A Comparison of the CARATKids and CARAT10 Questionnaires for the Evaluation of Control of Asthma and Allergic Rhinitis in Adolescents

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Palabras clave: CARAT. Asma. Rinitis alérgica.

The Control of Allergic Rhinitis and Asthma Test (CARAT) was introduced to assess control of allergic rhinitis and asthma (ARA) simultaneously. It is the first tool to implement ARIA guidelines in clinical practice [1-5].

CARAT10 was developed for adults [5], and CARATKids was designed for children aged 6 to 12 years [6]. There is no validated questionnaire to assess control of ARA in patients between the ages of 12 to 17 years.

This study compares the psychometric properties of the 2 currently available questionnaires for assessment of control of ARA in a population of adolescents aged 12-17 years.

Approval was obtained from the Ethics Committee of Braga Hospital and from the Ethics Committee of the School of Medicine of the University of Minho, Braga, Portugal.

A nonrandom consecutive sample of participants aged 12-17 years with a diagnosis of ARA was recruited from patients attending the Pediatric Allergology Clinic at Braga Hospital. Patients with other coexisting chronic or respiratory diseases that could influence the results were excluded.

The adolescents were asked to complete the Asthma Control Test (ACT) [7] and the CARAT10 [5] and CARATKids [6] questionnaires. Participants were assessed by their doctor, and the researcher conducted a short interview with the participants to assess the acceptability of the questionnaires.

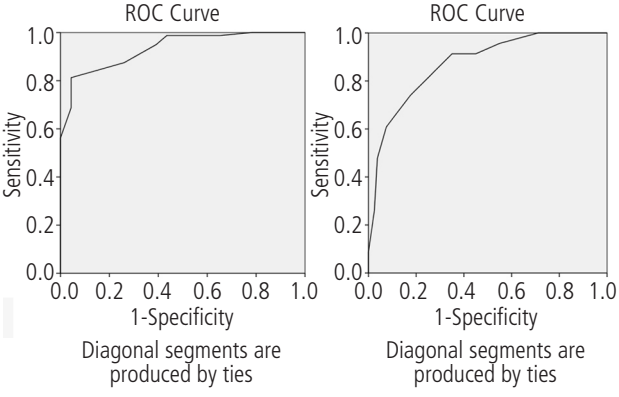
Medical assessment covered 6 parameters: (*1*) the classification of rhinitis as intermittent or persistent and mild or moderate/severe, as described in the ARIA guidelines; (*2*) a 10-cm visual analog scale (VAS, from 1 to 10) for rating disease control in the previous 4 weeks; (*3*) a classification of asthma control, according to the GINA criteria, as controlled, partly controlled, and uncontrolled; (*4*) a VAS for rating disease control in the previous 4 weeks; (*5*) atopy; and (*6*) treatment.

Categorical variables were expressed as absolute and relative frequencies. The Pearson or Spearman and intraclass correlation coefficient (ICC) were used to study the correlation and agreement between the CARAT and ACT scales and the CARAT and the medical evaluation, which included the VAS scores and the ARIA and GINA classifications.

The study included 103 patients (64% males). The most frequent comorbidities were a personal and/or family history of atopy.

Associations between the questionnaires and the medical evaluation were lower than expected (Pearson correlation $r < 0.40$, and ICC < 0.5). The correlation between the CARAT10 scores and VAS scores for the 14-15 and 16-17 year groups met the a priori prediction ($r > 0.40$). No significant differences were found for the associations between questionnaires and the medical evaluation before and after the consultation. Similarly, no association was found with the parents' level of education.

Most participants (62%) said they preferred CARATKids to CARAT10. They found it easier to complete (36 participants),



	CARAT10a	CARATKids
Area under the curve	0.933	0.873
Cut-off	14	6
Sensitivity	0.8775	0.913
Specificity	0.739	0.650

Figure. Receiver operating characteristic curves of the ACT with CARAT and with CARATKids.

faster to complete (14 participants), more appealing (7 participants), more complete, and more user-friendly than the CARAT10.

The results suggest that both CARAT10 and CARATKids can be used to assess the control of asthma in patients aged 12 to 17 years. The CARAT10 questionnaire can be used in patients from age 14 years to evaluate control of ARA.

The correlation coefficients met the a priori predictions for these instruments, suggesting that they can be used to evaluate the control of asthma in this population. The CARAT10a subscore had a higher correlation with the ACT, as expected, because, like the ACT, it only assesses the control of asthma, while CARATKids assesses the control of ARA. Our results favor the use of CARAT10 among patients aged 14 to 17 years [8].

ROC curves were constructed for the CARATKids and CARAT10 scores against the ACT (Figure). For adolescents, new cut-off values for these questionnaires may need to be considered. For CARATKids, we suggest a cut-off score of >6 points for uncontrolled asthma, with a sensitivity of 91% and a specificity of 65%. This is in agreement with previous proposals for this questionnaire [6].

