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Barrett's esophagus and eosinophilic esophagitis in a young pediatric patient with esophageal atresia



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ABSTRACT

We report the case and follow up of a 4 year old girl who was born with esophageal atresia and was found to have concomitant Barrett's esophagus and eosinophilic esophagitis. Development of metaplasia has generally been regarded as a chronic, long term complication post esophageal atresia repair, however this case highlights the need for early and regular endoscopic surveillance in this vulnerable patient population. In addition to this, eosinophilic esophagitis has only rarely been reported in patients with concomitant Barrett's esophagus. Our patient is the youngest in reported literature with Barrett's changes post esophageal atresia repair, and the first such reported patient with both eosinophilic esophagitis and Barrett's esophagus.

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Esophageal atresia (EA) affects 1:2400 live births, and is therefore a relatively common congenital anomaly [1]. Expectant management of long term complications such as strictures, esophageal dysmotility, gastroesophageal reflux disease (GERD) and an increased risk of Barrett's and cancer [2] has become increasingly relevant with improved survival rates. Eosinophilic esophagitis (EoE) is an emerging entity as a chronic inflammatory condition associated with esophageal dysfunction [3] which has only rarely been reported in EA patients [4]. Here we report the case and follow up of a young girl with EA diagnosed with EoE and Barrett's esophagus (BE) 4 years after her primary repair.

1. Case report

Our patient was born with long gap, Type A esophageal atresia. A gastrostomy was created shortly after birth and sutures were placed as per the esophageal growth augmentation technique first described by Foker [5]. Delayed primary anastomosis was performed at 3 months. Fundoplication was not performed as it is not routine practice at our center following a Foker long gap EA

repair. She was prescribed proton pump inhibitor (PPI) therapy but was non compliant. Her gastrostomy was closed at age 2. She had recurrent anastomotic strictures requiring thirteen radiological dilations, mostly in her first year of life. The patient also had eczema and asthma, but no food allergies were detected on skin prick testing.

In August 2013 she was referred to the newly established multidisciplinary EA-TEF clinic at our hospital by her treating surgeon for increasing dysphagia, regurgitation and food impaction. She had been recommenced on PPI therapy for her symptoms shortly before but was still symptomatic. She underwent a barium swallow which showed a mild anastomotic stricture with no hold up of contrast.

Her first gastroscopy at age 4 years 5 months showed a thickened distal esophagus with multiple erosions, mild furrowing and white exudate (Fig. 1).

There was a slight ledge at the site of previous EA repair but no strictures. The lower esophageal sphincter (LES) appeared to be lax. There was no hiatal hernia. Biopsies from the proximal esophagus showed spongiosis and parakeratosis, patchy basal zone hyperplasia and elongation of some lamina propria papillae, accompanied by intraepithelial eosinophils numbering up to 55/High Power Field (HPF). Distal esophageal biopsies showed similar changes with eosinophils numbering up to 80/HPF in addition to

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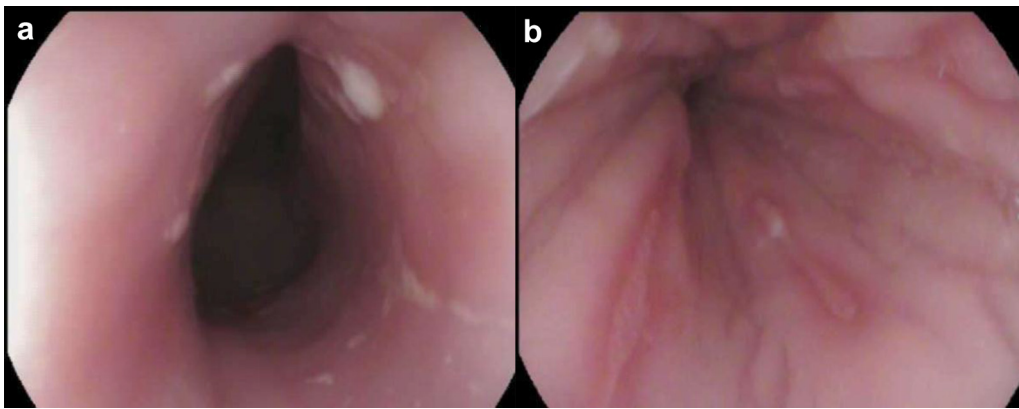


