Eosinophilic esophagitis, Barrett's esophagus and esophageal neoplasms in the pediatric patient: a narrative review

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Abstract: There are several esophageal disorders that can occur in the pediatric population. Eosinophilic esophagitis (EoE) is an eosinophil predominant inflammatory disease of the esophagus that was first characterized in the early 1900's. EoE is the most common pediatric esophageal inflammatory condition after gastroesophageal reflux disease (GERD). Longstanding GERD is a known risk factor for the development of Barrett's esophagus (BE) in both children and adults. BE is associated with the development of dysplasia and, if left undiagnosed, may progress to the development of esophageal adenocarcinoma (EAC). EAC and esophageal squamous cell carcinoma (ESCC) comprise the majority of childhood esophageal malignant neoplasms. The prevalence of EoE continues to rise within the pediatric population. On the other hand, both BE and esophageal neoplasms remain extremely rare in children. The relationship between a chronic inflammatory condition like EoE to BE and/or esophageal neoplasms remains unclear. The current research of these disease entities is prioritized to further understanding the disease pathogenesis and disease progression, exploring new diagnostic modalities, and developing novel treatments or less invasive therapeutic options. The focus of the following narrative review is to provide a summary of the current clinical practices, future research and their implications on these various esophageal disorders.

Keywords: Barrett's esophagus (BE); eosinophilic esophagitis (EoE); esophageal adenocarcinoma (EAC); esophageal cancer

Introduction

Several esophageal disorders occur in the pediatric population. Eosinophilic esophagitis (EoE) is the most common pediatric esophageal inflammatory condition after gastroesophageal reflux disease (GERD). EoE is an eosinophil-predominant inflammatory disease of the esophagus that affects both pediatric and adult populations.

Although clinical presentation and endoscopic features of EoE may vary between both populations, similarities do exist. These similarities include the association with atopic conditions, underlining pathogenesis and disease complications. The relationship between GERD and EoE is quite complex and will not be covered in this narrative review. However, longstanding GERD is a known risk factor for the development of Barrett's esophagus (BE) in

both adults and children. BE is associated with development of dysplasia and, if left undiagnosed, may progress to esophageal adenocarcinoma (EAC). The prevalence of EoE is increasing in the pediatric population. On the other hand, both BE and esophageal neoplasms remain extremely rare in children.

Current research of these disease entities is prioritized to understanding disease pathogenesis and progression, new diagnostic modalities, and developing novel therapeutic options. In this narrative review, we will examine the current epidemiology, clinical practices and recent research and their implications on future practices.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tgh-20-223).

Methods

We conducted a literature review search on PubMed and MEDLINE using the terms "Pediatric", "Barrett's Esophagus" "Eosinophilic esophagitis", "esophageal adenocarcinoma" and "esophageal cancer" from January 1989 through April 2020.

Eosinophilic esophagitis

Epidemiology and clinical presentation

EoE involves antigen-mediated eosinophilic inflammation of the esophagus leading to esophageal dysfunction and clinical symptoms (1-5). In the United States, the prevalence of EoE is estimated at 57 per 100,000 with a male predominance of 3:1 (4,6,7). EoE affects all racial and ethnic groups, with increased prevalence in Caucasians (2,3,6).

Age-related differences in the clinical presentation of EoE in children and adults are appreciated (4,8). In younger children, symptoms include emesis, abdominal pain, nausea, reflux, feeding dysfunction, and failure to thrive (4,9). Feeding difficulties may present as dysphagia, food aversion, choking, gagging, or food impaction (10). Solid food dysphagia is the most common presenting symptom in adolescents and adults, and as many as 50% of adults initially present with food impaction (2,4). For this reason, an adolescent or adult with food impaction warrants further diagnostic evaluation for EoE (8). Other symptoms displayed in adults include reflux, chest discomfort, and upper abdominal pain (4,11). Atopic comorbidities, including asthma, allergic rhinitis, atopic dermatitis, and food allergies, are common (70–80%) in pediatric patients with EoE (2,5).

