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Specific Immunotherapy can be a Useful Treatment in Seasonal Pollen Induced Esophagitis

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Abstract

Background: *Although pollen allergy is a very frequent finding in patients with eosinophilic esophagitis (EoE), it was doubted that it was an etiological agent to consider. Many EoE patients present rhinoconjunctivitis, atopic dermatitis and associated asthma, in addition to dysphagia and food impaction. EoE exacerbations are often seasonal.*

Methods: *We selected 255 patients suffered from esophagitis with seasonal exacerbation, and performed a real life study on the efficacy of immunotherapy with the detected pollen and avoidance of food, if was also detected. Allergens involved in EoE were identified by prick, specific IgE and component resolved diagnosis (CRD) by microarrays. Microscopic examination of esophageal biopsies of patients with EoE were made to verify the presence of callose (polysaccharide abundant in the polinic tubes during germination, but absent in animal tissues) in the esophagus. Callose was detected using histological sections stained with sirofluor fluorochrome. Endoscopy and biopsy were performed ever six months of treatment. Esophageal mucosal sections were analyzed by scanning electron microscope.*

Results: *Diagnosis of hypersensitivity using molecular microarray analysis CRD and biopsy study was efficient in esophagitis and was useful to decide the treatment (avoidance or targeted immunotherapy). This treatment allowed us a more reasonable restriction of food in the diet and specific immunotherapy aimed at the suspected allergens responsible for the disease. After immunotherapy, 188 (74%) patients were discharged whit negative biopsy, no symptoms, no medication, without relapse.*

Conclusion: *Specific immunotherapy can achieve clinic resolution and objective improvement by normal biopsy in patients with seasonal eosinophilic esophagitis.*

Keywords: Pollen Tubes, Eosinophilic Esophagitis, Seasonal Esophagitis, Callose, Germination, Biopsies, Specific Immunotherapy

Abbreviations

EOE- Eosinophilic Esophagitis
SPT- Skin Prick Tests
SIGE- Specific Immunoglobulin E
CRD- Component Resolved Diagnosis (Molecular Analysis By Microarrays)
AIT- Allergen Specific Immunotherapy

1. Introduction

Eosinophilic esophagitis (EOE) is associated with atopic diseases including asthma, allergic rhinitis, and atopic dermatitis and is considered as an atopic disease of unclear etiology [1]. As in allergic asthma, mucosal barrier dysfunction has been reported [2]. Many EOE patients present dysphagia and food impaction. EOE exacerbations are often seasonal and recently has been described as a late manifestation of the allergic march [3,4]. In a previous study we hypothesized that the inflammatory response of the esophageal mucosa in patients with high levels of antibodies to pollen allergens and worsened seasonal EOE might be due to swallowing and germination of airborne pollen in esophagus mucosa [5]. We thought it might be possible the intrusion into the esophageal mucosa of pollen allergens through the tubes emitted after pollen germination, which encounter a pH and humidity resembling the stigma of spermatophytes during the pollination. Microscopic examination of esophageal biopsies of 129 adult patients with EOE, 82 of them with seasonal exacerbation, and 100 controls with gastroesophageal reflux without eosinophilic infiltrate, were made to verify the presence of callose (polysaccharide abundant in pollen tubes but absent in animal tissues) in the esophagus [4]. Callose was detected using histological sections stained with sirofluor fluorochrome. Esophageal mucosal sections were analyzed by scanning electron microscope to detect pollen or spores. Allergens involved in EOE were identified by prick, specific IgE and component resolved diagnosis by microarrays [6].

Callosal was detected in 82 (67%) EOE patients with positive CRD to group 1 grass pollen. All these patients suffered clinical exacerbation in pollen season. Exacerbation was observed at the same time only in 4 control patients. Clinical evaluations and esophageal biopsies were made every six months. Gastrointestinal (dysphagia, heartburn, stomach upset, vomiting, constipation, diarrhea, failure to thrive) and allergic (rhinitis, asthma, dermatitis, anaphylaxis) histories were reviewed.

Pollen allergens were detected in 87.6% of patients with EOE. The predominant allergens were group 1 grass (55%), Art v 3 (11.3%) and lipid transfer proteins (LTPs) (19.4%) of common Mediterranean foods such as peach, hazelnuts, walnuts and wheat. This finding aimed us 3 years ago to study more patients suffered from esophagitis and seasonal exacerbation, and to carried out a treatment with specific immunotherapy with the detected pollen and/or avoidance of the detected food guided by CRD.

