

Scientific Letters

Non-IgE-mediated Asthma After Zinc Exposure[☆]



Asma inmunológica no mediada por IgE tras exposición ocupacional a cinc

To the Editor,

Various metals have been described as causing occupational asthma (OA), mostly chromium, nickel, and cobalt. The mechanism of action by which these metals can produce OA is generally immunological, either IgE-mediated or not.^{1,2} To date, only 2 cases of OA caused by zinc have been described, and in both cases, an IgE-dependent mechanism was involved in the pathogenesis of the disorder.^{3,4}

We describe, for the first time, a worker exposed to zinc who developed OA via a non-IgE-mediated immunological mechanism. Our patient was a 30-year-old man, former smoker of 5 pack-years, whose only clinical history consisted of a diagnosis of bronchial asthma in childhood, which had remitted, and for which he had not required treatment for 15 years. He had been working for 4 years as an industrial mechanic, making metal parts, and was in regular contact with copper, cadmium, zinc, and manganese dust. The patient consulted due to a 5-month history of cough, expectoration, wheezing, and dyspnea. Symptoms appeared some time after start of exposure and improved during the weekends and periods of sick leave. He had had to attend the emergency department on 5 occasions since the onset of symptoms. Chest radiograph was normal. Clinical laboratory tests showed a total IgE of 140 kU/l. Skin tests for airborne allergens were positive for house dust mites, while contact skin tests for metal, including nickel sulfate, potassium dichromate, cadmium, cobalt chloride, and zinc 2.5%, were negative. Forced spirometry showed FVC 6360 ml (112%), FEV₁ 4390 ml (98%), and FEV₁/FVC 69%. A methacholine challenge was positive with a PC₂₀ of 4 mg/ml. A provocation test was performed, according to standard methodology for testing metals,^{1,5} for which concentrations of 0.1 mg/ml, 1 mg/ml, and 10 mg/ml of zinc sulfate were prepared. The 0.1 mg/ml solution was nebulized for a total of 5 min, split into periods of 1, 2, and 2 min. Four hours after exposure, a 23% reduction in FEV₁ from baseline was observed (Fig. 1), along with cough, wheezing, and dyspnea. These symptoms abated after administration of a β_2 agonist. Ten hours after exposure, the patient presented the same symptoms, with a 29% reduction in FEV₁, requiring administration of intravenous corticosteroids in addition to β_2 agonist, and a 12-h stay in the emergency department.

Clinical and lung function data suggested that the patient had zinc-related OA, mediated by a non-IgE-dependent immunological mechanism. This diagnosis was supported by the latency period

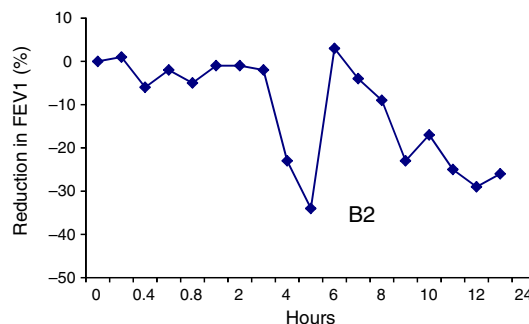


Fig. 1. Result of specific bronchial provocation test with zinc. A late-onset reduction in FEV₁ of 23% from baseline was observed after inhalation of zinc sulfate at a concentration of 0.1 mg/ml for 5 min, requiring administration of a β_2 -agonist (B2).

before the onset of symptoms after initiation of exposure, late onset of symptoms during the working day, the negative specific IgE test and skin tests, and the late reaction after the provocation test. Indeed, 2 recent studies have shown that low molecular weight agents are usually associated with late-onset reactions in which, although the immunological mechanisms are unclear, a non-IgE-dependent immunological mechanism is likely if no early or dual reaction is observed.^{6,7}

Currently, OA is classified as immunological and non-immunological or irritant-induced, the most representative form being reactive airways dysfunction syndrome.⁸ Immunological OA is further subdivided into IgE-mediated and non-IgE-mediated, depending on its physiopathological origin.⁹ Although low molecular weight agents can cause immunological OA by both mechanisms, the IgE-mediated mechanism is generally exceptional, while a non-IgE-mediated mechanism is more common; this is the case with isocyanates and persulfates.¹⁰ However, the situation appears to differ when OA is caused by exposure to metals, in which some authors report that a non-IgE-mediated mechanism is observed in only 30%–40% of patients.¹ In the specific case of zinc, the 2 cases reported to date suggested an IgE-mediated mechanism, as an early response was observed in the specific bronchial provocation test (SBPT), with a reduction in FEV₁ of 23% and 28% 10 and 20 min after inhalation, respectively.^{3,4} In this context, our observation supports the notion that, while there is no evidence of zinc sensitization, it must be considered as a possible causative agent of OA, and this diagnosis must not be ruled out. It is also important to mention that the presence of asthma before the occupational exposure, such as the childhood asthma reported by our patient, does not exclude the OA diagnosis, if the presence of an immunological mechanism (IgE or otherwise) is shown between exposure to the causative agent and the patient's asthma.¹¹ In our case, this mechanism was confirmed by the provocation test.

