ORIGINAL ARTICLE

# Molecular Profile of Sensitization to *Dermatophagoides pteronyssinus* Dust Mite in Portugal

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## Abstract

*Objective:* To analyze component-resolved diagnosis of sensitization to *Dermatophagoides pteronyssinus* (Der p) in patients with respiratory allergy and the association between diagnostic findings and clinical severity in different geographical areas.
*Methods:* The study population comprised 217 patients (mean age, 25.85 [12.7] years; 51.16% female) selected from 13 centers in Portugal (5 from the North, n=65). All had allergic rhinitis with or without asthma and positive skin prick test results to at least 1 dust mite. Specific IgE (sIgE) to Der p, *Dermatophagoides farinae, Lepidoglyphus destructor*, Der p 1, Der p 2, Der p 10, and Der p 23 was determined using ImmunoCAP. The Mann-Whitney test was applied for the following comparisons: rhinitis vs rhinitis and asthma; mild vs moderate-to-severe rhinitis; North vs South.
*Results:* The prevalence of sensitization was 98.2% for Der p, and 72.4%, 89.4%, 9.7%, and 77% for Der p 1, Der p 2, Der p 10, and Der p 23, respectively. The corresponding median sIgE levels were 8.56, 17.7, 0.01, and 3.95 $kU_A/L$. sIgE to all allergens was higher in patients with moderate-to-severe rhinitis and rhinitis with asthma (nonsignficant). Concentrations of sIgE to Der p 2 were significantly higher in the South than in the North (*P*=.0496).
*Conclusions:* The most common sensitization in Portugal was to Der p. The highest prevalence and median sIgE level were observed for Der p 2. All sIgE values for molecular components were higher in more symptomatic patients (nonsignificant). Concentrations of sIgE to Der p 2 were higher in the South, probably because of the warmer temperature and/or the larger sample size.

Key words: Allergy. Asthma. Component Resolved Diagnosis. *Dermatophagoides pteronyssinus*. Dust Mites. Rhinitis. Specific IgE.

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## Resumen

*Objetivo*: Analizar el diagnóstico por componentes para *Dermatophagoides pteronyssinus* (Der p) en pacientes con alergia respiratoria y su relación con la gravedad clínica en diferentes áreas geográficas.
*Métodos:* Se incluyeron 217 pacientes (edad media 25,85±12,7 años; 51,16% mujeres), seleccionados de 13 centros en Portugal (5 del Norte, n = 65). Todos tenían rinitis alérgica, con o sin asma, y tenían pruebas positivas en *prick* a al menos un ácaro del polvo. La IgE específica (sIgE) para Der p, *Dermatophagoides farinae, Lepidoglyphus destructor*, Der p 1, Der p 2, Der p 10 y Der p 23 se determinaron por ImmunoCAP. El análisis estadístico (prueba U de Mann Whitney) comparó pacientes con rinitis frente a rinitis y asma; rinitis leve frente a moderada-grave; Norte frente a Sur.
*Resultados:* La prevalencia de sensibilización fue del 98,2% para Der p, y del 72,4%, 89,4%, 9,7% y 77% para Der p 1, Der p 2, Der p 10 y Der p 23, respectivamente. Las medianas de sIgE fueron de 8,56, 17,7, 0,01 y 3,95 $kU_A$/ L. Las medianas de sIgE de todos los alérgenos fue mayor en pacientes con rinitis de moderada a grave y rinitis con asma, pero no estadísticamente significativo (NSS). El valor de Der p 2 fue significativamente mayor en el Sur en comparación con el Norte (p = 0,0496).
*Conclusiones:* La sensibilización a Der p es la más común en Portugal. Der p 2 tuvo la prevalencia más alta y los niveles medios más altos. Todos los componentes moleculares fueron mayores en pacientes más sintomáticos (NSS). El valor de Der p 2 fue mayor en el Sur, lo que puede estar relacionado con la temperatura más cálida y/o el tamaño de muestra más grande.


Palabras clave: Alergia. Asma. Diagnóstico por componentes. *Dermatophagoides pteronyssinus*. Ácaros del polvo. Rinitis. IgE específica.

