Pulmonary Hemorrhage in an Infant Following 2 Weeks of Fungal Exposure

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Background: Exposure to indoor fungus growth and tobacco smoke has been epidemiologically linked to unexplained pulmonary hemorrhage in infants.

Objective: To describe the 40-day-old male infant who had been exposed to fungi for a discrete 2-week period followed by acute exposure to environmental tobacco smoke prior to development of a life-threatening pulmonary hemorrhage.

Patient and Methods: History and clinical evaluation of the infant immediately followed the pulmonary hemorrhage. Air and surface sampling for isolation and identification of fungal growth in the dwelling where the infant resided before the acute hemorrhage was accomplished when the homeowner returned from vacation 4 months after the clinical event.

Results: Two fungi associated with mycotoxin production were cultured from surface samples collected in the residence: *Penicillium* (possibly *Penicillium purpurogenum*) and a *Trichoderma* species. *Stachybotrys atra* was not isolated from air or surface samples. Environmental tobacco smoke exposure occurred over a discrete several-hour period prior to onset of the acute pulmonary hemorrhage.

Conclusions: Avoidance of unnecessary exposure of infants to fungus growth in water-damaged environments or exposure to tobacco smoke is prudent. Further investigation into the toxic effects of indoor fungi as causes of infantile pulmonary hemorrhage is warranted.


Editor's Note: This is a somewhat frightening case report because it might be heralding yet another emerging infectious "horrendiomia."

Catherine D. DeAngelis, MD

Pulmonary Hemorrhage has been reported in infants following exposure to water-damaged environments and tobacco smoke. The epidemiological association of unexplained acute infantile pulmonary hemorrhage and exposure to mold has been most closely linked to the fungus *Stachybotrys atra*. Temporality and duration of exposure to toxigenic fungi that typically precede onset of acute infantile pulmonary bleeding is unknown. We describe an infant who had pulmonary hemorrhage after exposure to fungi other than *S. atra* for a discrete 2-week period prior to the onset of clinically evident, life-threatening disease.

REPORT OF A CASE

In November 1997 a 40-day-old Hispanic-Filipino boy who lived in Key West, Fla, visited his grandfather’s home in St Louis, Mo, for a 2-week period. He was healthy and growing on a cow-milk protein–based formula supplemented by breast milk. Throughout the visit to St Louis the infant’s health continued to be excellent. During the return trip home the infant suffered a sudden onset of life-threatening pulmonary hemorrhage.

The homeward journey began on a passenger train in a public compartment that was intermittently permeated with tobacco smoke. Several hours after boarding the train the infant awoke crying with a dry sounding cough. The infant had fed well just 45 minutes earlier. No formula was visible in the oropharynx either before or during the coughing episode. Tachypnea and respiratory distress gradually developed over the ensuing hour. On arrival at the emergency department dried blood was noted on the infant’s lips; blood was suctioned from the mouth and posterior pharynx. The infant’s respirations were 58/min, pulse oximeter saturation was 76% on room air, and subcostal retractions were present. Initial arterial blood gas levels measured PaCO₂ of 46 mm Hg; pH, 7.19; and PaO₂, 74 mm Hg on nasal
The infant was almost 2½ years old and has remained clinically healthy without clinical evidence of recurrent pulmonary hemorrhage or obstructive reversible airway disease.

Medical History was remarkable for a full-term uncomplicated pregnancy and delivery. Birth weight was 3.07 kg with an Apgar score of 9 at 1 minute and 10 at 5 minutes. No trauma had been reported. No illness characterized by cough, respiratory distress, decreased perfusion, or cyanosis had been observed by family members. The mother had been adopted and no family history was available about her lineage. The family history on the father's side was negative for connective tissue disorders, kidney or lung diseases, pulmonary hemorrhage, or sudden infant death syndrome. The father had smoked cigarettes outdoors but never in the presence of the infant. No direct environmental tobacco smoke exposure of the infant had otherwise occurred. No exposure to volatile organic compounds or pesticides was identified in Key West, Fla, or in St Louis, Mo. The mother, father, and grandfather of the infant suffered no illness before, during, or after the pulmonary hemorrhage of the infant.

