Case report

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Chacinero's lung – hypersensitivity pneumonitis due to dry sausage dust

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Objective Hypersensitivity pneumonitis (HP) comprises a large group of diseases that occur secondary to inhalation of a variety of antigens. This report describes a little-known cause of HP, previously unreported in the English literature.

Methods Five patients (three women) with a mean age of 41 years who fulfilled the criteria for HP due to exposure to dry sausage dust were studied. The clinical findings, immunologic testing, results of the specific inhalation challenge, and follow-up are described.

Results Three patients developed an acute form of disease and two patients a subacute form. A diffuse micronodular centrolobular pattern was seen on high-resolution computer tomography scanning of four patients. A restrictive pattern was identified on pulmonary function testing of four patients and decreased lung diffusion of carbon monoxide (DLCO) among three. In bronchoalveolar lavage specimens from three patients, lymphocytosis was 17%, 40%, and 40%, with a CD4/CD8 ratio of <0.6. Specific immunoglobin G (IgG) antibodies to *Penicillium frequentans* and *Aspergillus fumigatus* were positive for three patients. Performed on three patients, the specific inhalation challenge was positive for dry sausage dust extract in two cases and *Penicillium frequentans* in the third. Resolution of clinical, radiologic, spirometry, and DLCO alterations occurred among the three patients who avoided exposure following the diagnosis.

Conclusions A short patient series affected by a little-known cause of occupational HP is described. *Penicillium frequentans* may be the causative agent in some cases, but other fungi were found that could also be implicated in the etiology of this disease.

Key terms extrinsic allergic alveolitis; occupational disease; *Penicillium frequentans*; specific inhalation challenge; specific skin test.

The term hypersensitivity pneumonitis (HP) encompasses a group of lung diseases produced by inhalation of certain substances, mainly organic, which, among susceptible individuals, can trigger an inflammatory reaction at the level of the alveoli, bronchioles, and pulmonary interstitium, with a marked lymphocytic-histiocytic component (1). The clinical presentation is heterogeneous, and thus HP may present as an acute, subacute, or chronic disease, depending – among other factors – on the intensity of inhaled antigens and frequency of exposure (2–3). Patients with acute or subacute HP usually respond to treatment, whereas those with chronic disease at the time of diagnosis are often at the point of no return and progress to irreversible lung destruction with fibrotic or emphysematous changes (2, 4–5).

Most authors agree that HP is likely under-diagnosed because of the difficulty in establishing the diagnosis and the fact that there is still a general lack of knowledge about this condition (6). Several diagnostic criteria have been reported (7–9), but their accuracy is not well established. A previous study (3) identified exposure to a known offending antigen, *serum precipitins*, recurrent episodes of symptoms, inspiratory crackles, symptoms occurring 4–8 hours after exposure, and weight loss as significant predictors of HP. Nevertheless, specific

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inhalation challenge (SIC) is considered the reference standard diagnostic method (10).

The prevalence and distribution of HP can vary considerably between countries and geographical locations due to local customs and occupational and climatic conditions (11). Farmers' and bird fanciers' lung are the most commonly reported forms of HP, but more than 30 types of exposure and antigens have been described as a cause of this condition (2, 11). It is known that HP can progress clinically and histologically with features of non-specific interstitial pneumonia, idiopathic pulmonary fibrosis/usual interstitial pneumonia, or organizing pneumonia (12). Therefore, it is reasonable to think that many unrecognized types of exposure may be at the origin of HP, both in the acute and chronic forms. The description of new causative exposures would increase the possibility of reaching an early diagnosis of these conditions.

This report describes the clinical features, the diagnostic tests conducted, including SIC, and the follow-up of five patients with HP due to inhalation of dry sausage dust at their workplace, a very little known type of occupational exposure causing HP. In Spain, workers in the dry pork sausage industry are known as c*hacineros,* the name we propose to link with this disease.

