

Eosinophilic esophagitis due to allergy to sheep and goat milk proteins

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RESUMEN

La esofagitis eosinofílica, entidad caracterizada por la infiltración de la mucosa esofágica por más de 20 eosinófilos por campo de gran aumento, se suele presentar en forma de disfagia intermitente de larga evolución, pudiendo estar asociada a sensibilización alérgica a aeroalérgenos y/o alimentos. Presentamos el caso de un varón con clínica de disfagia intermitente coincidiendo con la toma de quesos curados de oveja y cabra que precisó asistencia urgente tras la impactación de un comprimido de ibuprofeno a 30 cm de la arcada dentaria. El estudio practicado demostró la existencia de estenosis en el esófago a ese nivel con infiltración eosinofílica difusa y sensibilización a proteínas de la leche de cabra, oveja y vaca, con especial relevancia para la IgG bovina, lactoferrina y albúmina sérica. Tras tratamiento con fluticasona deglutida y medidas de evitación se consiguió la resolución del cuadro clínico y la desaparición de los eosinófilos en la mucosa.

Palabras clave: Esofagitis eosinofílica. Disfagia. Alergia. IgG bovina. Lactoferrina. Albúmina bovina sérica.

ABSTRACT

Eosinophilic esophagitis is an inflammatory disease of the esophagus characterized by the presence of high numbers of eosinophils in the esophageal mucosal layer (> 20 high-power field). It is uncommon in adults but in such cases intermittent dysphagia and food impaction are the most common presenting symptoms. We report the case of a male with long-standing intermittent dysphagia after eating selected goat and sheep cheese types, who required medical help following the impaction of an ibuprofen pill in the esophagus. A biopsy demonstrated the presence of eosinophilic inflammation, and allergy testing showed specific IgE against proteins in the milk of goats and sheep. Topical steroid therapy with oral fluticasone, and the elimination of these dairy products from the diet induced complete symptom resolution, and biopsy specimens taken 4 months later showed no eosinophils.

Key words: Eosinophilic esophagitis. Dysphagia. Allergy. Bovine IgG. Lactoferrin. Bovine serum albumin.

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INTRODUCTION

Eosinophilic esophagitis (EE) is an inflammatory disease of the esophagus that has become increasingly recognized over the last decade. EE is a primary disorder of the esophagus characterized by the presence of high numbers of eosinophils in the mucosal layer of the esophagus (> 20 high-power field) in the absence of

pathological gastroesophageal reflux disease (GERD). The proximal esophagus is more frequently affected (1,2). Even though the etiology of EE is not known, a majority of patients have evidence of IgE-mediated food and aeroallergen sensitization. In fact, the disease predominantly involves the pediatric atopic population (1-3). EE is uncommon in adults, but in these cases intermittent dysphagia and food impaction are the most common presenting symptoms. Episodes of long-standing symptoms such as chest pain and vomiting have been reported in some patients (4,5). EE should be considered in patients with symptoms of GERD, especially in those with dysphagia and/or food impaction and poor response to acid blockade treatments. The observation

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that many patients have specific IgE against food and aeroallergens, and symptomatic improvement after removing that food from the diet, strongly suggest the role of allergic sensitization in the pathogenesis of EE (6). For that reason it is mandatory to explore the role of IgE sensitization in patients with this disease.

CASE REPORT

A 31 year-old male with a history of food allergy to cow milk proteins in early life, seasonal rhinoconjunctivitis, and mild intermittent bronchial asthma was referred to the Allergy Service, Hospital de Conxo, Santiago de Compostela, Spain, after being diagnosed with EE for allergic sensitization testing. The patient had been previously treated for an IgE-allergic disease to cat dander and required oral antihistamines during the spring season due to pollen allergy. He has had no problems with milk derivatives since childhood. During the past 4 years he noted several episodes of dysphagia after eating some kind of cheese from goat and sheep milk but no treatment was needed to solve these symptoms. On January 2005, and few minutes after taking a 400-mg ibuprofen pill, he experienced acute chest pain with dysphagia for beverages and even his own saliva. Hours later he required medical care. At the Emergency Department of Hospital Xeral-Calde, Lugo, Spain, an endoscopy examination was performed. This endoscopy was extremely difficult due to the narrowness of the esophagus, and the ibuprofen pill was detected at 30 cm from the teeth. Esophageal edema was so marked that the pill could not be entirely extracted, and had to be fragmented into small pieces. Biopsy specimens obtained from the middle and upper esophagus showed eosinophilic infiltration in the esophageal squamous epithelium at > 20 eosinophils per high power field (Fig. 1). Topical steroid therapy with swallowed fluticasone 500 μ g, one puff twice daily for 3 months, induced complete symptom resolution, and biopsy specimens taken 4 months later showed no eosinophils.

