



Refractory Pediatric Fibrostenotic Eosinophilic Esophagitis Treated With Dupilumab

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ABSTRACT

Eosinophilic esophagitis (EoE) is a progressive inflammatory disease of the esophagus. Untreated or uncontrolled disease over time can lead to the development of fibrosis and formation of strictures. Once the patient develops strictures, it is difficult to treat with the available medical therapies and will often require esophageal dilations. The Food and Drug Administration recently approved dupilumab for the treatment of EoE in patients older than 12 years. The clinical trials excluded patients with esophageal strictures. We describe a case of EoE with fibrostenotic stricture who had stricture resolution while on dupilumab therapy.

INTRODUCTION

Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory disease of the esophagus affecting both children and adults.¹ EoE is diagnosed when a patient presents with symptoms of esophageal dysfunction, with esophageal biopsies showing at least 15 eosinophils per high-power field in the absence of other causes of esophageal eosinophilia.² Standard therapy includes proton pump inhibitors (PPIs), topical corticosteroids, and diet elimination.³ Poorly controlled esophageal inflammation can lead to stricture development.⁴ Fibrostenotic EoE is difficult to manage. Narrow-caliber EoE responds poorly to standard medical therapy. Dupilumab is the first Food and Drug Administration-approved treatment of EoE for children 12 years and older, but clinical trials looking at its efficacy excluded patients with strictures. We present a case of a refractory fibrostenotic EoE who responded to dupilumab.

CASE REPORT

A 14-year-old adolescent boy with a history of allergic rhinitis and asthma presented to the emergency department with esophageal food impaction and inability to tolerate oral secretions. He gave a 2-year history of progressive dysphagia. He required frequent Heimlich maneuvers to dislodge impacted food. His mother had fibrostenotic EoE that was treated with esophageal dilations every 6 months. We performed an emergent esophagoscopy and observed ring trachealization and a very narrow diffuse stricture of the esophagus (Figure 1A). The narrowest portion was <5.4 mm (Figure 1B). An ultra-slim endoscope (diameter 5.4 mm) could not be advanced past the distal esophagus because of significant resistance. Esophageal biopsies confirmed EoE. His esophagram noted subtle narrowing of the mid esophagus from T2 to T3. He was immediately started on a burst of oral systemic steroids for a week along with daily swallowed steroids and high-dose PPIs. After 3 months, severe diffuse fibrostenotic disease was still present on endoscopy. The ultra-slim endoscope (diameter 5.4 mm) was only just able to pass through the esophagus with mild resistance. Over the course of the next year, we tried combinations of high-dose PPIs, swallowed topical steroids in both inhaled and viscous forms, milk elimination, esophageal dilations with bougie dilators, and several courses of systemic steroids (oral prednisone 2 mg/kg/d) including a 10-week taper.⁵ The patient's symptoms, abnormal histology, and stricture did not resolve. Histologic findings improved somewhat on systemic steroids, but his stricture persisted. Owing to his refractory disease, we started dupilumab 300 mg

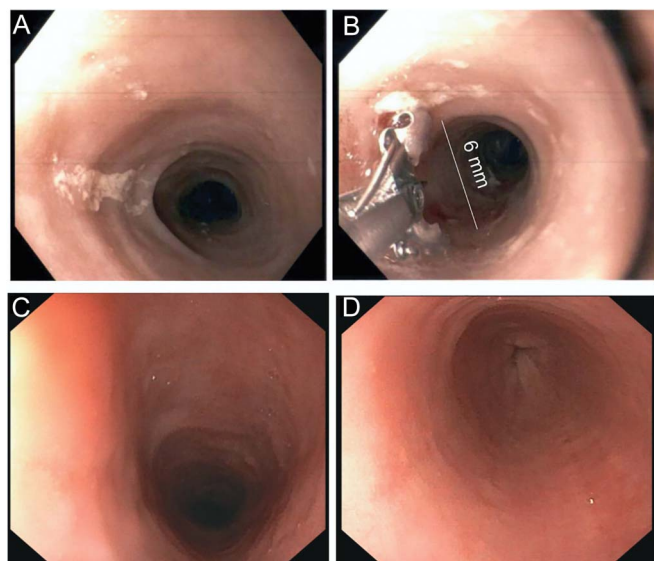


Figure 1. (A) Esophagoscopy showing pale esophageal mucosa with trachealization and diffuse esophageal stricture. (B) Distal esophageal stricture with diameter <6 mm. (C) Esophageal mucosa with normal vascularity and absent trachealization and strictures after starting dupilumab. (D) Absence of distal esophageal strictures with visualization of the lower esophageal sphincter after starting dupilumab.

