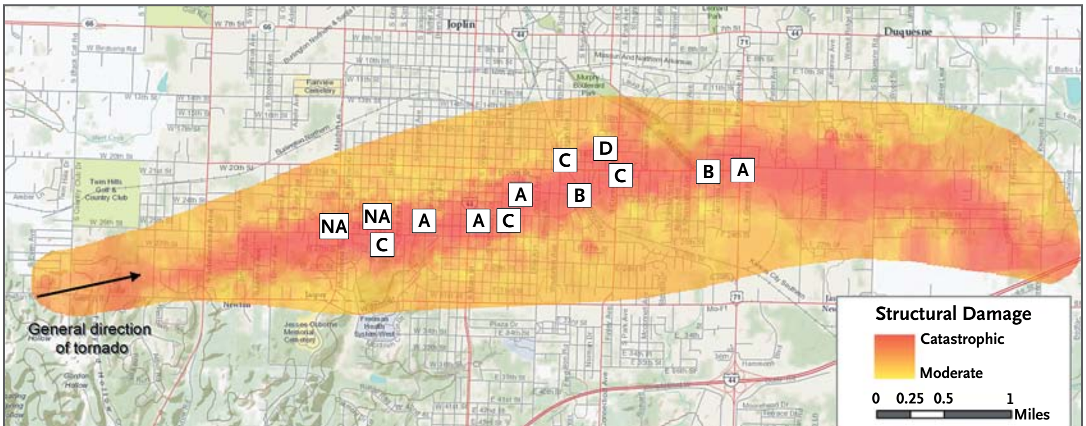

Figure 2. Locations of Case Patients at the Time of the Tornado and Genotype Groups.
The letters A through D denote the subtype groups of *Apophysomyces trapeziformis* clinical isolates from 11 patients; for 2 patients, data on the subtype group were not available (NA). On this map, the locations of case patients at the time of the tornado have been randomly shifted from 0.2 to 0.4 km (0.1 to 0.25 mi) in order to protect patient confidentiality. Data are from the U.S. Army Corps of Engineers and Esri.

tio, 7.3; 95% confidence interval [CI], 1.7 to 31.8; P=0.008). The median number of wounds was higher among case patients than among controls (5 vs. 2, P<0.001). Case patients were also more likely to have puncture wounds (odds ratio, 9.1; 95% CI, 1.8 to 45.7; P=0.007), penetrating trauma (odds ratio, 6.7; 95% CI, 1.3 to 33.9; P=0.03), and rhabdomyolysis (odds ratio, 25.3; 95% CI, 3.1 to ∞; P=0.002) at hospital admission. Case patients had a risk of death that was 6.7 times as high as that among controls (95% CI, 1.3 to 33.9; P=0.03); however, this association was not significant when we controlled for the number of wounds. The two groups were equally likely to have the incident wound sutured or stapled as treatment for the injury (odds ratio, 1.1; 95% CI, 0.3 to 3.9; P=1.00).

Location in the most severely damaged zone was not significantly associated with infection. Case patients were more likely than controls to have been in a single-family home instead of a vehicle or public building during the tornado (odds ratio, 6.0; 95% CI, 1.3 to 27.2; P=0.02). Interviews with 12 case patients and 30 controls showed that many persons were unable to locate or reach adequate shelter.

The final multivariate model showed that case status was independently associated with an increased number of wounds (adjusted odds ratio, 2.0 for each additional wound; 95% CI, 1.2 to 3.2; P=0.005) and with penetrating trauma (adjusted odds ratio, 8.8; 95% CI, 1.1 to 69.2; P=0.04) (P=0.67 for goodness-of-fit test).

LABORATORY ANALYSIS

All 13 case patients had laboratory evidence of a mucormycete on histopathological testing or culture; 8 patients (62%) had positive findings on both fungal culture and histopathological testing. The rare species *Apophysomyces trapeziformis* was identified in all 13 case patients by means of DNA sequencing of either an isolate or a tissue block. Of 50 specimens sent to the CDC from all 13 case patients, other fungi, including candida species (5 patients), fusarium species (2), aspergillus species (1), and *Mucor circinelloides* (1), were identified in specimens from 5 case patients (38%).

DNA samples from isolates were available from 11 of the 13 case patients for whole-genome sequencing. Three groups of distinct but genotypically similar or identical strains (denoted as A, B, and C), and an additional, closely related strain unique to 1 case patient (denoted D) were identified by means of SNP analysis. Case patients with isolates belonging to the A, B, and C groups were located throughout the tornado path (Fig. 2). One case patient with a strain from group A and one with a strain from group C were in the western portion of the path, closest to the touchdown site of the tornado.