For CARAT10, ROC curves were also analyzed in relation to the medical VAS assessment. A cut-off value of 21 indicated the best balance between sensitivity and specificity.

CARAT10 can be used for the evaluation of ARA in patients aged 14 years and onward. CARATKids and CARAT10 may both be used for the evaluation of asthma in patients aged 12 to 17 years. Further studies are needed to assess whether new cut-off values should be established for patients aged 14 to 17 years.

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Conflicts of Interest

The authors declare that they have no conflicts of interests.

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Successful Treatment of Corticosteroid-Refractory Hypereosinophilia With Reslizumab

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Palabras clave: Hipereosinofilia. Tratamiento. Reslizumab.

Hypereosinophilia, defined as a persistent absolute eosinophil count (AEC) of >1500/µL, has a broad differential diagnosis, with conditions ranging from benign to life-threatening. Causes of hypereosinophilia may be primary or secondary, such as infection, atopy, or drug reactions [1]. Hypereosinophilic syndrome (HES) is hypereosinophilia associated with end-organ damage and includes myeloproliferative, lymphoproliferative, and idiopathic variants. Corticosteroids are the first-line treatment for HES, although the response may be variable [2]. Alternative therapies include hydroxyurea, interferon α, imatinib, and monoclonal antibodies to IL-5, specifically mepolizumab [3,4]. We report on a patient with marked hypereosinophilia and respiratory failure that were refractory to high-dose corticosteroids. The patient was successfully treated with reslizumab, an intravenous IL-5 antagonist.

A 72-year-old Vietnam veteran with a history of relapsing polychondritis, myasthenia gravis, and hypertension and a remote history of seizure disorder presented to the emergency department with a 1-week history of dyspnea. He had been admitted 8 weeks previously with dizziness, left-sided hearing loss, and fatigue; at that time, his white blood cell count (WBC) was slightly elevated at 12.3×10^9/L, with no eosinophils. Following discharge, his long-term prednisone dose for myasthenia gravis (40 mg) was increased to 60 mg because of presumed peripheral vestibulopathy. Mycophenolate was changed to azathioprine 2 weeks prior to the current presentation because of dizziness. The patient saw his rheumatologist on the day of admission for progressive weakness, fatigue, weight loss (10 kg), and dyspnea. He was referred to the emergency department for respiratory distress and possible myasthenic crisis. He had an elevated WBC of 25.6×10^9/L with an AEC of 2.3×10^9/L (9% of differential) (Figure). A chest radiograph showed multifocal opacities, and within hours he developed respiratory failure requiring intubation and mechanical ventilation. Chest CT demonstrated patchy bilateral consolidations, ground-glass opacities, and scattered nodules.

He was treated with a single dose of intravenous methylprednisolone (125 mg) and subsequently maintained on prednisone 80 mg daily. He received multiple antibiotics for presumed infectious pneumonia. Testing for *Histoplasma, Cryptococcus, Legionella*, and *Cytomegalovirus* was negative. WBC trends showed rising eosinophilia, peaking at an AEC of 12.68×10^9/L (40% of WBC) despite high-dose prednisone. Therefore, bronchoscopy was performed and demonstrated 22% eosinophils in the bronchoalveolar lavage fluid. Cultures and cytology data from bronchoscopy were negative. The patient was treated empirically with ivermectin while awaiting the result of testing for *Strongyloides* antibodies (subsequently negative). The antineutrophil cytoplasmic antibody panel, rheumatoid factor, antinuclear antibody, and anti–cyclic citrullinated peptide studies were all negative. Tryptase was normal at 8 ng/mL, and vitamin B12 was slightly elevated at 1074 pg/mL. Cardiac studies were unremarkable, with no elevation in troponin and a normal ejection fraction on the echocardiogram. Preliminary histopathology of a bone marrow biopsy showed mild hypercellularity, with no evidence of lymphoma, leukemia, or increased blasts. There were varying stages of eosinophilic maturation and mild dyspoiesis. Peripheral blood flow cytometry showed no $CD34^+$ myeloblasts, although it did reveal many granulocytes including eosinophils.

Hypereosinophilia persisted despite treatment with high-dose prednisone and discontinuation of phenytoin, azathioprine, and all antibiotics (Figure). After 2 weeks of 80 mg prednisone daily and persistent eosinophilia, the patient received anti-IL5 treatment with reslizumab (3 mg/kg, 300 mg IV). His AEC prior to the reslizumab infusion was 8.73×10^9/L (43%); 6 hours after the infusion it fell to 4.53×10^9/L (25%) and 25 hours later it was 1000 cells/µL (6%) (Figure). He was transferred out of the intensive care unit the following day, and his oxygen requirement decreased from 10 L/min to 2 L/min. His WBC showed no detectable eosinophils 6 days after starting reslizumab, and he was discharged to a rehabilitation facility after 1 week. Following a brief stay in rehabilitation, he returned home with no residual oxygen requirement.

