

RESEARCH LETTER

Proton pump inhibitor-responsive oesophageal eosinophilia (PPI-REE): characteristics of a Spanish population in central Spain

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Updated guidelines in 2011 described a novel phenotype, proton pump inhibitor-responsive oesophageal eosinophilia (PPI-REE) [1, 2]. This disease refers to patients who clinically appear to have eosinophilic oesophagitis (EoE), but who achieve complete remission after PPI therapy [1]. It is currently unknown whether PPI-REE is an atypical variant of gastro-oesophageal reflux disease (GERD) or a variant of EoE, or whether it is a completely separate entity from these two pathologies [2].

We have prospectively studied patients diagnosed with PPI-REE during 2013 and 2014 in a specialized EoE oesophagitis office in a province of central Spain. The aim of the study was to analyse the epidemiological, clinical, serological, endoscopic/histological and allergological characteristics and comorbidities of these patients. The atopic and digestive comorbidities were obtained from the previous gastrointestinal and allergological database. Symptoms before and after treatment were assessed by the ELSA index (VAS-EoE score) [3], a visual analogue scale (0–10 points). The intensity of each seven symptoms was assessed as mild (1–3 points), moderate (4–6 points) and severe (7–10 points). A determination of blood eosinophils, total IgE serum levels, eosinophil cationic protein (ECP) and transglutaminase was done in all patients. Endoscopic signs (longitudinal furrows, concentric rings and micro-abscesses) and histologic findings were analysed. The hyperplasia of the basal layer and the number of eos/hpf in the upper, middle and lower segments were analysed in the biopsy specimens. We considered a remission to be complete when the number of eos/hpf ranged between 0 and 4 and partial when it was between 5 and 15 eos/hpf [4]. A series of standard tests were performed in all patients at the Allergy Department, following the recommendations of the EAACI (European Academy of Allergology and Clinical Immunology) [5]. Skin prick tests (SPT) included a battery of aeroallergens (AAs) and commercial foods, as well as the panallergens LTP and profilin. We also

measured serum-specific IgE (sIgE) (kU/L) to foods that have been shown to be related to the development EoE in our country [6].

sIgE levels were determined by ImmunoCAP test (ImmunoCAP250, Phadia, Uppsala, Sweden) and considered positive if figures were ≥ 0.35 kU/L. SPT with commercial food extracts and aerollergens (AAs) (Alk Abelló, Madrid, Leti, Barcelona, Spain) were performed on the forearm of patients by puncturing a drop of extract with standardized disposable lancets. Prick tests were positive if the resulting papules were ≥ 3 mm.

Results

Basal, clinical, analytical, endoscopic–histologic and allergological characteristics of the patients as well as atopic and digestive comorbidities are shown in Table 1.

Discussion

Eosinophilic oesophagitis (EoE) is a chronic, immune/antigen-mediated oesophageal disease characterized by symptoms related to oesophageal dysfunction and a eosinophil-predominant inflammation of the oesophagus [1]. PPI-REE is considered by some authors a phenotype of EoE as it causes symptoms indistinguishable from this pathology and shows at least 15 eos/hpf in the oesophageal biopsy, but with the peculiarity that both the clinical and histological features resolve after 2 months of treatment with proton pump inhibitors (PPIs) [7]. We report a series of 32 patients diagnosed with PPI-REE. These patients account for 32% of those previously diagnosed with EoE in our service, a proportion similar to that reported by other authors [7].

It predominates in atopic men, and we have not found that habitat influences the onset of disease. It is significantly associated with asthma and rhinoconjunctivitis (hay fever), while the association with eczema, anaphylaxis and/or urticaria–angio-oedema remains low. Despite remission with PPIs, it is associated with immediate, IgE-mediated food allergy (sensitization and

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Table 1. Basal characteristics of the patients and clinical and endoscopic changes after PPI therapy

