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A challenging case of invasive pulmonary aspergillosis after near-drowning: a case report and literature review

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Abstract

Near-drowning, a relatively common event, is often complicated by subsequent pneumonia. While endogenous and exogenous bacteria are typical pathogens, rarely fungi are as well. We report a complicated case of invasive pulmonary aspergillosis in a 30-year-old man after a near-drowning event. We also review the medical literature for similar cases. All cases of invasive pulmonary aspergillosis after near-drowning reported in the literature involve *Aspergillus fumigatus*. The majority of cases involved submersion in stagnant water after a motor vehicle accident (MVA). Treatment varied considerably, with amphotericin B used in the majority of cases. Morbidity was considerable with prolonged hospitalization occurring in every case, and mortality occurring in fifty percent of the reported cases. Although a rare complication of near-drowning, invasive pulmonary aspergillosis can occur and lead to significant morbidity and mortality. After near-drowning *A. fumigatus* isolated from the respiratory tract should be assumed to be a true pathogen and treated accordingly.

Keywords

near-drowning; invasive pulmonary aspergillosis; *Aspergillus fumigatus*

Introduction

Near-drowning is thought to occur much more frequently than actual drowning. While an estimated 449,000 people died worldwide from drowning in 2000, many more were seen in emergency departments and admitted to hospitals after near-drowning [1]. Pneumonia is a common complication of near drowning, related either directly to the aspiration of contaminated water and foreign material, or to aspiration from the upper respiratory tract. The pathogens related to pneumonia in near-drowning are numerous and include endogenous and exogenous bacteria and rarely fungi [2]. We report a complicated case of invasive pulmonary *Aspergillus fumigatus* infection in a 30-year-old man after a near-drowning episode. We also review the pertinent literature for additional cases.

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Case Report

An intoxicated 30-year-old man was admitted after being submerged for about 3 minutes in the San Diego River following a roll over motor vehicle accident (MVA). Upon arrival to the emergency department (ED) of our hospital he was spontaneously breathing but saturating at 59% on high-flow oxygen, and was intubated for acute respiratory failure. He had no known medical history aside from heavy alcohol use and did not routinely take any medications. No other history was obtainable.

Physical exam on admission was notable for an afebrile, unresponsive man with diminished bilateral breath sounds. Laboratory investigation was most remarkable for an alcohol level of 219 mg/dL and a white blood cell (WBC) count of 17.6×10^9/L (4.0 – 10.0 1000/mm^3). His human immunodeficiency virus (HIV) rapid antibody test was negative and glycohemoglobin (HbA1c) test was within normal limits. An extensive trauma workup was negative aside for a computed tomography (CT) scan of the thorax which revealed bilateral lower lobe infiltrates consistent with an aspiration event.

He was started empirically on vancomycin intravenous 1.25g every 6 hours and piperacillin/tazobactam intravenous 4.5g every 8 hours. In the intensive care unit he underwent bronchoscopy with bronchoalveolar lavage (BAL) which was remarkable for hyperemic airways and thick mucopurulent secretions in the right mainstem bronchus, without significant particulate matter noted. Initial respiratory cultures grew only one colony of methicillin-sensitive *Staphylococcus aureus* (MSSA). Follow-up BAL two days later was remarkable for thick, purulent, foul-smelling secretions in all airways with black particulate matter resembling sand. Repeat aerobic culture was negative.

Over the ensuing seven days he had intermittent high fevers with an up-trending leukocytosis to 24.0×10^9/L with 94% segmented leukocytes. Chest x-ray was compatible with acute respiratory distress syndrome (ARDS) superimposed on an underlying pneumonia. He underwent repeat BAL on hospital day six from which aerobic cultures grew *A. fumigatus*, and was started on voriconazole oral suspension 400mg every 12 hours. Two days later this same respiratory culture yielded an *Absidia* mold species, and his voriconazole was discontinued in favor of posaconazole suspension 400mg twice daily for empiric coverage of the *Absidia*. He continued to be febrile with leukocytosis, and liposomal amphotericin B intravenous 550mg daily was added five days later.