## Introduction

House dust mites (HDMs) are a major perennial allergen source and a significant cause of allergic rhinitis and allergic asthma. The incidence of sensitization to HDM allergen varies from 65 to 130 per million persons in the general population worldwide. The prevalence and the relative abundance of the different species varies from one region to another [1-3]. Dust mite allergens, namely those of *Dermatophagoides pteronyssinus* (Der p), are the most prevalent allergens in Portugal [4,5].

Currently, 30 allergens of Der p have been identified and sequenced [6]. The "major" allergenic molecules are Der p 1, Der p 2, and Der p 23, which are responsible for IgE-mediated responses in more than 50% of HDM-allergic patients [7-10].

The term *respiratory allergic disease* refers to a unifying allergic mechanism underlying the pathogenesis of allergic subtypes within asthma and rhinitis [11]. Identification and treatment of HDM allergy is a worthwhile investment in terms of future patient outcomes, and component-resolved diagnosis (CRD) offers the possibility of higher diagnostic accuracy and better management of the individual patient [1,12,13].

The aim of this study was to analyze CRD for Der p in patients with respiratory allergy to HDMs and to determine its possible association with clinical severity and geographical area.

## Methods

### *Study Design and Population*

A multicenter study was conducted with a total of 217 HDM-allergic patients followed in 13 allergy and clinical immunology departments/units in different areas of Portugal (5 from the North [n=65] and 8 from the South [n=152]). The patients were randomly selected from January to December 2018. All the patients had a medically confirmed diagnosis of allergic rhinitis, which was classified as mild or moderate-to-severe, with or without asthma, according to the Allergic Rhinitis and its Impact on Asthma (ARIA) and Global Initiative for Asthma guidelines [11,14]. Patient selection was based on the following criteria: allergic respiratory symptoms (rhinitis with or without asthma) after exposure to HDM; positive skin prick test (≥10 mg/mL) to Der p and/or *Dermatophagoides farinae* (Der f) and/or *Lepidoglyphus destructor* (Lep d) (Diater); and age between 3 and 60 years. None of these patients had previously been treated with immunotherapy based on dust mite allergens.

The study was approved by the local ethics committees, and written informed consent was obtained from all patients or from the parents or legal guardians of those under 18 years old.

### *Laboratory Analysis*

We determined serum specific IgE (sIgE) to Der p, Der f, and Lep d, as well as the molecular components of Der p, specifically, Der p 1, Der p 2, Der p 10, and Der p 23, in all patients (n=217) using the ImmunoCAP system (Thermo Fisher Scientific), according to the manufacturer's instructions. Results ≥0.35 $kU_A$/L were considered positive. Prevalence was defined as the percentage of patients with positive serum sIgE.

Western blot with the Der p extract revealed all the allergens according to the liquid chromatography mass spectrometry analysis described by the World Health Organization/ International Union of Immunological Societies [6], ensuring that any patient sensitized to this source was correctly diagnosed. Therefore, proteins from Der p extract were separated using sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) according to Laemmli [15] in 15% polyacrylamide gels under reducing conditions and transferred onto a polyvinylidene difluoride membrane (Trans-Blot Turbo, BIO-RAD). IgE antibody binding to allergens was analyzed using Western blot based on all the patients' sera from each center and antihuman IgE peroxidase conjugate (SouthernBiotech). Der p sIgE was distributed according to 3 levels: 0.35-3.5 $kU_A$/L; 3.5-50 $kU_A$/L; 50->100 $kU_A$/L.


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Chemiluminescence detection reagents (Western Lightning Plus-ECL, PerkinElmer) were added according to the manufacturer's instructions.

### *Statistical Analysis*

The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp.). Descriptive parameters such as mean (SD) were calculated for normally distributed continuous data; frequencies and percentages were calculated for categorical data. Parametric quantitative data were presented as mean (SD). Nonparametric quantitative data were presented as median (IQR). Categorical data were reported as a percentage showing the proportion of positive results. The Mann-Whitney test was used to compare serum IgE between groups (patients with rhinitis vs rhinitis with asthma, mild vs moderate-to-severe rhinitis, patients from northern centers vs southern centers). Differences were considered statistically significant if $P<.05$.

