
Case report

Fatal hypersensitivity pneumonitis

Michael Zacharisen, MD,* and William Schoenwetter, MD†

Background: Hypersensitivity pneumonitis (HP) is an uncommon, non-IgE-mediated interstitial lung disease caused by the inhalation of a variety of organic dusts, most commonly from exposure at work or in the pursuit of hobbies. Typically, after the disease is recognized, the causative allergen or environment is identified and treatment initiated through avoidance measures and corticosteroids. Progression of the disease is then usually halted and even reversed. Fatal cases of HP are unusual.

Objective: To report a case of progressive and deadly HP in a 40-year-old printer who developed subacute bird fancier's disease with its clinical characteristics and positive precipitins to pigeon proteins.

Methods: Chest x-ray examinations and tests of lung function were performed in the patient. Two months after initial consultation, when the diagnosis was still elusive, an open lung biopsy was performed and the patient was treated with prednisone for 3 months. A subsequent chest x-ray examination was performed 4 months after the biopsy.

Results: With avoidance of birds and treatment with corticosteroids, the patient's symptoms resolved and lung function normalized. He was subsequently diagnosed as having asthma followed by bronchitis and 2 episodes of pneumonia. He did not fully recover from these but developed progressive dyspnea. After linking his symptoms to work by history, he underwent lung biopsy with findings consistent with chronic HP. Serum antibody titers were positive for *Aspergillus* but not pigeon proteins. Based on exposure to water-based coolants, he was suspected of having chronic occupational HP, although this could not be confirmed. Despite aggressive treatment, he developed a progressive course that was ultimately fatal.

Conclusions: This report details the progressive disease course in an individual who presented initially with subacute HP. Unfortunately, even after appropriate diagnosis and management, the course of the disease can be fatal.

Ann Allergy Asthma Immunol. 2005;95:484–487.

INTRODUCTION

Hypersensitivity pneumonitis (HP) is an uncommon, non-IgE-mediated inflammatory interstitial and alveolar pulmonary disease that primarily affects adults and is caused by the inhalation of any of a wide variety of organic dusts.¹ The classic forms of HP are related to recurrent or prolonged inhalation exposures of thermophilic bacteria as in farmer's lung² or avian antigens as in pigeon breeder's disease.³ Other causes include a wide variety of fungi⁴ and low-molecular-weight chemicals.⁵ With early and aggressive treatment, the prognosis for acute and subacute HP is generally favorable without regard to the causative antigen.^{6,7} Even in the chronic form of avian HP, most patients achieve remission.⁷ However, fatalities have been reported.^{8–14} Herein, we report a case of subacute bird fancier's disease that despite appropriate treatment progressed to chronic HP that was ultimately fatal.

CASE REPORT

The patient was a 51-year-old white man who worked as a pressman at a printing company for 28 years. At the age of 40

years, he developed an influenza-like illness with fever, dyspnea, and cough. Chest x-ray films revealed bilateral, interstitial pulmonary infiltrates. Lung function showed restrictive ventilatory impairment with a forced expiratory volume of 1 second (FEV₁) of 66% and a forced vital capacity (FVC) of 59%. Diffusion capacity was impaired at 36% and hypoxemia was demonstrated on room air with a Pao₂ of 62 mm Hg. After 2 months, when the diagnosis was still elusive, an open lung biopsy was performed and the results were consistent with HP. Ouchterlony double diffusion technique documented a very high antibody titer to pigeon serum. During the preceding year, he had kept several doves in his house. Pigeon serum is antigenically similar to dove antigen, thus confirming significant relevant bird antigen exposure. His symptoms improved after the birds were removed and he was treated with prednisone for 3 months. A subsequent chest x-ray examination performed 4 months after the biopsy showed improvement, but mild infiltrates were still present bilaterally. Spirometry results improved to an FEV₁ of 100% and an FVC of 88%.

The patient was concomitantly diagnosed as having asthma, because spirometry results demonstrated an obstructive pattern with reversibility with albuterol. He was treated with daily inhaled corticosteroids and albuterol as needed and did well. Two years later his lung function was normal (FEV₁ of 99% and FVC of 83%), and a chest x-ray examination revealed stable diffuse bilateral interstitial fibrotic changes

* Department of Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin.

