

Fulminant Invasive Pulmonary Aspergillosis After a Near-Drowning Accident in an Immunocompetent Patient: A Case Report

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1–5

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Abstract

Objective: To report on invasive aspergillosis infection in an immunocompetent adult after a near-drowning event, which allowed this pathogen to easily gain access to the human respiratory system and result in rapid, severe infection.

Case Summary: A 51-year-old female developed severe pneumonia after a near-drowning accident. Two days after admission, a bronchial alveolar lavage (BAL) was performed and was positive for *Aspergillus fumigatus*. After a 30-day hospital course, multiple antifungals, and various routes of administration, the patient expired. **Discussion:** Pneumonia is particularly common because of the aspiration of contaminated water. Whereas pneumococci, staphylococci, and Gram-negative bacteria are all common pathogens for this type of infection, fungi such as *Aspergillus* spp can also be involved and may be life threatening. Typically, these cases are reported in individuals with an immunodeficiency such as from receipt of myelosuppressive chemotherapy, bone marrow transplants, or lung transplants. Despite initiation of an appropriate empirical antifungal regimen, the rapid recovery of *A fumigatus* from pulmonary alveolar lavage and BAL samples as well as extremely elevated levels of galactomannan and (1→3)- β -D glucan may have indicated an invasive fungal infection (IFI).

Conclusion: IFIs are uncommon in immunocompetent adults, but in the event of a near-drowning accident, environmental fungi can gain access to the human respiratory system and result in rapid, severe infection. Based on this case and the others described, it appears that near-drowning patients need an early initial evaluation for IFI.

Keywords

near-drowning, aspergillosis, immunocompetent, invasive fungal infection

Patients suffering from near-drowning or drowning events may show rapid decompensation after an apparently normal presentation and unremarkable chest X-ray findings.¹ Aspiration of fluid into the lungs impairs pulmonary surfactant and interferes with alveolar function and can result in inflammation, edema, impaired gas exchange, and ultimately acute respiratory distress syndrome (ARDS).² Pneumonia is typically rare after a near-drowning event; however, early-onset pneumonia can occur as a result of chemical and microbiological contaminants in the water or as a result of aspirating gastric contents.² Shallow water has the potential to contain more particulate matter, including mud and human or environmental waste, which can increase and alter the pathogen content.³ A wide range of bacterial and fungal pathogens that can survive in soil or water have been reported as causes of pneumonia after near-drowning events; however, they have never been systematically characterized. The most common fungal species recovered are *Pseudallescheria boydii* and *Aspergillus* species.³ The patient described in this case aspirated water from a shallow

ditch alongside the road resulting in a severe and fatal respiratory infection.

Case Report

An otherwise healthy 51-year-old woman presented to a small, community hospital after a near-drowning experience following a motor vehicle accident. According to her own report, she lost control of the car and was submerged in ditch water for an unknown amount of time. She

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subsequently escaped out the back hatch window and onto the main road where paramedics found her and took her to the community hospital. No significant skeletal or solid organ trauma was noted.

On presentation, she was tachycardic and had bilateral rales greatest at the right base. She reported shortness of breath and anxiety because she felt like there was water in her lungs. She developed altered mental status and respiratory distress, and an arterial blood gas analysis showed a moderate acidosis (pH = 7.24; pCO₂ = 58 kPa; pO₂ = 63 kPa; and HCO₃⁻ = 24 mmol/L). At this time, she was emergently intubated and transferred to a tertiary care academic medical center for further management. Her weight on admission was 108.8 kg, white blood cell count was elevated at 14.5 k/μL, oxygen saturation was 95%, Glasgow Coma Score was 3, and her temperature was 99.4°F. Her white blood cell count subsequently decreased to 2.2 k/μL on repeat labs. It is unclear whether the resultant infection or the primary injuries she sustained played a larger role in this patient's rapid decline.