Two weeks after starting reslizumab, final cytogenetic studies showed no clonal abnormalities, with negative results in *FIP1L1-PDGFRA, JAK2*, and *BCR-ABL* testing. However, next-generation targeted sequencing revealed a missense mutation in *SRSF2* and a frameshift mutation in *TET2*. These results supported the diagnosis of chronic eosinophilic

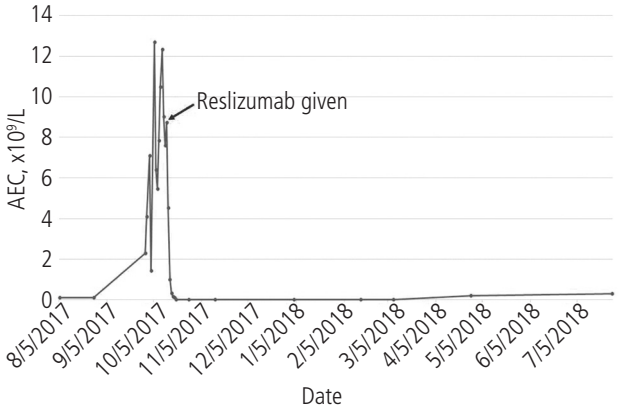

Figure. Absolute eosinophil count (AEC) over time.

leukemia, not otherwise specified (CEL-NOS), as *TET2* mutations have previously been associated with CEL-NOS [5]. However, idiopathic HES (I-HES) was considered as an alternative diagnosis, given the lack of increased blasts and chromosomal abnormality in bone marrow histopathology. Six months after starting reslizumab, the patient's AEC remains suppressed (Figure). Prednisone for treatment of myasthenia gravis was tapered to 10 mg/d.

This case illustrates a clinical dilemma involving the classification of primary hypereosinophilia. Next-generation targeted sequencing identified a mutation in *TET2* that has been seen in CEL-NOS [5]. On the other hand, the lack of blasts in peripheral blood and bone marrow would argue against an underlying neoplasm and favor a classification of I-HES with a mutation. Although inferior to the survival rate for I-HES without a mutation, the survival of patients with I-HES and a mutation is similar to that of patients with CEL-NOS [5].

Reslizumab was selected because it could be administered intravenously and dosed based on body weight. At the time of this patient's treatment, mepolizumab was only available for subcutaneous dosing at a significantly lower dose (100 mg) than that used in clinical trials for HES (700 mg IV) [4]. More recently, higher subcutaneous dosing (300 mg) of mepolizumab was approved for eosinophilic granulomatosis and polyangiitis [6], although there are no data on this dose in HES. There is scant literature regarding the use of reslizumab in HES. In a small study of 4 patients with HES who were treated with reslizumab (1 mg/kg), 2 of the 4 patients presented an initially favorable clinical response. However, the AEC and symptoms rebounded within 8 weeks in these 2 patients, who required 5 additional monthly doses, with transient and diminished subsequent responses [7]. In another study [8], a patient with eosinophilic dermatitis received reslizumab 3 mg/kg monthly, with a significant improvement in symptoms, although the response to AEC was not reported. In the case we present, the improvement in symptoms and suppression of eosinophils lasted at least 9 months without relapse after a single reslizumab infusion at 3 mg/kg, although the exact mechanism of this lasting remission remains unknown. To our knowledge, this is the first report of reslizumab being used to induce a successful and sustained treatment response in symptomatic I-HES with a mutation/CEL-NOS. Additional studies are required to further explore the efficacy of higher-dose reslizumab for treatment of hypereosinophilic disorders.

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Conflicts of Interest

Mark Gladwin is a shareholder, advisor, and director of Globin Solutions, Inc. He has had research funded by Bayer. He has been a consultant for Actelion, Epizyme, and Jenesis.

Andrej Petrov has participated on advisory boards for Genentech and CSL Behring.

The remaining authors declare that they have no conflicts of interest.

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A Possible New Mushroom Allergen in a Case of Occupational Asthma

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Palabras clave: Alergia a champiñón. Asma relacionada con el trabajo.

Basidiomycetes is the largest fungal complex. It comprises mushrooms, puffballs, toadstools, and bracket fungi, which are rarely considered allergenic [1,2]. However, a high prevalence of work-related respiratory morbidity has been reported among mushroom farm workers, including upper airway symptoms, asthma, and a specific form of hypersensitivity pneumonitis known as "mushroom worker's lung" [3]. Most reports come from eastern Asia, where mushrooms are extensively cultivated and consumed [4]. However, the increase in exotic mushroom consumption in Europe has led to an expansion of local production, with a higher risk of work-related diseases in various geographic areas [5].

We report the case of a 32-year-old woman from Jaén (Andalusia, southern Spain) who had been residing in Portugal for 7 years. The patient was referred to our Allergy Department for worsening of chronic nasal symptoms and new, recurrent episodes of dyspnea and wheezing (starting 12 months earlier). She had been working on a mushroom farm for 7 years and was involved in the growing and packing of 6 mushroom species. Respiratory symptoms were exacerbated in the workplace, especially inside the greenhouse where the mushrooms were grown. The patient had a personal history of grass pollen allergic rhinitis since childhood, although this was controlled with immunotherapy.