Methods

Study population

The study included five patients (three women), with a mean age of 41 years (range 24–53 years), who fulfilled the criteria for HP (10) due to exposure to dry sausage dust (table 1). Three patients (cases 1, 4, and 5) were diagnosed at our occupational respiratory disease unit in 1994 and 2008. Cases 2 and 3 were diagnosed in the Hospital Universitario de Salamanca in 1994 and 2004, respectively. All patients were actively working in the food industry, involved in the production of dry sausages. To improve the flavor of these products, the sausages are dipped in a bath containing molds, and then left to ferment and dry for 3–4 months in humidity- and temperature-controlled rooms. At the end of the process, the mold covering the product is removed by brushing (figure 1). Three of our cases carried out this task. Patients 1, 2, and 3 worked with a mechanical brush, manually guiding the sausages into the brushing machine to clean them. They did this task daily for eight hours a day, worked without respiratory protection, and were constantly exposed to high levels of brushing dust. Patient 4 was a secretary and worked in an office close to the industrial area. Patient 5 was a supervisor of the process who circulated through different areas of the factory. For these two patients, the exposure was light, but persistent.

At the time of the diagnosis, a complete clinical and occupational history was taken, and radiologic studies, pulmonary function tests, blood analyses, fiber bronchoscopy with bronchoalveolar lavage, immunologic studies, and SIC were performed. The tests were carried out in the acute form of HP during the last exacerbation for patients 1, 2, and 3, and in subacute disease in relation to the diagnostic process for the remaining two patients.

Pulmonary function testing

In both centers, pulmonary function tests were carried out according to the European Respiratory Society guidelines (13, 14) on a MasterLab instrument (MasterLab, Jaegger, Germany). Static lung volumes were measured using the plethysmography method, and lung diffusion of carbon monoxide (DLCO) was measured using the single breath-hold method (15). The reference spirometric values were those proposed for the Mediterranean population (16) and the predicted values for static lung volumes and DLCO were those proposed by the European Respiratory Society (13, 14). An obstructive ventilatory pattern was established on the basis of a forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio <70%. The DLCO was considered decreased at values of <90% of the predicted value.

Antigen extract preparation

An antigenic extract was prepared from the dust obtained by brushing the fermented sausage. Soluble proteins were extracted with ammonium bicarbonate buffer 0.2 M (pH 7.9) overnight at 4 ºC. The solution was centrifuged and the supernatant dialyzed at 4 ºC against H_2Od using a 3500 D pore-size membrane [(Spectra/Por) Spectrum Medical Industries, Los Angeles, CA, USA]. The material obtained from the dialysate was lyophilized and the protein concentration determined by the bicinchoninic acid method (Pierce, Rockford, IL, USA). Before preparing the antigen extract, a portion of the dust was cultured to determine what types of fungi were present.

Immunologic testing was performed with commercial extracts of *Penicillium frequentans, Aspergillus fumigatus, Mucor mucedo,* and *Rhizopus nigricans* (Bial-Aristegui, Bilbao, Spain).

Determination of specific IgG antibodies

For patient 2, specific precipitating antibodies to fungi and sausage dust extract were determined exclusively by countercurrent immunoelectrophoresis, as previously described (10). For the remaining patients, specific IgG antibodies to fungi were determined by an enzyme-linked immunoabsorvent assay (ELISA) technique based on a

Table 1. Clinical characteristics of patients studied [CT=computer tomography; BAL=bronchoalveolar lavage; CD=cluster of differentiation; DLCO=decreased lung diffusion of carbon monoxide; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; L=lymphocytes; M=macrophages; N=neutrophils; ND=not determined; PPD=purified protein derivative; RV=residual volume; TLC=total lung capacity; VA=alveolar volume.]

