

were performed: (1) basophil activation test⁶ revealed 0% activated basophils in basal conditions, 89.5% in response to anti-IgE and 86.5% in response to PPC extract; (2) the level of serum specific IgE antibodies to PPC (enzyme allergosorbent test [EAST]; Hytec Specific IgE EIA kit, Hycor Biomedical Ltd, Garden Grove, California) was less than 0.35 kU/L but greater than the value obtained with a pool of sera from nonatopic individuals (negative control); and (3) sodium dodecyl sulfate–polyacrylamide gel electrophoresis immunoblotting assay with and without 2-mercaptoethanol revealed 2 IgE-binding bands of approximately 35- and 55-kDa molecular weight in both electrophoretic conditions (Fig 1 and eAppendix).

PPC (*Thaumetopoea pityocampa*) is a Lepidoptera of the Thaumetopoeidae family, commonly found in Europe forests, particularly in Mediterranean areas. PPC has urticating hairs that frequently induce local reactions, such as contact dermatitis, urticaria, or keratitis and, more rarely, systemic symptoms, including anaphylaxis, mostly in the context of occupational exposures.^{7–10} Although an irritant mechanism can be involved in local reactions, IgE-mediated hypersensitivity has been demonstrated, particularly in patients with anaphylaxis, by SPT, enzyme allergosorbent test, and sodium dodecyl sulfate–polyacrylamide gel electrophoresis immunoblotting.⁷ Several allergens with different molecular weights have been reported so far,^{7–9} among which a 15-kDa protein called thaumetopoein (Thau p 1) has been suggested to be one of the most clinically relevant allergens.^{7,8} Although both IgE-binding bands of approximately 35 and 55 kDa detected with the serum of our patient have been already described,⁹ these have not been previously reported to be detected within the same patient serum. Noteworthy, our results indicate that basophil activation test might be also a complementary method that supports the hypersensitivity to PPC in this patient.

Similarly to other patients with ISMs[–] (eg, ISMs[–] associated with Hymenoptera venom anaphylaxis), the implication of PPC as the culprit trigger of anaphylaxis in our patient is supported by the demonstration of specific IgE to PPC together with the temporal association between the exposure to PPC and the development of symptoms and also by the absence of further anaphylactic episode while the patient has been using adequate protection to avoid new contacts to PPC. To the best of our knowledge, this is the first report on the coexistence of systemic mastocytosis and anaphylaxis attributable to PPC. Moreover, this case highlights the utility of the REMA score as a predicting tool for ISMs[–],^{3,4} even if the culprit elicitor of anaphylaxis has not been previously recognized in patients with mastocytosis.

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Supplementary Data

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References

- [1] Gonzalez de Olano D, de la Hoz B, Nunez-Lopez R, et al. Prevalence of allergy and anaphylactic symptoms in 210 adult and pediatric patients with mastocytosis in Spain: a study of the Spanish Network on Mastocytosis (REMA). *Clin Exp Allergy*. 2007;37:1547–1555.
- [2] Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy*. 2008;63:226–232.
- [3] Álvarez-Twose I, González de Olano D, Sánchez-Muñoz L, et al. Clinical, biological and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. *J Allergy Clin Immunol*. 2010;125:1269–1278.
- [4] Álvarez Twose I, González de Olano D, Sánchez-Muñoz L, et al. Validation of the REMA score for predicting mast cell clonality and systemic mastocytosis in patients with systemic mast cell activation symptoms. *Int Arch Allergy Immunol*. 2011;157:275–280.
- [5] Fuentes Aparicio V, de Barrio Fernández M, Rubio Sotés M, et al. Non-occupational allergy caused by the Pine Processionary Caterpillar (*Thaumetopoea pityocampa*). *Allergol Immunopathol*. 2004;32:69–75.
- [6] Maitta G. Basophil activation test: do not lose control. *Eur Ann Allergy Clin Immunol*. 2015;47:36–37.
- [7] Vega JM, Moneo I, Armentia A, et al. Anaphylaxis to a pine caterpillar. *Allergy*. 1997;52:1244–1245.
- [8] Moneo I, Vega JM, Caballero ML, Vega J, Alday E. Isolation and characterization of Tha p1, a major allergen from the pine processionary caterpillar *Thaumetopoea pityocampa*. *Allergy*. 2003;58:34–37.
- [9] Santos-Magadán S, González de Olano D, Bartolomé-Zavala B, Trujillo-Trujillo M, Meléndez-Baltana A, González-Mancebo E. Adverse reactions to the processionary caterpillar: irritant or allergic mechanism? *Contact Dermatitis*. 2009;60:109–110.
- [10] Siracusa A, Folletti I, Gerth van Wijk R, et al. Occupational anaphylaxis—an EAACI Task Force consensus statement. *Allergy*. 2015;70:141–152.

Severe adverse drug reactions induced by hydrochlorothiazide A persistent old problem



Hydrochlorothiazide has been used for years alone or in combination with other antihypertensive drugs in the treatment of hypertension. Although severe adverse reactions with systemic

involvement may occur with its administration, in most cases, these reactions are not initially attributed to this drug.¹

We describe 4 women aged 63 to 76 years with a medical history of hypertension who were admitted to the emergency department with acute onset of fever, chills, dyspnea, and gastrointestinal symptoms of nausea, vomiting, and diarrhea. On