A urine drug screen was negative. Urine and blood cultures were obtained in the emergency department. A urinalysis showed cloudy urine with 1+ bacteria, and her chest X ray revealed diffuse, bilateral, patchy opacities compatible with pulmonary contusions and aspiration pneumonia. Empirical broad-spectrum antibiotics, cefepime 2 g intravenously (IV) every 12 hours, levofloxacin 750 mg IV daily, and vancomycin 1500 mg IV every 12 hours, were initiated. In addition, IV methylprednisolone 100 mg daily was initiated for ARDS.

On hospital day (HD) 3, levofloxacin was discontinued, and colistin 200 mg IV every 12 hours was added because the admission urine culture grew 2 biotypes of meropenem and/or levofloxacin-resistant *Pseudomonas aeruginosa*. The next day, colistin was changed to tobramycin 550 mg IV (5 mg/kg) daily because both biotypes were susceptible. On HD5, mold with septate hyphae grew from the patient's bronchial alveolar lavage (BAL) sample from HD2, and liposomal amphotericin B (LAmB) 300 mg IV (3 mg/kg) daily was initiated for empirical fungal coverage. The mold was ultimately identified as *Aspergillus fumigatus*. The patient also experienced a suspected drug rash to cefepime and was changed to meropenem 1 g IV every 8 hours, despite resistance in 1 *Pseudomonas* biotype.

Furthermore, her serum fungal antigen tests were both highly positive, with (1→3)-β-D glucan >500 pg/mL and galactomannan index of 7.11. The patient had a Foley catheter in place, and after 2 days of treatment, LAmB was changed to voriconazole 600 mg IV (6 mg/kg) every 12 hours for 2 doses followed by 400 mg IV every 12 hours. Intravenous steroids were discontinued because of infection and to prevent further immunocompromise; she received steroids for 5 days before discontinuation. At this point, the hospital infectious diseases team was consulted to assist

with the treatment of her suspected fungal pneumonia. Although it was not entirely clear that *A. fumigatus* was a pathogen, voriconazole was continued, and nebulized amphotericin B 25 mg twice daily was initiated because of her poor clinical disposition. The patient remained febrile, and the nebulized amphotericin B was discontinued after 4 days.

Because the patient did not show clinical improvement while on voriconazole after 4 full days of treatment, she was switched back to LAmB 300 mg IV daily. She subsequently developed acute renal failure on HD10; therefore, tobramycin and vancomycin were discontinued because no bacteria were recovered in cultures other than her initial urine culture. Meropenem was continued and renally adjusted to 1 g IV every 12 hours. On HD11, the nephrology service was consulted and placed the patient on continuous renal replacement therapy, which continued most days for the remainder of her hospital stay. Antibiotic and antifungal doses were all appropriate based on the patient's renal function and severity of illness. A methylprednisolone continuous infusion was also initiated at 1 mg/kg/d for continued ARDS.

Over the course of the next 2 weeks, the patient's status remained critical but largely unchanged with continuous renal replacement therapy continuing and the occasional use of vasopressors for vascular support. She had transient fever with temperatures between 100°F and 100.9°F and consistent leukocytosis between 20 and 30 k/μL. Minimal changes were made to her antimicrobial regimen during this period; meropenem was discontinued on HD18 because of the appearance of a diffuse maculopapular rash. On that same day, the patient was discovered to have a pneumothorax, and 2 chest tubes were placed on her right side.

On HD21, her third computed tomography (CT) scan showed pulmonary necrosis and severe bilateral pneumonia worse on the right side. No medication changes were made at that time. On HD26, she again became febrile with a temperature of 102.9°F, and vancomycin, cefepime, and metronidazole were initiated. The patient's pleural fluid collected on HD25 was also found to have septate hyphae, and nebulized amphotericin B 25 mg twice daily was restarted. She developed a rash again, possibly from the cefepime, necessitating a change to aztreonam. A single dose of amphotericin B irrigation was administered through the chest tubes bilaterally in an attempt to maximize concentrations at the site of the infection. An endotracheal aspirate drawn on HD26 grew *Achromobacter xylosoxidans*, which was susceptible to and treated with levofloxacin. Unfortunately, the patient steadily deteriorated over the next several days experiencing severe, bilateral pneumothoraces, which required additional chest tubes. She expired on HD30 from complications related to severe pulmonary aspergillosis.

