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Eosinophilic esophagitis with refractory response in a pediatric patient: A case report

Esofagitis eosinofílica en un paciente pediátrico resistente al tratamiento: reporte de un caso

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Resumen

Antecedentes: El tratamiento de pacientes con esofagitis eosinofílica consiste en dieta o fármacos, y cualquiera de ambas opciones puede considerarse de primera línea. Los inhibidores de la bomba de protones o los corticosteroides tópicos deglutidos se indican de forma convencional, y recientemente se ha descrito la prescripción de dupilumab como opción terapéutica.

Reporte de caso: Paciente pediátrico, con esofagitis eosinofílica de difícil control, diagnosticada antes de los 2 años, en quien fue necesario la prescripción de un esquema triple de tratamiento (dupilumab, inhibidores de la bomba de protones y corticosteroides tópicos deglutidos) para el control histológico de la enfermedad.

Conclusión: El caso aquí expuesto resulta interesante, puesto que en las guías actuales no se recomienda ni se describe por completo el tratamiento farmacológico combinado. No obstante, dupilumab fue efectivo, aunque no cumple con los criterios de indicación de la ficha farmacológica, en cuanto a edad y peso.

Palabras clave: Esofagitis eosinofílica; Pacientes pediátricos; Inhibidores de la bomba de protones; Corticosteroides; Dupilumab; Dieta.

Abstract

Background: The treatment of eosinophilic esophagitis (EoE) is based on diets or drugs, with either being the first choice. Proton pump inhibitor (PPI) or swallowed topical corticosteroids (STC) are classically used, and more recently the use of dupilumab has been described as a therapeutic option.

Case report: A pediatric patient with difficult-to-manage eosinophilic esophagitis, diagnosed before the age of 2 years, in which the simultaneous use of triple pharmacological therapy (Dupilumab, PPI and STC) has been necessary for the histological control of the disease.

Conclusions: It is a case of interest since in current guidelines the use of combined pharmacological therapies is not recommended or fully described. In addition, it is a case in which a good response to treatment with dupilumab is observed despite not meeting the indication criteria of the pharmacological label, in terms of age and weight.

Keywords: Eosinophilic esophagitis; Pediatric patients; Proton pump inhibitor; Corticosteroids; Dupilumab; Diet.

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus characterized by symptoms of esophageal dysfunction and histologically by eosinophil-predominant inflammation.[1-3] The treatment recommended by the guidelines includes diets or drugs, with either being the first choice.[1-6] As a second-line treatment, the only biological agent approved by the United States Food and Drug Administration for the treatment of EoE is dupilumab.[7] The management guidelines recommend the use of any of the therapies and replace them with another line in case of therapeutic failure, which is insufficient for some patients. We present the case of a pediatric patient with EoE, in whom simultaneous multidrug management was necessary for disease control. Therapeutic decisions were made between the digestive and allergology departments and supervised by the Hospital Universitario La Paz in Madrid, Spain. Informed consent was signed by the parents for review of the medical history and publication.

CASE REPORT

An 18-month-old male was referred to allergy consultations in June 2013. He was fed exclusively with breast milk until the first month of age, changing by recommendations of his pediatrician to hydrolyzed milk formula due to poor growth, decrease from the 50th to 3rd percentile, associated lack of appetite and vomiting. At six months, with the introduction of complementary feeding, he had multiple reactions. Upon introducing eggs and lentils, he immediately developed generalized urticaria, cough, and vomiting, requiring emergency care. From 11 months old, he had daily vomiting immediately after meals.

His personal history included mild to moderate atopic dermatitis. From the first months of life he had eczematous, erythematous and itchy lesions on the face and extremities, for which he underwent treatment with emollient creams and topical corticosteroids in the outbreaks, with good control of the disease.

An allergology study was carried out with skin tests using commercial extracts for milk, eggs and legumes, considering as positive a welt greater than 3x3mm. Testing positive for cow's milk, alpha-lactalbumin, beta-lactoglobulin, goat's milk, egg white, egg yolk, ovalbumin, ovomucoid and lentils. In addition, the study was completed with total and specific IgE. The results were: total IgE 39.6kU/L, cow's milk 1.84kU/L, sheep's milk 0.54kU/L, ALA 0.00 kU/L, BLG 0.33 kU/L, casein 1.17 kU/L, egg white 0.37kU/L, OVA 0.20kU/L, OVM 0.00kU/L, lentils 0.20kU/L. Following referral to the pediatric gastroenterology service, an endoscopy with sedation and biopsy was performed, revealing macroscopic mucosal furrows and trachealization, with more than 25 eosinophils/HPF in the biopsy pathology.

After the anamnesis and the result of complementary tests, this 18-month-old infant was diagnosed with eosinophilic esophagitis, allergy to cow's milk, egg and lentils as well as mild atopic dermatitis.

The management of this patient for symptomatic and histological control of EoE was a challenge. **Table 1** shows the different treatments performed and the results of the biopsies.