Spirometry at her first visit revealed normal baseline lung function, with a positive bronchodilation test result. Skin prick tests (SPTs) with extracts of common inhalant allergens (LETI) were positive to house dust mite (*Dermatophagoides farinae*), tree pollen (plane tree, birch, and olive tree), grass pollen mix, weed pollen mix, and pellitory. Testing of *Cladosporium herbarum* and *Aspergillus fumigatus* extracts yielded negative results. SPT with nAlt a 1 extract (Diater) was positive (mean diameter, 4 mm; histamine 10 mg/mL, mean diameter, 5 mm).

Serum specific IgE (ImmunoCAP Specific IgE, Phadia AB) was below the detectable level for *C herbarum, A fumigatus*, and *Penicillium notatum*, but elevated for *Alternaria alternata* (3.69 kU/L). These results were confirmed by ImmunoCAP ISAC (Phadia AB) for rAlt a 1 (17.9 ISU-E).

The diagnosis of occupational asthma was confirmed based on serial FEV_1 and PEF monitoring at work (mean FEV_1, 1.47 L [53%]; mean PEF, 201 L/min) and away from work (mean FEV_1, 3.39 L [123%]; mean PEF, 517 L/min) [6].

The patient sampled 6 mushroom species (Supplementary material) from her workplace (*Flammulina velutipes* [enoki], *Agaricus bisporus, Agaricus brunnescens, Lyophyllum shimeji, Lentinula edodes*, and *Pleurotus ostreatus*). SPTs were performed with the cap, stalk, and gills, eliciting positive results to all parts of *F velutipes, A bisporus, A brunnescens, L shimej*i, and *P ostreatus* (all were negative in 6 nonatopic negative controls). Allergen extracts were produced from the sampled mushrooms (10 mg/mL; Diater) for SPTs, which elicited a positive reaction (4 mm) with both *A bisporus* and *A brunnescens*. Samples were used to perform SDS-PAGE followed by immunoblotting, as described elsewhere [7,8]. A high intensity 12-kDa IgE-binding protein was identified from *L shimeji*; 3 other lower intensity bands with molecular weights of 12, 30, and 45 kDa were identified in *F velutipes* (Figure).

The patient was able to tolerate oral intake of all the mushrooms tested and denied any contact symptoms elicited by these species.

We report a case of occupational asthma induced by IgE-mediated sensitization to mushrooms, supported by the identification of IgE-binding proteins in an immunoblotting assay.

L shimeji, F velutipes, A bisporus, and *A brunnescens* seem to be the relevant allergen sources. Although SPT results were positive to *A bisporus* and *A brunnescens*, we were unable to identify any IgE-binding proteins in vitro. Despite the negative SPT results, immunoblotting revealed a high-intensity 12-kDa IgE-binding band from *L shimeji* and 3 fainter bands of about 12, 30, and 45 kDa from *F velutipes*. The extracts used in the SPTs were specially produced for this patient at a concentration that was validated in 6 negative controls, thus potentially explaining the discrepancies found.

Cross-reactivity with *A alternata* does not explain our findings, since the patient seemed to be sensitized exclusively via Alt a 1, which has a higher molecular weight (15-16 kDa

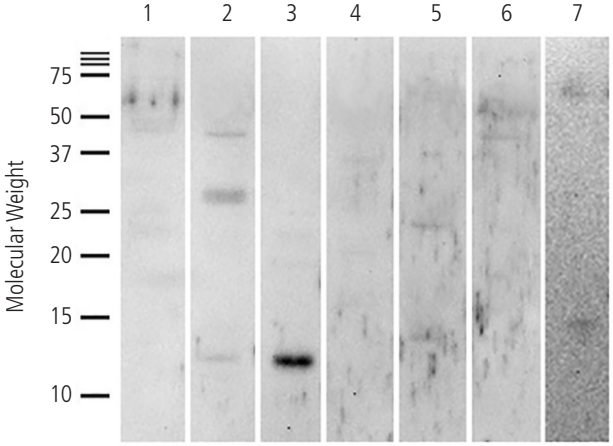

Figure. Immunoblotting results. Lane 1, *Lentinula edodes*. Lane 2, *Flammulina velutipes*. Lane 3, *Lyophylum shimeji*. Lane 4, *Pleurotus ostreatus*. Lane 5, *Agaricus brunnescens*. Lane 6, *Agaricus bisporus*. Lane 7, Alt a 1.

under reducing conditions) than the proteins identified in mushrooms (Figure). Mushrooms are macrofungi with edible bodies that belong to the Basidiomycota phylum, whereas molds such as *A alternata* are classified as Ascomycota. It has been suggested that the cross-reactivity between these 2 classes is minimal [10], consistent with our results.