Fig. 1. Initial gastroscopy findings. (a) White exudates in the distal esophagus. (b) Furrowing with erosions in the distal esophagus.

hyalinization of subepithelial stroma. She was formally diagnosed with EoE. Her PPI was optimized to regular oral pantoprazole 20 mg BD (weight 14 kg) and commenced on budesonide slurry 0.5 mg BD with marked improvement in symptoms.

A progress gastroscopy was performed after 3 months. This showed abnormal salmon colored mucosa suggestive of BE arising 1 cm from the LES at the 12, 6 and 9 o'clock positions, which had not been present previously (Fig. 2).

The furrowing and exudates seen previously had resolved. Four quadrant biopsies taken from the abnormal sites confirmed the histological presence of goblet cells, consistent with a diagnosis of BE intestinal metaplasia (Fig. 3). There was no evidence of dysplasia.

The number of intraepithelial eosinophils however had reduced proximally to 10/HPF and distally to 50/HPF (Table 1).

LK also had her first impedance study which showed an acid reflux index (ACI) of 2.1% on her current treatment. This, along with the detection of BE intestinal metaplasia, led to further optimization of LK's acid suppression from pantoprazole to esomeprazole 30 mg each morning and 20 mg each evening.

Three months later, biopsies from her third follow up gastroscopy showed residual EoE changes with 35 eos/HPF proximally and 24 eos/HPF distally. Gastric metaplasia was reported but this time there was no intestinal metaplasia. The budesonide slurry was increased from 0.5 mg BD to 1 mg BD. Despite adequate fasting there was a significant amount of bile and food in the stomach at time of gastroscopy. Hence LK was commenced on domperidone 5 mg BD as a prokinetic.

Her subsequent progress gastroscopy after three months revealed a moderate hiatal hernia for the first time. In addition, there was macroscopic erosive esophagitis. Biopsies revealed that her EoE was in remission (eosinophil count < 6 per HPF both proximally and distally). Biopsies taken above the Z-line showed only gastric metaplasia, with no sign of intestinal metaplasia. LK also had a repeat impedance study which again showed an elevated acid reflux index of 3.1% (Table 2) despite an increase in her acid suppression therapy three months prior. There was no improvement in the number of retrograde bolus movements (RBM), and LK continued to have prolonged acid reflux episodes and prolonged acid clearance time.

A High Resolution Esophageal Manometry (HREM) was performed. Significant esophageal dysmotility has been reported in all EA patients but HREM has only recently been used to delineate motility patterns [6]. The HREM was performed using a 36 channel solid state catheter (MD Solutions). This showed a hypotensive LES (6 mm Hg) and a moderate sized hiatal hernia. There were three different motility patterns seen with the wet and bread swallows. Peristalsis was seen only in the distal esophageal segment with 69%

of the wet swallows and 60% of the bread swallows. Complete absence of peristalsis was seen with 31% of the wet swallows. Pressurizations were seen with 40% of the bread swallows (Figs. 4–6). Based on these results, and the presence of a moderate hiatal hernia and erosive esophagitis, LK is planned for a floppy Nissen fundoplication.

2. Discussion

EoE has only recently been described in patients post EA/TEF repair [7]. This patient required frequent dilations for her symptoms in the first years of her life; more than would normally be expected even for a post Foker technique long gap repair. This raises the possibility that she may have already developed eosinophilic esophagitis earlier on. Unfortunately as she only had her first gastroscopy at age 4, there are no baseline biopsies to confirm or rule this out. A condition termed PPI-responsive Esophageal Eosinophilia (PPI-REE) has been described [8] however as our patient was already on PPI at the time of diagnosis of EoE it is more likely that she had true EoE rather than PPI-REE.