2. Methods

We performed a real life study in all EOE patients referred to our Allergy Clinic. Informed consent and the approval of the Rio Hortega Hospital Research Ethics Committee were obtained (Ref. CEIm:2011/PI02). A total of 327 patients met clinical and biopsy criteria of EOE with seasonal exacerbations. In all these patients conventional EoE treatment (PPi , diet or steroides) produce little improvement. Allergens involved in EOE were identified by prick, specific IgE and component resolved diagnosis (CRD) by microarrays (Thermofisher diagnostic, Sweden). We began allergen specific immunotherapy (AIT) with a commercial polymerized pollen extract in 291 patients that met criteria of pollen hypersensitivity (Positive clinical data, Prick, specific IgE, and CRD) and callosa in diagnostic biopsy, who suffered from esophagitis with seasonal exacerbation. The mean age was 36± 18.34 years and 72% were males. Thirty-six patients reused this immunotherapy or not finished 2 years of treatment due to different reasons. Clinical evaluations and esophageal biopsies were made every six months and we finished this therapy after a clear clinical and biopsy improvement. The immunotherapy had been applied for two years at the time of analysis of results. Patiens treated with immunotherapy and patients that denied this treatment were included in a statistical analysis.

3. Results

In our patients, CRD detected allergen hypersensitivity in more than 80% of patients with EOE. The predominant allergens were grass group 1 (65%) and lipid transfer proteins (LTP) of peach, hazelnuts and walnuts. Callose from pollen tubes was found in 86% of their biopsies and in all the selected patients for specific pollen immunotherapy. After two years of CRD-guided elimination diet and/or AIT, EOE patients showed significant clinical improvement ($p<0.017$) and 188 (74%) patients were discharged whit negative biopsy, no symptoms, no medication, without relapse. Evolution of EOE patients is show in table 1.

Intervention 255 patients with EoE	No AIT/ no avoidance	AIT only	Avoidance only	AIT+ avoidance	Pollen/pollen tubes	Callose
AIT	36	204	19	68	238	240
Group 1 grasses pollen		182		68	207	182
Other pollen mixtures		25		1	25	21
Avoidance						
Hazelnut			1			
Hazelnut+walnut			2			
Peach/fruits			16			
AIT/avoidance						
Hazelnut				23		
rCor a8/hazelnut				22		
Peach/fruits				15		
Sea food				8		
Significant biopsy improvement at 2 years	1 (0.3%)	188 (74%)	14 (73.7%)	64 (94.1%)		
Symptom free at 2 years	1 (0.3%)	188 (74%)	11(57.9%)	64 (94.1%)		

Table 1: Evolution of Eoe Patients after two Years of Specific Allergen Immunotherapy (Ait) and/or Elimination Diet

CRD-directed AIT and/or elimination diet was efficient in treating EOE patients and was well tolerated. AIT-treated patients had also better outcomes (odds ratio 177.3, 95% CI 16.2-1939.0). We frequently observed pollen tubes surrounded by eosinophils in the proximal and middle esophageal mucosa, resulting in micro-abscesses. Eosinophils seemed to act as if they were responding to parasitic infections. In figures 1,2 we add images from biopsies obtained during pollen season before Immunotherapy. Figure 3 shows histological changes after immunotherapy.