Sex M/F	23/9		
Age mean; range	40.7; (17–68)		
Rural habitat	17/32		
Personal history of atopy	28/32		
Serological markers	Mean and range		
Serum eosinophils count (cells/cm ³)	234 (50–800) (22% eosinophilia)		
ECP (mcg/l)	30 (2–121) (76% high)		
Total IgE (KU/l)	268 (11–2900) (44% high)		
Transglutaminase antibody	0		
Global ELSA (mean and range)	Pre-therapy	Post-therapy	
Clinical findings			
Dysphagia	4.6 (0–9)	1.2 (0–7)	
Food impactions	4.7 (0–10)	1.2 (0–6)	
Regurgitation	2.3 (0–10)	0.7 (0–5)	
Lump in the throat	4.2 (0–10)	0.6 (0–5)	
Heartburn	4.4 (0–10)	1.1 (0–6)	
Stomach pain	3.5 (0–10)	1.1 (0–5)	
Chest pain	1.9 (0–8)	0.3 (0–5)	
Endoscopic/Histological findings			
Eos/hpf upper tract	29 (16–100)	0	
Eos/hpf lower tract	68 (15–100)	0	
Basal hyperplasia	9 (28%)	2 (6%)	
Furrows	3 (12.5%)	0	
Rings	11 (46%)	5 (21%)	
Exudates	2 (8.3%)	0	
	Positive SPT to aeroallergens	Positive sIgE to aeroallergens	
Mites	21%	21%	
Pollens	86%	86%	
Fungi	14%	14%	
Epithelia	18%	18%	
	Positive SPT to foods	Positive sIgE to foods	
Milk	3.5%	11%	
Egg	7%	14%	
Wheat	18%	28%	
Lentils	18%	21%	
Prawn	7%	18%	
Hake	3.5%	3.5%	
Peanut	25%	21%	
Positive SPT panallergens			
LTP		32%	
Profilin		11%	
Atopic comorbidities	Digestive comorbidities		
Asthma	56%	Hiatal Hernia	30%
Rhinoconjunctivitis	72%	<i>Helicobacter Pylori</i>	27%
Atopic dermatitis	9.4%		
Urticaria/angio-oedema	3%		
Anaphylaxis	3%		
Food allergy	22%		

SPT, skin prick test; sIgE, specific IgE.

symptoms after eating the food involved) in 20% of the patients, with plant foods being more involved [8] than milk, egg or fish. These results may be explained because all the patients in our series are adults and, at this age, allergy to milk and egg is less prevalent. We did not detect association between coeliac disease and PPI-REE, perhaps because of the age of the patients and also because these data were only available in 12 patients of our series [9].

Although in most patients, the number of eosinophils is greater at the lower end of the oesophagus than in the other two segments, which would support the view that this is an atypical form of GERD, the latest evidence is that both the EoE and the PPIs-REE are closely related and GERD may be a cofactor in some patients [7]. As both conditions may coexist, pH monitoring is not required for the diagnosis in these patients.

Genetic studies support the involvement of allergy in the pathogenesis of EoE [9]. Any AA such as pollens, very prevalent in our area, could cause lesions when coming in contact with the oesophageal mucosa, similar to those which occur in the airways. Something similar could happen with food allergens, especially those of plant origin, as they share allergenic proteins with pollen [8].

The fact that the patients in our series had a larger number of sensitizations and atopic comorbidities than those in series published by other authors [10] could be explained because most had been treated previously in our allergy clinics for another atopic pathology; this could have led to a selection bias. The systematic implementation of a broad and comprehensive allergy study may have also contributed to the increased detection of atopy in our patients.

We conclude that PPI-REE predominates in atopic males and many of them are allergic to AAs and foods. Controversy continues on whether PPI-REE is a distinct entity, a subtype of GERD or a phenotype of EoE. We agree with many other authors [9] in that more longitudinal studies are warranted to clarify this question.

Patients with PPI-REE should be assessed by a multi-disciplinary team that should include allergists to take into account all the systemic manifestations of the allergic disease. Allergists should include in their daily practice a clinical history aimed at discovering symptoms of oesophageal dysfunction, as this disease is more common in atopic population. This may help to achieve an early diagnosis of these patients and provide prompt treatment with PPIs, thus leading to a significant improvement in their quality of life.

Conflict of interest

The authors declare no conflict of interest.

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