There have been recent reports in literature of a higher incidence of EoE in EA when compared to the general population. Our own group recently reported a 17% incidence of EoE in EA patients in a cohort of 103 EA patients [4]. One theory is that chronic



Fig. 2. Second gastroscopy showing abnormal salmon colored mucosa arising from LES.

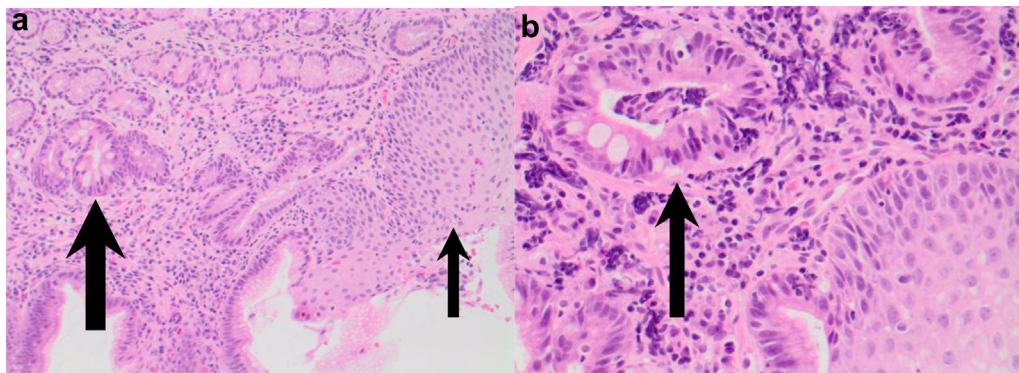


Fig. 3. Distal esophageal biopsies from second gastroscopy showing (a) eosinophilic infiltration of squamous mucosa (thin arrow) and intestinal metaplasia within glandular mucosa (thick arrow; H&E 200×) and (b) intestinal metaplasia confirmed by presence of goblet cells (thick arrow) in biopsy taken from abnormal colored mucosa (H&E 400×).

Table 1
Summary of our patient’s histological findings of sequential esophageal biopsies with follow-up gastroscopies.

Endoscopy (3 monthly intervals)	Eosinophils per high power field	Metaplasia present
1	55 proximally 80 distally	None
2	10 proximally 50 distally	Intestinal +ve
3	35 proximally 24 distally	Gastric +ve Intestinal –ve
4	<6 proximally and distally	Gastric +ve Intestinal –ve

Table 2
Summary of impedance study results.

	1st impedance study	2nd impedance study
Acid Clearance Index	2.2	3.1
Longest acid reflux episode (>5 min)	7.8 min	13.3 min
Mean acid clearance time (s)	60	114
Total RBM	25	27
Acidic RBM	10	15

exposure to acid damages the natural barrier of the esophageal epithelium, increasing permeability to foreign antigens. Esophageal dysmotility also prolongs exposure of the damaged mucosa to potential allergens [6] which may result in eosinophil chemotaxis secondary to activation of a T_H2 immune response. Another hypothesis is that some patients with EA have a genetic predisposition for developing EoE later in life. This is based on animal studies which showed that mice with EA have increased expression of eotaxin-3, which is also seen in patients with EoE [6].

The concomitant finding of EoE and BE (intestinal metaplasia) has also only rarely been reported. Ravi et al. [9] demonstrated EoE in 7% out of 200 adults with BE. A 2008 review of 1174 pediatric biopsies found EoE and BE coexisted in only 2 patients [10].

The prevalence of BE in children who have had EA repair has been estimated between 5%–15% [6]. It had previously been extrapolated that the lapse between primary EA repair and development of metaplasia is 10 years [11], hence the finding of intestinal metaplasia in our patient at this early age is of grave concern. The patient is the youngest in reported literature to have had Barrett’s changes post EA repair, and the first reported EA patient with both EoE and BE. She is also the first reported case of Barrett’s in a long gap EA patient who had primary repair using the Foker procedure.