DISCUSSION

We describe a large cluster of cases of mucormycosis, with 13 *A. trapeziformis* infections in persons injured during a tornado. Morbidity and mortality among the case patients were substantial; the primary risk factors for infection were penetrating trauma and an increased number of wounds, as compared with controls. Our findings suggest that clinicians should consider environmental fungi as potential agents of soft-tissue infections in injured patients after disasters.

Cutaneous mucormycosis after natural disasters is not unprecedented. Eight cases were reported after a 1985 volcanic eruption in Colombia.[18] Apophysomyces was identified as the agent of soft-tissue infections in two persons injured during the 2004 Indian Ocean tsunami.[19,20] These and other reports implicated penetrating trauma as the most common risk factor, which is consistent with our findings.[4,21] Although prior investigations of mucormycosis outbreaks have implicated contaminated medical equipment, including adhesive bandages,[22] wooden tongue depressors,[23] and ostomy bags,[24] we did not find evidence of risk related to equipment exposure. In addition, the 13 case patients received medical attention at six different hospitals, making a common nosocomial source unlikely.

We did not find that post-trauma medical practices, including wound closure immediately after injury, were associated with apophysomyces infection. The risk of complex wounds with foreign-body contamination during natural disasters is high, and wound management can pose a considerable clinical challenge in post-disaster settings, especially when the local health care infrastructure has been damaged.[25-27] Basic principles of emergency wound care dictate that contaminated wounds should be left open, since suturing in an unsterile environment or insufficient irrigation and débridement can increase the risk of infection.[25] Although it is unclear whether closure of contaminated wounds increased the risk of infection in general, we did not find that this practice increased the odds of apophysomyces infection.

Unlike other mucormycetes, apophysomyces has been associated primarily with infection in immunocompetent hosts.[5,6,20,28-32] Similarly, various underlying medical conditions were not risk factors for infection in this cluster. Rhabdomyolysis was associated with case status in the bi-

Table 3. Odds Ratios for Selected Characteristics of Case Patients with Mucormycosis, as Compared with Controls.

Characteristic	Case Patients (N=13)	Controls (N=35)	Unadjusted Odds Ratio (95% CI)
Age — yr			—
Median	48	52	
Range	13–76	14–91	
Male sex — no. (%)	6 (46)	16 (46)	1.0 (0.3–3.5)
White race — no. (%)	13 (100)	34 (97)	0.8 (0.0–82.7)
Underlying medical condition — no. (%)*	5 (38)	13 (37)	1.1 (0.3–3.9)
Immunocompromise — no. (%)	0	4 (11)	0.5 (0.0–4.1)
Tornado-related soft-tissue injury			
No. of wounds			
Median	5	2	1.9 (1.3–3.0)†
Range	1–7	1–6	
Laceration — no. (%)	12 (92)	30 (86)	2.0 (0.2–19.0)
Fracture — no. (%)	11 (85)	25 (71)	2.2 (0.4–11.8)
Puncture wound — no. (%)	6 (46)	3 (9)	9.1 (1.8–45.7)‡
Crush injury with rhabdomyolysis — no. (%)	5 (38)	0	25.3 (3.1–∞)‡
Penetrating trauma as the mechanism of injury — no. (%)	5 (38)	3 (9)	6.7 (1.3–33.9)§
Features of hospitalization and outcomes — no. (%)			
ICU admission	10 (77)	11 (31)	7.3 (1.7–31.8)‡
Sepsis	7 (54)	5 (14)	19.3 (3.2–116.0)†
Death	5 (38)	3 (9)	6.7 (1.3–33.9)§

Table 3. (Continued.)

Characteristic	Case Patients (N=13)	Controls (N=35)	Unadjusted Odds Ratio (95% CI)
Wound management — no. (%)			
Irrigation	13 (100)	25 (71)	6.7 (0.9–∞)
Surgical débridement	13 (100)	19 (54)	11.2 (1.7–∞)‡
Suturing or stapling	8 (62)	21 (60)	1.1 (0.3–3.9)
Removal of foreign matter	6 (46)	14 (40)	1.3 (0.4–4.6)
Microbiologic assessment of wound — no. (%)¶			
Bacteria recovered	10 (77)	14 (40)	5.0 (1.2–21.5)§
Nonmucormycete fungi recovered	7 (54)	3 (9)	12.1 (2.4–60.3)‡
Location at time of injury — no./total no. (%)‖			
Zone of most severe tornado damage	13/13 (100)	28/29 (97)	1.4 (0.0–140.1)
Type of structure or shelter at time of injury			
Home	9/13 (69)	10/30 (33)	6.0 (1.3–27.2)
Motor vehicle	2/13 (15)	8/30 (27)	0.5 (0.1–3.1)
Public or commercial building	1/13 (8)	10/30 (33)	0.2 (0.0–1.6)
Unknown	1/13 (8)	2/30 (7)	—