Patient number	Age / gender	Smoking habit (Pack-years)	Latency (exposure time in dyas until onset symptoms)	Duration of exposure up to diagnosis (years)	Symptoms	Radiography/ CT findings	Pulmonary function test	BAL cells %	Delayed cutaneous hypersensitivity test (+ positive) (- negative)
1	48 / Female	No	8 days	4	Fever, dry cough, anorexia, weight loss (3 kg), acute form	Diffuse micronodular pattern predominating in upper lobes	FVC: 3.00 (106%); FEV_1: 2.60 (109%) FEV_1/FVC%: 87% TLC: 5.98 (129%) RV: 2.55 L (171%) DLCO: 9.12 (118%) DLCO/VA: 1.75 (102%) SaO_2: 98%	M: 50%; L: 40%; N: 10%; CD8: 60%; CD4: 27%; CD4/CD8: 0.4%. Transbronchial biopsy: interstitial lymphocytic infiltrate	PPD+ Candida + Varidase +
2	53 / Male	Ex-smoker (30)	1 month	17	Malaise, myalgia, fever, dry cough, (acute form) chest thickness, dyspnea (acute form)	Left upper lobe infiltrate	FVC: 2.30 (62%): FEV_1: 1.58 (53%); FEV_1/FVC%: 69%; TLC: 5.00 L (84%); RV: 2.48 L (118%); DLCO: 120%; DLCO/VA: 119%; PO_2: 66 mmHg; PCO_2: 36 mmHg	L: 57.5%; M: 17%; N: 25; CD4: 25%; CD8: 57%; CD4/CD8: 0.43	PPD -
3	24 / Male	No	4.5 years	5	Asthenia, fever, cough, dyspnea (acute form)	Ground glass with some centrilobular nodules	FVC: 3.20 (70%); FEV_1: 2.88 (74%); FEV_1/FVC%: 90%; TLC: 4.26 (71%); RV: 1.07 (79%); DLCO: 77%; DLCO/VA: 112%; PO_2: 82 mmHg; PCO_2: 40 mmHg	M: 95%; L: 84%; CD4: 29%; CD8: 40%; CD4/CD8: 0.56	ND
4	39 / Female	Smoker (21)	9 years	15	Dry cough, dyspnea (subacute form)	Bilateral centrilobular nodular pattern	FVC: 3.54 (99%); FEV_1: 2.48 (87%); FEV_1/FVC%: 70%; TLC: 5.03 (107%); RV 1.50 L (97%); DLCO: 5.81 (74%); KCO: 1.24 (71%); SaO_2: 98%	M: 96%; L: 2% N: 2%	PPD - Candida + Trichophyton -
5	39 / Female	Ex-smoker (12)	5 years	6	Fever, dry cough, dyspnea, chest thickness, myalgia (subacute form)	Bilateral centrilobular nodular pattern	FVC: 2.16 (69%); FEV_1: 1.72 (68%); FEV_1/FVC%: 79%; TLC: 3.65 (90%); RV: 1.36 L (103%); DLCO: 5.05 (68%); KCO: 1.62 (84%); SaO_2: 97%	ND	ND

Figure 1. Removel of the mold covering the product by mechanical brush.

previously described method (10). Results were expressed as absorbance units at 450 nm. Values above the mean [standard deviation (SD) 2] of the results obtained in a control population of 30 healthy individuals previously studied in our laboratory were considered positive.

Specific skin tests

Immediate hypersensitivity skin tests were performed by intradermal injection in the forearm of 0.1 ml of solutions (1/100 w/v) of the following extracts: *Penicillium frequentans, Aspergillus fumigatus, Mucor mucedo, Rhizopus nigricans,* and sausage dust extract. An induration with a maximum diameter greater than 10 mm at 15 minutes (immediate reading) was the criterion defining a positive test (17–18).

Delayed hypersensitivity skin tests were performed by intradermal injection in the forearm of 0.1 ml of each of the following antigen extracts solutions: candidin 1/100 w/v (Laboratorios Leti, Barcelona, Spain), tuberculin [PPD Evans RT-23 (Evans Medical España, Madrid, Spain)] 0.1 mL=2 UT (Medeva-Pharma SA, Switzerland), and *Trichophyton mentagrophytes* 100 µg/mL (Laboratorios Leti). Development of a papule with a maximum diameter greater than 5 mm by 48 hours after extract injection was considered positive (19).