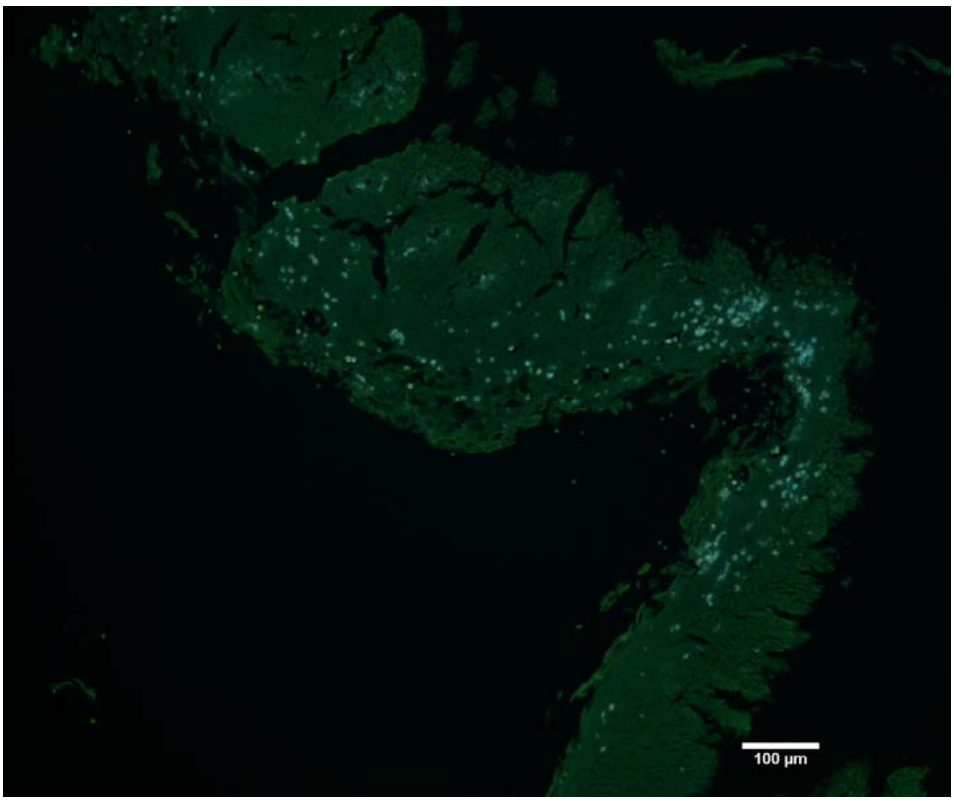

Figure 1: A: Damaged Epithelial Cells and Intercellular Spaces Points Shows Pollen Tube

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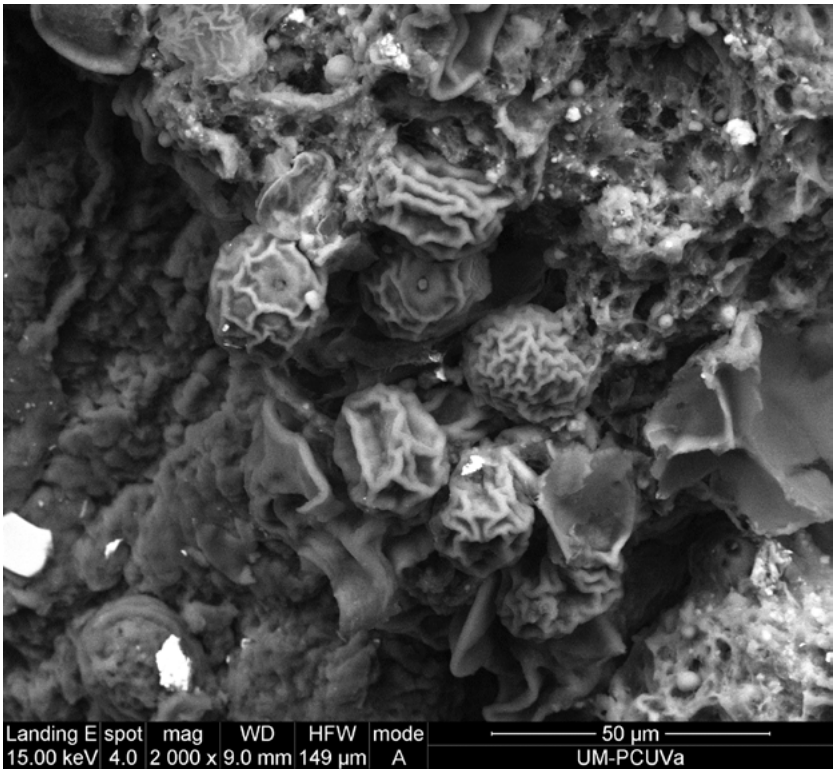

Figure 2: B: Micro-Impaction Mainly Composed of Pollen Grains of the *Poaceae* Family Infiltrating Intercellular Spaces Arrow Shows Characteristic Annulus of Grass Pollen