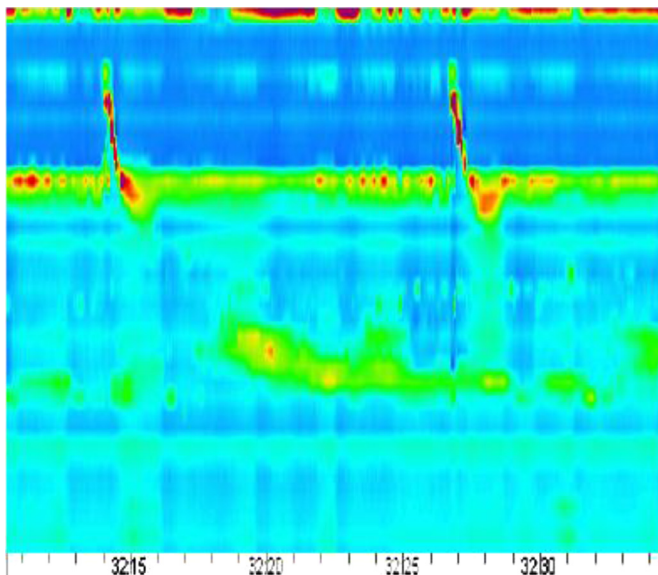


Fig. 4. Cookie swallow during our patient’s HREM showing only distal segment peristalsis.

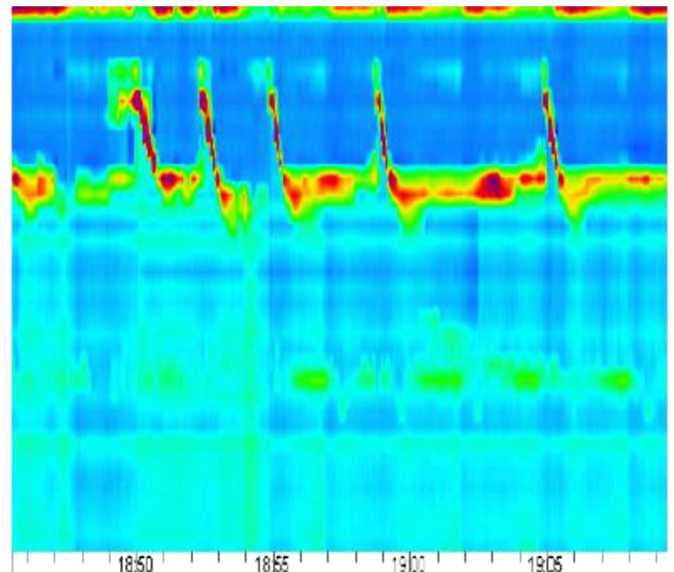


Fig. 5. Wet swallow during our patient’s HREM showing esophageal aperistalsis.

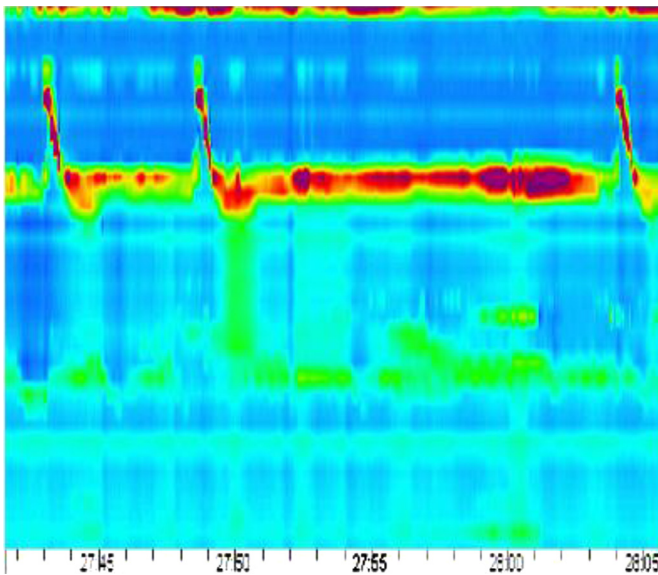


Fig. 6. Our patient's HREM showing pressurization with cookie swallow.