Allergic reactions to the mushroom species mentioned are extremely rare. *L shimeji* belongs to the species complex *Lyophyllum decastes*, within which taxonomic confusion is frequent, both in the scientific literature and in herbaria [9]. This is probably explained by the micro- and macromorphology of the species included and by the considerable intraspecific plasticity in terms of basidiocarp size and shape, gill attachment to the stem, and coloration [9]. While there are several reports in the literature regarding shimeji-induced respiratory disease in this setting, to our knowledge, none refers specifically to *L shimeji*, but rather to *Tricholoma conglobatum* (also known as *Lyophyllum fumosum*) or *Lyophyllum aggregatum* (Supplementary material).

Two cases of allergic reactions after ingestion of *F velutipes*, with involvement of a 75-kDa IgE-binding protein are shown in the Supplementary material. *A bisporus* has been involved in 2 cases of work-related asthma, with immunoblotting showing 2 intense IgE-binding bands of 15.8 kDa and 13.8/14.5 kDa, as well as several minor bands of 24-39 kDa (see Supplementary material). It has also been reported that 23.6% of mushroom farm workers were sensitized to *A bisporus* (Supplementary material).

In this report, we add *L shimeji, F velutipes*, and, potentially, *A brunnescens* and *A bisporus* as new allergenic sources that could elicit work-related asthma and rhinoconjunctivitis. Furthermore, immunoblotting revealed IgE-reactive proteins in *L shimeji* and *F velutipes* that have not been described in the literature. However, this report is limited by the absence of characterization of specific proteins from fungal spores and parts of the mushroom body. Various allergenic proteins have been described in mushroom spores and basidiocarps and reported to cause IgE-mediated reactions (Supplementary material).

To our knowledge, this is the first report of a case of occupational asthma and rhinoconjunctivitis with suspected involvement of *L shimeji, F velutipes*, and *A brunnescens*, and the third with involvement of *A bisporus*.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Duck Egg Allergy in an Adult Patient Without Allergy to Chicken Egg

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Palabras clave: Alergia alimentaria infrecuente. Huevo de pato. Ovalbumina.

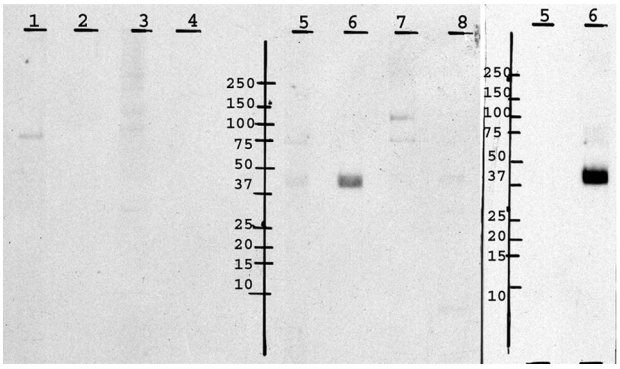

Figure. IgE-immunoblotting of egg extracts. Lane 1, hen egg white + c. negative. Lane 2, hen egg white + patient serum. Lane 3, hen egg yolk + c. negative. Lane 4, hen egg yolk + patient serum. Lane 5, duck egg white + c. negative. Lane 6, duck egg white + patient serum. Lane 7, duck egg yolk + c. negative. Lane 8, duck egg yolk + patient serum. Molecular weight markers are indicated in the center (10, 15, 20, 25, 37, 50, 75, 100, 150, and 250 kDa).

Egg is a basic ingredient in our diet because it provides essential nutrients of high biological value that are easily assimilated by the human body. Duck egg allergy is an uncommon food allergy that has been commonly associated with allergies to other types of egg, usually chicken [1].

We present a case of food allergy after ingestion of duck egg in an adult patient with no previous allergy to chicken egg.

The patient was a 25-year-old woman with a medical history of urticaria to dog dander who experienced abdominal pain, diarrhea, and loss of consciousness within 60 minutes after ingestion of a fried duck egg. She tolerated hen egg with no problems. No symptoms of rhinitis or asthma were reported.

Skin prick tests were performed with commercially available extracts of common inhalant allergens (house dust mites, molds, animal dander, and pollens) and hen egg proteins (egg white, egg yolk, ovalbumin, and ovomucoid) (Leti). Prick-prick testing was performed with fresh homemade uncooked white and yolk from duck egg (*Anas domesticus*) according to the Dreborg and Foucard method [2].

Specific and total IgE were determined using ImmunoCAP (ThermoFisher Scientific) to hen egg proteins (yolk, white, ovalbumin, and ovomucoid) according to the manufacturer's instructions, with negative results (ImmunoCAP <0.35 kU/L)

Fresh homemade extracts of white and yolk of duck egg were prepared in phosphate buffer at 10% (wt/vol) and kept for 90 minutes at 4ºC with magnetic shaking. They were then centrifuged, the resultant supernatant was filtered through a 0.2-µm membrane, and glycerin was added up to 50% before use. Commercial extracts of ALK from hen's egg were also used.

