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Bioaerosol Lung Damage in a Worker with Repeated Exposure to Fungi in a Water-Damaged Building

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There has been increased concern over health effects related to potential exposure of building occupants to bioaerosols. We report the case of a worker with a respiratory illness related to bioaerosol exposure in a water-damaged building with extensive fungal contamination. We performed environmental tests to evaluate potential exposure to fungi, and we used mycotoxin-specific IgG antibody in serologic studies in the attempt to evaluate exposure to mycotoxins. Extensive fungal contamination was documented in many areas of the building. *Penicillium*, *Aspergillus*, and *Stachybotrys* species were the most predominant fungi found in air sampling. Our serologic test was not useful in differentiating workers who were probably occupationally exposed to mycotoxins from those who were not; however, it did yield evidence that individuals may make specific IgG antibodies to macrocyclic tricothecene mycotoxins. Further research is needed concerning health effects related to bioaerosol exposures, particularly regarding markers of exposure to specific fungi that may produce mycotoxins. In the absence of clinical tools specific for evaluation of mycotoxin-related illness, a systematic clinical approach for evaluating persons with suspected building-related respiratory illness is warranted. **Key words:** bioaerosol, building-related illness, fungi, hypersensitivity pneumonitis, mycotoxin, *Stachybotrys*, water damage. *Environ Health Perspect* 109:641–644 (2001). [Online 15 June 2001] <http://ehpnet1.niehs.nih.gov/docs/2001/109p641-644trout/abstract.html>

Physicians are increasingly being asked to evaluate persons who report symptoms thought to be associated with indoor (nonindustrial) environments where various types of environmental problems have been identified. Although occupants of moisture-damaged buildings may experience increased respiratory symptoms (1), the clinical importance of moisture damage remains unclear in situations where occupants report nonspecific building-related illnesses (2). There has been particular concern over potential health effects from exposure to fungi that produce mycotoxins (3). This concern has received much public attention (4) and has led to recommendations for the remediation of buildings based in part on the reported association of various health effects with exposure to mycotoxins (5).

In October 1998, the National Institute for Occupational Safety and Health (NIOSH) received a request from a local health department to assist in the evaluation of potential occupational exposure to fungi among workers at a hotel. A preliminary visual inspection of the hotel revealed that many areas of the building had widespread fungal growth,

which appeared to be the result of frequent and severe water damage. Our subsequent activities included an environmental survey to assess potential fungal exposure and a pilot serologic survey to assess exposure of workers to mycotoxins. During the same period, clinical evaluation of a worker who developed chronic restrictive lung disease related to work duties in the hotel was performed by physicians not directly related to the NIOSH evaluation.

Case Presentation

Clinical evaluation. A 48-year-old white male, without a prior history of pulmonary disease or tobacco use, presented to his primary care physician in July 1998 with a 2-month history of dry cough and a 1-week history of fever and dyspnea. A chest exam revealed scattered rhonchi and crackles on the right side; an initial chest X ray was unremarkable. Over a period of several months, the patient was treated with several courses of azithromycin for a pneumonitis of uncertain etiology. Pulmonary function testing (Table 1) revealed a reduced forced vital capacity, (FVC), forced expiratory volume in the first

second of exhalation (FEV₁), and total lung capacity (TLC). The diffusing capacity corrected for alveolar volume (DLCO/VA) was normal.

Occupational history revealed that the patient had been a hotel manager at one hotel for the previous 14 years. Two months before initial presentation, he and a co-worker began assessing the extent of water damage and fungal growth in hotel rooms after hotel guests complained of water leakage and odors (Figure 1). These assessments included stripping wallpaper and making holes in walls; no respiratory protection was worn. Shortly thereafter, the patient reported the onset of a nonproductive cough. The patient performed these types of duties until the hotel was closed in October 1998, 5 months after the initial assessment for water damage. However, as the primary supervisor for remediation of the damaged areas, the patient continued to enter all parts of the hotel. The patient had no prior history of exposure to farms or other environments where he would have been exposed to excessive amounts of fungi.

