

## Letter to the Editor

**Possible eosinophilic esophagitis induced by milk oral immunotherapy**

To the Editor:

New therapeutic strategies to treat food allergy have emerged in recent years.<sup>1</sup> At present, oral immunotherapy (OIT) with food is one of the most widely researched treatments for food allergy.<sup>2</sup> Immediate adverse reactions during therapy have been widely described,<sup>3,4</sup> and most of them were mild. However, long-term effects of OIT have been barely reported.<sup>5</sup> We describe 3 cases of esophageal eosinophilia in 110 patients treated with milk OIT at our outpatient clinic during the last 5 years.

Our milk OIT protocol consisted of increasing weekly doses of milk in the hospital and daily maintenance of the tolerated dose at home. Once a dose of 200 mL/d was achieved, continued daily intake of this dose at home was compulsory and consumption of dairy products was allowed.<sup>4</sup> OIT was performed in 110 milk-allergic children aged 2 to 16 years (mean, 6.8 years) who were followed up for 5 years. IgE-mediated allergy was previously confirmed by using skin prick tests, specific IgE (sIgE) levels, and oral food challenges. After successfully achieving a daily intake of 200 mL of milk, 3 children who were previously asymptomatic developed malaise and gastrointestinal symptoms.

Case 1: An asthmatic boy had been diagnosed with milk allergy at age 6 months because of vomiting immediately after drinking milk. He was treated with an elimination diet. He had an egg allergy that resolved spontaneously when he was 2 years old. Endoscopy and biopsy performed at 26 months revealed cardia insufficiency and no inflammatory signs with no eosinophils, leading to a diagnosis of gastroesophageal reflux disease (GERD). He was treated with cycles of omeprazole. At the age of 3 years and 9 months, milk and casein sIgE levels were 55.6 and 67.3 kU<sub>A</sub>/L, respectively, and an oral challenge with milk was positive. The patient underwent an OIT protocol. After 29 weeks of treatment, he had successfully achieved a 200 mL milk intake, with milk and casein sIgE levels of 23.2 and 25.8 kU<sub>A</sub>/L, respectively. After 14 months of daily milk intake and dairy products consumption, he began to eat slowly and experienced general weakness, low physical activity, sleep disturbances, and slow growth for 5 months. Markers for celiac disease and *Helicobacter pylori* were negative. A complete blood cell count revealed 420 eosinophils/mm<sup>3</sup>, and esophageal endoscopy showed rings and white mucosal exudates with a peak of 35, 35, and 40 eosinophils/hpf in mucosa from the upper, middle, and lower esophagus, respectively. After treatment with omeprazole and oral fluticasone (250 mg/12 h) for 2 months and a milk-free diet for 3 months, he was asymptomatic and endoscopy and biopsy findings were normal. The child remains symptom free after 20 months.

Case 2: A boy with atopic dermatitis and asthma vomited after drinking milk. He was diagnosed with milk allergy and GERD at age 7 months, and he was treated with milk-free diet and omeprazole. When he was 11 years old, his milk and casein sIgE levels were 35.1 and 46 kU<sub>A</sub>/L, respectively, a persistent milk allergy was confirmed by oral challenge, and the patient was included in a milk OIT protocol. He successfully achieved a daily intake of 200 mL in 19 weeks, with no gastrointestinal symptoms and milk and casein sIgE levels of 32.3 and 32.1

kU<sub>A</sub>/L, respectively. Three months later, he began to experience retrosternal pain and dysphagia related to food ingestion. Markers for celiac disease and *H pylori* were negative. A complete blood cell count revealed 1270 eosinophils/mm<sup>3</sup>, and esophageal endoscopy disclosed rings and white mucosal exudates with a peak of 30, 25, and 25 eosinophils/hpf in mucosa from the upper, middle, and lower esophagus. He was treated with omeprazole and oral fluticasone (250 mg/12 h) for 2 months, and a milk-free diet for 3 months. After the 3-month milk-free diet, endoscopy findings were macroscopically normal and biopsies showed a peak of 7, 5, and 5 eosinophils/hpf from the upper, middle, and lower esophagus, respectively. He complained of mild abdominal pain for 15 days, which resolved with a cycle of omeprazole. One year later, he remains asymptomatic. A pH-monitoring test was performed, and it showed no alterations.