The extracts and the molecular weight markers were analyzed using glycine SDS-PAGE (acrylamide concentration, 16%) under nonreducing conditions. The extract proteins separated by SDS-PAGE were transferred onto nitrocellulose membranes as described by Towbin et al [3]. Immunoblotting of IgE-binding protein was achieved by enhanced chemiluminescence according to the manufacturer's instructions (ECL-Amersham Bioscience). As negative controls, the blots were also incubated with dilution buffer.

Skin prick tests were positive for pollens of grass, olive, *Plantago*, cypress, and dog dander and negative to the remaining inhalant extracts and hen's egg. Prick-prick testing was only positive to duck egg white, with a wheal measuring 22 mm in diameter.

The Figure shows the result of IgE Immunoblotting for the different egg extracts.

Duck egg allergy is an uncommon allergy. Allergy to egg is associated with different species, although 2 cases of specific allergy to duck egg in patients with no hen egg allergy have been reported. In both, a lysozyme and ovalbumin were identified as the responsible allergens [4,5]. In the case presented in this study, the protein detected by immunoblotting has a molecular weight that suggests that ovalbumin could be the allergen responsible for the allergic reaction. The patient's IgE recognized this protein in duck egg but not in hen egg. These findings seem to indicate that the patient's IgE can recognize specific epitopes of duck egg ovalbumin.

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Autoimmune Diseases and Asthma

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Palabras clave: Asma. Enfermedades autoinmunes. Respuesta T1 y T2.

Cellular immune mechanisms comprise 2 types of response, namely the T1 response and the T2 response [1]. Asthma is a heterogeneous disease characterized by chronic inflammation of the airways. Various cells and cytokines, mainly those of the T2 profile [2], intervene in the pathogenesis of asthma, whereas the T1/T17 profile predominates in autoimmune diseases. The immunologic paradigm TI/T2 predicts a negative association between autoimmune (T1) and allergic diseases (T2) [1]. However, some authors propose autoimmunity as the key pathological mechanism of so-called intrinsic asthma, while others consider it an additional phenomenon to allergy in the development of asthma. Co-occurrence of allergy and autoimmunity in the same patient and the presence of autoantibodies in both entities support the hypothesis of autoimmunity in asthma [3-5]. Other factors that corroborate this hypothesis are the role that T-cell dysregulation and mast cells have in both diseases [2-5].

With the aim of analyzing the inflammatory profile of patients with asthma and autoimmune diseases, we describe a series of consecutive asthmatic patients (diagnosed according to GINA criteria [2] at least 1 year before inclusion in the study) with a known concomitant autoimmune disease attended during the year 2016 in a certified multidisciplinary severe asthma unit.

After signing the informed consent document, patients were included in the study and phenotyped as T2-high or T2-low according to the following criteria proposed by Woodruff et al [6] and Kraft [7]: the T2-high phenotype was defined as total IgE >100 IU/mL and peripheral blood eosinophilia >140/mm^3; the phenotype was considered T2-low if only 1 or neither of these 2 criteria was met. Pulmonary function parameters and other inflammatory biomarkers (fractional exhaled nitric oxide [FeNO] and serum periostin) were registered. Asthma control was assessed based on the presence of at least 1 exacerbation during the previous year and on the results of the Asthma Control Test (ACT).

Table. Concomitant Autoimmune Diseases

Autoimmune Disease	No.[a]
Autoimmune thyroiditis	5
Psoriasis	4
Rheumatoid arthritis	3
Systemic lupus erythematosus	2
Sjögren syndrome	2
Autoimmune hepatitis	2
Autoimmune gastritis	1
Raynaud syndrome	1
Antiphospholipid syndrome	1
Chronic immune thrombocytopenia	1
Myasthenia gravis	1
Amyopathic dermatomyositis	1
Guillain-Barré syndrome	1
	25

[a]A patient could have more than one autoimmune disease.

We included 18 asthmatic patients with at least 1 concomitant autoimmune disease (Table). The median (IQR) age was 52.5 (27-78) years, and 83% were female. Nine patients had been smokers (current smokers, 3; ex-smokers, 6; median pack-years, 15) and 5 patients fulfilled the criteria for asthma-COPD overlap syndrome. Eight patients (44%) were atopic and 6 (33%) had aspirin-exacerbated respiratory disease. The associated comorbidities were chronic rhinosinusitis (33%), sleep apnea-hypopnea syndrome (11%), gastroesophageal reflux (33%), bronchiectasis (28%), and psychiatric disorders (28%). The inflammatory biomarker values (expressed as median [minimum-maximum value]) were as follows: blood eosinophils, 200/mm^3 (100-800); blood neutrophils, 3200/mm^3 (2400-6600); total IgE, 94 IU/mL (2-2717); FeNO, 20 ppb (12-50); and serum periostin, 29.91 ng/mL (15-85.99). Spirometric values (expressed as median [minimum-maximum value]) were as follows: forced vital capacity (FVC), 3120 mL (1780-4580); %FVC, 101% (71-126); forced expiratory volume in the first second (FEV_1), 2315 mL (1320-3890); $\%FEV_1$, 92% (64-129); and $\%FEV_1$/FVC, 70% (63-91). Seven patients (39%) had chronic airflow limitation (all 7 had been smokers).