Specific inhalation challenge

Only patients 1, 4, and 5, who were studied in Barcelona, underwent SIC. The tests were carried out in the hospital after patients gave their written consent. Patients 1 and 5 underwent inhalation challenge to the dust extract from their source of exposure, whereas patient 4 underwent challenge to *Penicillium frequentans* because the culture of the dust she was exposed to and serum IgG were positive only for this fungus. The SIC was performed as previously described (10, 20). Briefly, using a dosimeter (Mefar MB3, Ele H_2O, Medicali, Brescia, Italy), the patient was requested to inhale 2 ml of the suspected antigen at a dilution of 1/100 (0.01 mg/ml). FVC, FEV_1, DLCO, and the patient's temperature were recorded at 20 minutes after the inhalation and every hour for the following 8 hours thereafter. When the test proved negative, inhalation of a new antigen dilution of 1/10 (0.1 mg/ml) following the same procedure was performed the next day. In all cases, SIC with a placebo solution was carried out one day before testing with the suspected antigen.

The test was considered positive when any of the following post-inhalation responses was elicited: (i) FVC decrease >15% or DLCO decrease >20% as compared with baseline values; (ii) 10–15% FVC decrease plus the at least one of the following criteria related to clinical status and baseline analytical values (21–22): (a) white blood cell increase ≥20%, (b) 3% decrease in O_2 saturation; (c) significant radiologic changes; (d) rise in body temperature >0.5 ºC; or (e) evident clinical symptoms (eg, cough, dyspnea); or (iii) FVC decrease <10%, but with evidence of ≥3 of the previously-mentioned clinical and analytical criteria (10, 20).

Follow-up

All patients were advised to avoid exposure to the antigen. Post diagnosis medical visits that included pulmonary function testing by spirometry and DLCO measurement were conducted at 1, 3, and every 6 months thereafter. Radiologic studies were performed every 6 months until complete recovery was observed.

Results

The clinical characteristics of the patients are shown in table 1. The physical examination was strictly normal in all cases. The mean time of contact with dry sausage dust before the diagnosis was 9.4 years (range, 4–17 years) and the mean time that elapsed between the onset of symptoms and diagnosis was 3.7 years (range, 8 days–9 years). Three cases (patients 1, 2, and 3) developed acute symptoms after exposure to dry sausage dust and patients 4 and 5 developed a subacute form of HP. Three patents were smokers or ex-smokers, and none of the patients had experienced any respiratory disease before initiating contact with sausage dust.

The results of the complementary tests are also shown in table 1. Blood analysis was normal for all patients. Chest X-ray and/or computed tomography revealed a diffuse micronodular centrilobular pattern among four patients (figure 2) and an alveolar infiltrate in the left-upper lobe of patient 2. Pulmonary function

Figure 2. High-resolution chest computed tomography of patient 1. A diffuse micronodular pattern is seen on the inspiratory scan.

tests showed a normal pattern for 2 patients and a mild DLCO decrease among 3 patients. Hypoxemia (PO_2<80 mmHg) was documented for only one patient. Analysis of bronchoalveolar lavage (BAL) specimens was carried out for four patients and lymphocytosis >40% was documented for two of them. Differential T lymphocyte counts performed on three patients disclosed a CD4/CD8 ratio of <0.6.

The immunological test responses and results of dry sausage dust culture from the workplace are shown in table 2. Positive SIC responses were obtained to sausage dust extract in cases 1 and 5, and to *Penicillium frequentans* in case 4; that is, all 3 patients for whom SIC was performed. A decrease of 29%, 15%, and 15% in FVC and 24%, 28%, and 24% in DLCO, as well as an increase in temperature of 1ºC, 0.6ºC, and 0.9ºC were observed in cases 1, 4, and 5, respectively (figure 3). The flu-like symptoms and pulmonary function changes recovered in 48 to 72 hours in all patients without the need for treatment. The positive response of patients 1 and 5 was elicited when a concentration of 1/10 was administered, whereas for patient 4, the response occurred at a concentration of 1/100. No changes were observed with the placebo in any of the 3 patients.