† Park Nicollet Clinic, St Louis Park, Minnesota.

Received for publication April 19, 2005.

Accepted for publication in revised form May 1, 2005.

and bilateral upper lobe bullae. While being evaluated during a bout of bronchitis 1 year later, spirometry results suggested mild restriction, with an FVC of 76% and an FEV₁ of 77%. He had bilateral rales and slight wheezing and was treated with a short course of prednisone and azithromycin with symptomatic improvement. However, he experienced recurrence of symptoms that required a slow taper of prednisone.

Two years later, or 5 years after the initial diagnosis, he reported mild dyspnea with exertion, he had bilateral crackles on auscultation, and his spirometry results had reduced to an FEV₁ of 83% and an FVC of 68%. He continued to take asthma medications. One year later he developed right lower lobe pneumonia and was treated with high-dose prednisone and antibiotics, and he improved. However, during the next 3 weeks, his symptoms recurred, he was hospitalized, and his condition was shown to have further deteriorated (FVC of 47% and FEV₁ of 51%). He exhibited hypoxemia with exertion, with a Pao₂ decreasing to 71 mm Hg while receiving 3 L of oxygen. Although the results of chest computed tomography and chest x-ray examination were unchanged, he was treated with oxygen, antibiotics, high-dose corticosteroids, and bronchodilators. There was no measurable response to bronchodilator therapy, but he symptomatically improved and was discharged after 3 days. He continued to have a marked restrictive pulmonary function defect and reduction in diffusion capacity. He was treated with daily oral and inhaled corticosteroids and bronchodilators for 3 months with continued symptoms. A subsequent serum analysis revealed precipitins to *Aspergillus niger* and *Aspergillus fumigatus* but not pigeon serum. He was unable to taper oral steroids, because his clinical status and lung function would deteriorate. He exhibited hypoxemia after walking short distances.

After 4 months he complained of progressive fatigue and dyspnea, with a subsequent chest computed tomogram revealing improvement in lung infiltrates, yet the remainder of the abnormalities persisted. Another open lung biopsy specimen revealed chronic HP with fibrosis. He reported increased symptoms at work with improvement on weekends and vacations. It was suspected that he had developed occupational HP and was removed from work.

Further evaluation of the workplace revealed that the ink had changed to a soy base 10 years earlier and that recycled water collected in a 600-gallon reservoir was used for cooling the high-speed printing presses. Although the coolant system was cleaned biannually, it was noted that "ropy scum" was removed from the surface, despite the addition of biocides. This material was not cultured. An industrial hygiene analysis performed nearly 2 years after he was removed from the workplace revealed that the culturable bacteria and fungus were greater in the outdoor air compared with the indoor air, although the total spore count was slightly higher indoors. The types of fungi were similar and included *Cladosporium*, *Penicillium*, *Aspergillus versicolor*, *A. fumigatus*, basidiomycetes, *Micrococcus luteus*, and *Rhodococcus*. Bacterial and fungal cultures from the coolant tank were negative. Other exposures at the worksite included dust from paper rolls and

oil mist that was sprayed onto the gears of the printing press. Although this lubricating process was enclosed, the patient had intermittent exposure during inspections and he did not wear respiratory protection. A detailed search through the Material Safety Data Sheets revealed exposure to phthalic anhydrides, diatomaceous earth, cobalt, aluminum, and barium; no exposure was in excess of the Occupational Safety and Health Administration permissible limits where identified. Despite workplace avoidance and daily prednisone, there was no appreciable improvement in lung function and his dyspnea and fatigue increased. A subsequent chest x-ray examination identified new interstitial infiltrates. Seven months later he developed a pneumothorax presumed to be a ruptured bleb.

Additional history revealed that he had experimented with inhaling or sniffing drugs and smoking marijuana many years ago. He had a 17-pack-year history of cigarette smoking but had stopped 6 years before his symptoms developed.