The molecular asthma phenotype was T2-low in 61% of patients (n=11). As for severity, no patients had mild asthma, 33% (n=6) had moderate asthma, and 67% (n=12) had severe asthma. According to the ACT scores, disease was controlled in 55% of patients, partially controlled in 27%, and uncontrolled in 18%. In the previous year, 67% of patients had had at least 1 exacerbation, none of which required admission to the intensive care unit.

When considering patients according to asthma severity, we found that 50% of patients with moderate asthma had a T2-low phenotype and median serum periostin of 16.28 ng/mL. According to the ACT scores, disease was controlled in 75% and partially controlled in 25%. At least 1 exacerbation during the previous year was recorded in 67%. All patients were treated with low or medium doses of inhaled corticosteroids and a long-acting $ß_2$-agonist; 33% were also treated with tiotropium.

Sixty-seven percent of patients with severe asthma had a T2-low phenotype and median serum periostin of 34.06 ng/mL. According to the ACT scores, disease was controlled in 43%, partially controlled in 28%, and uncontrolled in 29%. Severe asthma guidelines (ERS/ATS [8] and SEPAR [9]) consider an ACT score <20 as uncontrolled asthma; therefore, 57% of patients with severe asthma had uncontrolled disease. At least 1 exacerbation during the previous year was recorded in 67%. All patients were treated with high doses of inhaled corticosteroids and long-acting $ß_2$-agonists. Additionally, 58% were treated with tiotropium, 67% with a leukotriene receptor antagonist, 8% with macrolides, 8% with omalizumab, and 25% with mepolizumab.

The results of the series we present show that the T2-low profile predominated and was associated with low levels of serum periostin [10]. However, 44% of patients were atopic, thus contradicting the theory that the T1 profile suppressed the development of atopy. Evidence of T2 inflammation was detected in 39% of patients, and in 33% of those with severe disease, leading us to believe that these patients could benefit from anti-T2 monoclonal antibodies. Nonetheless, asthma was uncontrolled in >50% of patients with severe asthma, and 67% had had at least 1 exacerbation during the previous year. These results support our hypothesis that the association between asthma and autoimmune disease leads to more severe and difficult-to-treat asthma. Given that the pathophysiology has yet to be established, we think it is important to determine the inflammatory profile of these patients when we consider a biological treatment, because they could be good candidates for new therapies, even though they have a concomitant autoimmune disease.

Our study is limited by the fact that the case series is small and heterogeneous. Nonetheless, it tries to highlight the importance of the association between asthma and concomitant autoimmune disease, which, to our knowledge, has not been suitably addressed elsewhere. It would be interesting to perform prospective studies with larger samples to clarify the complex underlying mechanisms of asthma in these patients and, consequently, to identify the best therapeutic targets.

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Conflicts of Interest

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Amoxicillin-Induced Aseptic Meningitis: 2 Case Reports and Appraisal of the Literature

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Palabras clave: Meningitis aséptica. Amoxicilina. Meningitis inducida por fármacos.

Drug-induced aseptic meningitis is an uncommon adverse reaction caused by different agents, particularly nonsteroidal anti-inflammatory drugs, antimicrobials, intravenous immunoglobulin, intrathecal agents, OKT3 monoclonal antibodies, and vaccines. The term aseptic meningitis refers to patients who have clinical and laboratory evidence of meningeal inflammation with negative routine bacterial cultures [1]. Amoxicillin-induced aseptic meningitis is an extremely rare adverse reaction, with only 14 reported cases [2-10]. We report 2 additional cases and review the literature.

Case 1. A 62-year-old man presented to the emergency department with fever and headache 48 hours after initiation of amoxicillin for dental pain. Physical examination, routine laboratory tests, and a computed tomography (CT) scan of the brain were unremarkable. Blood pressure was 160/105 mmHg, and body temperature was 37.7°C. The patient was discharged, although amoxicillin-clavulanic acid and analgesics (if needed) were prescribed. Four days later, the patient returned to the hospital with persistent headache and fever (37.8°C). Physical examination including detailed neurological examination, routine laboratory tests, and a cranial CT scan and magnetic resonance imaging (MRI) were unrevealing. Cerebrospinal fluid (CSF), which was obtained by lumbar puncture, showed lymphocytic pleocytosis (red blood cells, 5/µL; white blood cells [WBC], 44/µL; polymorphonucleocytes, 20%; mononuclear cells, 80%; glucose concentration, 50 mg/dL; and protein concentration, 80 mg/dL). Bacterial and fungal cultures of CSF were negative. Serology testing for herpes simplex virus type 1 and type 2 infection yielded negative results. The patient was diagnosed with acute viral meningitis and discharged from the hospital after 4 days. Two years later, he was seen at the Allergy Unit of our institution because of 2 similar episodes of fever, nausea, vomiting, and headache after taking amoxicillin for a dental procedure. The symptoms observed in both episodes resolved completely

after discontinuation of amoxicillin. In these episodes, a CSF analysis was not performed. Skin tests with penicilloyl-poly-L-lysine, minor determinant mixture, benzylpenicillin, and amoxicillin were performed according to the ENDA/EAACI Drug Allergy Interest Group protocol and yielded negative results. Rechallenge was not performed. The patient was diagnosed with amoxicillin-induced aseptic meningitis.