Workup for causes of persistent fever, including CT scan of the head to evaluate for evidence of invasive fungal disease and CT scan of the abdomen/pelvis to evaluate for abscess were negative. CT scan of the thorax demonstrated bilateral pleural effusions with empyema. He underwent thoracentesis and eventual bilateral chest tube placement, with pleural fluid cultures growing *A. fumigatus*. His posaconazole trough came back low at 0.2 (therapeutic >= 0.8 ug/mL) and was sub-therapeutic on repeat testing, so he was transitioned to voriconazole intravenous 500mg every 12 hours, micafungin intravenous 150mg daily, and inhaled amphotericin 10mg every 8 hours.

He eventually underwent left-sided video-assisted thoracoscopic surgery (VATS) with decortication and intrapleural amphotericin irrigation. Operative findings were notable for a

thick rind covering the lung and parietal pleura with over 300cc of purulent fluid collected in the rind. After his initial positive BAL culture, *A. fumigatus* consistently grew from repeat BAL, sputum, and pleural fluid cultures over the ensuing two-and-a-half weeks. BAL and sputum cultures were not initially sent for anaerobic culture, although pleural fluid was eventually sent and negative for anaerobic pathogens. In addition, he had an *Aspergillus* galactomannan antigen titer from a BAL specimen that was positive to 10.51 (positive >= 0.05). The *Absidia* species failed to grow again in culture and was not thought to be the primary pathogen causing his pulmonary disease.

Treatment was further complicated by sub-therapeutic voriconazole levels of 0.8 and 0.4 ug/mL (therapeutic 1.0 – 6.0 ug/mL). Upon further testing he was found to be an ultra-fast voriconazole metabolizer via an increased-function cytochrome P450 2C19*17 allele, and adequate voriconazole levels were eventually achieved with high-dose voriconazole intravenous 700mg every 12 hours. After 3 weeks of treatment the inhaled amphotericin was discontinued. After 4 weeks of anti-fungal treatment his respiratory cultures eventually turned negative for *A. fumigatus*. Of note, after one month of hospitalization he had a BAL culture that grew *Ochrobactrum antrhopi*, a pleural fluid culture that grew rare *Aspergillus terreus*, and an *Achromobacter* species that grew from one sputum culture. None of these organisms were thought to be true pathogens, although the *A. terrus* was already being targeted with antifungal therapy and the two bacterial species were treated with a 7-day short-course of antibiotics.

He was transitioned from intravenous voriconazole to voriconazole tablets 400mg every 8 hours and continued on micafungin intravenous 150mg daily at discharge from the hospital. In total he spent almost 2 months in the hospital. On follow-up in the Infectious Diseases clinic as an outpatient his initial voriconazole level was therapeutic at 1.9 ug/mL, but subsequent levels were sub-therapeutic at 0.2 and <0.1 ug/mL. His voriconazole was discontinued and he was started on posaconazole tablets 300mg three times daily. Once his serum level was therapeutic for posaconazole the intravenous micafungin was discontinued. He was continued on monotherapy with posaconazole for an additional 8 weeks with therapeutic posaconazole levels to 0.9 and 1.6 ug/mL (therapeutic >= 0.8 ug/mL).

Five months after his near-drowning episode he was doing well clinically. At that time he underwent repeat CT scan of his thorax which demonstrated marked improvement and his anti-fungals were discontinued. At around 9 months of follow-up after his initial aspiration event he was nearly back to baseline with only mild dyspnea on exertion but no other symptoms.

Discussion

Pneumonia is a common complication of near-drowning, with the likelihood of developing pneumonia related to multiple variables, including a known aspiration event, the chemical composition of the water, submersion in contaminated water, and higher water temperature. Bacterial pathogens such as *Aeromonas hydrophilia* and *Burkholderia pseudomallei* have been most commonly associated with pneumonia after near-drowning events, with other

bacterial pathogens less common, and fungal pathogens such as *A. fumigatus* rarely reported in the literature [2].

Aspergillus species, including *A. fumigatus*, is a mold that is ubiquitous in the environment and common to soil, seawater, polluted water, plant matter, and sewage [2–3]. Given how widespread it is in the environment, one would expect this to be more commonly associated with pneumonia after near-drowning. However, invasive pulmonary aspergillosis is uncommonly reported with few cases documented in the literature (Table 1). Although samples from the site of the near-drowning episode were not sent for *A. fumigatus* culture, aspirated seawater and surrounding particulate material were presumed to be the source of his infection. We reviewed all cases of invasive pulmonary aspergillosis reported in the English literature, with one additional case in Japanese that was documented in another reference [9].