Physical examination revealed a mildly dyspneic man, with a pulse oximeter that measured 95% on 3 L of oxygen by nasal cannula. Head and neck examination results were normal. Chest auscultation revealed distant breath sounds and mild wheezing but no rales. He exhibited mild clubbing of his digits without cyanosis. Spirometry revealed an FVC and FEV₁ of 49%. The results of allergy skin testing to common inhalant allergens were negative. The patient continued to experience progressive respiratory impairment with increasing oxygen requirement and ultimately died of respiratory insufficiency.

DISCUSSION

Hypersensitivity pneumonitis is an uncommon cause of interstitial and alveolar lung disease that can present in acute, subacute, or chronic forms.¹ When identified early, treatment typically halts or reverses the process and most patients recover regardless of the antigen implicated. Deaths related to HP typically occur in adults with avian-induced HP or farmer's lung,⁸⁻¹⁴ perhaps because these are the most common categories of HP.

The natural history of bird fancier's lung suggests that once treated and without further antigen exposure, most patients improve.⁷ Conversely, individuals who continue to be exposed to the bird antigen have continued symptoms and decline in pulmonary function. Mexican pigeon breeders with chronic disease had a mortality rate of 29% at 5 years despite treatment.⁸

Fatal avian-related cases include a 47-year-old pheasant gamekeeper who presented with 8 months of insidious dyspnea after 1 year of rearing pheasants.⁹ This individual continued to care for pheasants for 2 years wearing respiratory protection but experienced progressively worsening symptoms. Deterioration continued despite avoidance measures, and he died 8 years after initial diagnosis. A 68-year-old man died of acute alveolar injury (patchy consolidation and organized exudates in some alveoli) following years of slowly progressive pulmonary deterioration. Mild airflow obstruc-

tion was followed by the development of pulmonary fibrosis and honeycombing.¹⁰

An additional case report was that of a 49-year-old man with chronic bird fancier's lung who was stable while avoiding birds but deteriorated acutely after intermittent exposure during 1 year to budgerigars in his wife's office. Despite hospitalization and aggressive treatment, he died within 8 months. Autopsy findings revealed diffuse alveolar damage, fibrosis, and extensive honeycombing.¹¹

The first fatal case of bird fancier's lung reported in North America was a 45-year-old woman who presented with chronic cough, shortness of breath, and dyspnea on exertion.¹² She had subacute disease related to a parakeet she had kept for 7 years, although she had bird exposure since the age of 7 years. Despite removal of the parakeet and pharmacologic treatment, she developed severe wheezing and end-stage pulmonary fibrosis. She died postoperatively after a single lung transplantation 5 years after diagnosis.

Although avoidance of the allergen is the primary nonpharmacologic treatment for HP, complete avoidance of animal allergens is problematic. It is well established that animal allergens, such as cat and dog dander, can be detected within a home despite removal of the pet and even in homes that have not had pets.¹³ This environmental distribution of dander is related to aerodynamic properties and passive transfer of allergen. Bird antigens from cockatiels and parakeet can persist for up to 18 months after bird removal, especially in homes where the bird was kept in one room despite extensive environmental control measures.¹⁴

Farmer's lung has rarely been associated with fatal outcomes, with no cases reported in major follow-up studies from 1980 to 1997. This includes 29 cases followed up for 10 years,¹⁵ 61 cases with 1- to 11-year follow-up,⁶ 86 cases with 5-year follow-up,¹⁶ 101 cases followed up for 5 years,¹⁷ and 33 cases followed up for 6 years.¹⁸ In 1997, 3 Canadian farmers (2 brothers and 1 wife) died of progressive pulmonary fibrosis related to farmer's lung caused by newly causative antigens *Penicillium brevicompactum* and *Penicillium olivicolor*.¹⁹ None were smokers, and the brothers had mild symptoms episodically for nearly 50 years. In Finland, 13 terminal cases of farmer's lung were identified based on death certificates during more than 10 years (1980 to 1990), with an estimated mortality rate of 0.7%. All but 1 of these patients had chronic disease, and most experienced symptoms for at least 1 year before the diagnosis was established.²⁰ Death occurred on average 8 years after the diagnosis. The incidence however may have been underreported, because death certification was 0% to 70% (overall 26%) when standard case histories for farmer's lung were reviewed by physicians in 8 European countries.²¹

