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CASE REPORT

Gastroenterology: Eosinophilic Gastrointestinal Disorders

Pediatric eosinophilic gastritis treated with benralizumab: A case report

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Abstract

We report one of the first cases of eosinophilic gastritis (EoG) in a child under 12 years treated with benralizumab. At 7 years, our patient was started on benralizumab after failing to respond to various combinations of high-dose omeprazole, milk elimination diet, oral viscous budesonide, and oral systemic steroids. He had a complete depletion of gastrointestinal tissue eosinophils with improved symptoms but had symptomatic flares with tapering of background therapy. However, after 4 years on benralizumab he became symptomatic again. Benralizumab may be a viable option for EoG refractory to systemic steroids but only as a short-term adjunct therapy. More robust studies with long-term data are needed, especially in this younger population.

KEYWORDS

biologic, children, eosinophil, stomach

1 | INTRODUCTION

Eosinophilic gastritis (EoG) is a rare, chronic, immune-mediated inflammatory disorder with an estimated prevalence in children <20 years of 4.4/100,000.[1] It is characterized by eosinophilic predominant inflammation of the stomach.[2]

There are no clinical trials examining the use of benralizumab for EoG in children younger than 12 years, and its use in this population has not been previously reported. We present a case of a 7-year-old with EoG treated with benralizumab.

2 | CASE REPORT

Our patient presented at 20 months of age with periorbital edema and severe iron deficiency anemia (IDA) requiring packed red blood cell transfusion for a hemoglobin of 5 g/dL (normal 10.9–15 g/dL). He had comorbid allergic rhinitis and eczema. He was initially evaluated by hematology and then followed by his primary provider, who managed his IDA with oral iron supplements. He was referred to gastroenterology at 5 years of age to evaluate for gastrointestinal (GI) blood loss causing persistent IDA with minimal GI symptoms. He had positive stool heme occults, hypoalbuminemia from protein-losing enteropathy, and repeat iron transfusions for IDA. He was diagnosed a few months later, when he turned 6 years old, with hypereosinophilic syndrome (HES) involving the GI tract, including eosinophilic esophagitis (EoE) and EoG. At presentation, absolute eosinophil count (AEC) was 1330/mm^3 (normal 180–465/mm^3) and remained elevated for the next 5 years. Since diagnosis, his AEC ranged from 970 to 2170/mm^3 (normal 40–650 mm^3). His first upper endoscopy and colonoscopy at 6 years noted linear furrowing of the esophagus, mild erythema with erosions in the antrum, and lymphoid hyperplasia of the distal colon. Biopsies showed esophagitis with predominant eosinophil infiltration (>100 and 65/HPF [high power field] in the distal and mid esophagus, respectively) with eosinophil surface layering and clustering, epithelial hyperplasia, and spongiosis. Antral lamina propria eosinophils count was >100/HPF.

Colonoscopies evaluating for sources of GI blood loss, concurrent eosinophilic enteritis (EoN)/colitis, and

inflammatory bowel disease (IBD) were normal. Bone marrow biopsy with FIP1L1-PDGFRA gene analysis was done to identify a cause of his HES, and it was normal. Studies done to identify other HES organ involvement and other causes of hypereosinophilia included stool parasites, *Strongyloides*, *Toxocara*, *Trichinella*, *Ascaris* serology, tryptase, vitamin B12, troponins, T-cell receptor clonality studies, and chest and abdominal computed tomography, all of which were normal. Immunoglobulin E was >1000 IU/mL (normal 0–90 IU/mL).

Evaluations for other causes of hypoalbuminemia were negative, including morning urinary protein and microalbumin, serum protein electrophoresis, immunoglobulin G, thyroid function tests, gastrin level, transaminases, and liver synthetic function testing.

