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## Occupational Asthma to Dried Tobacco Leaves: A Very Delayed Diagnosis

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**Palabras clave:** Asma ocupacional. Tabaco. Prueba específica de provocación por inhalación.

A 59-year-old woman who had never smoked and had no known history of atopy was seen in our department in 2011 for a possible diagnosis of occupational asthma. The patient had not been employed since 2000 and had worked as a production agent at a cigarette manufacturing facility between 1986 and 2000. Her work primarily consisted of manually filling small bags with dried, milled tobacco leaves. She described the factory as very dusty, particularly during the early years, but no atmospheric measurements were available. The patient reported the appearance of rhinitis, cough, dyspnea, and wheezing, closely related to work periods, some months after starting to work at the factory. An initial check-up in 1991 led to a diagnosis of asthma, but a skin prick test (SPT) to tobacco leaves yielded a wheal of just 2 mm in diameter and was considered doubtful. The patient continued to work until 2000 without any change in her exposure to tobacco leaves; she described progressive worsening of her asthma, despite short-acting  $\beta_2$ -agonist treatment. The patient stopped working at the factory in 2000 and was no longer exposed to respiratory allergens or irritants. Her respiratory symptoms decreased, but did not disappear completely. In 2008, she experienced worsening of dyspnea and received inhaled corticosteroid therapy, with only slight improvement due to poor treatment adherence. In 2011, the patient was referred to our department for a possible diagnosis of occupational asthma. Clinically, she had bronchial hyperresponsiveness, but no wheezing under treatment. SPTs to airborne allergens and tobacco leaves (after humidification) were negative. The blood count was normal and total IgE was 1451 IU/mL. Specific IgE levels were 0.21 kU<sub>A</sub>/L for tobacco leaves and 0.12 kU<sub>A</sub>/L for eggplant. The results were negative for latex, tomato, and potato allergens. The baseline functional respiratory test demonstrated a slight reversible obstructive syndrome (forced expiratory volume in the first second [FEV<sub>1</sub>], 2.11 L; 91% of predicted; FEV<sub>1</sub>/forced vital capacity [FVC], 70%; forced expiratory flow at 50% relative to FVC, 1.97 L/s; 54% of predicted). A methacholine challenge was

positive with a 36% decrease in FEV<sub>1</sub> for a cumulative dose of 160 µg of 1% methacholine (approximately 0.5 mg/mL). An inhalation control test to lactose powder (stepwise handling of lactose powder for 1, 2, 3, 4 and 5 minutes) was strongly negative. In the specific inhalation challenge (SIC) to tobacco, the patient was asked to pour 2 cups of 20 g of tobacco leaf powder according to the same schedule as that used for lactose powder. A strong immediate positive reaction appeared after 10 minutes of cumulative exposure, with a 42% decrease in FEV<sub>1</sub> relative to baseline. No delayed symptoms were observed before discharge from our department 8 hours after the SIC, but the general practitioner reported some wheezing the following morning. To rule out nonspecific irritant reactions, we performed SICs with tobacco leaves in the same conditions in 2 volunteers, using a positive methacholine test as a control. These 2 SICs were strongly negative. A possible diagnosis of occupational asthma to tobacco leaves was established.

Occupational asthma to tobacco dust was first described by Gleich et al [1] in 1980. Since then, many authors have reported cases of occupational asthma as well as alterations in respiratory function in cigarette facilities. In 1988, for instance, Lander et al [2] reported a significant change in daytime peak flow expiratory in tobacco workers compared with controls. More recently, Mustajbegovic et al [3], following the systematic examination of 121 tobacco workers, reported 6 cases of occupational asthma to tobacco dust, interestingly all in women (total women, 97). To date no tobacco allergens have been identified. Although contamination of tobacco by fungi was initially hypothesized, more recent findings suggest that a profilin-like protein, or a villin-like protein [4] belonging to the cytoskeletal of plants, may be involved, as there have been several (but inconsistent) reports of cross-reactivity between several allergens from the Solanaceae family [5-6] as well as latex [7] in individuals with tobacco leaf asthma. Although our case is consistent with previously reported cases, the diagnosis of occupational asthma is questionable considering that the source of occupational exposure was eliminated a long time ago. The absence of atopy or previous asthma, intense occupational exposure to tobacco leaves for more than 10 years, and the patient's clinical history all support this potential diagnosis but may not be sufficient. The strongest diagnostic evidence is the positive SIC to tobacco leaf powder. However, this may also correspond to a simple immediate reaction to a nonspecific irritant. The absence of a reaction to the control test to lactose powder using the same procedure, the severity of the specific response (fall of 42% in FEV<sub>1</sub> relative to baseline), and the existence of a slight delayed reaction at 24 hours all support a diagnosis of occupational asthma rather than a simple immediate irritant reaction to tobacco leaf dust. Nevertheless, specific IgE to tobacco leaves was low, but this might be explained by the long period without exposure. We therefore believe that a diagnosis of occupational asthma to tobacco leaves is the most plausible diagnosis. Consequently, even though end of exposure is often proposed as an explanation for a negative SIC, our observation suggests that positive reactions may still occur many years later. Clinicians should also be aware that functional respiratory reactions could still be severe in such cases.

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#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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