Hypersensitivity Pneumonitis Caused by Domestic Exposure to Molds

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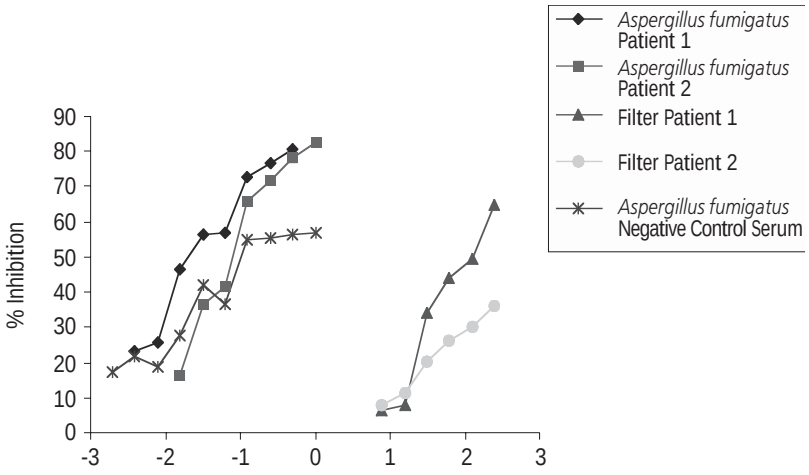
Hypersensitivity pneumonitis (HP) is an allergic lung disease related to repeated inhalation of a variety of etiologic agents, many of which have been reported in certain occupations and hobbies, but also in the home environment [2,3].

A 40-year-old woman, a smoker and homemaker, was seen in the emergency room with a history of progressive dyspnea and cough lasting 10 days. The physical examination revealed bilateral crackles. Blood tests showed leukocytosis and hypoxemia. Chest X-ray revealed interstitial infiltrates. She showed a marked improvement within a few days of hospital admission. After discharge home, she returned to the hospital within 24 hours with a similar clinical picture. High-resolution computed tomography scanning (HRCT) showed bilateral diffuse micronodular infiltrates. Spirometry revealed a forced vital capacity (FVC) 61 % of predicted, a forced expiratory volume in 1 second (FEV_1) 42 % of predicted, and a FEV_1/FVC ratio of 59 %. Lung diffusion capacity (single breath carbon monoxide transfer factor) was 76.2 % of predicted uncorrected but was normal when corrected for alveolar volume. The bronchoalveolar lavage fluid revealed lymphocytosis with a $CD4^+/CD8^+$ ratio of 1.1. A transbronchial lung biopsy sample showed interstitial pneumonitis and non-necrotizing microgranulomas. Precipitating antibodies to *Aspergillus fumigatus* were detected in the patient's serum. She reported that her bathroom was being refurbished because of plumbing problems. A walk-through visit to her house revealed evident water damage and visible mold growing. Cultures of the indoor air obtained by placing agar plates in the house grew mainly *A fumigatus* and *Aspergillus niger*. Environmental sampling was performed using a volumetric air sampler and airborne particles were collected onto polytetrafluoroethylene filters [3].

A 39-year-old man, a nonsmoker and waiter, had suffered from dyspnea, cough, fever, and weight loss for the last month. Physical examination revealed bilateral crackles. Blood test showed leukocytosis and hypoxemia. Chest X-ray revealed interstitial infiltrates. Clinical and radiological signs disappeared within 24 hours. After discharge home, he returned with similar symptoms several hours later. Chest HRCT showed bilateral micronodular infiltrates and patchy ground-glass opacities. Pulmonary function tests and diffusion capacity were normal. Lymphocytosis and a reduced $CD4^+/CD8^+$ ratio (0.2) in the bronchoalveolar lavage fluid were observed. Lung biopsy revealed a diffuse interstitial infiltrate comprised of T-lymphocytes and microgranulomas. Precipitating antibodies to *A fumigatus* were detected. The patient reported that the rental apartment where he lived had water leakage and dampness.

Neither of these subjects kept pets at home or had hobbies or jobs with exposure to suspected antigens. Serologic tests to common respiratory pathogens were negative. Both patients remained symptom free after moving to a different dwelling or remodeling the house. Enzyme-linked immunosorbent assay (ELISA) inhibition studies of immunoglobulin (Ig) G response to *A fumigatus* showed dose-dependent inhibition with the mold extract and with the extract obtained from the air samples collected at home (figure).

A diagnosis of HP is made by a combination of clinical, radiological, physiological, and immunological studies. The results of the investigations carried out in our patients indicated that they had developed HP caused by indoor molds (*Aspergillus* species). Exposure to specific domestic indoor fungal spores is considered an unlikely cause of HP [4] except in Japan where summer-type HP caused by home contamination of *Trichosporon* species is common. In our patients, however, the natural challenge during re-exposure at home, as well as the response to avoidance of exposure strongly suggested that the domestic environment was the cause of HP. Demonstration of precipitating antibodies to *A fumigatus*, as well as the dose-dependent inhibition of the IgG to this mold with an



Dose-dependent enzyme-linked immunosorbent assay and inhibition of immunoglobulin (Ig) G to *Aspergillus fumigatus* in 2 patients with extracts from this mold and from domestic air samples.

air sample extract collected in the patients' homes, supported the diagnosis.