Seven months after his initial presentation, the patient was referred for further evaluation. Dyspnea and cough were noted to be temporally related to his presence in the hotel. His white blood cell count and erythrocyte sedimentation rate were normal. His total IgE level was 346 IU/mL (normal range 0–99 IU/mL). Precipitating antibodies were positive only to *Thermoactinomyces vulgaris*. Specific IgG and IgE antibody responses to *Stachybotrys* sp. were not elevated. A repeat chest X ray was unremarkable, as was high-resolution computed tomography (HRCT) of the chest. A methacholine challenge test

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was performed and was equivocal [the cumulative dose of methacholine (in milligrams) that causes a 20% fall in FEV₁ = 25 mg/mL methacholine]. A repeat HRCT of the chest performed several weeks later with inspiratory and expiratory views was suggestive of an interstitial mosaic pattern consistent with bronchiolitis. Spirometry remained notable for a moderate restrictive defect (Table 1). Based on the patient's history and laboratory findings, he was advised to completely avoid all exposure to his workplace (11 months after the initial investigations for water damage).

The patient was subsequently referred for bronchoscopy. Transbronchial biopsy was unremarkable. Bronchoalveolar lavage (BAL) initially was not performed. The patient was given a provisional diagnosis of restrictive lung disease consistent with a chronic form of hypersensitivity pneumonitis, and treatment was begun with high-dose prednisone (120 mg/day). Repeat bronchoscopy (4.5 months after the initial bronchoscopy) revealed 12% lymphocytes in the BAL fluid (normal < 20%) and a CD4/CD8 ratio of 0.8 (laboratory reference > 1). On the basis of continuing symptoms, evidence of advancing restrictive lung disease (despite removal from the workplace), and concern over the side effects of prednisone, treatment with methotrexate was initiated at 10 mg/week and was subsequently increased to 7.5 mg twice weekly as the prednisone was gradually decreased. A repeat HRCT of the chest was normal. The patient's symptoms gradually improved, while his lung function remained stable (Table 1).

Environmental evaluation. Beginning in November 1998, we conducted environmental surveys (including bulk and air sampling) in a total of 19 rooms of the 10-story hotel. Rooms that had experienced water damage

but that had not yet been remediated were chosen for sampling; the objective was to sample from a representative group of affected rooms. We collected 14 bulk samples of materials that appeared to be contaminated with fungi for analysis with culture techniques (all fungal samples were analyzed by P & K Microbiology Services, Inc., Cherry Hill, NJ) (6). Using previously described methods (6,7), we collected 18 samples to be analyzed for mycotoxins (specifically trichothecenes, atranones, griseofulvins, and phenylspirodrimanes), which can be produced by *Stachybotrys chartarum* (synonyms *atra* or *alternans*) and other fungi.

We collected air samples over a 2-day period using culturable and nonculturable methods. Concentrations of culturable airborne fungi were determined for 14 interior building locations and 1 outdoor location using the Andersen single-stage viable cascade impactor (Andersen Instruments, Smyrna, GA) at a calibrated flow rate of 28.3 L/min. We used the Air-O-Cell (Zefon Analytical Accessories, St. Petersburg, FL) at a calibrated flow rate of 15 L/min (6) to determine airborne concentrations of total spores (nonculturable method) at 13 locations throughout the building at the same locations as the culturable samples and at an outdoor location.

Fungal concentrations from the bulk material samples ranged from 8.8×10^4 to 5.2×10^7 colony forming units (CFU) per gram of material. The predominant fungi identified included *Acremonium* sp., *Alternaria* sp., *Aspergillus niger*, *Aspergillus sydowii*, *Mucor* sp., *Penicillium* sp., *Phoma* sp., *Stachybotrys chartarum*, *Ulocladium chartarum*, and yeasts. Among the identified fungi, *Aspergillus* sp., *Penicillium* sp., and *Stachybotrys chartarum* are known to be capable of producing

mycotoxins. Mycotoxins produced by *Stachybotrys chartarum* (or *Memnoniella echinata*) were identified in 8 of 18 samples. The complex trichothecenes, satratoxin and roridin, produced by *Stachybotrys chartarum*, were found in minute quantities. Atranones, spirocyclic compounds (phenylspirodrimanes) produced by *Stachybotrys chartarum* and *M. echinata*, and epidechlorogriseofulvin, produced by *M. echinata*, were also identified.

Results of the culturable air samples are presented in Table 2. Two of the samples were overloaded with fungal growth so colonies could not be counted; results in Table 2 reflect the 12 samples that could be counted. In water-damaged areas, *Penicillium* sp. and *Aspergillus* sp. were the predominant genera detected. *Stachybotrys* was identified from 5 of 12 sampling locations. Results of the nonculturable techniques were consistent with those obtained by culturable sampling, with *Stachybotrys* identified from 13 of 14 sample locations.