The house that the infant visited in St Louis was located in a neighborhood established in 1950. The residence was ranch style and had a fully sunken basement. Since initial construction of the dwelling, moisture had repeatedly saturated the basement walls following rainstorms. A black discoloration described as “black measles” covered approximately 12 square feet of a basement wall and had first appeared in approximately 1970. Despite repeated efforts to clean the walls, the growth would routinely reappear. Reportedly, moisture had regularly condensed on the windowpanes of the upper stories of the house. During his stay in St Louis the infant had resided in a bedroom where “mold” grew in the paint and in the crevices of the walls below the windowpanes. The grandfather's house remained closed and was unavailable for inspection until 4 months after the pulmonary hemorrhage. At that time a thorough examination was accomplished. Chronic water entry, water damage, and fungal growth were observed in the upper level (infant's bedroom and living room) and in the basement.

Surface samples and paint chips from stained walls were gathered and cultured. Air was sampled for fungal spores using both plate exposure and volumetric Burkard aerosampler. During collection of fungal spores agitation of dust was augmented by motion caused by the investigators as they traversed the residence. Airborne fun-
gal spores were collected on culture plates containing maltose extract agar with 0.5-g/L chloramphenicol. Fungi were allowed to grow under banks of cool-white and gro-lux fluorescent tubes for 7 to 15 days. Some of these fungi were later isolated and grown on sabouraud dextrose agar (to facilitate identification).

Penicillium (possibly purpureogenum) species and a nonsporulating unidentifiable fungus were isolated from paint chips taken from a mold stain on the lower one-third section of the southern wall in the infant's bedroom in St Louis. Near a crack in the basement wall several other species of Penicillium and of Trichoderma were isolated. A large patch of actively growing fungi was present on the southern wall of the basement and a culture from it grew an almost pure isolate of Cladosporium sphaerospermum. This mold along with Ulocladium were isolated from paint chips in the living room that adjoined the bedroom where the infant had slept. Visible air sampling in the basement collected Alternaria, C sphaerospermum, and Pseudallescheria colonies. Upstairs Epicoccum and Alternaria species were captured in the child’s bedroom and Cladosporium herbarum spores were collected from the living room. Particles collected indoors with a volumetric air sampler included Alternaria species, Cladosporium species, Curvularia species, and slime-mold spores, ascospores, basidiospores, a few pollen, and some organic/inorganic debris. Water damage was reported to have been present in the Key West home from a leak in the upstairs bathroom prior to the trip to St Louis but no fungus was visible when the dry-wall was removed and replaced.

**COMMENT**

Pulmonary hemorrhage occurred in this infant without any recognizable association to infection, trauma, foreign body, congenital heart defect, congenital lung abnormality, or bleeding diastasis. Cow-milk protein allergy has been proposed as a cause of infantile pulmonary hemorrhage. In this infant, however, no milk precipitins were detected. A lack of significant amounts of hemosiderin in pulmonary macrophages suggested that the presenting illness had not been preceded by previous pulmonary bleeding. The lack of evidence for previous pulmonary hemorrhage did not support a diagnosis of idiopathic pulmonary hemosiderosis.

Exposure to various fungi and fungal toxins has been associated with disease of animals and humans. Ramazzini,1 the father of occupational medicine, accurately described diseases of workers inhaled “foul and mischievous powder” from handling food, fodder, and fiber crops in 1705. Exposure of humans to straw contaminated with the fungus S atra was recognized to have been associated with the occurrence of hemorrhagic lesions of the mouth and lung since 1972.2 More recently S atra has been epidemiologically and environmentally linked to the occurrence of unexplained pulmonary hemorrhage and hemosiderosis in infants who were clustered in several midwestern US cities.5,4 In the Cleveland case study, infants were more likely to have come from homes that were water damaged, moldy, and contaminated with tobacco smoke.3 In our case report a 40-day-old infant boy was exposed for a discrete 2-week period to a chronically water-damaged, moldy environment. On the passenger train he was briefly exposed to tobacco smoke before he became symptomatic from pulmonary hemorrhage. The exposure of this young infant boy to the environmental risk factors of a chronically moist or water-damaged environment and tobacco smoke may have been relevant to the occurrence of pulmonary hemorrhage.