Risk factors for fatal HP are not clearly defined; however, patients who present with pulmonary fibrosis apparent on lung biopsy specimens had diminished survival (7.1 years) compared with patients without fibrosis.²² The group with pulmonary fibrosis was also older and had greater restrictive lung physiology. Using age-adjusted regression analysis, an-

tigen, symptom duration, and lung function had no effect on survival. The best predictors of mortality in chronic pigeon breeders' disease were age older than 44 years, male sex, honeycombing apparent on x-ray film, and severity of fibrosis on lung biopsy specimen.⁸ Although smoking has appeared to be a protective factor against developing HP,²³ farmers with farmer's lung who smoked had significantly lower 10-year survival rates, more symptomatic recurrences, and lower vital capacities when compared with nonsmoking farmers with farmer's lung.²⁴

This current case represents a patient who developed progressive and fatal HP. After appropriate treatment for subacute bird fancier's disease related to doves, he developed obstructive lung disease that may have been mistaken for asthma as it has been in other reports.^{12,25,26} The chronic HP present for at least 6 years may have represented an extension of the avian HP either from low-grade persistent bird antigen exposure or progression of disease without ongoing bird exposure. Furthermore, other antigens, such as *Aspergillus* or phthalic anhydride, related to work were raised as a possible cause, although this was not clearly established. There has been only 1 case report of HP related to 2 different causative antigens.²⁷ Contaminated water-based cooling fluid systems have been implicated in cases of HP in machinists²⁸ but not in pressman who operate printing presses.

The patient's history of smoking may have contributed to symptoms of airway obstruction as is seen in chronic obstructive pulmonary disease or contributed to the progressive chronic nature. The patient's history of inhaling illicit drugs also complicates this case. Inhaled heroin has been reported to result in HP.²⁹ This patient denied using heroin but had smoked marijuana. There is insufficient published data to recommend treatment with immunosuppressive agents for progressive and intractable HP, although individual reports have included treatment with cyclosporine A.¹¹

In conclusion, although HP can be challenging to diagnose, once the source or causative antigen is identified, treatment is usually successful with avoidance measures with or without oral steroids. Symptom progression and clinical deterioration after initiation of avoidance and pharmacologic treatment in the presence of fibrosis appear to be common themes in patients with poor outcomes. Unfortunately, despite treatment, HP can be fatal.

REFERENCES

1. Fink JN, Zacharisen MC. Hypersensitivity pneumonitis. In: Adkinson NF, Yunginger JW, Busse WW, et al, eds. *Middleton's Allergy: Principles and Practice*, 6th ed. New York, NY: Mosby Inc; 2003:1373-1390.
2. Dickie HA, Rankin J. Farmer's lung: an acute granulomatous interstitial pneumonitis occurring in agricultural workers. *JAMA*. 1958;167:1069-1076.
3. Fink JN, Sosman AJ, Barboriak JJ, et al. Pigeon breeders' disease. *Ann Intern Med*. 1968;68:1205-1219.
4. Blyth W, Grant WB, Blackadder ES, Greenberg M. Fungal antigens as a source of sensitization and respiratory disease in Scottish maltworkers. *Clin Allergy*. 1977;7:549-562.