Laboratory evaluation. Because there are currently no useful biological monitoring techniques to assess exposure to mycotoxins, we conducted a pilot serologic evaluation using a test under development to identify specific IgG and IgM antibodies to roridin (a trichothecene mycotoxin known to be produced by several different fungi including *Stachybotrys* species). Trichothecene mycotoxins are potent irritants and may act as haptens, which bind constitutive proteins exerting an immune response similar to what has been described for other xenobiotics. *De*



Figure 1. Water damage and fungal growth in a room with wallpaper stripped from walls.

Table 1. Pulmonary function testing of case patient (height 74 in; weight 226 lb).

Date	Dec 1998	Feb 1999	Aug 1999	Dec 1999	Feb 2000
FVC (L)	3.60 (66%)	3.48 (64)	3.31 (59)	3.19 (57)	3.17 (57)
FEV ₁ (L)	2.91 (66%)	2.86 (65)	2.76 (63)	2.55 (58)	2.59 (59)
FEV ₁ /FVC	0.81 (100%)	0.81 (99)	0.83 (106)	0.80 (102)	0.82 (104)
DLCO/VA (L/min/mmHg)	5.98 (139)	5.66 (131)	ND	ND	ND
TLC (L)	5.0 (66)	4.8 (63)	ND	ND	ND

ND, not done. Values in parentheses are observed values expressed as a percentage of predicted values.

Table 2. Results of air sampling for culturable fungi ($n = 12$).

Agar media ^a	Median indoor concentration (CFU/m ³) ^b	Outdoor concentration (CFU/m ³)	Predominant ^c genera/species indoors	Predominant ^c genera outdoors
Cornmeal agar	1,200 (294–2,690)	380	<i>Penicillium</i> sp. (100) ^d <i>Aspergillus</i> sp. (83) <i>Cladosporium</i> sp. (100) <i>Stachybotrys chartarum</i> (42)	<i>Cladosporium</i> sp.
Dichloran glycerol	1,350 (319–2,745)	419	<i>Penicillium</i> sp. (100) <i>Aspergillus</i> sp. (100) <i>Cladosporium</i> sp. (100)	<i>Cladosporium</i> sp.

^aCornmeal agar is a selective nutrient medium to promote the growth of *Stachybotrys* species; dichloran glycerol is a selective nutrient medium to promote the growth of low-moisture tolerating fungi (i.e., xerophiles). ^bValues in parentheses indicate range. ^cGenera most frequently found across all samples. ^dValues in parentheses indicate the percentage of samples in which each fungus was found.

novo biosynthesis of antibodies from mycotoxin exposure has been shown for related mycotoxins such as aflatoxins found in food (8). In addition, cows exposed to mycotoxins in their feed have been shown to produce anti-mycotoxin antibodies (9). Roridin-A IgG antibodies, generated in animals, have been shown to be specific for macrocyclic tricothecenes (roridin is a type of macrocyclic tricothecene) (10).

In a study approved by the NIOSH Human Subjects Review Board, personnel lists of former hotel employees (total of 90 full- or part-time employees) were reviewed with hotel management to determine exposed (persons who had routinely worked in the fungi-contaminated areas) and unexposed (persons who had worked in areas found not to be grossly contaminated with fungi) workers. Employee recruitment was difficult because the hotel was closed at the time of our evaluation and employees were no longer employed at the hotel. Eight employees agreed to participate in the survey, including six exposed and two unexposed employees. The two hotel employees who participated in the discovery and initial mitigation of the water problem (including the hotel manager), and who were the persons most highly exposed to the fungal contamination, were included among the six exposed employees. After informed consent was obtained, a serum sample was collected from each participant. A brief questionnaire to assess job duties, medical history, and current symptoms was also administered to participants. We did not perform clinical examinations of study participants.