Case 3: A boy presented with vomiting and mild urticaria after drinking milk at the age of 4 months and was diagnosed with milk allergy. He had no other atopic diseases. When he was 14 years old, he experienced mild wheezing and urticaria after several unintentional ingestions of milk traces and was treated with a milk OIT protocol. He successfully achieved a 200 mL intake after 39 weeks on the protocol, with milk and casein sIgE levels of more than 100 kU<sub>A</sub>/L. After 3 months of taking at least 200 mL of milk per day, he began to experience abdominal pain immediately after ingestion of milk and other foods, anorexia, and weight loss (6 kg) for 4 months. Markers for celiac disease and *H pylori* were negative. A complete blood cell count revealed 920 eosinophils/mm<sup>3</sup>, and esophageal endoscopy showed rings and white mucosal exudates with a peak of 100 eosinophils/hpf in mucosa from the upper, middle, and lower esophagus. He was treated with a milk-free diet. Omeprazole was prescribed, but he decided not to follow the treatment by his own risk. Other drugs were not prescribed until the etiology of the disease had been determined. After 8 months, the patient was asymptomatic although he decided to continue to eat foods with milk traces. Endoscopy showed an improvement, and biopsies revealed a peak of 10, 5, and 19 eosinophils/hpf from the upper, middle, and lower esophagus, respectively. After 12 months, a pH-monitoring test result was normal and the patient remains asymptomatic.

All 3 patients stopped drinking milk. A summary of the main findings is shown in Table 1.

We report 3 patients who developed gastrointestinal symptoms 3 and 14 months after a final dose of 200 mL of milk was achieved during milk OIT. Esophageal eosinophilia was confirmed by endoscopy and histologic findings. The recovery observed after a milk-free diet suggested that esophageal eosinophilia was caused by milk during the OIT protocol. Although the 3 patients should have been treated exclusively with proton-pump inhibitors to discard GERD and/or proton-pump inhibitors-responsive esophageal eosinophilia, as a recent guideline indicates,<sup>6</sup> clinical features along with endoscopic and histologic findings point out eosinophilic esophagitis as the most likely diagnosis. We performed pH-monitoring tests in cases 2 and 3 after 15 months and 1 year of esophageal eosinophilia diagnosis, respectively, and the results were normal, which may point to discard a baseline GERD. Because pathogenesis and long-term evolution of esophageal eosinophilia and eosinophilic esophagitis is still uncertain, we suggest this reaction as an absolute contraindication to