It is also interesting to note that the patient's asthma presented clinically as severe, reflected by his attending the emergency department on 5 occasions during the 5-month period between the

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onset of asthma and diagnosis. The severe asthmatic reaction presented by the patient during the provocation test, requiring him to remain in the emergency department for 12 h, is also remarkable. Moreover, this reaction occurred after exposure to 0.1 mg/ml of zinc sulfate, a concentration not previously associated with severe asthmatic reactions in provocation tests with metals.^{5,12–14} In the 2 cases of OA caused by zinc reported to date, the reaction occurred when doses of 1 and 10 mg/ml, respectively were used, and no severe reactions were observed.^{3,4} This observation is in line with the evidence of Meca et al.⁷ who suggested that when low molecular weight agents act by non-IgE-mediated mechanisms, the asthma can be more severe.

In conclusion, this case shows that zinc can cause OA by a non-IgE-mediated mechanism, and that this diagnosis must not be excluded when specific IgE and contact skin tests are negative. We also stress the possibility that asthma caused by this agent can be particularly severe, and recommend caution when performing the SBPT.

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Spontaneous Regression of Pulmonary Emphysematous Bulla[☆]



Regresión espontánea de una bulla enfisematosa pulmonar

To the Editor,

Pulmonary bullae are defined as air spaces greater than 1 cm in diameter with no epithelial wall. They can appear in normal pulmonary parenchyma, or more commonly, in the context of generalized emphysema. The natural course of pulmonary bullae is characterized by progressive growth, but it is not uncommon for them to present long periods of stability. In contrast, spontaneous regression is unusual.¹

We report the case of a 55-year-old man, former smoker of 50 pack-years who gave up 16 years previously, who attended our hospital in June 2012 with cough, daily expectoration, and dyspnea MRC grade 1, with no significant exacerbations. Lung function tests showed a moderate obstructive pattern, with a forced vital capacity (FVC) of 4890 cc (106%), forced expiratory volume in 1 second (FEV1) of 2740 cc (74%), FEV1/FVC ratio of 56% and normal carbon monoxide diffusion (DLCO). Computed tomography (CT) revealed severe bilateral mixed centrilobular and paraseptal pulmonary emphysema, primarily involving the upper lobes, containing frank areas of pulmonary parenchymal destruction and a large paraseptal emphysematous bulla in the anterior segment of

the right upper lobe (RUL), longest diameter 9 cm (Fig. 1). Given these findings and persisting symptoms, surgical bullectomy was proposed, which the patient refused.

In November 2015, a follow-up chest CT was performed, which revealed a nodular image with slightly spiculated margins in the paramediastinal region of the RUL, in close contact with the fat of the anterior line of pleural reflection, measuring 18 × 21 mm in the anteroposterior and transversal diameter on the axial plane, and 4 cm in length on the sagittal plane. Extensive areas of parenchymal pulmonary destruction could still be observed, associated with the prevailing emphysema pattern in the upper lobes. Of particular interest was the disappearance of the large bulla in the anterior segment of the RUL (Fig. 1). Given the suspicion of a malignant solitary pulmonary nodule, a positron emission tomography (PET) was requested that showed a moderately hypermetabolic pulmonary lesions in the RUL, consistent with malignancy, so the lesion was surgically removed. Video-assisted thoracoscopic wedge resection was performed, and pathology study found the lesion to be a residual sclerotic pulmonary nodule, consistent with thrombosed cavernous hemangioma, forming organized dystrophic calcification. In the subsequent lung function tests after resolution of the bulla, no improvement was found on spirometry, with FVC 4600 cc (100%), FEV1 2690 cc (74%) and a FEV1/FVC ratio of 58%.

As mentioned above, the natural course of bullae is progressive growth, to the extent that giant bullae can become so large that they even cause adjacent parenchyma to collapse.² Treatment of choice is surgery, which has been shown to improve dyspnea, gas exchange, lung function, and exercise capacity.³ A few cases of spontaneous regression of an emphysematous bulla have been reported, the first of which was probably that published by Douglas

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