Diagnosis

EoE is a clinicopathologic disease, requiring both clinical and histologic findings consistent with the diagnosis. Thus, endoscopic evaluation by esophagogastroduodenoscopy (EGD) with esophageal mucosal biopsies is necessary. Endoscopic features suggestive of EoE include presence of edema, fixed esophageal rings, white exudates, linear longitudinal furrowing, mucosal fragility, and esophageal narrowing (Figure 1) (5,12). In the pediatric EoE population, inflammatory endoscopic features of edema, exudates, and furrowing are more common (4). Features may also be subtle and in some cases, the esophageal mucosa is normal in appearance (4,13). Progressive disease with chronic inflammation can lead to esophageal remodeling, which can lead to fibrostenotic endoscopic features such as rings, strictures, narrowing, and mucosal tears (10-12). On histology, findings of esophageal intraepithelial eosinophilia (≥15 eosinophils/high power field), basal cell hyperplasia, elongation of vascular papillae, intercellular edema (spongiosis), and degranulation of eosinophils are findings consistent with active EoE disease (Figure 2) (2,5,8,10,14-16). Pathologists can also identify subepithelial fibrosis when there is sufficient lamina propria in biopsy specimens (16). Histopathologic changes in EoE can be patchy; therefore multiple biopsies obtained from three levels (i.e., proximal, middle, and distal) of the esophagus are recommended to maximize diagnostic yield of EoE and to detect subepithelial fibrosis (16).

Both the diagnosis and management of EoE are dependent on mucosal biopsy for accurate diagnosis and to assess the response to therapy. Mucosal evaluation is most commonly performed by EGD. Less invasive modalities for monitoring EoE disease activity and response to therapy are being investigated. The Esophageal String Test (EST) is a minimally invasive technique that utilizes the Enterotest string device which is a gelatin capsule containing a nylon string that is swallowed and later withdrawn through the mouth. EST can detect active EoE inflammation by measuring biomarkers such as eotaxin-3 and major basic protein-1 (8,17,18). Luminal concentrations of eosinophil-
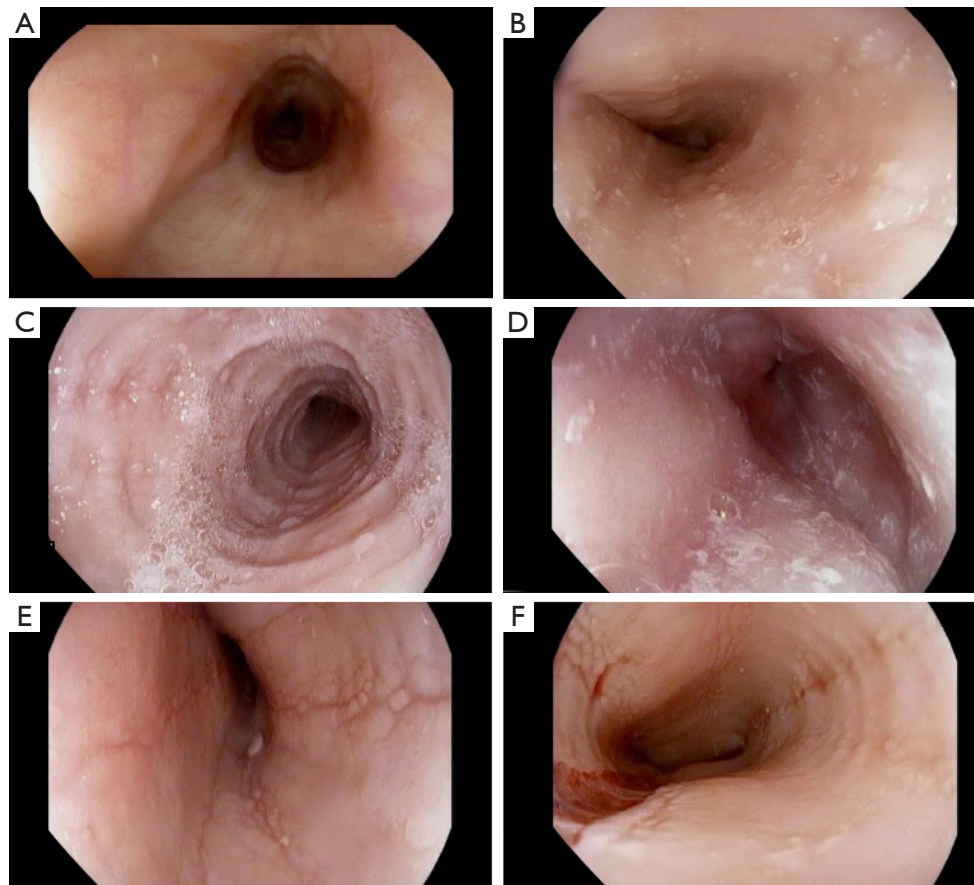
Figure 1 Endoscopic features in pediatric EoE. (A) Normal esophagus for comparison. Endoscopic features in pediatric cases with EoE include (B) esophageal mucosal edema with loss of vascular markings, (C) circumferential rings or trachealization, (D) exudates or white plaques, (E) vertical, longitudinal linear furrowing, or (F) crepe paper esophagus with mucosal fragility upon passage of the endoscope. EoE, eosinophilic esophagitis.

