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Occupational asthma caused by high- and low-molecular weight agents in an auto body worker



We report the case of a 35-year-old Ecuadorian man who presented at our center with shortness of breath on moderate exertion, wheezing, dry cough, and thoracic oppression. The symptoms worsened at the end of the work day; they had been progressing for 2 years. He had been hospitalized for an asthma exacerbation 1 year earlier and was since treated with on-demand albuterol, which he used 3 times weekly, usually at night. He also presented with rhinoconjunctivitis symptoms in the spring and was asymptomatic during his summer vacation in Ecuador. The patient smoked occasionally and had no prior diagnosis of asthma.

The patient had been working in an auto body shop since moving to Madrid 10 years before the start of symptoms. His work mainly consisted of spray-painting cars, using a paint-gun. He wore respiratory protection equipment, including a mask with a double-filter (3M 7000 series half-mask respirator, Madrid, Spain), but not consistently. When using latex gloves in the workplace, he experienced cutaneous pruritus, contact urticaria, rhinitis, and asthma symptoms within a few minutes. A clear-cut relationship between exposure to latex objects and immediate cutaneous and respiratory symptoms was established.

The product labels of the substances used in the workplace included 2-dimethylaminoethanol; nafta-, methyl-, and butyl-methacrylates; 1,6-diisocyanatohexane, and 3-isocyanatomethyl-3,5,5-trimethylcyclohexyl isocyanate.

Skinprick testing was positive for pollens (grass pollen, *Cupressus arizonica*, *Olea europaea*, *Plantago lanceolata*, *Chenopodium album*), and latex extracts from 2 laboratories (Stallergenes and ALK-Abelló). Total serum immunoglobulin E (IgE) levels were of 195 kU/L. Specific IgE antibodies (ImmunoCAP, ThermoFisher, Uppsala, Sweden) for hexamethylene diisocyanate (HDI), toluene diisocyanate, methylene diphenyl diisocyanate, and Hev b 5 Latex were negative, but positive for natural rubber latex (NRL) (1.94 kU/L) and Hev b 6.01 latex (0.75 kU/L). Specific IgE antibodies to related fruits were elevated: avocado 1.35 kU/L, kiwi 1.25 kU/L, banana 1.16 kU/L, and chestnut 1.11 kU/L, but their ingestion was well tolerated.

Methacholine challenge testing was performed after 1 day off work and was positive, with a provocation concentration that caused a decrease in forced expiratory volume in 1 second (FEV₁) of 20% of 0.75 mg/mL. Specific inhalation challenge (SIC) with HDI was performed after 2 days off work, in a 7-m³ dynamic challenge chamber.¹ A dual asthmatic response was observed, with an immediate decrease in FEV₁ of 15%, associated with symptoms of cough and shortness of breath, and a late decrease in FEV₁ of 20%, 8 hours after exposure. Specific inhalation challenge to NRL was suggested to the patient, who refused further testing once the diagnosis of HDI-induced occupational asthma (OA) was reached. His insurance company also declined further investigations once the work-related disability status was awarded.

At the time of the first visit, the patient was still working, his Asthma Control Test score was 14, with an FEV₁ of 3.21 L (90.4%), and FEV₁/forced vital capacity ratio of 75%, while on treatment with salmeterol/fluticasone propionate 50/500 twice daily. Two months later, he was removed from work, awaiting medical board evaluation for occupational illness. Asthma remained uncontrolled, with an Asthma Control Test score of 11, FEV₁ 2.68 L (77%), FEV₁/forced vital capacity of 72%, and a positive bronchodilation response (FEV₁ rising of 510 mL and 19%). Asthma control remained poor, with persistently positive bronchodilator responses despite treatment with high-dose inhaled corticosteroids and 2 add-on controllers (albuterol and tiotropium bromide), and functional limitations have precluded our patient from returning to work.

To our knowledge, this is the first case of OA caused by 2 agents of different molecular weight categories. A diagnosis of OA to HDI was first confirmed. Although the clinical history was also highly suggestive of OA to latex, we were not able to confirm it with SIC.

However, the identification of specific IgE reactivity to recombinant NRL allergen components strongly supports the diagnosis of NRL-induced asthma. An NRL-specific IgE concentration cutoff of 0.75 kU/L was previously suggested for the diagnosis of NRL-induced asthma, showing a sensitivity and specificity of the ImmunoCAP assay of 84% and 50%, respectively.² This is supported by a recent study showing that high levels of recombinant NRL allergen components have high positive predictive values (PPV) for positive SIC to NRL.³ In this study, the highest PPV (96%) was observed when the sum score of rHev b 5 plus rHev b 6.01 or 6.02 was of 1.46 kU/L or more. Isolated NRL-specific IgE values over 1.12 kU/L and over 0.35 kU/L for rHev b 6.01 had 92% and 89% PPV, respectively. Our subject exceeded both cutoffs, supporting a diagnosis of NRL-induced OA.