Discussion

Aspergillus spp is a mold that is ubiquitous in the environment and is found in soil and plant matter. The most common species that causes invasive infection in humans is *A fumigatus*. Typically, cases are reported in individuals with an immunodeficiency, such as receipt of myelosuppressive chemotherapy, bone marrow transplants, or lung transplants. The most common form of infection is invasive pulmonary aspergillosis, but it can also cause disseminated disease, including osteomyelitis, and meningitis.⁴ Although it is not typically a pathogen in immunocompetent individuals, reports of near-drowning victims have demonstrated rapid and serious infection resulting in prolonged hospitalization and/or death.⁵⁻¹⁰ Table 1 highlights these previously reported cases.

Voriconazole was found to have better response rates and survival than amphotericin B deoxycholate with less toxicity, and it is considered the drug of choice to treat invasive aspergillosis (IA).^{4,11} Since this patient's condition was declining, however, it was felt that LAmB would provide broader mold coverage than voriconazole against other potential pathogenic fungi, such as the mucorales, which were not recovered. van Dam et al⁹ previously reported a case where the patient was infected with both *A fumigatus* and *Rhizopus microsporus* var. *rhizopoidformis*. A majority of previously reported cases used amphotericin B formulations as the cornerstone of definitive therapy.

Although the patient described here was not previously immunocompromised, it is important to note that her medication regimen included steroid use at the beginning and near the end of her hospitalization for ARDS, and this may have contributed to progression of the fungal infection. Despite initiation of an appropriate empirical antifungal regimen on HD5, the rapid recovery of *A fumigatus* from pulmonary alveolar lavage and BAL samples as well as extremely elevated levels of galactomannan and (1→3)-β-D glucan may have been indicative of an invasive fungal infection (IFI). Positive findings for both galactomannan and (1→3)-β-D glucan have been associated with a sensitivity of 69%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 81%.¹² Vieira et al⁵ reported a case with rapid identification and treatment initiation similar to this scenario; however, that patient survived after a 41-day hospitalization. Other cases have also reported CNS involvement.^{7,8} However, there was no indication that this patient suffered from a disseminated CNS infection based on several CT images conducted during her course of therapy.

Although developed to identify IFI for clinical and epidemiological research purposes, the EORTC/MSG Guideline updated in 2008 has been used to provide a

clinical diagnostic framework as well.¹³ Unfortunately, a limitation of the guideline is that it is only applicable to immunocompromised patients and not those who have critical illness caused by a fungal pathogen. As a result, it is extremely difficult to use this scoring system on the patient presented in this case because she was immunocompetent. However, she did meet the remaining criteria for probable fungal infection (except for endemic mycoses) based on clinical criteria of chest CT scan findings; mycological criteria, with the presence of a mold in BAL culture; and positive results on the galactomannan and (1→3)-β-D glucan tests. This underscores the importance of recognizing a near-drowning event as a risk factor for fungal infections outside of the framework presented in these guidelines.

Because of the patient's unstable condition, a pulmonary biopsy was not performed. This would have ruled out the possibility of colonization, established *A fumigatus* as a definitive pathogen, and met the criteria for proven fungal infection.

The β-D glucan assay is indicated for the presumptive diagnosis of IFI through detection of elevated serum levels of (1→3)-β-D glucan, a component of the fungal cell wall. Therefore, levels of (1→3)-β-D glucan provide a convenient surrogate marker for IFI, as was true for this patient's significantly elevated result of >500 pg/mL, when values as low as 80 pg/mL are interpreted as positive. The *Aspergillus* galactomannan EIA is a test commonly used with other diagnostic procedures, such as microbiological culture, histological examination of biopsy specimens, and radiographic evidence, to aid in the diagnosis of IA. Patients with an index ≥0.5 are considered to have a positive galactomannan antigen, and this patient presented with values distinctly above the positive threshold, at an index of 7.11 initially and then 2.93 when measured 21 days later. However, the EORTC/MSG guidelines note that elevated levels of non-culture-based diagnostic tests are not sufficient at present and may not correlate with increased mortality. Other factors such as prior or concurrent antifungal treatment, certain β-lactam antibiotics, albumin, and hemodialysis filters can affect (1→3)-β-D glucan and galactomannan results.^{14,15} Much of the literature about these assays studied patients with hematological malignancies; however, the findings should be generalizable to other patients with IFI. Previous studies have found that when used properly and in conjunction with other clinical indicators of fungal infections, these assays are helpful diagnostic tools.^{16,17} The extremely positive values in this patient combined with the positive cultures would have precluded any confounding of these factors.