We performed enzyme-linked immunosorbent assays (ELISA) for roridin-hemisuccinate-human serum albumin (RH-HSA)-specific IgG antibodies on each serum sample. Fifty microliters of a 50 µg/mL solution of RH-HSA was placed in each well and incubated overnight at 4°C. Each well was then washed three times with phosphate-buffered saline (0.02 M phosphate buffer, pH 7.4) containing 0.91 M sodium chloride and Tween; a similar wash was repeated between all subsequent steps. Aliquots (200 µL) of each diluted serum sample (1:10 in 5% bovine serum albumin–deionized water) were added to the wells and allowed to incubate at room temperature for 2 hr. After washing, 100 µL of goat anti-human IgG or IgM (whole molecule) alkaline phosphatase conjugate (Sigma Chemical Co., St. Louis, MO) was added to each well and incubated for 2 hr at room temperature. The plates were again washed and 100 µL of 0.6 mM disodium *p*-nitrophenyl phosphate (Sigma Chemical Co.) substrate solution, diluted in alkaline glycine buffer (0.05 M glycine and 0.5 mM magnesium chloride, pH 10.4), was

added. After 10–15 min, the reactions were read on an automated ELISA plate reader. Each serum was tested in triplicate. We used seven stored sera obtained from unrelated NIOSH studies (from persons living in the same geographic area as the hotel but with no known contact to this hotel or excessively moldy environments) as assay controls. A response was defined as positive if a subject's serum optical density (OD) was greater than the assay control sera's mean OD + 3 SD.

The participants in the survey included three males and five females. The median length of employment at the hotel was 4 years (range: 1–14 years). Persons considered exposed worked in housekeeping, maintenance, or supervisory jobs, whereas the two unexposed persons worked in the bar/restaurant area. Among the eight sera samples, two had elevated IgG antibody titers to RH-HSA. The two individuals with elevated levels included one who was considered exposed and one who was considered unexposed. The hotel manager (case patient) did not have an elevated antibody level. No exposed or unexposed individuals gave evidence of specific IgM antibodies to RH-HSA.

Although exposed workers reported a spectrum of symptoms, some of which were reported to improve away from work, none of the workers were identified during our interview as having a clinical illness similar to that of the case patient. We did not perform systematic clinical evaluations of survey participants.

Discussion

Fungi are ubiquitous in the environment, and most individuals are exposed to them on a daily basis. Many fungi are capable of producing mycotoxins, which suggests that most people have some level of regular exposure to mycotoxins. An important aspect of evaluating whether health effects may be related to mycotoxin exposure is documentation of exposure (11). This is difficult because there are currently no reliable exposure indicators for mycotoxins. The standard used to associate health effects to mycotoxin exposure is the measurement of mycotoxins in bulk samples obtained from materials such as walls, ceiling tiles, and air ducts (12,13). Although the identification and quantification of several mycotoxins has been recently accomplished using monoclonal antibodies and enzyme immunoassays, these methods have had limited use in field evaluations (10,14–16). The pilot serologic survey of this investigation was not able to distinguish between exposed and unexposed workers in a building heavily contaminated with mycotoxin-producing fungi. Although this laboratory testing did yield evidence that individuals may make specific

IgG antibodies to roridin, the source of the exposure that led to this response cannot be determined from our data. Further studies are needed to determine the validity and specificity of this antibody testing in humans.

This case report emphasizes the importance of a careful occupational and environmental history because earlier recognition and avoidance of exposure to the suspected causal antigens may have reduced the degree of the patient's pulmonary disease. Furthermore, this case illustrates the complexity of establishing a definitive relationship between a specific illness and exposure to bioaerosols in general, or to any specific component of a bioaerosol (such as a mycotoxin).

In this case, the worker who developed chronic lung disease was likely exposed to an unusually high concentration of airborne fungi while investigating water incursion into the building. Although a specific diagnosis or cause of his pulmonary disease could not be confirmed, environmental sampling revealed heavy growth and airborne dissemination of many fungi, including several known to cause hypersensitivity pneumonitis (HP) (17,18). This worker fulfilled several of the major criteria required for the diagnosis of HP (19), including chronic respiratory symptoms compatible with HP, prolonged exposure to a putative antigen, and recurrence of symptoms upon reentry into the contaminated workplace. Although there was no absolute lymphocytosis on BAL, the CD4/CD8 ratio was decreased, which is consistent with HP.

The difficulty in making a definitive diagnosis of HP is due in part to the incomplete understanding of the pathogenesis of this disorder (20). A diagnosis of HP is further complicated because HP can present in acute, subacute, or chronic forms (21,22). Prolonged, low-dose exposure to inciting agents has been thought to predispose to a more chronic presentation (21). The clinical manifestations of the chronic form of HP, which often include cough and dyspnea without the systemic manifestations more commonly seen in the acute form (20,21), are compatible with the case patient's presentation.