A review of the published literature revealed one report of OA caused by 2 low molecular weight agents, isocyanates and epoxy resin, resulting from mixed exposure in different work areas.⁴ One series of 5 subjects working in food production companies who were exposed to various dry aerosol agents suggested that subjects sensitized to 1 proteinaceous agent could be more likely to develop sensitization to a second one.⁵ This was also suggested by a report of subjects sensitized to grass pollens and wheat flour.⁶ These findings could be explained in the context of the “danger hypothesis” (an immune response is triggered by certain agents, depending on their ability to cause cell damage).⁷

Our case underlines the importance of pursuing investigations and objectively diagnosing OA to suspected workplace agents even in the presence of clinical suspicion of OA to multiple agents. The cornerstone of treatment of OA, aside from asthma treatment as per current guidelines, is the avoidance of the causal agent, with significant financial consequences for the patient.⁸ The avoidance of ulterior expositions and symptom progression relies on a complete etiologic diagnosis. Subjects diagnosed with OA also can be relocated to different work areas or change work fields entirely.

Unfortunately, agent avoidance leads to clinical improvement in fewer than half the subjects⁹ and to remission in less than one third of subjects.¹⁰

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Treatment of hypereosinophilic syndrome and eosinophilic dermatitis with reslizumab



Hypereosinophilic syndrome (HES) is a heterogeneous group of disorders defined by peripheral eosinophilia of at least 1,500/μL and eosinophil-related end-organ manifestations. The HES subtypes have been broadly defined as idiopathic, primary (neoplastic), and secondary (reactive) HES,¹ and treatment is guided by clinical variant. Idiopathic HES can be a therapeutic challenge. The first line of treatment is high-dose corticosteroids. Hydroxyurea and interferon-α are used in refractory disease or as steroid-sparing therapy.

Herein we present a patient with hypereosinophilia and steroid-refractory eosinophilic dermatitis, in whom continued treatment with interleukin-5 (IL-5) blockade proved successful in long-term follow-up.

A 55-year-old woman presented for evaluation of longstanding dermatitis of the bilateral shins, ongoing for the past 8 years. The lesions consisted of coalescent ulcerated violaceous plaques. She complained of severe pruritus as well as swelling and a sensation of tenseness in eczematous lesions. The rash was chronic and unremitting, without spontaneous regression at any point. Her clinical course was also punctuated by recurrent admissions for lower extremity “cellulitis.”

Over the years, she had undergone evaluation by allergists, dermatologists, and by an oncologist. Various local and systemic treatment modalities failed except for transient improvement on high doses of oral corticosteroids. At the time of presentation, she was on prednisone 10–20 mg/day, on most days with continued dermatitis symptoms.

She also described a 3-month history of episodic nausea, vomiting, belching, and diarrhea, occurring about once a week. Esophagogastroduodenoscopy had revealed eosinophilic infiltration of the esophagus (50 per high-power field) and she was diagnosed with eosinophilic esophagitis (EoE).

On examination, a violaceous eruption with edema and ulcerations was found to be distributed in a symmetrical fashion and confined largely to bilateral shins.

Laboratory workup revealed moderate peripheral eosinophilia despite ongoing oral steroid therapy (absolute eosinophil count of 1,200 cells/μL). Histologically, skin biopsy demonstrated a psoriasiform/spongiotic dermatitis with a diffuse eosinophilic infiltrate.

Evaluation included immunoglobulin E (IgE) elevated at 802 kU/L, normal tryptase, negative peripheral blood fluorescence in situ hybridization for abnormalities of *PDGFRA*, negative polymerase chain reaction of peripheral blood for c-kit D816V, and normal peripheral blood flow cytometry for lymphocyte subsets.

She presented for further management of steroid-refractory eosinophilic dermatitis. A trial of monthly infusions with reslizumab, a humanized IL-5 blocker, was instituted at a dose of 255 mg (3 mg/kg) per month. Because of the severity of pruritus, the patient initially received reslizumab in combination with prednisone. Response to treatment was assessed by improvement in clinical disease (dermatitis and pruritus), and ability to reduce or discontinue corticosteroid use.

At 2 months, there was progressive improvement with healing of ulcerations (Fig 1A). Prednisone was subsequently tapered and discontinued over 3 months. Follow-up at 7 months confirmed the efficacy of treatment with IL-5 blockade without requirement for supplemental steroids. Dermal plaques and ulcerations had resolved, with residual erythema and hyperpigmentation (Fig 1B). Of note, she also reported complete recovery of chronic gastrointestinal symptoms after IL-5 blockade.

Cutaneous involvement occurs in HES in up to 70% of cases and is manifested by a multitude of alterations, including eosinophilic cellulitis, urticaria, mucosal ulcerations, and pruritus.²

Use of monoclonal antibodies is now emerging as a safe and efficacious therapy for the treatment of HES. IL-5 is the key driver of eosinophil activation, survival, proliferation, and maturation.³ In the setting of systemic eosinophilic inflammation, monoclonal antibodies against IL-5 could be a promising therapeutic strategy.

Garrett et al⁴ first undertook an open-label trial of mepolizumab in 4 patients with HES over 28 weeks. Therapy was well tolerated and lowered peripheral blood eosinophilia, and improved clinical and quality-of-life measurements.