

Table 1
Immunology Laboratory Test Results

Test	Results and interpretation	Age-based reference range
IgG, mg/dL	60–<270	400–1200
IgA, mg/dL	<4	30–215
IgM, mg/dL	178–225	30–122
Absolute neutrophils $\times 4$, / μ L	220–2300	1500–7800
Total lymphocyte count, / μ L	5388	4000–10,500
CD3, / μ L	4795	2030–5150
CD4, / μ L	2728	1220–3550
CD8, / μ L	2133	530–1590
CD19, / μ L	0	830–1880
CD4/CD8 ratio	1.28	1.40–3.90
NK cells, / μ L	111	
BTK flow cytometry	BTK protein is normally present in B cells and monocytes	Normal
CD40L flow cytometry	CD40L (cd154) expression on activated CD4 cells is normal and binding of CD40L to the soluble receptor; CD40 μ immunoglobulin is also normal	Normal
BTK mutation analysis	See the text	

Abbreviations: BTK, Bruton's tyrosine kinase; CD40L, CD40 ligand; IgG, immunoglobulin G; NK, natural killer.

Our hypothesis is that this novel mutation with resulting frameshift and premature stop codon seems to impair BTK activity (rather than completely blocking BTK expression) resulting in a leakage of some peripheral B cells, which may not be detected on routine flow cytometry.⁶ Some of these leaky B cells were mature enough to cause higher IgM levels with the possibility of defective class switch recombination, leading to very low IgG and IgA levels.

In conclusion, this phenotypical picture of high IgM levels in a patient with XLA might be related to the novel BTK mutation. To the best of our knowledge, this is the first case of XLA associated with cardiomyopathy.

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Analysis of the allergen profile of patients sensitized to shrimp based on ImmunoCAP immune solid-phase allergen chip results



Tropomyosin is the main allergen found in crustaceans, with high interspecies homology; it is also found in house dust mites (HDMs). In ImmunoCAP immune solid-phase allergen chip (ISAC), there are only 3 shrimp allergen components, which are as follows: Pen m 1, Pen m 2, and Pen m 4. The possibilities of establishing the level of immunoglobulin E (IgE) specific to other shrimp allergen components is still only possible by using experimental methods. The aim of this study was to analyze the sensitization profile of patients with allergy to shrimps.

A total of 290 patients (176 women, 114 men) with symptoms of persistent allergic rhinitis were selected for screening. Patients with serious, chronic diseases and on medication that could influence the results of this study were excluded. Interviews and physical examinations were conducted. All patients were subjected to skin prick tests (SPTs) with HDM, *Dermatophagoides pteronyssinus* and *D farinae* (Allergopharma, Reinbek, Germany), and prick by prick tests with frozen giant

tiger prawn and the concentration of HDM and shrimp specific IgE (sIgE) (Singleplex, quantitative ImmunoCAP, extracts and single components; reference value of >0.35 kU/L). A total of 71 patients had elevated levels of shrimp sIgE, and 50 patients had shrimp sIgE greater than or equal to 0.51 kU/L; in these cases, ImmunoCAP ISAC (semiquantitative, fixed multiplex platform with 112 allergen components) was performed (reference value of >0.3 ISU-E).

Notably, 30 patients with negative allergy history were included in the control group. Statistical analysis was done by performing Mann–Whitney and Kruskal–Wallis tests with Dunn's test post hoc analysis, using the R 3.3.1 and Microsoft Excel 365 (Microsoft, Redmond, Washington). Approval was obtained from the local bioethical committee (no. 147/2015); patients gave informed, written consent to participate in the study.

In the group of 50 patients with shrimp sIgE 0.52 to 100 kU/L, 41 had an elevated concentration of sIgE *D pteronyssinus* and 37 had an elevated sIgE *D farinae* concentration. A total of 42 patients received positive SPT results for shrimp, 45 received for *D pteronyssinus*, and 44 received for *D farinae*. General characteristics of the group and results of the immunoassay are presented in Table 1.

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Table 1
General Characteristic of Population and Immunoassay Results