In our report the sampling from air and from surfaces in the home resulted in the isolation of several fungi but not S atra. Although a 4-month period had elapsed between the time of the infant’s visit and sampling procedures, the history of long-time mold growth at the residence suggests that similar kinds of fungi would have been identified had sampling been conducted earlier. Moreover, this residence had remained mostly unoccupied during this interval. Methods employed in the fungal home survey have successfully isolated S atra from other homes in the St Louis area.2 During bioaerosol sampling activities to release dusts from household surfaces were not performed. Though agitation was not used to simulate household activities, surface sampling was conducted to help isolate slimy molds as S atra. If S atra had been present, it escaped detection by methods that likely would have been identified by the isolation techniques employed.

The occurrence of pulmonary hemorrhage in humans and in animals has been associated with disease caused by other fungi as well. Pulmonary bleeding caused by mycelia of Aspergillus2 species or Penicillium species invading lung parenchyma of immunocompromised human hosts. This form of fungal disease would have been unlikely in this otherwise healthy infant. Absence of fungal growth from bronchoalveolar lavage and rapid clinical recovery during therapy with systemic steroid would argue against the presence of an invasive fungal infection.

It has been proposed that human disease may also be caused by exposure to mycotoxins which are secondary metabolites elaborated by various fungi. The production of mycotoxins and the role of those substances in the genesis of human and animal disease continues to be an area of intense research. Several mycotoxins implicated in human and animal diseases have been listed in the Table.

The occurrence of pulmonary hemorrhage in the human infant has been epidemiologically linked to exposure to S atra. Stachybotrys atra was not isolated from cultures obtained from the residence that the our report describes. The recovery of Trichoderma species from the basement wall was consistent with a chronic water-damaged environment.8,6 Both S atra and Tricho-derma species have been reported to produce dustborne trichothecene mycotoxins that are lipid soluble and readily absorbed by the intestinal lining, airways, and skin.8,10 Trichothecene compounds are potent inhibitors of protein synthesis in animal cells9 and are postulated to be causative in pulmonary vascular injury in the immature lung. Trichoderma species have also been identified in rare cases to be an invasive pathogen in immunocompromised children.12 Though the possible relation of the Trichoderma species isolated from this residence and the pulmonary hemorrhage is speculative, the simi-
larity of *Trichoderma* and *Stachybotrys* is notable. The possible association of exposure to *Trichoderma* species and the incidence of idiopathic infantile pulmonary hemorrhage needs to be further explored.

Other fungal isolates from the home included species of *Penicillium* (possibly *Penicillium purpurogenum*) and *Alternaria* species. Both of these fungi have been associated with the occurrence of pulmonary hemorrhage in animals. As indicated in the Table, rubratoxin, produced by *P. purpurogenum* have been most closely associated with hemorrhagic disease in animals. To date neither of these 2 fungi which are common isolates from the indoor environment have been implicated in the causation of human lung injury. Notably, *C. sphaerospermum* was another fungus isolated from the house where the infant who suffered the pulmonary hemorrhage had resided. The toxic effects of several *Cladosporium* species has been demonstrated and 2 toxic metabolites have been isolated.44 Although a causal relationship between the presence of *Cladosporium* species and infantile pulmonary hemorrhage has not been established, *Cladosporium* has been more frequently isolated from residences of infants with pulmonary hemorrhage than from residences of case-matched controls.

Toxic effects from an individual mycotoxin or the synergistic action of several mycotoxins on the immature pulmonary vasculature of this infant may have triggered a pulmonary bleed. The exposure to fungi in the St Louis residence was for a brief 2-week period; the infant was not present at the residence when the bleeding became clinically evident. Further investigation and monitoring of fungi present in the environment of infants who have experienced idiopathic pulmonary hemorrhage is warranted. Meanwhile, avoiding unnecessary exposure of infants to water-damaged and/or mold-laden environments would be prudent.

Accepted for publication July 22, 1999.

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REFERENCES