## Results

### *Characteristics of Study Patients*

The study population comprised 217 patients with respiratory allergy and sensitization to at least 1 dust mite. Seventy-six were children (35%). Mean age was 25.8 (12.7) years (minimum, 3; maximum, 58; median, 24 years) and 51% were female. According to the ARIA guidelines, all the patients had allergic rhinitis, which was mild in 43.8% (n=95) and moderate-to-severe in 56.2% (n=122). Furthermore, 52% (n=113) of patients had concomitant asthma.

### *Sensitization Profile*

With respect to dust mites, the prevalence of positive serum sIgE was higher for Der p, followed by Der f and Lep d. Der p was by far the allergen with the highest median sIgE level, followed by Der f and Lep d (Table 1). Regarding CRD, Der p 2 was the most prevalent, followed by Der p 23, Der p 1, and Der p 10. The highest sIgE level was found for the Der p 2 molecular component, followed by Der p 1, Der p 23, and Der p 10 (Table 1). The sensitization profile was similar in children and adults (Table 1).

Among the 213 patients sensitized to Der p, 7.5% (n=16) were monosensitized to Der p 2, 2.8% (n=6) to Der p 23, and 0.9% (n=2) to Der p 1.

### *Component-Resolved Diagnosis and Clinical Severity and Geographical Areas*

With respect to clinical severity, median sIgE levels ($kU_A/L$) to Der p 1, Der p 2, Der p 10, and

Der p 23 tended to be higher in patients with moderate-to-severe rhinitis than in those with mild rhinitis (18.15 vs 14.20, 22.10 vs 17.65, 5.76 vs 1.36, and 6.87 vs 6.14, respectively), although the difference was not statistically significant. In this context, we also observed that Der p 2 had the highest IgE value. In addition, sIgE ($kU_A/L$) levels to Der p 1, Der p 2, Der p 10, and Der p 23 were higher in patients with concurrent rhinitis and asthma than in those with rhinitis alone (20.35 vs 17.20, 23.50 vs 20.00, 7.29 vs 5.69, and 7.32 vs 6.65, respectively), although the difference was not statistically significant. Once again, IgE levels were higher for Der p 2 (Table 2).

Table 1. Dust Mite Sensitization and Dermatophagoides pteronyssinus Molecular Profile by In Vitro Tests

| | ImmunoCAP (sIgE) | Prevalence, No. (%) | Mean (SD) sIgE, $kU_A/L$ | sIgE, maximum/ minimum, $kU_A/L$ | sIgE, median, $kU_A/L$ |
|---|---|---|---|---|---|
| Total | Der p | 213 (98.2) | 42.5 (37.9) | 100/0.03 | 31.9 |
| | Der f | 211 (97.2) | 30.6 (32.3) | 100/0.02 | 17.5 |
| | Lep d | 184 (84.8) | 22.6 (30.3) | 100/0.02 | 8.12 |
| | Der p 1 | 157 (72.4) | 21.7 (29.7) | 100/0 | 8.56 |
| | Der p 2 | 194 (89.4) | 30.6 (34.0) | 100/0 | 17.7 |
| | Der p 10 | 21 (9.7) | 1.6 (9.2) | 100/0 | 0.01 |
| | Der p 23 | 167 (77) | 12.1 (19.9) | 100/0 | 3.95 |
| Children (<18 y) | Der p | 76 (100) | 61.72 (37.72) | 100/0.54 | 66.5 |
| | Der f | 76 (100) | 44.2 (35.63) | 100/0.32 | 31.2 |
| | Lep d | 63 (83) | 30.16 (31.2) | 100/0.02 | 12.1 |
| | Der p 1 | 67 (88) | 35.16 (35.83) | 100/0 | 20.4 |
| | Der p 2 | 74 (97) | 47.36 (36.85) | 100/0 | 35.5 |
| | Der p 10 | 8 (10.5) | 2.20 (12.5) | 100/0 | 0.01 |
| | Der p 23 | 60 (78.9) | 22.61 (26.40) | 100/0 | 10.5 |
| Adults (≥18 y) | Der p | 136 (97.1) | 31.78 (33.77) | 100/0.03 | 17.3 |
| | Der f | 135 (96.4) | 23.33 (28.17) | 100/0.02 | 11.3 |
| | Lep d | 121 (86.4) | 18.74 (26.73) | 100/0.02 | 6.89 |
| | Der p 1 | 95 (67.8) | 13.92 (26.73) | 100/0 | 5.01 |
| | Der p 2 | 122 (87.1) | 21.07 (28.40) | 100/0 | 9.09 |
| | Der p 10 | 13 (4.2) | 1.25 (7.27) | 100/0 | 0 |
| | Der p 23 | 109 (77.8) | 6.51 (12.28) | 100/0 | 2.33 |