Number of patients in each population group	General population = 290	Population with IgE shrimp > 0.51 kU/L = 50	Control group = 30	
Age, y	18-75 ± 15.49, av. 40.6	18-73 ± 13.33, av. 38.8	18-50 ± 11.39, av. 37.4	
Sex	175 women and 115 men	25 women and 25 men	15 women and 15 men	
Elevated level of specific IgE (≥0.35 kU/L) ImmunoCAP				
<i>Dermatophagoides pteronyssinus</i>	156 patients, 0-100 kU/L (av. 8.2)	41; 0-100 kU/L (av. 26.3)	IgE < 0.35 kU/L	
<i>Dermatophagoides farinae</i>	157 patients, 0-100 kU/L (av. 11.8)	37; 0-100 kU/L (av. 26.0)	IgE < 0.35 kU/L	
Shrimp	71 patients, 0.35-100 kU/L (av. 1.57)	50; 0.52-100 kU/L (av. 9.42 kU/L)	IgE < 0.35 kU/L	
Results of immunoassay in the group of 50 patients who underwent ImmunoCAP ISAC				
ImmunoCAP Singleplex, allergen extract based	Number of patients with IgE > 0.35 kU/L	ImmunoCAP ISAC	Number of patients with IgE > 0.3 ISU-E/% of patients sensitized in ImmunoCAP	Total number of sensitized patients detected in ImmunoCAP ISAC, %
IgE shrimp	50	IgE Pen m 1 IgE Pen m 2 IgE Pen m 4	14 (28%) 8 (16%) 5 (10%)	22/44%
IgE <i>Dermatophagoides pteronyssinus</i>	41	IgE Der p 1 IgE Der p 2 IgE Der p 10	25 (61%) 32 (78%) 17 (41.5%)	40/97.6%
IgE <i>Dermatophagoides farinae</i>	37	IgE Der f 1 IgE Der f 2	25 (67.6%) 32 (86.5%)	34/91.9%

Abbreviations: av, average; IgE, immunoglobulin E; ISAC, immune solid-phase allergen chip.

NOTE: There are no significant differences in sex between the study and control groups ($P < .05$).

ImmunoCAP ISAC was able to detect elevated levels of at least one shrimp allergen component in 22 of 50 patients sensitized to shrimp (14: Pen m 1; 8: Pen m 2; 5: Pen m 4). ImmunoCAP ISAC had better detecting ability for HDM sensitization.

Interviews revealed that 28 patients had symptoms related to sensitization to shrimp and 16 experienced anaphylaxis (definition of the World Allergy Organization).¹ In symptomatic patients, ImmunoCAP ISAC detected 13 patients with elevated levels of at least 1 shrimp allergen component (8: Pen m 1; 3: Pen m 2; 4: Pen m 4), giving the detectability rate of 48.2%. In patients with anaphylaxis, 9 (56%) had elevated levels of at least 1 shrimp allergen component (6: Pen m 1; 1: Pen m 1 and Pen m 4; 1: Pen m 2; 1: Pen m 4) and 7 were suspected of being sensitized to allergen components unavailable in ImmunoCAP ISAC, for example hemocyanin. Shrimp sIgE greater than 1.04 kUA/L had 100% sensitivity in reported anaphylaxis and 89% sensitivity in all symptomatic patients, with 58% specificity.

In the control group, SPT results were negative and the level of sIgE was not elevated. In the research group, there was a high prevalence of cosensitization to HDMs. Notably, 82% of patients were sensitized to shrimp and *D pteronyssinus* and 74% to *D farinae*. Tropomyosin (Der p 10) is considered to be a minor HDM allergen that triggers allergy in as few as 5.6% of patients. Boquete et al² indicated that 71% of patients with allergy to HDMs also had IgE for shrimp, and 55% of them had increased level of IgE specific for shrimp tropomyosin. Canadian studies found that 90.5% of patients with allergy to shrimp had positive SPT results for HDMs.³

In ImmunoCAP ISAC, the detectability rate of HDM sensitization was high (*D pteronyssinus*: 97.6%; *D farinae*: 91.9%). New multiplex platforms (FABER and ALEX) include more HDM allergen components, but in most cases, the evaluation of IgE specific to mite allergen groups 1 and 2, as available in ImmunoCAP ISAC, should be sufficient. Yadzir et al⁴ compared SPT results with those of ImmunoCAP ISAC. In 40 patients with positive SPT results to HDM allergen extract, the elevated level of sIgE to at least 1 of the HDM allergen components was found in 34 patients (85%).⁴ Panzner et al⁵ analyzed the results of the ImmunoCAP ISAC involving 1766 patients and found an elevated level of IgE specific for at least

1 tested allergen component in 1255 cases, with 2.2% sensitized to tropomyosin.

Compared with shrimp sIgE, ImmunoCAP ISAC had only 44% detectability rate. This indirectly proves that there are other shrimp allergen components responsible for sensitization. Tuano et al⁶ analyzed 12 patients with shrimp allergy and 18 patients with tolerance to shrimp. In their series, in the patients who were non-HDM sensitized, a shrimp sIgE level of greater than 3.55 kUA/L indicated 100% sensitivity and Der p 10 sIgE of greater than 3.98 kUA/L indicated 100% specificity for shrimp allergy.⁶ In our study, shrimp sIgE level of greater than 1.04 kUA/L indicated 100% sensitivity in shrimp-related anaphylaxis and 89% specificity and 58% specificity in all symptomatic patients. Elevated levels of IgE, Der p 10 sIgE of greater than 3.5 ISU-E/L, indicated 72.7% specificity for shrimp allergy. In both studies, the size of population was limited, and further research is necessary to establish the sensitivity and specificity of immunologic assay in shrimp sensitization.