Follow-up data and the results of radiologic studies and pulmonary function tests are shown in table 3. The mean duration of follow-up was 3.6 years (range, 1–12 years). Following the diagnosis, 3 patients avoided exposure to sausage dust, and the clinical, radiologic, spirometric, and DLCO alterations resolved in all of them. Cases 4 and 5 have continued working in the same company, using respiratory protection. An obstructive ventilation pattern was documented on lung function testing at the last follow-up visit in patient 4. Cough and dyspnea have been observed in both patients.

Table 2. Culture of dry sausage dust and immunological response to various antigens [IgG=immunogloblin G; ND=not determined; OD=optical density; SIC=specific inhalation challenge]

Patient number	Sausage dust culture findings	Positive immediate specific skin test	Positive specific IgG antibodies (OD 450nm)	SIC (positive result)
1	*Penicillium spp, Mucor spp, Absidia, Candida parapsilosis*	Dust extract 21 × 17	*Penicillium frequentans* (1990), *Aspergillus fumigatus* (1100)	Dust extract
2	*Mucor spp, Candida parapsilosis, Candida lipolytica*	Dust extract 20 × 20	*Aspergillus fumigatus* (3 arcs), dust extract (1 arc)	ND
3	*Mucor spp, Candida sp*	ND	*Aspergillus fumigatus* (1828), *Penicillium frequentans* (2171), *Mucor mucedo* (2154), *Rhizopus nigricans* (1187)	ND
4	*Penicillium spp, Aspergillus spp*	*Penicillium frequentans* 13 × 13	*Penicillium frequentans* (1100)	*Penicillium frequentans*
5	ND	*Penicillium frequentans* 8 × 3, *Aspergillus fumigatus* 2 × 2	ND	Dust extract

Discussion

The present study describes a little known type of occupational exposure as the cause of HP. Very few cases of this condition have been previously reported, all in the French literature (23–24). In 3 of the 5 patients we describe, the symptoms were acute and exposure was massive, since their work involved cleaning the fungi covering the product by brushing. The fourth and fifth patients, who experienced a subacute disease course, worked as a secretary and supervisor in the respective companies implicated. Although there was environmental exposure in these cases, inhalation of the antigens was not as massive as in the other patients. It is reasonable that high-intensity exposure to the causative antigen would trigger acute forms (25), whereas low-grade, prolonged exposure would be associated with a subacute or chronic presentation. In this line, it is worthy of note that in cases 4 and 5 the latency period between the start of exposure and the development of symptoms was long, whereas in patients 1 and 2, it was a matter of days.

The radiologic presentation in our 5 patients can be considered typical. Lobar alveolar infiltrates are common in the acute form, and diffuse centrilobular nodular infiltrates are seen in all the presentation forms (26). Pulmonary function tests in HP usually show restrictive ventilatory impairment with a reduction in lung volumes and frequent alterations of CO diffusing capacity (7). Although these findings were seen in some of the patients described herein, pulmonary function studies were all normal in 1 case (patient 1), a situation that is not infrequent in HP. In one recent study, undertaken in 86 patients with bird fancier's lung, 10% of the patients showed no ventilatory alterations, and in 15%, the CO diffusing capacity was normal (10). The pulmonary function findings in patient 2 were also interesting: the CO diffusing capacity was normal, and the combination of forced spirometry and lung volume study by plethysmography suggested an obstructive ventilatory disorder. Although a clinical presentation of bronchial obstruction is unusual, the possibility of encountering an obstructive disorder in patients with HP has been estimated at 9–16% (10, 27).