The goals of therapy for our patient's EoE and EoG included histological improvement of EOE, improvement of protein losing enteropathy (PLE) (improved hypoalbuminemia), and resolution of IDA. EoE and EoG failed to respond to various combinations of high-dose omeprazole, milk elimination diet, oral viscous budesonide, and oral systemic steroids. During this first year after diagnosis, on these various therapies, the patient underwent four more upper endoscopies, which revealed persistent esophageal and gastric eosinophilia, continued hypoalbuminemia, and IDA. There are no Food and Drug Administration-approved medications for EoG. An appeal was made to insurance for a biologic with reported use in HES and other eosinophilic disorders, given our patient's refractory symptoms. A year after diagnosis, benralizumab 30 mg subcutaneously every 4 weeks was prescribed along with omeprazole and prednisolone. IDA, hypoalbuminemia, and histology improved. His first endoscopy 3 months after adding benralizumab (his sixth upper endoscopy overall) showed an absence of eosinophils in the esophagus and stomach, mild to focal moderate epithelial hyperplasia, and spongiosis of the esophagus, reactive gastropathy, and mild chronic inflammation of the stomach body. Prednisolone was discontinued, but a year later, crushed budesonide was added for the return of IDA, down-trending hypoalbuminemia, and worsening gastric histology, which included severe reactive gastropathy with no eosinophils. Esophageal biopsies showed minimal epithelial reactive changes. A second colonoscopy was done 2 years after diagnosis to evaluate for another source of his IDA. There were no concerns about medication compliance. IDA resolved, and hypoalbuminemia improved 4 months after the addition of budesonide.

The patient's AEC normalized for the first time to 40/mm^3 just hours after receiving the first dose of benralizumab. His AEC remained normal or low except for three instances where levels spiked but normalized with subsequent repeat lab draws. Our patient had good weight gain since presentation at 20 months old. Length at presentation was around 40% and slowly trended down to 7% over the next 3 years where it remained for another 2 years. After prednisolone and benralizumab were started, his height increased from 9% to 21% over 3 months. Prednisolone was stopped, and he continued to grow well, reaching 31% after 1 year. With the initiation of crushed budesonide, he grew less than 1.5 inches over the subsequent 2.5 years. His height stunted, and he fell to 3%.

Our patient is now 11 years old and has been on benralizumab for 4 years. He had 2 years of good symptom control with benralizumab, omeprazole 20 mg daily, and crushed budesonide 9 mg daily but began to have down-trending iron stores and worsening PLE. Repeat biopsies noted minimal histological findings with chronic inactive gastritis, abundant oxyntic cells, and superficial acute esophagitis. Fecal alpha-1-antirypsin (A1AT) and calprotectin were both strongly elevated at >1.13 mg/g (normal <0.5 mg/g) and 1570 µg/g (normal <50 µg/g), respectively. A wheat elimination diet was incorporated into his therapy plan. Stool studies were repeated after 6 weeks, which showed a decrease of fecal A1AT and calprotectin to 1.08 mg/g and 755 µg/g, respectively. He was unable to maintain a wheat elimination diet, and his fecal A1AT and calprotectin increased to >1.13 mg/g and 1020 µg/g, respectively.

Our patient's course has been further complicated by adrenal insufficiency from crushed budesonide. He is presumed to have iatrogenic adrenal insufficiency based on stunted growth in the setting of chronic steroid use and a morning cortisol level <0.1 µg/dL (normal 6–18.4 µg/dL). A growth hormone stimulation test was negative for growth hormone deficiency but could not be interpreted for adrenal insufficiency as he was on a hydrocortisone taper at the time of the study. He remains on stress dose steroids as needed until his hypothalamic–pituitary–adrenal axis can be reevaluated after the removal of steroids.

Our patient became more symptomatic with weaning of budesonide, with intermittent abdominal pain and vomiting, persistent hypoalbuminemia, and low iron stores. A change in biologic to dupilumab is being pursued.

3 | DISCUSSION

Our patient's presentation was atypical as he presented with IDA, PLE, and without any GI symptoms suggestive of EoE/EoG. He did not develop GI symptoms until several years into his treatment. His new GI symptoms of vomiting and abdominal pain, however, may be due to adrenal insufficiency, as these symptoms occurred when budesonide was discontinued. Though atypical, his IDA and PLE are thought to be due to EoG. IDA can stem from GI blood loss or poor absorption due to mucosal involvement. Iron absorption is affected in gastric diseases by altering gastric acid secretion as seen in gastric resection,

atrophic gastritis, and *H. pylori* gastritis.[3] Occult blood loss is suspected in our patient's case as his IDA persisted despite iron infusions unless his EoG was treated.

