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Diagnosis of eosinophilic esophagitis in an infant undergoing milk oral immunotherapy - a case report

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Summary

Although the standard of care for cow's milk (CM) allergy is strict food avoidance, oral immunotherapy (OIT) is being widely investigated as an alternative management option in certain cases. Immediate adverse reactions to OIT have been described, but its long-term effects are much less often reported.

We present the case of a girl diagnosed with IgE-mediated CM allergy that was proposed for our CM OIT protocol at the age of 3 years. The first sessions (dose escalation up to 5 ml) were well tolerated, however eight hours after her daily morning dose of 5ml CM the child developed late episodes of vomiting. No other symptoms, particularly immediately after CM ingestion, were reported. These episodes became progressively worse and on the third day she presented mild dehydration and blood eosinophilia. After OIT interruption, a progressive clinical improvement was observed. An esophageal endoscopy was performed, showing signs of eosinophilic esophagitis (EoE) with peak 20 eosinophils/hpf. After treatment with topical swallowed fluticasone (500 mcg bid) and a CM-free diet for 4 months, the child was asymptomatic and endoscopy and biopsy findings were normal.

The long-term effects of milk OIT are still in part unknown. We hypothesize that eosinophilic esophagitis may have been a consequence of OIT in this case. The findings seem to indicate that food allergy may play a role in the pathogenesis of esophageal eosinophilia and stress the importance of a well programmed long-term follow-up of patients that have undergone milk OIT.

Case Report

Cow's milk (CM) allergy is a common disorder for which the standard of care is strict food avoidance. In recent years, CM oral immunotherapy (OIT), achieved by oral exposure to increasing doses of the food, has received particular attention as an alternative in cases where spontaneous tolerance acquisition is unlikely (1), increasing both quality of life and safety in the event of accidental ingestion of the offending food. Immediate adverse reactions during OIT have often been reported and

seem to occur in 50 to 100% of cases (2-5). Delayed reactions, however, are much less often reported (3,5).

We present the case of a 3-year old girl with atopic eczema and CM allergy. This condition manifested at 2 months of age in association with several episodes of urticaria, angioedema and vomiting following CM ingestion. IgE-mediated allergy was confirmed by skin prick tests, positive serum specific IgE (sIgE) and a positive oral food challenge. A complete eviction of CM from her diet resulted in resolution of all symptoms.

At the age of 3 years and 9 months, after several immediate reactions with cutaneous and gastrointestinal involvement associated with unintentional CM ingestion, and since sIgE levels were persistently elevated (milk: 60 KUA/L; casein: 29 KUA/L), the child was proposed to undergo a OIT protocol (6). Consent from our institution's review board and from her parents was obtained prior to protocol start.

It consisted of administration of increasing doses of CM in our outpatient allergy center at 2 to 3 week intervals followed by daily consumption of the tolerated dose at home. In the first session, a dose of 1 ml was reached and mild immediate reactions (facial urticaria, oral itching) were observed. No reactions occurred during the maintenance period at home, thus a new dose escalation was done from 1 to 5 ml after 3 weeks. Thereafter, parents were instructed to maintain a daily morning dose of 5 ml at home. On the following day however, the child developed vomiting episodes approximately eight hours after CM ingestion. No other symptoms, particularly immediately after the dose, were reported. These episodes became progressively worse and on the third day she returned to the hospital. She looked ill and mildly dehydrated. A complete blood cell count revealed 1020 eosinophils/mm³ (prior levels were 340 eosinophils/mm³). At this time point, OIT was interrupted and progressive clinical improvement was observed on the course of the following days. Five days later an esophageal endoscopy was performed, showing rings and white mucosal exudates with a peak of 20 eosinophils/hpf in mucosal biopsies from the upper, middle and lower esophagus. Gastric and duodenal biopsies had no alterations and *Helicobacter pylori* (HP) and *Giardia lamblia* were absent. Markers for celiac disease and HP were negative. A pH-monitoring test was attempted but not tolerated by the child. Subsequent skin tests with other foods commonly associated with eosinophilic esophagitis (EoE) were negative.

Treatment was started with lansoprazol but there was an episode of vomiting and urticaria immediately after the first dose, and therefore a decision was made to initiate topical swallowed fluticasone therapy (500 mcg bid) immediately. After a 4 month treatment with fluticasone and a CM-free diet, the child was asymptomatic and a new endoscopy with multiple biopsies found no alterations. Fluticasone was stopped and CM avoidance was maintained until now. At present, the child remains symptom-free 28 months after fluticasone discontinuation. Control endoscopies and biopsies performed at 12 and 27 months showed no sign of esophagitis. Specific IgE measured 14 months after the interruption of OIT was slightly higher (milk: 70 KUA/L; casein: 41 KUA/L) and presently a spontaneous decrease is observed (milk: 34 KUA/L; casein: 27 KUA/L).

We describe a patient with a typical history of IgE-mediated CM allergy, who developed a different clinical profile after the beginning of OIT: initial immediate skin and gastrointestinal

reactions associated with CM ingestion developed into late gastrointestinal symptoms at the third week of OIT protocol.

EoE is an immune-mediated disorder in which the esophagus is infiltrated by eosinophils, presumably through a TH₂-driven process (7). In this case, diagnosis was confirmed by endoscopy and biopsy findings. Recovery following withdrawal of CM suggests a probable causal relation with CM ingestion during OIT. As no endoscopy was performed prior to OIT, we can only speculate that EoE developed during the treatment. However, symptoms of recurrent vomiting and malaise were absent previously, and blood eosinophilia also developed only after initiation of the protocol. According to recent guidelines (7) proton-pump inhibitor therapy was attempted, in order to discard gastroesophageal reflux disease or proton-pump inhibitor-responsive esophageal eosinophilia. Unfortunately, it had to be interrupted due to an apparent adverse reaction and a decision was made not to delay swallowed fluticasone therapy. It was therefore not entirely possible to exclude those diseases. However, we consider that the fact that the child remained asymptomatic and free of histologic abnormalities long after interruption of pharmacological treatment, strongly supports the diagnosis of CM induced EoE. It has been hypothesized that exposure of the esophagus of predisposed individuals to high antigen loads may be the core mechanism responsible for the development of EoE (8). In animal models, mice with respiratory, oral or epicutaneous sensitization that are rechallenged with intranasal exposure to allergens, develop esophageal eosinophilic infiltrates which mimic EoE (9,10). In humans, cases of EoE have been attributed to large volume allergen exposures (8), aeroallergen sublingual immunotherapy (11) and OIT (12-14).

Our review has found reports of 4 patients who developed EoE following CM OIT protocols (12,13). Furthermore, OIT protocols with peanut (3) and egg (13,14) have also been implied. Although this condition is probably underdiagnosed, the scarcity of reports suggest that EoE associated with OIT is likely rare. This is the first suggestive case in over 30 CM OIT performed in our center.

Although a favorable outcome seems to have occurred in this case, long-term evolution of esophageal eosinophilia and EoE is still uncertain. We agree with authors (12) who suggest that in the presence of this reaction, OIT should be interrupted.

The long-term effects of CM OIT are still in part unknown and adverse reactions may be more common than previously expected. The findings in this case seem to indicate that food allergy may play a role in the pathogenesis of esophageal eosinophilia and possibly of EoE and stress the importance of a well programmed long-term follow-up of patients that have undergone CM OIT.

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