associated proteins obtained by EST were found to correlate with esophageal mucosal eosinophilic inflammation (17,18). A prospective, multisite study evaluating 134 subjects (both pediatric and adult) by Ackerman *et al.* demonstrated that a 1-hour EST accurately distinguishes active *vs.* inactive EoE in a less invasive and safe manner compared to endoscopic examination with biopsies (18). Unsedated transnasal endoscopy (uTNE) utilizes a small flexible endoscope for sampling esophageal mucosa and can be performed without anesthesia or sedation in select patients. Studies in pediatrics have shown that it is an adequate, well-tolerated, and cost-effective method of mucosal evaluation for monitoring disease activity in EoE (19,20). Currently the suitability of uTNE in pediatrics is an area under investigation by a network of academic pediatric gastroenterology centers. The Cytosponge is an encapsulated compressed mesh

sponge attached to a string. Once swallowed and in the stomach, the capsule dissolves and the sponge expands. Upon withdrawing the sponge through the mouth by the attached string, cells are sampled from the esophagus (8,21). Katzka *et al.* compared the adequacy and diagnostic accuracy of esophageal sample collection by endoscopy versus the Cytosponge in adult patients and found that samples collected by Cytosponge were adequate in evaluating epithelial activity in adult patients with EoE (21).

In contrast to the tests that sample the mucosa, the endoscopic functional luminal imaging probe (EndoFLIP) serves as an additional diagnostic modality that phenotypically characterizes EoE by assessing esophageal distensibility (i.e., 'stiffness') through the use of high resolution planimetry during endoscopy (8,22). Distensibility is defined as the measure of the esophageal
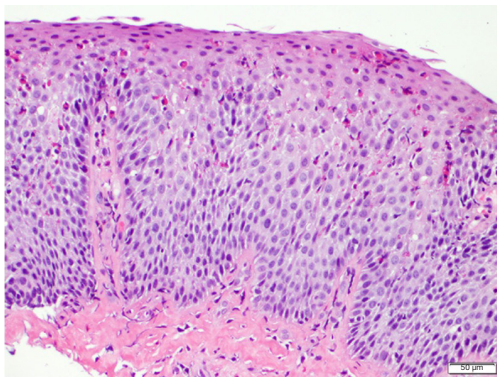
Figure 2 Histologic features of active EoE in a pediatric patient. Esophageal biopsy with evidence of intraepithelial eosinophilia (≥15 eosinophils/high power field), spongiosis, rete papillae elongation, and basal cell hyperplasia. Subepithelial fibrosis is seen in the lamina propria (H&E stain, 100× magnification). EoE, eosinophilic esophagitis.

luminal cross sectional area and distending pressure (23). In patients with EoE, esophageal distensibility is reduced compared to controls (23,24). The EndoFLIP might serve as an adjunctive tool to assess the extent of esophageal remodeling in EoE by measuring esophageal narrowing, strictures, and rigidity (23). Although there continues to be evolving technologies for the future of diagnosis and monitoring of EoE, upper endoscopy with biopsy remains the current standard of practice.

Treatment and management

The goal of EoE treatment is to mitigate ongoing esophageal inflammation, obtain symptom resolution, achieve histological remission, and prevent further esophageal remodeling. Treatment options include topical corticosteroids, proton pump inhibitor (PPI) therapy, and dietary therapy (14,25,26). However, there is no FDA-approved therapy for EoE.