subcutaneous injections weekly. His stricture resolved, and he required dilation only once more at the start of the dupilumab trial. His symptoms and endoscopic appearance of the esophagus improved (Figure 1C) without any evidence of stricture

(Figure 1D). Histologically, the eosinophil count at the mid esophagus normalized, but the distal esophagus continued to have active EoE (Table 1). At the time of this submission, he was on dupilumab for almost a year without any identified side effects, except for poor appetite, which has not been reported as a side effect in the literature.

DISCUSSION

Fibrostenotic EoE is difficult to treat and may require multiple mechanical dilations.⁶ Repeated esophageal dilations in managing fibrostenotic EoE is not without risks and does not address the underlying inflammatory process.⁷ Our patient had severe esophageal stricturing disease with an esophageal lumen of <6 mm requiring multiple dilations. There are limited options in managing the inflammation in severe fibrostenotic EoE.⁵ In pediatric patients, this leads to a significant number of endoscopic procedures and anesthesia exposure over their lifetime. There is a critical need for newer therapies to help these patients. Dupilumab is a biologic agent that may be a promising treatment option for narrow-caliber EoE, but data are lacking. It blocks interleukin (IL)-4/IL-13 signaling and, thereby, inhibits receptor signaling downstream the JAK-STAT pathway. There are studies showing that EoE is associated with T helper cell 2 (Th2)-type immune response to patient-specific antigens, predominantly to foods. Elevated levels of the Th2 cytokines; interleukins IL-4, IL-5, and IL-13; and mast cells have been found in the esophageal biopsies of patients with EoE.⁸ There is experimental evidence that IL-13 can directly stimulate

Table 1. Time line of treatment and endoscopic and histologic findings of the patient with fibrostenotic EoE

Date of endoscopy (mo/yr)	Therapy at the time of endoscopy	Stricture	Dilation	Endoscopic findings (EREFS)	Esophageal histopathology (EoEHSS) (grade/stage)	
July 2020	None	Diffuse esophageal stricture present Distal esophagus <5.4 mm	Not done	Edema grade 2 Rings grade 3 Exudate grade 1 Furrows grade 0 Stricture grade 1 Total 7	Mid (grade/stage) EI 2/2 BZH 2/3 DIS 3/2 LPF NA (no LP present) EA 1/1 SL 2/1 SEA 2/2 DEC 0/0	Distal (grade/stage) 3/3 N/A superficial fragments 2/2 NA (no LP present) 3/3 3/3 3/3 3/3
October 2020	Omeprazole 40 mg BID Prednisolone 40 mg OD × 1 wk Fluticasone inhaler 220 mg/puff 4 puffs BID	Diffuse esophageal stricture present	Not done	Edema grade 2 Rings grade 1 Exudate grade 2 Furrows grade 1 Stricture grade 1 Total 7	Mid EI 3/3 BZH 3/3 DIS 3/3 LPF 3/2 EA 3/3 SL 3/3 SEA 3/2 DEC 1/1	Distal 3/3 2/3 3/3 3/1 3/3 3/3 3/3 1/1

Table 1. (continued)