Two diets were carried out. The first in 2013 was based on the result of allergy skin tests, without success. The second diet was implemented during a hospital admission in 2014, initiating an elemental diet with amino acids through a nasogastric tube, without clinical or histological control. After the failure of the diet, it was reassessed in our allergology consultations in 2015, the study with skin prick-test and total and specific IgE was repeated. Absence of sensitization was observed to cow's milk, egg and lentils and oral food challenge tests were carried out with the foods involved, achieving the reintroduction of all foods.

In 2016, after the reintroduction of food, the patient had good clinical control and improvement in weight gain, performing treatment with PPI and STC (viscous budesonide 1mg every 12 hours and omeprazole 15mg every 12 hours) but control endoscopy was not performed until 2017.

In the following years between 2017 and 2020, an attempt was made to achieve the minimum effective dose. Multiple strategies were tried, but reducing or suspending the treatment with PPI or STC consistently resulted in clinical and histological relapses.

Table 1. Pathology results according to age, weight and treatment.

Endoscopy	Age (years, months)	Weight (Kg)	Treatment (dose)	Interval under treatment	Pathological anatomy	Symptoms
June 2013	1 year, 8 months	8.2	No treatment		25 Eos HPF	Difficulty gaining weight. Lack of appetite. Vomiting
November 2013	2 years	9.0	Food-free diet due to ST	5 months (June 2013-November 2013)	40 Eos HPF	Difficulty gaining weight. Lack of appetite. Vomiting
June 2014	2 years, 7 months	12.0	Elemental diet with NT	3 months (April 2014 – June 2014	12-50 Eos HPF	Repeated vomiting.
August 2014	2 years, 9 months	12.4	Elemental diet STC (0.5 mg/12 h) PPI (Omeprazole 12 mg/24 h)	2 months (July 2014-August 2014)	40-60 Eos HPF	Repeated vomiting.
June 2016	4 years, 7 months	13.10	STC (0.5 mg/24 h)	4 months (March 2016-June 2016)	Severe eosinophilia with micro-abscesses	Repeated vomiting. Abdominal pain. Dysphagia
September 2017	5 years, 10 months	15.2	STC (1 mg/12 h) PPI (Lansoprazole 15 mg/12 h)	3 months (July 2017- September2017)	0 Eos HPF	Asymptomatic
November 2017	6 years	15.3	PPI (Lansoprazole 15 mg/12 h)	2 months (October 2017-November 2017)	30-100 Eos HPF	Dysphagia with solid and liquid foods. Food impactions.
March 2018	6 years, 4 months	16.5	STC (1 mg/12 h) PPI (Lansoprazole 15 mg/24 h)	4 months (December 2017-March 2018)	0 Eos HPF	Asymptomatic
January 2019	7 years, 10 months	16.9	STC (1mg/12h) PPI (Lansoprazole 15 mg/24 h)	13 months (December 2017-January 2019)	0 Eos HPF	Asymptomatic
September 2019	7 years, 10 months	18.3	STC (1 mg/12 h) PPI (Lansoprazole 7.5 mg/24 h)	8 months (February 2019-September 2019)	0 Eos HPF	Asymptomatic
January 2020	8 years, 2 months	20	STC (0.5 mg/12 h)	2 months (October 2019-January 2020)	0 Eos HPF	Asymptomatic
June 2020	8 years,7 months	20.7	STC (0.5 mg/24 h)	5 months (February 2020-June 2020)	60-100 Eos HPF	Dysphagia with solid and liquid foods. Severe abdominal pain.
December 2020	9 years, 1 months	21	STC (1 mg/12 h) PPI (Lansoprazole 15 mg/12 h)	6 months (July 2020-December 2020)	0 Eos HPF	Asymptomatic
April 2022	10 years, 5 months	21.8	STC (1 mg/24 h) PPI (Lansoprazole 15 mg/24 h)	15 months (January 2021- April 2022)	1 Eos HPF	Asymptomatic
November 2022	11 years	23.5	STC (1 mg/24 h) PPI (Lansoprazole 15 mg/12 h)	6 months (June 2022- November2022)	40-150 Eos HPF	Refusal to eat food Food impactions. Severe abdominal pain.
January 2023	11 years, 2 months	25.6	Dupilumab 300mg/week STC DTC (1 mg/12 h) PPI (Lansoprazole 15 mg/12 h)	2 months (December 2022-January 2023)	0 Eos HPF	Asymptomatic
February 2023	11 years, 3 months	26	Dupilumab 300 mg/2 week STC (1 mg/12 h) PPI (Lansoprazole 15 mg/24 h)	1 month (February 2023)	4-6 Eos HPF	mild dysphagia to solids
May 2023	11 years, 6 months	27	Dupilumab 300 mg/2 week PPI (Lansoprazole 15 mg/12 h)	3 months (March 2023-May 2023)	24-77 Eos HPF	Abdominal pain Food impactions. Nausea. Vomiting
September 2023	11 years, 10 months	30.5	Dupilumab 300 mg/2 week STC (1 mg/24 h) PPI (Lansoprazole 15 mg/24 h)	4 months (June 2023-September 2023)	0 Eos HPF	Asymptomatic

Eos: eosinophils; NT: nasogastric tube; PPI: proton pump inhibitor; ST: Skin test; STC: swallowed topical corticosteroids.