Regular surveillance endoscopies are necessary in EA patients due to the lack of correlation between symptoms and histology in EA patients. Nowhere is this better exemplified than in our patient who was referred only at age four.

In our patient, the severe changes due to EoE at the time of the initial endoscopy could have masked the underlying BE changes which became apparent upon treatment of EoE. To date, it remains unclear if EoE is also an independent risk factor to GERD for the development of BE. However the persistence of gastric metaplasia even after achieving remission with her EoE (and in light of her persistent reflux) suggests that in LK, her BE was likely to be secondary to severe GERD.

3. Conclusion

Our case highlights the importance of regular surveillance endoscopies in EA patients not only to exclude GERD but also EoE. To date our patient is the youngest at age 4 in whom BE intestinal metaplasia has been reported. Given the increased risk of malignancy in patients with BE and the higher risk of BE in EA patients, these patients will continue to require lifelong surveillance.

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Conflicts of interest

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Author contribution

Conception and design: U.K., L.-Z.T., A.J.G. Data collection: L.-Z.T., U.K., A.J.G., C.C., G.H. Data interpretation: L.-Z.T., U.K., A.J.G., C.C. Drafting the manuscript: L.-Z.T., U.K. Contribution to the final manuscript and important intellectual content: L.-Z.T., U.K., A.J.G.

References

- [1] Kovcsi T, Rubin S. Long term complications of congenital esophageal atresia and/or tracheoesophageal fistula. *Chest* 2004;126(3):915.
- [2] Rintala RJ, Sistonen S, Pakarinen MP. Outcomes of esophageal atresia beyond childhood. *Semin Pediatr Surg* 2009;18:50.
- [3] Papdoulou A, Koletzko S, Heuschkel R, Dias JA, Allen KJ, Murch SH, et al, for the ESPGHAN Eosinophilic Esophagitis Working Group and Gastroenterology Committee. Management guidelines of eosinophilic esophagitis in childhood. *J Pediatr Gastroenterol Nutr* 2014;58:107–18.
- [4] Dhaliwal J, Tobias V, Sugo E, Varjavandi V, Lemberg D, Day A, et al. Eosinophilic esophagitis in children with esophageal atresia. *Dis Esophagus* 2014 May-Jun;27(4):340–7.
- [5] Foker JE, Linden BC, Boyle EM, Marquadt C. Development of a true primary repair for the full spectrum of esophageal atresia. *Ann Surg* 1997;226(4):533–43.
- [6] Aspirot A, Faure C. Esophageal dysmotility: characterization and pathophysiology. *Dis Esophagus* 2013;26:405–9.
- [7] Gorter RR, Heij HA, Van der Voorn JP, Kneepkens CMF. Eosinophilic esophagitis after esophageal atresia. Is there an association? Case presentation and literature review. *J Pediatr Surg* 2012;47:E9–13.
- [8] Wen T, Dellon ES, Moawad FJ, Furuta GT, Aceves SS, Rothenberg ME. Transcriptome analysis of a proton pump inhibitor-responsive esophageal eosinophilia reveals proton pump inhibitor-reversible allergic inflammation. *J Allergy Clin Immunol* 2015;135(1):187–97.
- [9] Ravi K, Katzka DA, Smyrk TC, Prasad GA, Romero Y, Francis DL, et al. Prevalence of esophageal eosinophils in patients with Barrett's Esophagus. *Am J Gastroenterol* 2011;106:851–7.
- [10] Francalani P, De Angelis P, Minnei F, Diomedei Camassei F, Torroni F, Dall'Oglio L, et al. Eosinophilic esophagitis and Barrett's Esophagus: an occasional association or an overlap disease? *Digestion* 2008;88:16–9.
- [11] Schenider A, Michaud L, Gottrand F. Esophageal atresia: metaplasia, Barrett. *Dis Esophagus* 2013;26:425.