There are reports of PLE due to EoG. There is a distinct possibility that in our patient and these cases, concomitant EoN was missed in the small bowel and not assessed. A limitation in our case was that a capsule endoscopy was not done. It was discussed with the family at diagnosis and again when his symptoms returned with elevated calprotectin. It was ultimately not pursued as it was not thought to significantly change his management course. Elevated calprotectin may suggest undiagnosed EoN but may also be due to severe EoG. Two studies have reported elevated fecal calprotectin in children with gastritis,[4,5] which is thought to represent gastric neutrophilic inflammation. While stricturing disease is an established outcome of uncontrolled EoE, normal histology may not be necessary as a therapeutic goal in non-EOE eosinophilic gastrointestinal disease (EGID), as data on prognosis is limited. Eosinophil count has been shown to be an inadequate correlate of disease remission. Superior histological markers are yet to be identified. Endoscopy comes with procedural and anesthesia risks. There is a need for noninvasive measures of disease response. Fecal A1AT and calprotectin may be such markers if abnormal.

Our patient developed adrenal insufficiency due to the use of budesonide. Budesonide is thought to have minimal systemic absorption because of its high first-pass metabolism. Adrenal insufficiency, however, has been reported in patients on budesonide for IBD and EoE.[6,7] Increased systemic absorption may occur due to a defective epithelial barrier of the diseased GI tract and a lower body mass index. Crushed budesonide allows for a greater surface area of absorption. Our patient's stunted growth was distinctly noted after budesonide was started. He continued to grow well while on prednisolone and was off prednisolone for approximately 1 year before stunting of growth began. It is unlikely prednisolone caused his adrenal insufficiency.

Treatment options for pediatric EoG are limited. Benralizumab is a recombinant monoclonal antibody that binds to the α-subunit of the interleukin (IL)-5 receptor expressed on eosinophils.[8] It causes rapid and near-complete depletion of blood and tissue eosinophils by attracting natural killer cells to induce apoptosis.[9,10]

A randomized controlled trial (RCT) assessing benralizumab in 20 adults with HES reported findings in a subset of seven patients with EGID, six of whom had EoG.[9] Complete depletion of blood and GI tissue eosinophils was noted. All patients had improved GI symptoms but symptomatic flares with liberalization of dietary restrictions and/or tapering of background therapy. Our case replicates these findings, with depletion of gastric eosinophils and clinical improvement, and worsening IDA and hypoalbuminemia when steroids were weaned. This suggests that benralizumab is not effective as monotherapy.

Another RCT assessing the efficacy and safety of benralizumab in 26 adolescents and adults with EoG reported induced histological remission with depletion of gastric eosinophils but no improvement in structural histological abnormalities, endoscopic severity, or symptom score.[11] Despite our patient's return of symptoms, his biopsies remained depleted of eosinophils. This suggests that depletion of eosinophils is not a sufficient goal in managing EoG and that another mechanism independent of eosinophils is contributing to symptom development. Benralizumab is ineffective as monotherapy further supports this theory. Complementary therapy is needed to manage the eosinophil-independent component.

Epithelial cells, mast cells, and T-cells have been identified as potential drivers of this secondary mechanism but robust data is lacking.[9,12] Lirentelimab (an anti-Siglec-8 antibody) reduces mast cell activation and contributes to eosinophil depletion. It has not shown clinical improvement in phase 3 trials, which suggests that mast cells may not be the secondary driver.[9,11] Omalizumab (an anti-IgE antibody) has shown statistically significant symptom improvement, but not improved histology.[13] A current clinical trial of dupilumab (an IL-4 and IL-13 inhibitor) holds promise as it may target both eosinophilic and IgE-mediated inflammation.[13]

These RCTs followed patients for 48 and 88 weeks, respectively. We describe our experience with over 200 weeks (4 years) of benralizumab use, with only 2 years of symptom control.

4 | CONCLUSION

To our knowledge, we present one of the first cases of a pediatric patient younger than 12 years with EoG treated with benralizumab. Our patient's course demonstrates: (1) benralizumab may be a viable option for treating pediatric EoG refractory to systemic steroids but only as adjunct therapy and may only provide short-term benefit, (2) stool testing with fecal A1AT and calprotectin may be viable options to monitor disease response, (3) adrenal insufficiency may develop with crushed budesonide use, and finally, depleting eosinophils is not sufficient to control disease, and future therapies with broader targets are necessary.

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CONFLICT OF INTEREST STATEMENT

Dr. Donna Cheung and Dr. Benjamin Davis are investigators in an industry-led clinical trial of dupilumab in pediatric patients with eosinophilic esophagitis by Regeneron Pharmaceuticals Inc. The remaining author declares no conflict of interest.

ETHICS STATEMENT

Informed consent was provided by the patient's mother for this case report.

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