* Underlying medical conditions included a history of chronic renal insufficiency, chronic liver disease, cardiovascular disease, chronic obstructive pulmonary disease, thyroid disease, or diabetes.

† $P<0.001$.

‡ $P<0.01$.

§ $P<0.05$.

¶ For case patients, organisms were recovered from the incident wound 5 days before or after the initial fungal culture that showed mucormycetes; for controls, organisms were recovered at any time during hospitalization.

‖ We were able to interview 30 of the 35 control patients regarding location at the time of injury; data regarding presence in the zone of most severe damage were missing for 1.

variate analysis but was not significant in the multivariate analysis. Elevated levels of serum iron due to hereditary iron-overload states and iron-chelation therapy with deferoxamine are risk factors for systemic mucormycosis, because iron uptake is an important factor in the pathogenesis of infection.[33,34] Rhabdomyolysis, which releases iron-binding myoglobin into the blood, could be a factor in the development of mucormycosis; further investigation of this condition as a risk factor is warranted.

Currently, only two Food and Drug Administration–approved antifungal agents, amphotericin B and posaconazole, are commonly used against mucormycetes, including apophysomyces.[35] In this cluster of cases, antifungal agents that are not active against mucormycetes were initially used in six case patients; in some patients, treatment was switched to amphotericin B when culture results became available. It is not known whether the outcomes for these case patients would have been different if mucormycete-active agents had been used initially. However, this situation shows the importance of rapid and accurate differentiation of mucormycetes from other molds, as well as from bacterial infection, necrotizing fasciitis, and post-trauma necrosis. The timely diagnosis of mucormycosis is essential for guiding therapy, because the early initiation of appropriate antifungal medication and aggressive surgical débridement are associated with improved outcomes.[34,36] Infection with aspergillus species, which can resemble mucormycetes on histopathological assessment, is often treated with voriconazole, an antifungal agent that is not active against mucormycetes. Given the difficulty in distinguishing among molds by means of histopathological examination, clinicians might consider obtaining appropriate specimens for culture or evaluating tissue with the use of immunohistochemical assessment or genetic sequencing.[37]

It is likely that one or more environmental sources of apophysomyces existed along the tornado path and that spores were aerosolized, carried along with debris, and inoculated along with the debris after penetrating trauma. Isolates from the case patients did not show strain-specific geographic clustering; instead, related genotypes were scattered throughout the tornado path, with two of the genotypes identified in isolates from the westernmost cases. This suggests either that there was a single environmental source, located in the westernmost portion of the tornado path and proximal to the first case patient, which contained multiple genotypes, or that there were sources at multiple points along the tornado path, each containing one or more genotypes. There are several small bodies of water in this area; apophysomyces has previously been implicated in an infection derived from an organ donation (the donor had been exposed to a retention pond).[38] Further research on the ecology of apophysomyces is needed in order to gain a better understanding of its habitat and the environmental factors that affect its growth and diversity.

There are several limitations of our study. First, recall bias may have affected results involving self-reported data from case patients. Second, it is possible that during the case-finding phase, undiagnosed or mild mucormycosis infections were missed. Third, the small sample in our study may have affected the associations between certain variables and case status. Finally, a validated injury-severity score was not used, and our ability to accurately assess the level of injury may have been affected.

Our findings have several important clinical and public health implications. Increased awareness of environmental fungi as a cause of necrotizing soft-tissue infection in patients injured during natural disasters is warranted, since early treatment may improve outcomes. Public health officials might consider surveillance for cutaneous mucormycosis after disasters in which persons have multiple penetrating traumas. To prevent cases of post-disaster mucormycosis, officials should emphasize emergency tornado-preparedness strategies to decrease the risk of injury, such as the implementation of early-warning systems, the promotion of emergency-shelter plans, and the reduction of household hazards (i.e., arranging and securing of furniture, appliances, and hazardous materials, such as solvents and poisons).[39]

The views expressed in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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