**TABLE I.** Summary of laboratory, endoscopic, and histologic findings

|                                               | Case no.                                                                                                                                 |                                                               |                                                               |
|-----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
|                                               | 1                                                                                                                                        | 2                                                             | 3                                                             |
| Blood eosinophilia, n (%)                     |                                                                                                                                          |                                                               |                                                               |
| Baseline                                      | 580 (6.9)                                                                                                                                | 660 (6.3)                                                     | 370 (7.2)                                                     |
| At time of esophageal eosinophilia            | 420 (4.9)                                                                                                                                | 1270 (14.4)                                                   | 920 (11.4)                                                    |
| Casein-IgG4                                   |                                                                                                                                          |                                                               |                                                               |
| Baseline                                      | 2.84                                                                                                                                     | 7.03                                                          | 2.43                                                          |
| At time of esophageal eosinophilia            | >30                                                                                                                                      | 23.6                                                          | 25.4                                                          |
| Endoscopy                                     |                                                                                                                                          |                                                               |                                                               |
| Baseline                                      | Distal esophagus showed erythema and some ulcerations covered by fibrin; cardia insufficiency; pyloro and duodenum showed no alterations | ND                                                            | ND                                                            |
| At time of esophageal eosinophilia            | Trachealization, white exudates                                                                                                          | Rings, white exudates                                         | Rings, linear erosion, white exudates                         |
| After treatment                               | Normal esophagus, cardia, pyloro, stomach and bulboduodenal junction                                                                     | Esophagus, cardia, pyloro, and duodenum showed no alterations | Esophagus, cardia, pyloro, and duodenum showed no alterations |
| Histology                                     |                                                                                                                                          |                                                               |                                                               |
| Baseline                                      | Stratified mucosa epithelium, no inflammatory signs observed                                                                             | ND                                                            | ND                                                            |
| At time of esophageal eosinophilia            | Intense spongiosis, inflammatory infiltrates consisted mainly of eosinophils, microabscesses                                             | Acantosis, spongiosis, eosinophils-forming microabscesses     | Acantosis, papylomatosis, basal hyperplasia, and spongiosis   |
| After treatment                               | No abnormalities                                                                                                                         | No alterations                                                | Occasional eosinophils through epithelium                     |
| Esophagus eosinophils count (peak number/hpf) |                                                                                                                                          |                                                               |                                                               |
| Baseline                                      |                                                                                                                                          |                                                               |                                                               |
| Upper                                         | 0                                                                                                                                        | ND                                                            | ND                                                            |
| Medial                                        | 0                                                                                                                                        | ND                                                            | ND                                                            |
| Distal                                        | 0                                                                                                                                        | ND                                                            | ND                                                            |
| At time of esophageal eosinophilia            |                                                                                                                                          |                                                               |                                                               |
| Upper                                         | 35                                                                                                                                       | 30                                                            | >100                                                          |
| Medial                                        | 35                                                                                                                                       | 25                                                            | >100                                                          |
| Distal                                        | 40                                                                                                                                       | 25                                                            | >100                                                          |
| After treatment                               |                                                                                                                                          |                                                               |                                                               |
| Upper                                         | 2                                                                                                                                        | 7                                                             | 10                                                            |
| Medial                                        | 2                                                                                                                                        | 5                                                             | 5                                                             |
| Distal                                        | 1                                                                                                                                        | 5                                                             | 19                                                            |

Peripheral blood eosinophilia was measured in eosinophils/mm<sup>3</sup> and casein-IgG4 in kU<sub>A</sub>/L by UNICAP, Phadia (Uppsala, Sweden).

ND, Not done.

reintroduce the treatment. In our population, 2.72% of children treated with milk OIT developed esophageal eosinophilia. In a recent study, a similar percentage (3.1%) of eosinophilic esophagitis was reported among milk-allergic children who overcame a baked milk challenge, but in these cases milk was not the causative food since avoidance diet did not improve eosinophilic esophagitis.<sup>7</sup> This condition has been suggested as a complication after desensitization protocols in patients with peanut allergy,<sup>8</sup> and there is one report of a patient who developed gastrointestinal symptoms suggestive of eosinophilic esophagitis after milk OIT<sup>5</sup>; however, in this case, esophageal eosinophilia was not confirmed by endoscopy or biopsy, which leads to an uncertain diagnosis. Eosinophilic esophagitis after egg OIT was recently observed in an 11-year-old boy who experienced anaphylactic reactions; the patient recovered from eosinophilic esophagitis after following an egg-free diet.<sup>9</sup> In this case, recovery was also confirmed by endoscopy. However, the authors do not state what percentage of the population their case represents; therefore, it is uncertain whether this is an incidental finding or a complication after egg OIT. To

our knowledge, this is the first report of a series of cases where a severe and nonimmediate adverse reaction occurred during this treatment protocol. These reports support the implication of food allergy in pediatric cases of esophageal eosinophilia, and moreover, in possible cases of eosinophilic esophagitis. Therefore, we highly recommend a strict and long-term follow-up of patients who regularly drink milk after being treated with milk OIT.

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