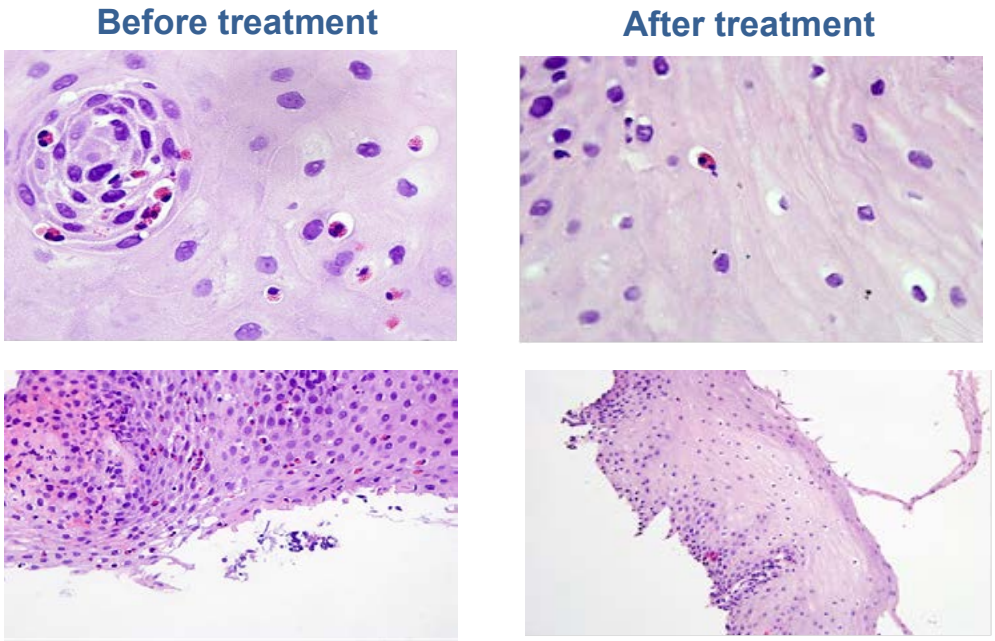

Figure 3: Human Histology Showed Eosinophilic Infiltration before Ait and Elimination Diet with Significant Decrease of Eosinophil Infiltrate at two Years EOE Biopsies Showed Eosinophilic Infiltration Gradually Lessened after Etiological Treatment with Diet and Specific Ait (Before Ait H/E 100x, > 15 Eo/Cga: after Ait (H/E 40x) *H/E: Hematosiline-Eosine Stain*

4. Discussion

Identification of environmental and food allergens in patients suffered from EOE is important and can guide therapy. Evidence supports a link between EOE, gut inflammation and environmental aeroallergens [7-10]. In a study by Ram including 160 pediatrics patients with EOE, 20% had biopsy examination-confirmed variation of EOE triggered by aeroallergens and 84% of them had allergic rhinitis and asthma [9]. Components of pollen grains are suspected to trigger changes in gut functions, something leading to inflammatory conditions. Buhner et al investigated the effect of aqueous pollen extracts on enteric and spinal sensory neurons from humans and guinea-pig and concluded that altered nerve signaling as a result of severe pollen exposure

may be a pathophysiological feature to allergic and non-allergic challenges [10]. Encouraged by our previous findings we treat patients with pollen germinated in their esophagus and with positivity in CRDs with pollen specific immunotherapy [5]. Those who also had an awareness of related foods, often described were selectively eliminated from their diet. After two years of specific immunotherapy achieved objective improvement by clinic and negative biopsy in 74% of patients [7].

Recent update suggests disease exacerbations owing to the increase in aeroallergens to which patients are sensitized. It was also recently postulated that treatment of allergic rhino-conjunctivitis with allergen specific immunotherapy can improve the symptoms of EOE our study aims to consider swallowed pollen in the triggering and exacerbation of EOE, since in addition to being airborne and inhalant, can also be ingested as food [11]. Currently, biomarkers and biologic therapies are not helpful for diagnosis or inducing clinical and histological remission of the disease [12]. So, we must try to identify the cause of the disease to ensure an etiological treatment of EOE. As of yet, no single agent has been approved by the US Food and Drug Administration to treat eosinophilic esophagitis [13]. Successful therapies exist, including different medications (budesonide effervescent tablet, biologics used for other Th2 mediated diseases) and dietary modifications, but disease typically recurs when the intervention is discontinued (14-16). Specific Immunotherapy can avoid disease recurrence and other treatment complications. We have not found relapse after one year of finishing the AIT. The efficacy of the treatment must be demonstrated. Endoscopy and biopsy are essential for diagnosis, assessment of response to therapy and ongoing monitoring of patients in histological remission [17]. We have been able to found in numerous patients germinated pollen in their esophagus, thanks to using a specific stain for plant cells that are different to the stains (hematoxilyn-eosin), normally used in human tissue [5,6]. Alteration of the mucosal barrier might cause the penetration of pollen grains tubes into the esophageal tissues. The subsequent germination of pollen and the release of highly-allergenic digestion-resistant molecules, such as group 1 grass (β-expansins) and LTPs, might be responsible for the increase in symptoms in these patients during periods of greater pollination. Stacks of rough endoplasmic reticulum are largely dissociated in heat-stressed pollen, consequently affecting protein processing and secretion.

In EOE patients, endoscopic and biopsy studies searching for intrusion to plant foods and pollen, and specific-guided diet and immunotherapy after plant structures detection in biopsies, might be effective. Emerging immunologic treatment with specific molecular targets are likely to change EOE management paradigms in the next years. A multidisciplinary approach (allergist, gastroenterologist, plant biologist, immunologist, dietitians and pathologist) is recommended, given the complexity of this disease [17].

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