Table 1
Drug Prescribed and Hydrochlorothiazide Dose Intake

Patient No.	Drug	Drug dose, mg	Hydrochlorothiazide dose intake, mg	Dose No.	Onset of reaction, min	Diagnosis at discharge	No. of previous reactions
1	Lisinopril/hydrochlorothiazide	20/12.5	12.5	First	30	Iatrogenic hypotension	1
2	Hydrochlorothiazide	50	25	First	10	Hydrochlorothiazide allergy	1
3	Amiloridine/hydrochlorothiazide	5/50	25	First	60	Pneumonia	2
4	Lisinopril/hydrochlorothiazide	20/12.5	12.5	First	30	Hydrochlorothiazide-induced noncardiogenic pulmonary edema	0

admission, hypotension and hypoxia were observed in all the patients, and endotracheal intubation was necessary in 1 of them. Initial chest radiography revealed diffuse interstitial lung infiltration suggestive of pulmonary edema. Common causes of shock and pulmonary edema were ruled out, and all patients had a fast recovery under supportive treatment. In all cases, the symptoms started within the first hour after taking the first dose of hydrochlorothiazide. This drug had been added to their usual antihypertensive treatment because of their uncontrolled blood pressure (Table 1). Three of the patients had already presented with severe reaction coinciding with the previous intake of a single dose of hydrochlorothiazide. The drug had not been used by patients between reactions. A hydrochlorothiazide adverse reaction was only suspected in 2 patients at discharge (patients 2 and 4). Patient 2 was diagnosed as having hydrochlorothiazide allergy because of her past clinical reaction, and patient 4 was diagnosed as having hydrochlorothiazide-induced noncardiogenic pulmonary edema after the case was discussed in a general clinical session. These 2 patients in whom hydrochlorothiazide was suspected as a cause of the reaction were referred to the allergy service, where severe adverse reactions to hydrochlorothiazide were confirmed. The other 2 patients were diagnosed with severe adverse reaction to hydrochlorothiazide in the allergy service while they were being evaluated for other reasons.

On the basis of the association between the intake of hydrochlorothiazide and the onset of characteristic symptoms,¹ the patients were diagnosed as having hydrochlorothiazide-induced noncardiogenic pulmonary edema. For ethical reasons, we did not consider performing a challenge with hydrochlorothiazide because 3 of the patients had presented with similar symptoms after a previous exposure to the same drug. The use of the Naranjo algorithm² yielded a score of 9 in 1 patient and 10 in the other 3 patients, indicating a definite adverse reaction to hydrochlorothiazide.

Severe adverse reactions related to hydrochlorothiazide are rarely described. In the last 50 years, there have been approximately 60 cases reported of noncardiogenic pulmonary edema induced by hydrochlorothiazide.^{3,4} We suspect that the number of severe reactions could in fact be higher than published because, as had occurred in our patients, the correct etiologic diagnosis is not often initially given.¹

The mechanism that induces these reactions is unknown. Some reports describe a significant percentage of neutrophils in the

bronchoalveolar lavage of patients with hydrochlorothiazide-induced pulmonary injury.^{5,6} Although allergic or other immunologic mechanisms have been proposed,^{3,7} they have not been demonstrated, so an idiosyncratic reaction has been suggested.^{8,9}

Although severe adverse reactions to hydrochlorothiazide are not initially preventable, clinicians should consider this potentially life-threatening adverse drug reaction early and withdraw administration of the drug in such an event. Clinicians must also inform the patients and amend the clinical history to prevent a new administration of the drug. The reporting of these events to epidemiologic surveillance services could contribute to their understanding and to determine their real prevalence.

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References

- [1] Knowles SR, Wong GA, Rahim SA, Binkley K, Phillips EJ, Shear NH. Hydrochlorothiazide-induced non cardiogenic pulmonary edema: an underrecognized yet serious adverse drug reaction. *Pharmacotherapy*. 2005;25:1258–1265.
- [2] Naranjo CA, Busto U, Sellers EM, et al. A method for stimulating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239–245.
- [3] Goetschalckx K, Ceuppens J, Van Mieghem W. Hydrochlorothiazide-associated noncardiogenic pulmonary oedema and shock: a case report and review of the literature. *Acta Cardiol*. 2007;62:215–220.
- [4] Lee PY, Salinas M, Lora P, Reynolds E, Enciso G. Hydrochlorothiazide-induced acute pulmonary edema: a rare adverse reaction. *Rev Chil Enferm Respir*. 2015;31:105–108.
- [5] Darwish OS, Criley J. Hydrochlorothiazide-induced noncardiogenic pulmonary edema: BAL fluid analysis. *Chest*. 2011;139:193–194.
- [6] Biron P, Dessureault J, Napke E. Acute allergic interstitial pneumonitis induced by hydrochlorothiazide. *Can Med Assoc J*. 1991;145:28–34.
- [7] Manso L, Heili S, Fernandez-Nieto M, Sastre B, Sastre J. Basophil activation in two cases of hydrochlorothiazide-induced noncardiogenic pulmonary edema. *Allergy*. 2009;65:135–136.
- [8] Gamboa PM, Achotegui V, Irigoyen J, Pérez-Asenjo J, Merino J, Sanz ML. Hydrochlorothiazide-induced acute non-cardiogenic pulmonary edema. *J Invest Allergol Clin Immunol*. 2005;15:299–301.
- [9] Vereda A, Cárdena B, Quirce S, de las Heras M, Cuesta J, Sastre J. Immunological studies in a case of hydrochlorothiazide-induced pulmonary edema. *J Invest Allergol Clin Immunol*. 2005;15:297–298.

Omalizumab and allergen immunotherapy in a patient with asthma and inhaled corticosteroid–induced adrenal suppression



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Inhaled corticosteroids (ICSs) represent the mainstay of long-term treatment for asthma.¹ With long-term use, even this cornerstone of asthma management has the potential for corticosteroid-induced adverse effects, such as decrease in linear growth and,