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Table 2. Association Between Component-Resolved Diagnosis of Allergy to *Dermatophagoides pteronyssinus* and Severity of Allergic Respiratory Disease

| | Median (IQR) sIgE, $kU_A/L$ | | | Median (IQR) sIgE, $kU_A/L$ | | |
|---|---|---|---|---|---|---|
| | Mild rhinitis | Moderate-to-severe rhinitis | *P* value | Rhinitis | Rhinitis with asthma | *P* value[a] |
| Der p | 28.30 (5.54-74.80) | 36.00 (8.20-99.78) | .354 | 32.80 (6.80-83.40) | 38.30 (9.00-100.0) | .259 |
| Der p 1 | 14.20 (5.43-42.20) | 18.15 (6.55-49.78) | .382 | 17.20 (5.96-46.15) | 20.35 (6.90-49.33) | .501 |
| Der p 2 | 17.65 (5.46-42.60) | 22.70 (6.41-66.90) | .192 | 20.00 (6.14-56.78) | 23.50 (9.29-67.20) | .232 |
| Der p 10 | 1.36 (1.13-23.50) | 5.76 (3.66-22.40) | .4 | 5.69 (1.38-22.60) | 7.29 (3.16-25.05) | .654 |
| Der p 23 | 6.14 (2.31-13.40) | 6.87 (2.26-23.60) | .416 | 6.65 (2.26-18.40) | 7.32 (2.56-27.40) | .489 |

[a]Mann-Whitney.

Table 3. Association Between Component-Resolved Diagnosis of Allergy to *Dermatophagoides pteronyssinus* and Geographical Area

| | Median (IQR) sIgE, $kU_A/L$ | | |
|---|---|---|---|
| | Northern centers | Southern centers | *P* value[a] |
| Der p | 20.80 (5.35-73.95) | 35.35 (7.17-84.18) | .192 |
| Der p 1 | 7.06 (0.04-23.30) | 8.84 (0.14-39.28) | .342 |
| Der p 2 | 11.30 (1.96-32.25) | 19.10 (4.71-56.08) | .0496[b] |
| Der p 10 | 0.00 (0.00-0.03) | 0.01 (0.00-0.03) | - |
| Der p 23 | 2.53 (0.28-9.16) | 4.99 (0.81-13.33) | .083 |

[a]Mann-Whitney.
[b]Statistically significant

According to geographical area, concentrations of Der p 2 sIgE ($kU_A/L$) were significantly higher in patients from the southern centers than in those from the northern centers (19.10 vs 11.30; *P*=.0496; Table 3 and Figure 1).

The IgE Western blot for Der p, which was carried out with all the blood sera from each center according to IgE levels, revealed that each group of patients presented a characteristic pattern of recognition, either by center or by the titration of sIgE to the source studied. Furthermore, all the groups presented more intense sIgE binding for the Der p 2 allergen, which proved to be the most prevalent and the one with the highest levels of sIgE (Figure 2).

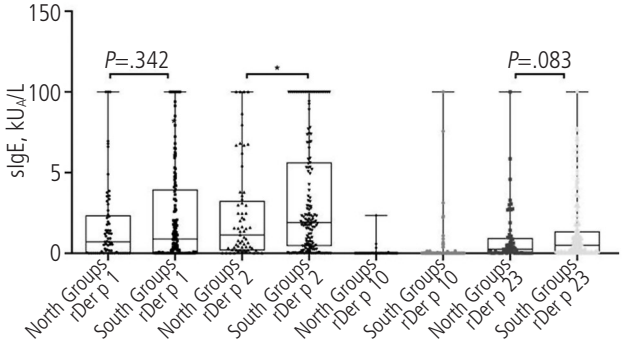


Figure 1. Levels of specific IgE to *Dermatophagoides pteronyssinus* based on component-resolved diagnosis and according to geographical area. *Statistically significant (*P*=.0496).

