

C A S E R E P O R T

Is a strict cow's milk-free diet necessary to treat milk oral immunotherapy-related eosinophilic esophagitis?

Mauro Calvani¹, Lucia Leonardi², Daniele Remotti³, Roberto Paparella², Annamaria Bianchi¹

¹U.O.C. di Pediatria, Azienda Ospedaliera San Camillo Forlanini, Roma, Italia, ²Dipartimento di Pediatria, Università La Sapienza, Roma, Italia; ³U.O.C di Anatomia ed Istologia Patologica, Ospedale di Belcolle, Viterbo, Italia

Abstract. We report the case of a 15-year-old boy who developed eosinophilic esophagitis (EoE) during cow's milk oral immunotherapy (CM-OIT). In order to not completely invalidate OIT benefits, baked milk-containing foods were allowed instead of a strict CM-free diet. However, histological remission of EoE was reached only after a strict cow's milk-free diet, not associated to pharmacological treatment. Nevertheless, given the limited data on real incidence of food OIT related EoE and potential beneficial treatment for this condition, we highlight the need of prospective studies aimed to evaluate if a strict CM free diet in OIT related EoE is always necessary to obtain remission of the disease or similarly to CM EoE, baked milk-containing foods" diet could be abeneficial treatment also in these patients. (www.actabiomedica.it)

Key words: eosinophilic esophagitis; oral immunotherapy; cow's milk hypersensitivity

Introduction

Eosinophilic esophagitis (EoE) is a chronic, multifactorial, immune-mediated esophageal disease, characterized clinically by symptoms related to esophageal dysfunction including dysphagia, bolus impaction and heartburn, but also abdominal pain, reflux, nausea, vomiting, reduced appetite, and failure to thrive. Clinical presentation of the disease is generally age related. EoE is histologically marked by eosinophilic predominant inflammation. At least 15 eosinophils/high power field (eos/hpf) in esophageal mucosa is the minimum threshold required for diagnosis (1).

EoE diagnosis and prognosis have become widely recognized in the past years. A recent Consensus statement of the Italian Society of Pediatric Allergy and Immunology for the management of allergic children during the COVID-19 pandemic reflects the burden of this condition by suggesting to postpone outpatient evaluation of most allergic patients while emphasizing

the need to promptly address any suspected case of eosinophilic esophagitis (2).

EoE is frequently associated with other allergic manifestations, such as atopic dermatitis, asthma, allergic rhinitis and above all food allergy (FA) (3). Indeed, food allergens exposure is emerging as the central feature of EoE pathogenesis. This assumption is confirmed by the fact that in many cases the elimination of the food trigger abrogates the disease, while its reintroduction causes disease recurrence (4). As a result, some authors include EoE in food allergy (5).

However, not all EoE patients achieve histological and/or symptomatic remission following elimination diets. This discrepancy may result from non-compliance to treatment, incomplete elimination of the food allergen or other allergic triggers.

A subset of patients with esophageal eosinophilia may respond to first step treatment with proton pump inhibitor (PPI). When resolution of esophageal eosinophilia is complete, patients can be treated with

PPI alone. On the contrary, dietary elimination and/or swallowed, topical steroid therapy are recommended for long-term management (6).

In the past decade, EoE has been reported in food oral immunotherapy (OIT) with an overall prevalence of 2.7% (7). Indeed, although OIT represents a promising treatment for FA, inducing desensitization and tolerance, heterogeneous clinical responses and adverse effects have been reported (8). Nevertheless, OIT-related EoE is reasonably an underdiagnosed complication due to the fact that a high percentage of children discontinue OIT because of gastroenteric symptoms onset without performing endoscopy (9). As a result, literature data on real incidence of food OIT-related EoE and potential beneficial treatment for this condition are still limited.

Cow's milk (CM) is one of the most common causative food described in pediatric EoE etiology, including OIT-related (4, 7).

The aim of the case report is to address possible allergen-free diet strategies in CM OIT-related EoE and to discuss the case in the light of the recent literature.

Case report

We report the case of a 15-year-old boy, with atopic dermatitis and seasonal rhinoconjunctivitis, who developed EoE during the maintenance phase of CM-OIT.

CM allergy was diagnosed at the age of three months, when he developed generalized urticaria soon after the first ingestion of a CM-containing food. Skin prick tests and serum-specific IgE level for CM were positive, requiring milk-free diet. At the age of three years he developed anaphylaxis after accidental ingestion of a goat's milk-containing food, thus a strict cow's and goat's (and any other mammals) milk-free diet was firmly confirmed. At the age of 8 years old, seasonal rhinoconjunctivitis was diagnosed by performing skin prick test resulting positive for grass pollen.