Molds have been described for years as a common cause of occupational HP [2,5] and mold-induced HP is increasingly being reported to be caused by contaminated humidifiers, heating–ventilation systems, and other home reservoirs [3-8].

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Erytema Multiform Due to Hyaluronic Acid (Go-On)

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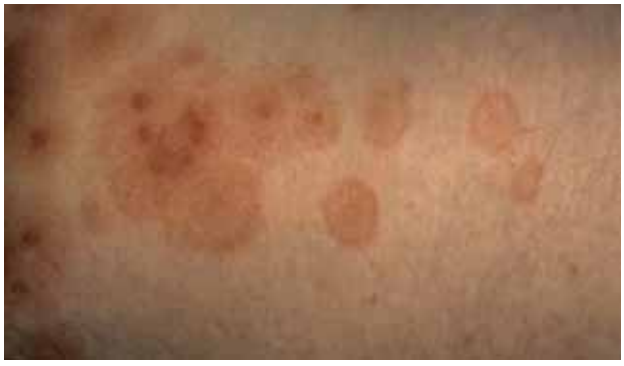
Palabras clave: Alergia a medicamentos. Hipersensibilidad retardada. Eritema exudativo. Hialurónico.

Hyaluronic acid (HA) is a high–molecular-weight polysaccharide found throughout extracellular tissues. Biopolymers made by crossing hyaluronate molecules are currently used for therapeutic purposes. Reported adverse events are unusual, the most frequent ones being transient local reactions at the inoculation site [1].

A 70-year-old woman with a history of osteoarthritis, hypertension, and pyrazolone allergy received a second weekly intra-articular injection of sodium hyaluronate 1%, sodium chloride, sodium monohydrogen phosphate, sodium dihydrogen phosphate (Go-On, Almazara, Valencia, Spain). Within approximately 12 hours, she suffered a general rash with confluent, edematous, pruritic, and papulous erythematous lesions symmetrically distributed on arms, palms, abdomen, gluteus, and thighs with typical target lesions without mucosal involvement or other symptoms. Other infectious or autoimmune diseases, common etiologies of erythema exudative multiform (EEM) were not suspected based on the reported history. The rash resolved in 10 days with antihistamines and oral corticosteroids, without desquamation or residual lesions.

Skin prick and intradermal tests with sodium hyaluronat (10 mg/mL) were negative at immediate and late readings. Twenty-four hours after the intradermal test, she developed itching erythematous papules on arms and the backs of her hands. The following day these became a generalized eruption with features and distribution similar to those observed after the therapeutic dose (figure). Histopathologic study of a lesion after the intradermal test showed a normal epidermis with dermal changes: vasodilatation of small vessels with edema and moderate perivascular and interstitial lymphohistiocytic and eosinophilic infiltrates compatible with dermal-type EEM [2]. The total immunoglobulin (Ig) E level was 147 kU/L by enzyme-linked immunosorbent assay, but results of testing for IgE specific to HA were negative. The blood cell count, serum biochemistry, and chest radiograph were normal. Antinuclear antibody levels were normal and herpes simplex, cytomegalovirus, and *Mycoplasma pneumoniae* serologies were negative.

HA allergic reactions have been described even though preliminary studies suggested this drug had no immunogenic properties [3]. The most common side effects, occurring especially after intra-articular injections, are transient local reactions at the inoculation point [1,4,5] characterized by pain, redness, swelling, and local heat; they appear 24 hours after the dose and may last for weeks. The pathogenic mechanism is unknown, although a foreign body reaction has been hypothesized [4]. Granulomatous reactions have been described after inoculation in the lips and a positive intradermal test and histological findings pointing to a hypersensitivity reaction were reported in 1 case [6].



Detail of the reproduced target lesions after skin tests.

Other investigators have observed lymphocyte transformation, and serum IgG and IgE antibodies against HA [7]. Exceptional systemic anaphylactoid reactions [5], generalized cutaneous vasculitis and localized exfoliative erythema [1] have also been reported.

In this first reported case of EEM after HA injection, the reaction was systemically reproduced in an intradermal test, which represented a minimal systemic challenge (0.3 mg), and EEM was confirmed by histology. As other possible nondrug-related causes of EEM were ruled out, the HA molecule was the main candidate as the etiologic agent. The drug presentation (Go-On) administered was purified from *Streptococcus equi*, but the possibility that proteins derived from the extraction process could be implicated, as has previously been suggested [3,7], cannot be ruled out. Many commercial preparations of this drug are purified from rooster comb, and it has been suggested that minute remains of avian proteins may be responsible for some allergic reactions. Specific antibodies to chicken or HA-coupled chicken proteins have been identified in the absence of antibodies to the isolated drug. Furthermore, HA reactions seem to be more frequent in patients sensitized to avian proteins [4].

This report of EEM caused by HA shows that HA can trigger systemic reactions and severe adverse effects in addition to local ones.

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