In November 2022, he had clinical worsening, presenting intense abdominal pain, as well as repetitive food impactions, despite the double therapy (viscous budesonide 1mg every 24 hours and omeprazole 15 mg every 12 hours). The patient required hospital admission after presenting food impaction in which an urgent endoscopy was performed, showed 150 eosinophils/HPF. In view of the poor clinical and histological control, it was decided to start treatment with dupilumab 200 mg subcutaneously (SC) weekly for compassionate use, as its indication for EoE was not approved at that time, and he did not meet age or weight criteria (age: 11 years, weight: 23.5kg).

Two months later, clinical and histological remission was achieved with the use of triple therapy (dupilumab 200 mg SC weekly, viscous budesonide 1 mg every 12 hours, and omeprazole 15 mg every 12 hours). A new attempt was made to achieve the minimum effective dose, leading to spacing dupilumab to 200 mg every 2 weeks and discontinue viscous budesonide, but again biopsy revealed histological relapse with 77 eosinophils/HPF. In this scenario, the reintroduction of swallowed corticosteroids was necessary. Currently, he maintains treatment with triple therapy (dupilumab 300mg every 14 days, viscous budesonide 1mg every 24 hours, and omeprazole 15mg every 24 hours), with clinical and histological control.

In relation to the evolution of other atopic comorbidities, atopic dermatitis remained well controlled in general even before the initiation of Dupilumab, with the use of topical corticosteroids being very sporadic. On the other hand, during 2018 and 2019 between the months of January and May, the patient began with rhinoconjunctival symptoms of moderate intensity without associating bronchial symptoms. He was treated with oral antihistamines and eye drops as well as nasal spray with mometasone. For this reason, in 2020 subcutaneous immunotherapy was started on a monthly regimen with a polymerized extract for *Cupressaceae* and grass pollens after verifying their sensitization through skin tests. He is currently continuing with immunotherapy and maintains a favorable evolution. Regarding food allergies, the patient currently follows a varied diet without restrictions and has not developed allergies to other foods.

We want to emphasize that during the follow-up, good adherence to treatment was always verified, Treatment with PPI, STC and Dupilumab was always well tolerated, with no notable adverse effects. Complementary diagnostic tests were carried out to rule out other diagnoses such as pHmetry, manometry and abdominal ultrasounds.

DISCUSSION

Controlling EoE can be challenging. Following the recommendations of the therapeutic algorithm of EoE published in 2017 by Lucendo et al,[1] elimination diet, STC or PPI therapy, are the first lines of treatment without preferences of one line over the other and it is recommended in the scenario of therapeutic failure to switch therapeutic lines, trying elemental diets or experimental drugs. But there is no reference to the possible use of combination therapies.

In our patient, the elimination diets based on the results of the skin tests were not effective. At the present time, it is known that their effectiveness is limited (response of around 45%). In our case, the elemental diet was not effective either, despite a 90.8% success rate is described.[4]

The use of pharmacological therapy with PPI and STC was temporarily successful only when their use was combined, until April 2022. Was histologically demonstrated on several occasions that the use in monotherapy was not sufficient for this patient. Later, the use of dual therapy was ineffective, so it was necessary to add a third drug to the treatment.

If we follow the proposed therapeutic algorithm by Lucendo et al,[1] the next step would be the use of experimental drugs such as Dupilumab. In our patient, the use of dupilumab was effective only if, again, it remained associated with the other treatments.

The use of combination therapy is discreetly suggested in the algorithm proposed by the British Society of Gastroenterology,[2] but is not developed within the manuscript. On the other hand, the American Gastroenterological Association[5] comments on the lack of evidence regarding combined therapies, highlighting it as an important field to be investigated.

In this clinical case, it is well reflected that the combined use of pharmacological therapies is an option that is not clearly proposed in clinical guidelines and can be the solution to the poor clinical control of our patients with EoE.

The use of dupilumab alone in adolescents and children has been presented by other authors,[8] but to our knowledge, no data have been presented on its effectiveness in combination with other treatments in patients under 12 years of age.

We believe it is important to emphasize the importance of updating the EoE management guidelines and including management with combination therapies before labeling them as refractory or non-responder.

CONCLUSION

The management of eosinophilic esophagitis presents significant therapeutic challenges. We report a complex case of EoE diagnosed in infancy, with concomitant multiple allergic comorbidities. Clinical and histological remission was achieved through a tailored triple therapy approach combining off-label Dupilumab, swallowed topical corticosteroids, and proton pump inhibitors. In this patient, there was no response to the treatment recommended by current management guidelines. Both dietary interventions and standard pharmacological treatments, including proton pump inhibitors and swallowed corticosteroids, failed when used individually or as dual therapy. The associated comorbidities, including atopic dermatitis, allergic rhino-conjunctivitis, and food allergy, demonstrated a favorable clinical course

Conflicts of interest

The authors declare no potential conflicts of interest with respect to research, authorship or publication of this article.

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