In 2012, Asero et al⁷ found that only 41% of patients had an elevated level of IgE against tropomyosin, whereas in 52% of cases, the serum indicated reactions with a protein of molecular weight greater than 60 kDa. It was later identified as hemocyanin and considered 1 of the allergens responsible for crossreactivity with HDMs, with higher IgE sensitization rate among shellfish-processing workers.⁸ In case of food-dependent, exercise-induced anaphylaxis, Tonomura et al⁹ described a 40-kDa shrimp allergen (fructose 1,6-bisphosphate aldolase) and Kimura et al¹⁰ identified a 43-kDa shrimp protein.

ImmunoCAP ISAC has a high detectability rate in patients sensitized to HDMs, but in the case of shrimp sensitization, it allowed to diagnose only 44% of patients, probably owing to a lack of clinically important shrimp allergens, such as hemocyanin, in this multiplex platform.

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COVID-19, severe asthma, and biologics



Coronavirus disease 2019 (COVID-19) is an acute respiratory syndrome that emerged in the city of Wuhan and rapidly spread throughout the world causing a global pandemic.¹ The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified as its causal agent.¹ Factors such as older age or presence of comorbidities are frequently identified as variables with a negative effect on patients' prognosis.² If we focus on the preexistent respiratory conditions, a higher risk of developing a severe infection has been reported in patients with chronic obstructive pulmonary disease.³ However, there is controversial evidence regarding the prevalence of asthma in patients diagnosed as having COVID-19 (eTable 1) or the effect of asthma and its treatment on the clinical evolution of COVID-19.

We report 2 patients with severe asthma on treatment with benralizumab, an antieosinophil monoclonal antibody, who have been affected by COVID-19.

A 56-year-old woman who has been followed at our severe asthma unit for late-onset, severe, eosinophilic asthma with bronchiectasis without criteria for asthma–chronic obstructive lung disease overlap syndrome. Her asthma was controlled with high-dose ICS, long-acting β_2 -agonist, montelukast, ipratropium, and benralizumab. On March 8, 2020, she went to the emergency department owing to a 24-hour episode of fever, arthralgia, myalgia, dyspnea, and brownish expectoration. On physical examination, no wheezing was found. Complementary tests revealed a unilobar opacity in the right lung, a slightly increased C-reactive Protein and lactate dehydrogenase (Table 1), and a positive polymerase chain reaction result for SARS-CoV-2. A dose of levofloxacin 500 mg for 14 days and systemic corticosteroids (1 mg/kg) were administered owing to the brownish expectoration and history of bronchiectasis (lopinavir/ritonavir and hydroxychloroquine were not started according to the hospital's protocol, at that moment, because the patient did not have hypoxemia). The patient was

discharged on the fourth day of admission owing to clinical stability, which was maintained without oral corticosteroids. After 1 week, the patient was asymptomatic. Notably, 4 of her relatives also received a diagnosis of COVID-19.

The other case is a 62-year-old man with severe eosinophilic asthma on treatment with benralizumab since July 2018. Previously, he had received treatment with omalizumab and mepolizumab, which were both discontinued because of poor response. As comorbidities, he had moderate obstructive sleep apnoea, chronic rhinosinusitis with nasal polyps, bronchiectasis, and obesity (body mass index of 33 kg/m²). He did not fulfill the criteria of asthma–COPD overlap syndrome. On March 25, 2020, he experienced cough, fever, and darker and thicker expectoration than his usual, therefore he self-medicated with a dose of levofloxacin 500 mg for 3 days. Owing to a lack of improvement in symptoms, he was evaluated at a primary care where a chest X-ray examination was performed, which revealed peripheral and bilateral opacities, more evident in mid/lower lung areas, compatible with COVID-19 pneumonia (Fig 1); thus, he was referred to the emergency department. One of his relatives, who lived with him, had the same symptoms. Complementary test results revealed lymphopenia with increased levels of lactate dehydrogenase, C-reactive protein, D-dimers, and fibrinogen (Table 1) and a baseline partial pressure of oxygen of 59 mm Hg. The diagnosis of SARS-CoV-2 pneumonia was assumed considering the epidemic context, symptoms, radiologic and laboratory findings, and following the recommendations of the Spanish authorities at that moment. The patient requested his voluntary discharge. He was placed at home isolation and was monitored by his primary care physician. He was treated with a dose of azithromycin 500 mg (3 days), hydroxychloroquine 200 mg twice a day (5 days), and amoxicillin-clavulanic acid 875/125 mg (7 days). After 1 week, he had no symptoms, and he completed 14 days more of isolation.

Owing to the respiratory nature of COVID-19, it could have been reasonable to expect that patients with asthma, especially severe ones, could have a worse prognosis. However, both patients had a good response to the infection, which could provide some support to the recommendations made concerning COVID-19 and asthma that encourage the continuation of maintenance therapies in patients with asthma. For example, the recent 2020 Global Initiative for Asthma report recommends advising

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