A skin prick test (SPT) was performed with extracts from a standard battery of aeroallergens including *Dermatophagoides pteronyssinus*, *Lepidoglyphus destructor*, *Tyrophagus putrescentiae*, *Euroglyphus maynei*, *Blattella germanica*, *Alternaria alternata*, *Aspergillus fumigatus*, *Penicillium notatum*, *Cladosporium herbarum*, latex, dog, cat, hamster and cow dander, and pollen from *Lolium perenne*, *Betula alba*, *Plantago lanceolata*, and *Parietaria judaica* (ALK-Abelló Laboratories, Madrid, Spain). All SPT reactions were read after 15 minutes, and a wheal diameter greater than 3 mm was considered positive (similar to that obtained from one histamine solution control). Positive results were obtained against grass pollen (*Lolium perenne*) and

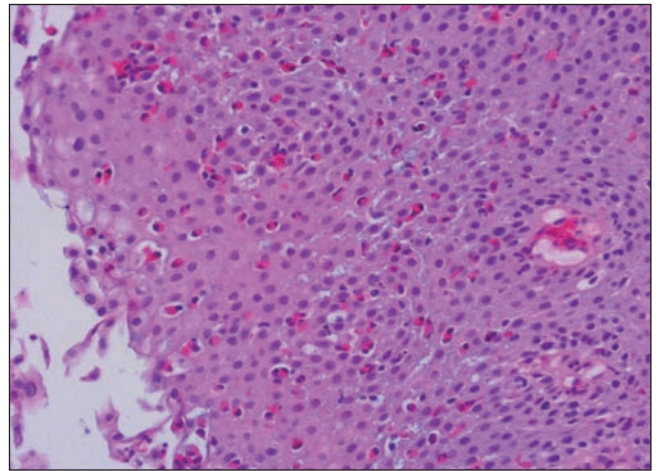


Fig. 1. Eosinophilic esophageal inflammation with evidence of more than 20 eosinophils per high power field.

Plantago lanceolata pollen, as well as cat epithelium. Skin prick tests against commercial food extracts, including clam, squid, prawn, mussel, oyster, cow milk, casein, egg, wheat, rice, corn, lentil, soybean, peanut, hake, sardine, kiwi, walnut, and hazelnut (Leti Laboratories, Madrid, Spain) were negative, as was a skin test with *Anisakis simplex* and latex extracts. Samples of cheese and yogurt from goat and sheep milk brought by the patient were used to perform prick-prick tests. For that purpose, lancets were pricked into each food and, immediately afterwards, pricked into the skin on the volar surface of the forearm. Prick-prick tests were positive to goat cheese, sheep cheese, goat yogurt, and sheep yogurt. In order to study the possible contribution to patient symptoms of a delay hypersensitivity mechanism, epicutaneous tests were performed. This kind of tests consisted of a small sample of antigen (cheese from goat and sheep milk in the case presented here) put on the back of the patient and occluded for 48 hours. After this time epicutaneous tests are removed and the presence of skin lesions are evaluated as positive if eczema-like lesions appear. No positive response was obtained in this patient, which ruled out a delayed hypersensitivity mechanism.