At the age of ten, referred to our unit, the patient showed positive skin prick tests to commercial extracts of β -lactalbumin (8 mm), β -lactoglobulin (6 mm), casein (6 mm) and grass pollen mix (6 mm) (Lofarma,

Italy). Fresh milk oral challenge failed at a dose of 30 ml because of generalized urticaria and vomit. Thus, a CM-OIT following local protocol was started, beginning with a single drop dose. The escalation phase was long lasting, due to recurrent abdominal pain, oral itching and transient skin rash after doses administration. Nevertheless, at the age of thirteen, he successfully achieved the maintenance dose of 200 ml of milk with skin prick tests positive to β -lactoglobulin (5 mm), casein (3 mm), β -lactalbumin (2 mm) and grass pollen (6 mm). Afterwards, not only he continued daily intake of this dose but the consumption of dairy products was also allowed. One year later, he started refusing milk, while eating dairy products and milk-containing foods.

At the age of fifteen, he presented with nighttime epigastric pain and heartburn. *Helicobacter pylori* stool antigen test was negative. Skin prick tests showed only persistence of β -lactalbumin sensitization (6 mm) and grass pollen (7 mm).

Therefore, an eight-week treatment with pantoprazole (40 mg/die) was performed twice leading every time to a complete remission of symptoms followed by a relapse two months after withdrawal. Histology from proximal, medial and distal esophageal biopsies was consistent for EoE, showing irregular basal cell hyperplasia and 25 eos/hpf; gastric and duodenal biopsies had no alterations.

Despite aeroallergens might be involved in EoE exacerbations (10, 11), in our case the absence of correlation between esophageal symptoms and seasonal aeroallergen exposure made unlikely the role of grass pollen in EoE pathogenesis.

CM-free diet was restarted, with the exception of baked milk-containing products, in the attempt to not completely invalidate OIT benefits. Rapid clinical remission was achieved without pharmacological treatment. However, six months later, biopsies from proximal, medial, and distal sections showed persistent inflammation (20 eos/hpf) of esophagus despite the patient was asymptomatic. Strict CM-free diet was therefore started including baked milk-containing foods avoidance. Twelve months later, persistent clinical remission and complete histological resolution were confirmed while skin prick tests were still showing sensitization to CM proteins and grass pollen.

Discussion

Our case seemingly suggests that only a strict CM-free diet, even if not associated to pharmacological treatment, can be effective in cow's milk OIT-related EoE.

However, we aim to highlight the need to investigate if in patients with milk OIT-related EoE, diet including baked milk food might be still beneficial while not completely invalidating OIT benefits or on the contrary if a strict cow's milk-free diet is always necessary to treat milk oral immunotherapy-related EoE. To date, no data of efficacy are available for diet including baked milk food in OIT-related EoE while few data are available on this diet when treating EoE due to cow's milk allergy (CM EoE).

Indeed, only a small number of milk OIT-related EoE cases (7 patients) has been exhaustively described in the literature and reported in a recent review (12). OIT was discontinued and a strict CM-free diet was recommended in all patients. Four out of seven were treated also with PPI and/or topical corticosteroid showing clinical and histological remission (13, 14, 15). Among the three children treated only with a strict CM-free diet (13, 14), all but one presented clinical and histological remission, too. Persistent slight esophageal inflammation was in fact reported in one patient, despite clinical improvement, being seemingly related to his decision to keep eating foods with milk traces (13). Similarly, our patient achieved clinical, but not histological remission, after six months of a CM-free diet except for baked milk-containing food, without any pharmacological treatment. However, a complete clinical and histological remission was reached only when a strict CM-free diet was followed.

On the contrary, in a retrospective study carried out by Leung et al. on fifteen children with CM EoE, baked milk was well tolerated in 64% of them, while 36% of patients had disease recurrence after at least sixteen weeks of baked milk ingestion (16). Another retrospective pediatric study investigated the degree of adherence to a strict elimination diet in CM EoE. Among 24 children undergoing strict CM diet, 16 achieved remission; subsequently eight patients remained on strict CM diet, while eight opted to a liberalized diet in which were allowed foods with traces of milk and baked goods with milk ingredients. Nev-

ertheless, histological remission was maintained in five patients (63%) of this latter group (17).