## Discussion

In this multicenter nationwide study, we not only confirmed that sensitization to Der p is the most common type of sensitization to HDM in Portugal, as previously described in the literature [4,5], but we also characterized, for the first time in Portugal, details of molecular sensitization and its relationship to clinical and geographical factors.

Our study highlighted the molecular sensitization profile of the most prevalent HDM [16,17]. The Der p 2 molecular component was the most prevalent, followed by Der p 23, Der p 1, and Der p 10, thus supporting the worldwide recognition of Der p 2, Der p 23, and Der p 1 as major allergens [7-9,18]. Similar studies were performed in other countries, where the prevalence of sensitization varied between 44.4% and 93% for Der p 1 [19-28], between 53.5% and 96% for Der p 2 [19-28], and between 45% and 71% for Der p 23 [22,24,25]. Several of these studies, especially those carried out in Europe, reported that the frequency of patients sensitized to Der p 2 was higher than that of patients sensitized to Der p 1, as we observed in this study [19,20,22-25,28]. It should be highlighted that, in comparison to similar studies, we obtained one of the highest levels of prevalence of sensitization to Der p 2, second only to those reported by Barber et al [20], with 96% in a center in Vizcaya, in northern Spain.

Although sIgE levels to the molecular components of Der p were higher in more symptomatic patients, that is, in patients with moderate-to-severe rhinitis and in patients with concomitant asthma, this trend was not statistically significant. According to studies of the prevalence of IgE recognition and allergen-specific IgE levels, Der p 1, Der p 2, and Der p 23 appear to be clinically relevant and there appears to be a correlation between higher levels of sIgE to molecular components and the severity of allergic respiratory disease [19-28]. Some studies have shown that IgE levels to Der p 1, Der p 2, and Der p 23 were significantly higher in patients with asthma (with or without concomitant rhinitis) than in patients with rhinitis alone [20,22,23,26,28]. On the other hand, Bonnert et al [21] found no association between the prevalence


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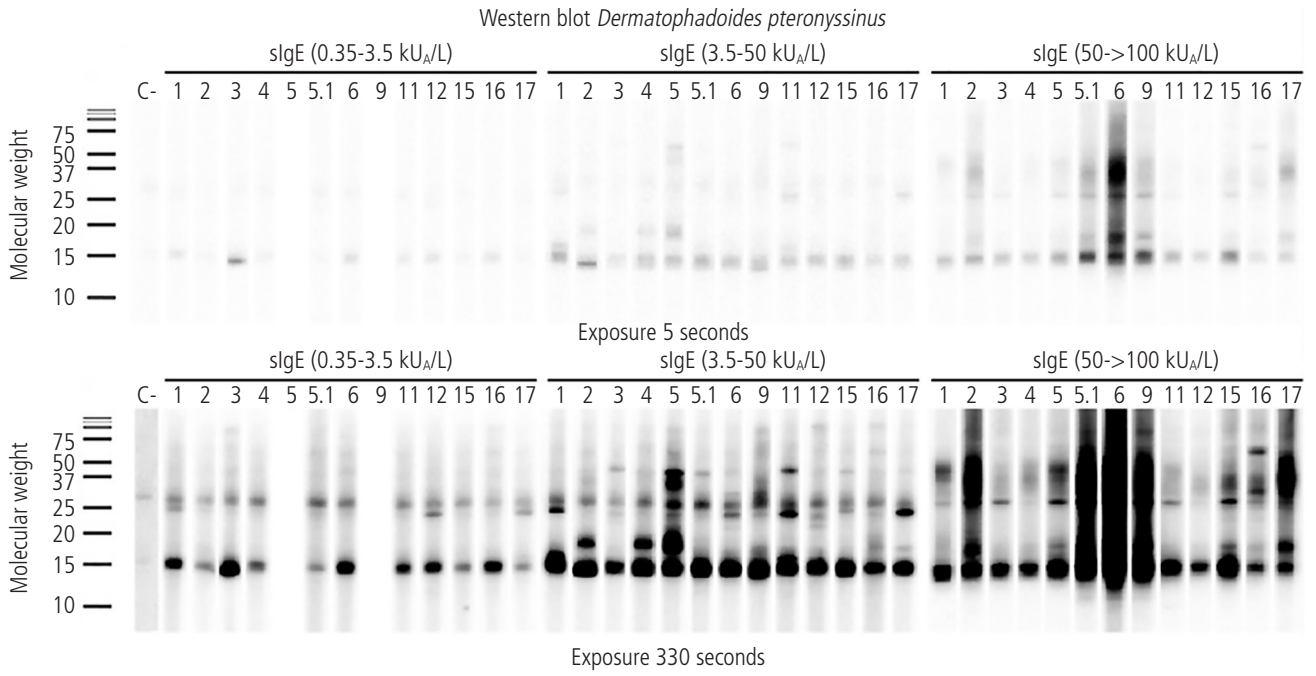