Total serum IgE was 422 kU/L (normal values below 100 kU/L), and specific serum IgE against goat, sheep, and cow milk (CAP System®, Phadia, Uppsala, Sweden) was 0.59, 0.43, and 0.77 kU/L, respectively. SDS-PAGE immunoblotting after incubation with patient serum revealed IgE binding bands of 85, 66, and 55 kDa in cow milk extract and milk, and yogurt and cheese from goat milk. Using the same technique, an immunoblotting study showed the presence of serum specific IgE that recognized bovine proteins recently described as important allergens in the hypersensitivity process (9,10) as lactoferrin, serum albumin, and immunoglobulin G; these

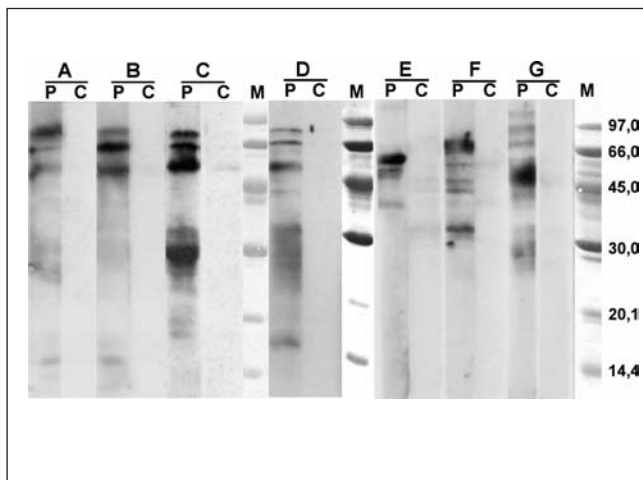


Fig. 2. SDS-PAGE immunoblotting. A: Cow milk extract; B: Sheep milk extract; C: Goat yoghurt extract; D: Sheep cheese extract; E: Bovine serum albumin; F: Lactoferrin; G: Bovine IgG. Lane P: patient's serum; Lane C: control serum (pool of sera from non atopic subjects); Lane M: molecular mass marker.

bands were also detected in sheep milk and derived dairy products.

Once a diagnostic was reached, and after following a restriction diet for dairy products from goat and sheep milk, the patient remained asymptomatic with normal endoscopic exploration results.

DISCUSSION

A relatively novel disease, EE is being recognized with increasing frequency, and some cases have been underdiagnosed because of difficulties to demonstrate the presence of eosinophilic infiltration in the esophagus. There are no macroscopic findings typical of the disease, and even some overlap between GERD and EE is possible since no feature can be classified as pathognomonic for EE, and a normal macroscopic appearance may be found (2,4). It has long been recognized that other entities are associated with a lesser degree of eosinophilic infiltrate, and for that reason a cut-off value has been established and the presence of more than 20 eosinophils per high power field strongly represents EE. Moreover, eosinophils can be found at distant points from the esophagus, such as the stomach, and some degree of peripheral eosinophilia can be detected (1).

It seems clear that there is an association between EE and allergy, as most patients with EE suffer from another allergic disease (3). Foods may act as a trigger of EE in some patients as has been suggested by the improvement after food exclusion from the diet, and by the presence of specific IgE against the related component (6,7). The hypersensitivity mechanism involved in those cases has not

been fully elucidated, and *in vivo* and *in vitro* tests are needed to investigate this issue. No published studies document whether or not total or specific IgE can serve as a surrogate marker for the disease (6-8). In some studies a delayed hypersensitivity reaction has been implicated, and epicutaneous tests recommended (6,7). Our patient showed positive results to prick tests and immunoblot studies lead us to identify the specific molecular band proteins probably responsible for the reaction, including serum albumine, lactoferrin and immunoglobulin G (9-11).

The clinical remission obtained after fluticasone treatment and the elimination of goat and sheep derivatives from the diet was in accordance to previous reports, in which more than 75% of cases improved if one or a few foods are involved (6). However, long-term outcome is difficult to predict since up to 40% of patients will have relapsing symptoms sooner or later (12,13). The use of an amino acid-based formula is currently the gold standard in determining whether food antigens are responsible for EE when a specific elimination diet causes no changes. The main problem of these regimens is their poor palatability, and a high cost that limits its use (8,14).

In conclusion, the patient reported here represents an example of the importance of allergological assessment in cases of suspected EE, and of the benefits obtained from collaboration between allergists and gastroenterologists in both diagnostic and therapeutic approaches.

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