-
5. Baur X. Hypersensitivity pneumonitis (extrinsic allergic alveolitis) induced by isocyanates. *J Allergy Clin Immunol.* 1995; 95:1004–1010.
 6. Cormier Y, Belanger J. Long-term physiologic outcome after acute farmer's lung. *Chest.* 1985;87:796–800.
 7. Zacharisen MC, Schlueter DP, Kurup VP, Fink JN. The long term outcome in acute, subacute and chronic forms of pigeon breeders disease hypersensitivity pneumonitis. *Ann Allergy Asthma Immunol.* 2002;88:175–182.
 8. Perez-Padilla R, Salas J, Chapela R, et al. Mortality in Mexican patients with chronic pigeon breeders' lung compared with those with usual interstitial pneumonitis. *Am Rev Respir Dis.* 1993;14:49–53.
 9. Partridge SJ, Pepperell JCT, Forrester-Wood C, et al. Pheasant rearer's lung. *Occup Med.* 2004;54:500–503.
 10. Tasaka S, Kanazawa M, Kawai C, et al. Fatal diffuse alveolar damage from bird fanciers' lung. *Respiration.* 1997;64: 307–309.
 11. Ohtani Y, Inase N, Miyake S, et al. Fatal outcome in chronic bird fancier's lung. *Am J Med.* 2002;112:588–590.
 12. Greenberger PA, Pien LC, Patterson R, et al. End-stage lung and ultimately fatal disease in a bird fancier. *Am J Med.* 1989;86: 119–122.
 13. Bollinger ME, Eggleston PA, Wood RA. Cat antigen in homes with and without cats may induce allergic symptoms. *J Allergy Clin Immunol.* 1996;97:907–914.
 14. Craig TJ, Hershey J, Engler RJM, et al. Bird antigen persistence in the home environment after removal of the bird. *Ann Allergy.* 1992;69:510–512.
 15. Cuthbert OD, Gordon MF. Ten year follow up of farmers with farmer's lung. *Br J Industrial Med.* 1983;40:173–176.
 16. Monkare S, Haahtela T. Farmer's lung: a 5 year follow-up of eighty-six patients. *Clin Allergy.* 1987;17:143–151.
 17. Kokkarinen JI, Tukiainen HO, Terho EO. Recovery of pulmonary function in farmer's lung: a five-year follow-up study. *Am Rev Respir Dis.* 1993;147:793–796.
 18. Lalancette M, Carrier G, Laviolette M, et al. Farmer's lung: long-term outcome and lack of predictive value of bronchoalveolar lavage fibrosing factors. *Am Rev Respir Dis.* 1993;148: 216–221.
 19. Nakagawa-Yoshida K, Ando M, Etches RI, Dosman JA. Fatal cases of farmer's lung in a Canadian family: probable new antigens, *Penicillium brevicompactum* and *P olivicolor*. *Chest.* 1997;111:245–248.
 20. Kokkarinen J, Tukiainen H, Terho EO. Mortality due to farmer's lung in Finland. *Chest.* 1994;106:509–512.
 21. Farebrother MJ, Kelson MC, Heller RF. Death certification of farmer's lung and chronic airway diseases in different countries of the EEC. *Br J Dis Chest.* 1985;79:352–360.
 22. Vourlekis JS, Schwarz MI, Cherniack RM, et al. The effect of pulmonary fibrosis on survival in patients with hypersensitivity pneumonitis. *Am J Med.* 2004;116:662–668.
 23. Cormier Y, Gagnon L, Berube-Genest, et al. Extrinsic allergic alveolitis, the influence of cigarette smoking. *Am Rev Respir Dis.* 1988;137:1104–1109.
 24. Ohtsuka Y, Munakata M, Tanimura K, et al. Smoking promotes insidious and chronic farmer's lung disease, and deteriorates the clinical outcome. *Int Med.* 1995;34:966–971.
 25. Bourke S, Carter R, Anderson K, et al. Obstructive airways disease in non-smoking patients with pigeon fancier's lung. *Clin Exp Allergy.* 1989;19:629–632.
 26. Selman-Lama M, Perez-Padilla R. Airflow obstruction and airway lesions in hypersensitivity pneumonitis. *Clin Chest Med.* 1993;14:699–714.
 27. Da Broi U, Orefice U, Cahalin C, et al. ARDS after double extrinsic exposure hypersensitivity pneumonitis. *Intensive Care Med.* 1999;25:755–757.
 28. Bernstein DI, Lummus ZL, Santilli G, et al. Machine operator's lung: a hypersensitivity pneumonitis disorder associated with exposure to metalworking fluid aerosols. *Chest.* 1995;108: 636–641.
 29. Suresh K, D'Ambrosio C, Einarsson O, et al. Hypersensitivity pneumonitis induced by intranasal heroin use. *Am J Med.* 1999; 107:392–395.
-
- Requests for reprints should be addressed to:*
Michael Zacharisen, MD
Department of Pediatrics
Medical College of Wisconsin
9000 W Wisconsin Ave
PO Box 1997
Milwaukee, WI 53201
E-mail: mzach@mcw.edu
-