Figure 2 provides an algorithmic approach that can be helpful in the clinical evaluation of a person who, based on a history and physical examination, is suspected of having an illness associated with bioaerosol exposure. After infectious processes are appropriately evaluated and found to be unlikely, then further evaluation is warranted. Hypersensitivity illnesses that must be considered in such an evaluation can be categorized broadly as having asthmatic or pneumonitis features, although there may be considerable overlap between the two. Although inhalation fevers (e.g., humidifier

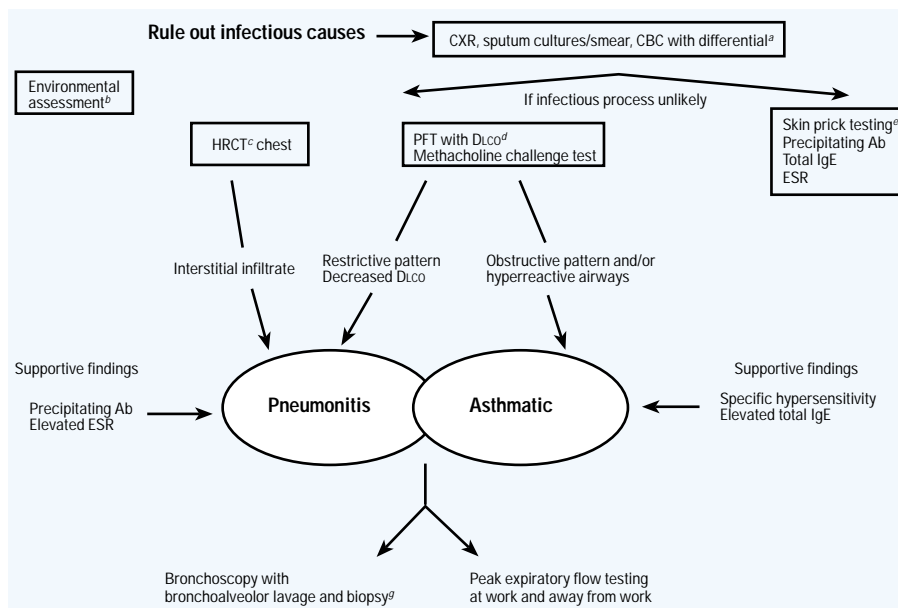


Figure 2. Approach to patients with suspected building-related illness from bioaerosol exposure: components of clinical evaluation when history and physical examination is suggestive of respiratory illness. Abbreviations: Ab, antibody; CBC, complete blood count; CXR, chest X ray; ESR, erythrocyte sedimentation rate; PFT, pulmonary function test.

^aSerology for histoplasmosis and Lp1 antigen (urine) to evaluate for Legionella infection should also be considered. ^bExtent of environmental assessment will depend on multiple factors. ^cHRCT should be performed even with normal CXR. ^dPFT (with bronchodilator administration) with lung volumes and diffusing capacity corrected for alveolar volume. ^eEvaluation for IgE-mediated immediate hypersensitivity. ^fEvaluation for precipitating antibodies to antigens present in the environment. ^gShould also include CD4/CD8 ratio, fungal/bacterial cultures, and histology.

fever) do not manifest primarily as respiratory illness, they should also be considered in the differential diagnosis. Detailed reviews related to the diagnosis of these illnesses are available to supplement the broad algorithm presented here (23).

In the last several years, reports have implicated exposure to *Stachybotrys chartarum* as being associated with acute pulmonary hemorrhage/hemosiderosis among infants or children (24). However, in a recent extensive review, the Centers for Disease Control and Prevention (13) concluded that evidence from currently available studies is not sufficient to support an association between acute pulmonary hemorrhage/hemosiderosis and exposure to *Stachybotrys chartarum*, and that further investigation of acute pulmonary hemorrhage/hemosiderosis in infants is needed. Our findings reinforce the difficulty investigators have had in attempting to determine actual exposure to mycotoxins.

Conclusion

Building-related illnesses include a variety of recognized disease entities that are characterized by objective clinical findings

related to specific exposures in the indoor environment (2). These illnesses are preventable if greater efforts at improving building design, construction, indoor environmental controls, and maintenance to prevent or reduce exposure to potential etiologic agents are implemented. The clinical and environmental evaluations we have presented emphasize the need for further research involving biomarkers and health effects related to bioaerosol exposure. Such research should focus on identifying acceptable levels of indoor airborne microorganisms and mycotoxins and developing better methods for assessing their effects on human health. In the absence of tools specific for evaluation of possible mycotoxin-related illness, the clinical evaluation of suspected building-related respiratory illness should follow standard guidelines.

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