Figure 2. Distribution of the pool of sera from each center according to specific IgE levels. Center 1 (South), center 2 (South), center 3 (South), center 4 (South), center 5 (South), center 5.1 (South), center 6 (South), center 9 (North), center 11 (North), center 12 (North), center 15 (South), center 16 (North), center 17 (North).

of IgE reactivity to HDM components and the diagnosis of asthma or rhinitis.

Regarding the geographical distribution of sensitization patterns, we found that concentrations of Der p 2 sIgE were significantly higher in the southern centers than in the northern centers, probably because of the warmer southern temperature and/or the larger sample size. Der p 1 is a cysteine protease located in the mite intestine and is more thermolabile, whereas Der p 2 is an intracellular lipid-carrier protein that is more thermostable, thus potentially explaining the higher intensity of sensitization in the warmer, southern regions of Portugal [7,29-31]. However, other reasons may underlie these differences since, in neighboring Spain, Barber et al [20] studied a total of 477 patients from 10 clinical groups throughout the Mediterranean and Atlantic regions, where mites are relevant allergenic sources, and observed no differences between the thermal pattern of each region and the prevalence or sIgE levels to Der p 2.

Our study has several limitations. First, there were more southern than northern centers, and this may have influenced our results. Second, we selected patients with a high level of sensitization to HDM based on skin prick test results (≥10 mg/mL) and not on serum levels of Der p–, Der f–, or Lep d–specific IgE. This may have biased our results, since correlations between CRD and skin prick testing may not have been optimal [28]. Third, we did not determine severity or control of asthma or fully characterize how long the patients had had asthma or rhinitis or the medication they were taking, and this may have hampered our capacity to adequately determine disease severity.

Nevertheless, our study is novel, multicenter, and thorough in terms of HDM-related CRD analysis. Furthermore, it attempted to characterize severity of allergic disease not only by comparing isolated rhinitis with concurrent rhinitis and asthma, but also in terms of ARIA-based severity and persistence of rhinitis.

In conclusion, our data support the relevant role of Der p 2 in mite allergy, associating it with the greatest intensity of sensitization, especially in more severe allergic respiratory disease and in the warmer southern regions of the country. We also confirm the importance of molecular components in improving diagnosis in mite-allergic patients. We provide evidence for the importance of major allergens in patients with respiratory allergy to HDM and the clinical implications of CRD. Finally, since mite immunotherapy represents approximately 50% of the total volume of the vaccine market, our study may contribute to the development of HDM immunotherapy with a more precise allergen content and potentially greater efficacy and safety [32-34].

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The authors declare that no funding was received for the present study.

### *Conflicts of Interest*

Pineda F was at the time of the study and is currently working for Diater Laboratorio de Diagnostico y Aplicaciones Terapeuticas SA. However, there are no direct conflicts with the data presented in this study. The remaining authors declare that they have no conflicts of interest.

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*Previous Presentation*

This study was presented as an oral communication at the European Academy of Allergy and Clinical Immunology Congress in June 2019 and at the 40th annual meeting of the Sociedade Portuguesa de Alergologia e Imunologia Clínica in October 2019.

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