Date of endoscopy (mo/yr)	Therapy at the time of endoscopy	Stricture	Dilation	Endoscopic findings (EREFS)	Esophageal histopathology (EoEHSS) (grade/stage)		
January 2021	Omeprazole 40 mg BID Milk-elimination diet Prednisolone 60 mg OD × 1 wk	Diffuse esophageal stricture present	Dilated to 12.8 mm with Savary dilators	Edema grade 2		Mid	Distal
				Rings grade 1	EI	3/2	3/3
				Exudate grade 2	BZH	3/3	3/3
				Furrows grade 1	DIS	3/3	3/3
				Stricture grade 1	LPF	3/2	3/3
				Total 7	EA	3/1	3/2
					SL	3/2	3/3
					SEA	3/2	3/3
	DEC	1/1	1/1				
April 2021	Omeprazole 40 mg BID Budesonide slurry 1 mg BID	Diffuse esophageal stricture present	Not done	Edema grade 2		Mid	Distal
				Rings grade 2	EI	3/3	3/3
				Exudate grade 2	BZH	3/3	3/3
				Furrows grade 1	DIS	3/3	3/3
				Stricture grade 1	LPF	3/2	3/1
				Total 8	EA	3/3	3/3
					SL	3/3	3/3
					SEA	3/3	3/3
	DEC	3/1	3/2				
August 2021	Omeprazole 40 mg BID Prednisolone 40 mg × 4 wk, followed by taper over 6 wk, followed by fluticasone inhaler 220 µg/puff 2 puffs BID	Diffuse esophageal stricture present	Dilated to 12.8 mm with Savary dilators	Edema grade 2		Mid	Distal
				Rings grade 2	EI	1/0	2/1
				Exudate grade 1	BZH	2/2	2/2
				Furrows grade 1	DIS	2/1	2/1
				Stricture grade 1	LPF	3/2	3/3
				Total 7	EA	0/0	0/0
					SL	1/1	1/1
					SEA	2/1	2/2
	DEC	1/1	1/1				
December 2021	Dupilumab 300 mg Q1week	Mid esophageal narrowing present but improved	Dilated to 12.8 mm with Savary dilators	Edema grade 2		Mid	Distal
				Rings grade 1	EI	1/1	2/1
				Exudate grade 0	BZH	1/2	1/2
				Furrows grade 1	DIS	2/1	2/1
				Stricture grade 1	LPF	2/1	3/1
				Total 5	EA	0/0	0/0
					SL	0/0	1/1
					SEA	1/1	1/1
	DEC	0/0	0/0				
March 2022	Dupilumab 300 mg Q1week	None	Not done	Edema grade 2		Mid	Distal
				Rings grade 1	EI	1/1	3/1
				Exudate grade 1	BZH	1/1	1/2
				Furrows grade 1	DIS	1/1	2/1
				Stricture grade 0	LPF	2/1	2/1
				Total 5	EA	0/0	1/1
					SL	0/0	2/1
					SEA	0/0	3/1
	DEC	0/0	1/1				
BID, twice daily; BZH, basal zone hyperplasia; DEC, dyskeratotic epithelial cell; DIS, dilated intercellular space; EA, eosinophil abscess; EI, eosinophil inflammation; EoE, eosinophilic esophagitis; EoEHSS, Eosinophilic Esophagitis Histologic Scoring System; EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; LPF, thickened lamina propria fiber; OD, once daily; Q1week, once weekly; SEA, altered tinctorial properties of surface epithelium; SL, eosinophil surface layering.							

BID, twice daily; BZH, basal zone hyperplasia; DEC, dyskeratotic epithelial cell; DIS, dilated intercellular space; EA, eosinophil abscess; EI, eosinophil inflammation; EoE, eosinophilic esophagitis; EoEHSS, Eosinophilic Esophagitis Histologic Scoring System; EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; LPF, thickened lamina propria fiber; OD, once daily; Q1week, once weekly; SEA, altered tinctorial properties of surface epithelium; SL, eosinophil surface layering.

fibroblasts to produce periostin, and overexpression of IL-13 stimulates collagen production in an EoE model. Both these processes may lead to stricture formation.⁹ Dupilumab works in fibrostenotic EoE likely by blocking the downstream effects of

IL-13 on dysregulation of epithelial barrier function and tissue repair/fibrosis and the downstream effects of IL-4 on Th2 differentiation and, thereby, the orchestration of an atopic response in the esophagus.

To the best of our knowledge, this is the first case report of successful treatment of EoE-related esophageal strictures using dupilumab and the second case report of refractory pediatric EoE responding to dupilumab.¹⁰ Of note, although promising, our patient was not in complete histologic remission, and it is too early to tell if dupilumab will prevent future stricture formation and recurrent esophageal dilations. More robust studies will be needed to assess the efficacy of dupilumab in managing severe fibrostenotic EoE and preventing stricture formation.

DISCLOSURES

Author contributions: GG Nambiar wrote the manuscript. D. Chueng and B. Davis edited the manuscript. Y. Xiong analyzed biopsies and edited the manuscript. R. Rahhal edited the manuscript. GG Nambiar and R. Rahhal performed the procedures. All authors performed critical review and editing of the manuscript. D. Chueng is the article guarantor.

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