Topical corticosteroids are quite effective for EoE and have demonstrated a disease remission rate of 50–60% (2,27). The challenge with use of topical corticosteroids is ensuring effective delivery of the medication to the entire luminal surface of the esophagus (2). Currently, oral viscous budesonide slurry and swallowed aerosolized fluticasone are the most common and accepted means of administration. A multicenter Phase 3 randomized, placebo-controlled, double-blind trial in adult patients evaluated the use of a newer formulation of budesonide in patients with active EoE (28). This study demonstrated the effectiveness of an orodispersable budesonide tablet formulation in inducing clinical, histological and endoscopic remission in EoE compared to placebo (58% *vs.* 0%, P<0.0001) (28).

PPI therapy has a 40–50% success rate for achieving histological remission in EoE (29,30). The potential anti-inflammatory and antioxidant properties of PPIs are thought to contribute to its efficacy (31). PPIs have anti-inflammatory properties that suppress expression of IL-13-induced-eotaxin-3, an eosinophil attractant, in the esophageal epithelium, thereby potentially reducing recruitment of eosinophils into the esophagus (3,32,33). Recent EoE guidelines consider PPIs a potential early or initial therapeutic option due to their low cost, safety profile, and efficacy (5,27,31).

Food allergens and aeroallergens play a role in the pathogenesis of EoE (14). Dietary modification is considered an acceptable treatment modality for EoE (14,34). Three distinct dietary approaches have been utilized including the elemental diet, empiric food elimination diet, and allergy testing-directed elimination diet (2,14,33). The elemental diet is restricted to an amino acid-based formula without any intact dietary protein (14,34). In a systematic review analyzing the efficacy of dietary interventions in inducing EoE disease remission, an elemental diet had a near 90% success rate (35). Empiric food elimination diets exclude the most common food allergens: cow's milk, egg, soy, wheat, peanut/tree nut, and fish/shellfish (14). In children with EoE, histological remission was seen in 74% of children treated with the six-food elimination diet (36). Allergy testing-directed diet therapy was less successful, exhibiting remission in only 45% of cases (35).

Due to the chronic inflammatory nature of EoE, esophageal strictures and narrowing may result from ongoing esophageal remodeling unresponsive to treatment (37). In these cases, esophageal dilation (bougie or balloon technique) may be used in the management of fibrostenotic lesions or as adjuvant therapy to aid in clinical symptomatic relief (33,37-39). While dilation can improve areas of stenosis, it does not treat the inflammation due to esophageal eosinophilia (30).

The pathogenesis of EoE involves inflammatory infiltrates including eosinophils, T-cells, mast cells, and their chemokines and cytokines, such as interleukin (IL)-4, IL-5 and IL-3 (33,39,40). Therapies have been developed to target these specific immune pathways (39). Dupilumab

is a human monoclonal antibody against the IL-4 receptor that inhibits IL-4 and IL-13 signaling and is an effective treatment of several allergic and atopic diseases (27). In a 12-week multicenter, randomized, double-blind, parallel group, placebo-controlled Phase 2 study of adult patients with active EoE, dupilumab reduced dysphagia and histological and abnormal endoscopic features of EoE compared with placebo, and was overall a well-tolerated drug (27). Participants enrolled in this study were required to remain on a stabilized diet 6 weeks before screening and throughout completion of the study. Additionally, they were prohibited to utilize concomitant medications for the treatment of EoE, immunotherapies, investigational drugs other than Dupilumab, and could not start PPI therapy unless having been using the medication in the 8 weeks before screening. Mepolizumab and reslizumab are monoclonal antibodies targeting IL-5. Despite a decrease in esophageal tissue eosinophilia with these drugs, symptomatic improvement has been inconsistent. Potential clinical benefit requires additional studies (27,41). Sialic acid binding immunoglobulin-like lectins (Siglecs) are transmembrane protein receptors expressed on eosinophils. AK002, an antibody directed against Siglec 8, causes apoptosis of human eosinophils (39,41). There is an ongoing phase 2/3 randomized, placebo-controlled trial to assess its safety and efficacy in adolescent and adult patients with active EoE (ClinicalTrials.gov. NCT04322708). Participants in this study are excluded if they have used of oral corticosteroids within 8 weeks prior to screening, had a change in dose in PPI therapy of dietary therapy within 4 weeks prior to screening, or used immunosuppressants or immunomodulatory drugs within 12 weeks prior to screening.