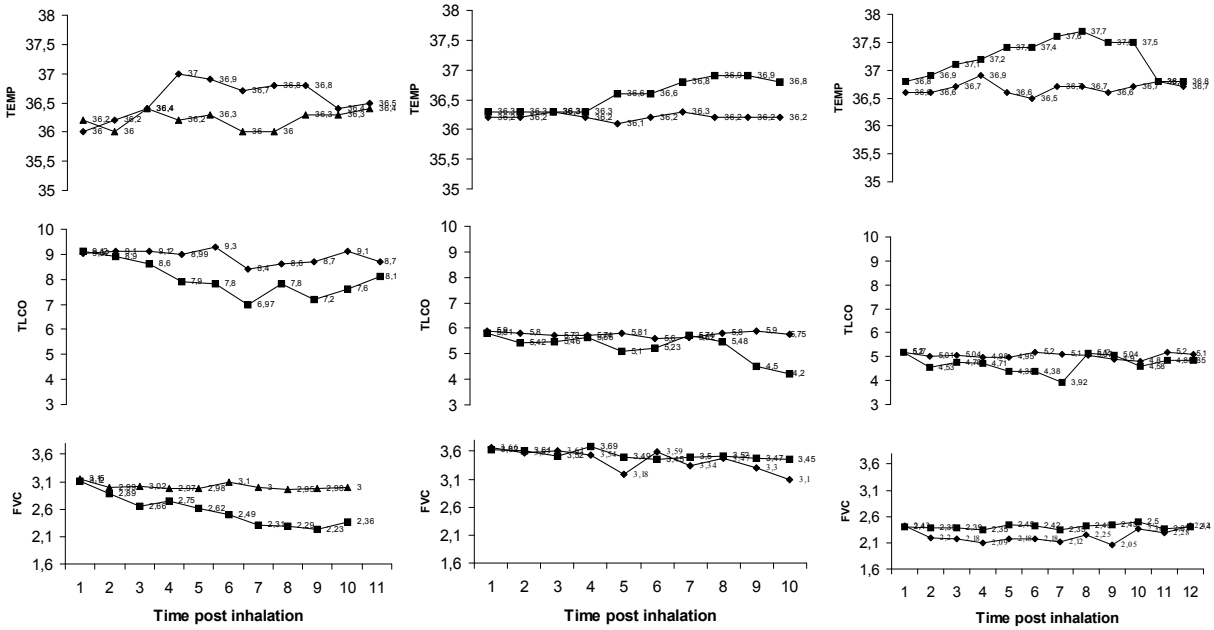

Figure 3. Specific inhalation challenge was positive in the three patients undergoing this test: patients 1 and 5 to dust extract (1/10) and patient 4 to *Penicillium* (1/10) (triangle, placebo; square, antigen) [FVC=forced vital capacity; TLCO=lung function test measuring the diffusing capacityof the lungs for carbon monoxide].

Table 3. Follow-up of patients studied [FVC=forced vital capacity; FEV_1=forced expiratory volume in one second; TLC=total lung capacity; RV=residual volume; DLCO=decreased lung diffusion of carbon monoxide; KCO=carbon monoxide transfer coefficient; PO_2=partial pressure of oxigen; PCO_2 partial pressure of carbon dioxide; ND=not determined]

Patient number	Mean follow-up time (years)	Radiography findings	Symptoms	Exposure post-diagnosis	Respiratory function
1	12	Normal	Asymptomatic	No	FVC: 3.04 (101%); FEV_1: 2.37 (107%); FEV_1%: 77%; TLC: 5.07 L (112%); RV: 1.93 L (108%); DLCO: 7.28 (104%); KCO: 1.44 (86%)
2	1	Normal	Asymptomatic	No	FVC: 2.63 (71%); FEV_1: 2.12 (71%); FEV_1% 82%; PO_2: 78 mmHg; PCO_2: 33 mmHg
3	4	Normal	Asymptomatic	No	Pulmonary function tests not performed; SaO_2: 99%
4	1	No changes	Cough and dyspnea	Yes (protective mask)	FVC: 3.18 (89%); FEV_1: 2.15 (76%); FEV_1%: 68%; TLC: 5.18 (66%); KCO: 1.27 (72%)
5	3	ND	Cough and dyspnea	Yes (protective mask)	ND

Bronchoscopy is commonly used in the diagnosis of HP. BAL fluid typically reveals lymphocytosis, usually (but not always) with a low CD4/CD8 T-cell ratio (28). These findings were documented in 3 of our patients, specifically those with an acute presentation, in whom the percentage of lymphocytes ranged from 17–84%. The CD4/CD8 ratio ranged from 0.4–0.56. Nevertheless, BAL yielded only 2% lymphocytes in patient 4. An absence of lymphocytosis in BAL is relatively uncommon in HP, although it does not exclude the diagnosis; nonetheless, some authors consider that a value of <30% makes the diagnosis of HP uncertain (2). It is important to keep in mind that very few patients demonstrate all the characteristic features of HP at the same time, and that the diagnosis is based on the combination of features in each particular case. In patient 4, the diagnosis was ultimately confirmed by SIC.