Case 2. A 58-year-old man was admitted to the emergency department with a 7-day history of fever (38°C) and headache that coincided with oral amoxicillin-clavulanic acid for whitlow on his toe. His blood pressure was 163/98 mmHg, and his body temperature was 37.6°C. The results of the physical and neurologic examination were normal, and routine laboratory tests, electrocardiogram, and cranial CT scan were unrevealing. Peripheral blood cultures were negative. CSF showed lymphocytic pleocytosis (red blood cells, 70/µL; WBC, 130/µL [100% lymphocytes]; glucose concentration, 48 mg/dL; protein concentration, 86 mg/dL; and adenosine deaminase activity, 9 IU/L). Bacterial and fungal cultures of CSF were negative. The patient reported 2 previous episodes of similar clinical symptoms during the previous year after taking amoxicillin-clavulanic acid for dental procedures, with lymphocytic pleocytosis documented in the CSF examination in both episodes. He was diagnosed with recurrent lymphocytic meningitis, probably due to the antibiotic agent. In one of these episodes, ampicillin, cefotaxime, and ceftibuten were administered for several days with good tolerance. The patient attended our Allergy Unit to confirm the diagnosis of amoxicillin-induced septic meningitis. Skin tests to penicilloyl-poly-L-lysine, minor determinant mixture, benzylpenicillin, and amoxicillin were performed according to the ENDA/EAACI Drug Allergy Interest Group protocol and yielded negative results for specific IgE to amoxicillin. Rechallenge was not performed. The patient was diagnosed with amoxicillin-clavulanic acid–induced aseptic meningitis.

Drug-induced aseptic meningitis secondary to amoxicillin is reported exceptionally and is not registered as a potential adverse effect on the package insert. The diagnosis is usually based on a temporal relationship with drug intake, CSF pleocytosis, negative microbiological tests, and rapid complete resolution after discontinuation. However, clinical signs and CSF findings may vary considerably. The exact pathogenesis is still unknown, but a delayed-type hypersensitivity reaction has been proposed. In the 2 cases reported here, an IgE-mediated mechanism could not be demonstrated because of the negative skin and serological test results. The literature contains no information on the underlying mechanism of this adverse reaction. Hypersensitivity syndrome related to amoxicillin is relatively frequent, although it typically includes gastrointestinal and dermatologic symptoms.

A review of the literature revealed 14 cases of amoxicillin-induced aseptic meningitis. The salient characteristics of these patients and of the 2 patients we report are summarized in the Supplementary Table. Ten of the 16 cases occurred in men, with a mean age of 64.4 years. Most patients reported 2 or 3 episodes of amoxicillin-induced aseptic meningitis, with symptoms of meningoencephalitis (cognitive disturbance, confusion, disorientation, and related neurological signs) in only 4 cases. Patients typically presented with fever and headache, which developed a few hours to 7 days after exposure to amoxicillin and mostly resolved within 2-4 days after discontinuation. Photophobia, nuchal rigidity, lethargy, myalgia, and general malaise were also present in some of the cases reported. Blood tests and brain CT or MRI scans were not diagnostic. Typical CSF findings consist of pleocytosis (lymphocytic or neutrophilic), which in some cases is accompanied by elevated protein and usually normal glucose levels. Normal CSF glucose levels may help to differentiate drug-induced aseptic meningitis from bacterial meningitis, in which glucose levels are usually low. CSF cultures are consistently negative. In some of the cases reported, treatment with other antimicrobials, including cefuroxime, ceftriaxone, cefotaxime, ampicillin, and ceftibuten was well tolerated.

Suggestive symptoms, a history of treatment with amoxicillin before appearance of clinical manifestations, a documented positive rechallenge result, CSF pleocytosis, and prompt resolution of symptoms, usually a few days after discontinuation of the drug, should alert clinicians to a diagnosis of amoxicillin-induced aseptic meningitis.

In the cases we report, allergy studies including skin tests and specific IgE levels to ß-lactam drugs were negative. However, allergy studies were not performed in previously published cases. Information about cross-reactivity with other penicillins or ß-lactams is lacking, although it seems reasonable to recommend avoidance of these agents in suspected cases of amoxicillin-induced aseptic meningitis. Clinicians should be aware that recognition and early diagnosis of amoxicillin-induced aseptic meningitis is very relevant in daily practice, since this condition is easily managed with discontinuation, thus obviating other, more aggressive diagnostic procedures and prolonged treatments, as well as the possibility of recurrent episodes related to the use of amoxicillin.

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