All reported cases of invasive pulmonary aspergillosis have been due to *A. fumigatus*. The majority of cases occurred following submersion in stagnant water after a motor vehicle accident (MVA), although one case involved a 10-month old girl who was found submerged in a pond, and another a 68-year old woman who experience a near-drowning event associated with a tsunami. Most cases involved a combination of serologic and microbiologic testing leading to the diagnosis of pulmonary aspergillosis. Three cases involved multiple pathogens in addition to *A. fumigatus* retrieved from pulmonary secretions. Treatment varied considerably, although amphotericin B was used in the majority of cases. Unfortunately, invasive pulmonary aspergillosis after near-drowning is associated with significant morbidity, leading to prolonged hospitalization in every case and mortality in 50% of reported cases [4 – 9].

Treatment in our patient was further complicated by difficulty maintaining therapeutic voriconazole levels secondary to an increased-function cytochrome P450 2C19*17 (CYP2C19*17) allele, resulting in increased drug metabolism and necessitating multiple changes in antifungal agents. CYP2C is a subfamily of CYP enzymes that is comprised of four main members, including 2C19. CYP2C19 is a metabolizer of multiple drugs including clopidogrel, proton pump inhibitors, some antimalarial drugs, and voriconazole, Voriconazole is primarily metabolized by CYP2C19, and to a lesser extent by CYP2C9 and CYP3A4 [10]. CYP2C19 polymorphisms vary widely based on ethnic groups, with an estimated 3% of Caucasians having decreased enzyme function and up to 20% in the Japanese population. The CYP2C19*17 allele is an autosomal recessive variant that leads to increased enzyme function in contrast to the other variants. In contrast, CYP2C19*9 and CYP2C19*10 alleles lead to decreased function, with multiple other variants resulting in no change in enzyme function. The frequency of the CYP2C19*17 allele has been found to be as high as 18% in Ethiopian and Swedish populations, and as low as 1.3% in the Japanese population [11].

Conclusion

Pneumonia, a complication of near-drowning, is typically caused by bacterial pathogens but rarely fungi. Invasive pulmonary aspergillosis, although a rare complication of near-

drowning, can result in significant morbidity, prolonged hospitalization, and high mortality rates. After a near-drowning event, workup for an invasive fungal infection should be initiated early, and *Aspergillus fumigatus* isolated from respiratory secretions should be considered a true pathogen and treated aggressively.

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Table 1

Published reports of invasive pulmonary *Aspergillus fumigatus* after near-drowning episodes

Date published	Age	Gender	Submersion Incident	Diagnostic studies/source	Other pathogens isolated	Treatment of fungal infection	Survival	LOS in hospital
1984[4]	27 yr	M	Ditch after a MVA	Serologic* and microbiologic (sputum)	No	Miconazole (IV/inh) followed by amphotericin B + flucytosine (IV/inh)	Yes	41 days
1996[5]	21 yr	M	Reservoir after a MVA	Serologic and microbiologic	No	Amphotericin B + itraconazole (PO)	Yes	N/A
2004[6]	22 yr	M	Ditch after a MVA	Microbiologic (BAL)	*A. hydrophilia* *A. sobria* *Rhizopus* spp *S. maltophilia* *Acinetobacter* sp *E. coli* *Nocardia farcinica* and *N. cyriacigeorgici*	Liposomal amphotericin B (IV)	Yes	2 months
2006[7]	10 mo	F	Pond	Serologic^ and microbiologic (endotracheal aspirate)	*A. sobria* *S. pneumonia* *S. maltophilia*	Itraconazole (IV)	No	16 days
2012[8]	68 yr	F	Tsunami	Serologic# and microbiologic (sputum)		Micafungin (IV)	No	18 days
2014[9]	51 yr	F	Ditch after a MVA	Serologic^# and microbiologic (BAL)	*P. aeruginosa* *A. xylosoxidans*	Liposomal amphotericin B (IV)	No	30 days

Abbreviations: motor vehicle accident, MVA; length of stay, LOS; bronchial alveolar lavage, BAL;

*IgA/IgG;

^*Aspergillus* galactomannan;

#*B*-D glucan

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