Serologic testing is an important component in the diagnostic evaluation of suspected HP. The utility of these tests depends in part on the number of antigens included in the test panel. The screening panel used in our laboratory to investigate a suspected fungal cause includes *Aspergillus fumigatus, Penicillium frequentans, Mucor mucedo,* and *Rhizopus nigricans* (21). In addition, the use of antigen extracts from the exposure source to perform skin prick tests and determination

of specific IgG is a part of the routine practice in our laboratory (10, 20, 29). The value of immediate hypersensitivity skin testing for diagnosing HP has been investigated by several authors. Our group showed that specific skin tests are effective for differentiating between HP patients and asymptomatic bird fanciers (17) and farmers (18), particularly in the case of an immediate reaction. The sensitivity and specificity of the test were 90% and 85%, respectively, using bird serum extract in bird fancier's lung, and 83% and 72%, respectively, using hay extract in farmer's lung. These immediate hypersensitivity reactions have been attributed to the role of an IgG subclass rather than IgE (17). In the patients described in the present report, skin tests were positive in 3 of the 4 patients on whom they could be performed. Two patients had a positive response to the extract derived from their source of exposure, whereas the third patient was positive to *Penicillium frequentans*. Serum determination of specific IgG was positive for *Penicillium frequentans* and *Aspergillus fumigatus* in 3 patients, and in patient 3, positive testing to IgG against *Mucor mucedo* and *Rhizopus nigricans* was documented in addition to *Penicillium frequentans* and *Aspergillus fumigatus*. Although positive serologic test results only confirm prior exposure and sensitization of the host to an antigen, two recent studies have shown that demonstration of positive precipitating antibodies to the offending antigen is one of the major predictive factors of HP (3, 30).

Considering the source of occupational exposure among the patients presented, as well as the serological results, it is evident that HP was caused by fungi, although, based on our findings, we could not establish which of the fungi found was the main agent. It is also possible that more than one fungus is implicated in the genesis of this entity, as has been demonstrated in other types of HP (2). It is likely, however, that *Penicillium frequentans* has an important role, since in one patient, it was the only fungus testing positive in the skin prick test, specific IgG determination, and SIC. In addition to being the reference standard for the diagnosis of HP, (10, 21–22), SIC also enables identification of the causative agent. With the use of this test, it has been established that in certain types of HP, various agents can be the cause in different individuals, and, although it is less common, different agents can be implicated in the same patient (20). In the few available case reports, several *Penicillium* species have been described as etiological agents of this type of HP (23–24), and one study has shown that sensitization to *Penicillium nalgiovense* is frequent among workers exposed to mold during brushing in dry sausage plants (31).

Based on the follow-up findings, this type of HP seems to have a good prognosis if patients avoid exposure to the causative agent. For the three patients who discontinued exposure, the clinical symptoms disappeared, radiologic findings normalized, and pulmonary function tests improved. For the two patients who did not avoid exposure, but only used a protective mask, there was mild bronchial obstruction at one year following the diagnosis and a decrease in diffusion capacity with respect to the tests realized at diagnosis for patient 4. Nonetheless, for this patient, exposure to tobacco smoke could also explain the ventilatory dysfunction. Progression of HP to bronchial obstruction or emphysema is well recognized (10, 32).

In conclusion, a work-related cause of HP is described in this study. Physicians should be aware of this association because in many countries such as ours, elaboration of raw food products derived from hogs is a widespread industry. Although *Penicillium frequentans* seems to be one of the main fungi involved in this cause of HP, a multifactorial origin cannot be ruled out, with other fungi such as *Aspergillus fumigatus, Mucor mucedo,* or *Rhizopus nigricans* being implicated.

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