Table 1. Published Reports of Invasive Aspergillosis After Near-Drowning Episodes.

Reference	Presentation	Site of Infection	Diagnostic	Imaging	Culture	ARDS	Complications	Treatment	Survival	LOS (days)
Vieira et al ⁵	27-yo Man; severe ARDS after near-drowning following a car accident	Pulmonary	N/A	CT of lungs	Sputum grew <i>Aspergillus fumigatus</i>	Yes		Amphotericin B + flucytosine (IV and inhalation)	Yes	41
Mizukane et al ⁶	21-yo Man; rapidly progressing respiratory failure after near-drowning in reservoir by a traffic accident	Pulmonary	Serological and microbiological studies	Chest roentgenograms	N/A	Yes		IV methylprednisolone + antibiotics IV amphotericin B + oral itraconazole	Yes	N/A
Leroy et al ⁷	10-mo Girl; near-drowning in a pond followed by respiratory arrest	Pulmonary, CNS	CNS Postmortem serum samples positive for <i>Aspergillus galactomannan</i>	Chest X ray, CT and MRI of brain	Sputum and cerebral pus grew <i>A. fumigatus</i>	Yes	Day 1: Streptococcus pneumoniae + <i>Aeromonas sobria</i> ; day 8: <i>Stenotrophomonas maltophilia</i>	IV antibiotics + salbutamol and prednisone; IV itraconazole	No	16
Kowacs et al ⁸	26-yo Man; near-drowning in mangrove swamp; treated for aspiration pneumonia but returned for CNS symptoms	CNS	CSF culture	CT and MRI of brain	Culture from CSF grew <i>A. fumigatus</i>	N/A	Subarachnoid hemorrhage	IV methylprednisolone + antibiotics; amphotericin B + IV itraconazole	No	56
van Dam et al ⁹	22-yo Man; near-drowning after car accident. Presented with respiratory insufficiency	Pulmonary	BAL	Chest X ray and CT of chest	Culture of BAL grew <i>A. fumigatus</i>	Yes	Day 7 BAL culture: <i>Rhizopus microsporus</i> var. <i>rhizopoidiformis</i> , <i>Stenotrophomonas maltophilia</i> , <i>Acinetobacter</i> sp., <i>Escherichia coli</i> . Day 17: <i>Nocardia farcinica</i> and <i>Nocardia cyriacgeorgici</i>	Antibiotics, liposomal amphotericin B	Yes	60
Kawakami et al ¹⁰	68-yo Woman; near-drowning during tsunami	Pulmonary	Sputum culture, (1→3)- β -D glucan levels	Chest X ray and CT of chest	Sputum culture grew <i>A. fumigatus</i>	Yes	Hemodynamic status continued to worsen as a result of septic shock; autopsy revealed microabscesses containing <i>A. fumigatus</i> in the heart; kidneys, stomach, gall bladder, mandibular gland, iliopsoas muscle, tongue, and adrenal glands	IV cefotiam for aspiration and near drowning in seawater; day 6, changed to Zosyn; day 13, micafungin; day 18, ciprofloxacin	No	18

Abbreviations: ARDS, acute respiratory distress syndrome; LOS, length of stay; CT, computed tomography; IV, intravenous; CNS, central nervous system; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; BAL, bronchial alveolar lavage.

Conclusions

Based on this case and others described, it appears that near-drowning patients need an early initial evaluation for IFI. Given the rapidity with which the culture grew and the highly positive results from the (1→3)- β -D glucan and galactomannan tests, a course of action consisting of lung culture and antigen tests with or without empirical antifungal coverage may be warranted. Despite not having traditional risk factors for IA, clinicians should not discount early findings of fungal infection in this patient population.

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