These findings suggest that there might be two different phenotypes in CM EoE treatment responders: those needing a strict diet and those who can tolerate baked milk. For this reason, it is tempting to speculate that also in a patient who develops EoE after successfully reaching a CM oral desensitization, in order to not completely invalidate OIT benefits, it would be beneficial to try a "baked milk-containing foods" diet followed by endoscopy to elucidate the patients response-profile before eventually shifting to a strict CM-free diet. In this perspective, prospective studies are warranted to further define the role of cow's milk-free diet in CM-OIT related EoE.

Conclusion

This case highlights the need of prospective studies aimed to evaluate if a strict CM-free diet in OIT-related EoE is always necessary to obtain remission of the disease or, similarly to CM EoE, baked milk-containing foods" diet could be a beneficial treatment also in these patients while not completely invalidating OIT benefits.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol.* 2011;128(1):3-20.
2. Cardinale F, Ciprandi G, Barberi S, et al. Consensus statement of the Italian society of pediatric allergy and immunology for the pragmatic management of children and adolescents with allergic or immunological diseases during the COVID-19 pandemic. *Ital J Pediatr.* 2020 Jun 16;46(1):84.
3. Capucilli P, Hill D.A. Allergic Comorbidity in Eosinophilic Esophagitis: Mechanistic Relevance and Clinical Implications. *Clin Rev Allergy Immunol* 2019 Aug;57(1):111-127.
4. Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy*

- Clin Immunol 2012;130(2):461-7.
5. Leung J, Beukema KR, Shen AH. Allergic Mechanisms of Eosinophilic Oesophagitis. *Best Pract Res Gastroenterol*. 2015 Oct;29(5):709-720.
 6. Ruffner MA, Spergel JM. Pediatric Eosinophilic Esophagitis: Updates for the Primary Care Setting. *Curr Opin Pediatr*. 2018 Dec;30(6):829-836.
 7. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol*. 2014 Dec;113(6):624-9.
 8. Mastrorilli C, Caffarelli C, Hoffmann-Sommergruber K. Food allergy and atopic dermatitis: prediction, progression and prevention. *Pediatr Allergy Immunol*. 2017 Dec;28(8):831-840.
 9. Mori F, Cianferoni A, Brambilla A, et al. Side effects and their impact on the success of milk oral immunotherapy (OIT) in children. *Int J of Immunopathol Pharmacol* 2017;30:182-7.
 10. Atkins A. Aeroallergens in eosinophilic esophagitis: Significant triggers or noise in the system? *J Pediatr Gastroenterol Nutr* 2017 Jan;64(1):1-2.
 11. Moawad FJ, Veerappan Gr, Lake JM, et al. Correlation between eosinophilic oesophagitis and aeroallergenes. *Aliment Pharmacol Ther*. 2010;31(4):509-15.
 12. Bianchi A, Cuomo B, Verduci E, et al. L'esofagite eosinofila: una possibile complicanza dell'immunoterapia orale per alimenti. *RIAP* 2019;1:20-29. ISSN: 0394-7939 (Print) – ISSN; 2531-3916 (On line).
 13. Sánchez-García S, Rodríguez Del Río P, Escudero C, Martínez-Gómez MJ, Ibáñez MD. Possible eosinophilic esophagitis induced by milk oral immunotherapy. *J Allergy Clin Immunol* 2012;129:1155-7.
 14. Gómez Torrijos E, Mendez Díaz Y, Moreno Lozano L, et al. Frequency and course of eosinophilic esophagitis during oral immunotherapy for cow's milk allergy in a series of 57 children. *J Investig Allergol Clin Immunol* 2017;27:132-3.
 15. Morais Silva P, Antunes J, Chambel M, Prates S, Leiria Pinto P. Diagnosis of eosinophilic esophagitis in an infant undergoing milk oral immunotherapy - a case report. *Eur Ann Allergy Clin Immunol* 2014;46:154-6.
 16. Leung J, Hundal NV, Katz AJ, Shreffler WG, Yuan Q, Butterworth CA, et al. Tolerance of baked milk in patients with cow's milk-mediated eosinophilic esophagitis. *J. Allergy Clin Immunol*. 2013 Nov;132(5):1215-1216.
 17. Teoh T, Mill C, Chan E, Zimmer P, Avinashi V. Liberalized Versus Strict Cow's Milk Elimination for the Treatment of Children with Eosinophilic Esophagitis. *J Can Assoc Gastroenterol* 2019 May;2(2):81-85.

Received: 15 June 2020

Accepted 6 February 2021

Correspondence:

Annamaria Bianchi

U.O.C. di Pediatria, Azienda Ospedaliera San Camillo Forlanini

Circonvallazione Gianicolense 87, 00152 Roma, Italia

tel. +39 06 58703360

fax +39 06 58704514

E-mail: annamaria.bianchi9@yahoo.it