Barrett's esophagus

Epidemiology and clinical presentation

BE is defined as the presence of metaplastic intestinal-type columnar epithelium that has replaced the normal squamous epithelium lining of the esophagus (42,43). BE predominantly presents in adults, with a prevalence of 1% to 2% of all patients referred for upper endoscopy. BE is seen in approximately 5–15% of patients exhibiting symptoms of gastroesophageal reflux (GER) (44-46). The prevalence of BE in children varies between 0.05% to 4.8%, with a mean age 12.4 years at diagnosis (46,47). The main risk factor in both adults and children is longstanding GER. BE

has been identified in children with reflux after a period of 5.3 years (46). Predisposing risk factors for children include tracheoesophageal abnormalities, neurological impairment, chronic lung disease, hiatal hernia, and increased body mass index in patients without underlying conditions (46,47). In adults, additional risk factors include male gender, central obesity, age over 50 years, tobacco usage, Caucasian race, and family history in a first-degree relative (43,45,48).

Since pediatric BE is rare, there is a paucity of data to suggest that pediatric BE portends a worse prognosis compared to adult BE. However, as previously mentioned, studies in adults have indicated that long duration of GERD symptoms are a risk factor for BE (44-46). Furthermore, there are no specific guidelines available for screening or treatment in children with BE. As the prevalence of pediatric BE increases, pediatric guidelines for screening and management will be warranted. Overall, practice guidelines on the diagnosis and management of BE in adults recommend screening in only patients that meet the identified risk factors including men with chronic reflux disease (>5 years) and two or more risk factors (42,43,45). The American College of Gastroenterology (ACG) suggests, in women, to screen those with multiple risk factors (42,45).

Diagnosis

The diagnosis of BE requires identification of salmon colored mucosa extending into the esophagus at least 1 cm proximal to the gastroesophageal junction (GEJ) combined with histological confirmation of intestinal metaplasia (IM) exemplified by the presence of goblet cells (*Figure 3*) (42). Biopsies from four-quadrants at 2 cm intervals should be obtained over the length of the BE segment during endoscopy (43,45). If BE is suspected, at least eight random biopsies from the segment should be obtained in order to maximize the yield of IM on histology (42,49). In the case of short segments (i.e., <3 cm) of suspected BE, at least four biopsies per cm of circumferential BE and one biopsy per cm in tongues of BE should be obtained (42). If BE is suspected, but there is lack of IM on histology, a repeat endoscopy should be considered in 1–2 years (42).

BE is associated with the development of EAC (43). The risk of cancer progression in BE is 0.2–0.5% per year in patients with nondysplastic changes and up to approximately 6% per year in patients with evidence of high-grade dysplasia (42). The goal of endoscopic
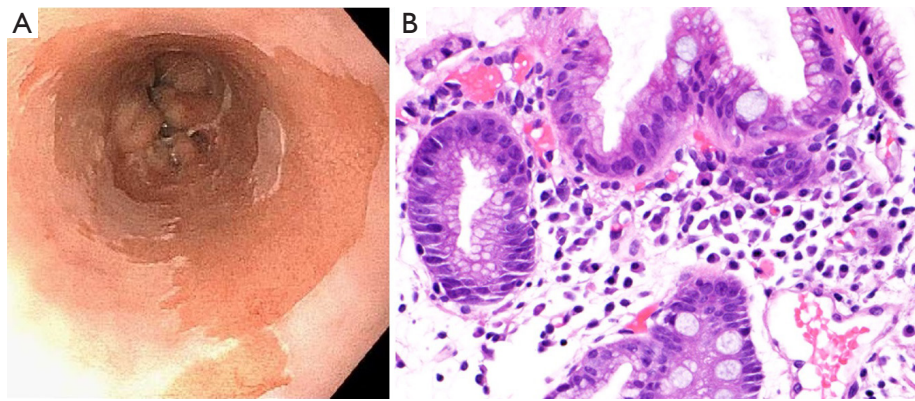
Figure 3 BE. (A) Endoscopic image of BE in an adult patient with evidence of salmon colored mucosa extending proximally into the esophagus. (B) Histology of BE in a pediatric patient includes columnar epithelium with IM and the presence of goblets cells (H&E stain, 400× magnification). BE, Barrett's esophagus; IM, intestinal metaplasia.

surveillance is to detect dysplasia at an earlier stage. The degree of dysplasia (no dysplasia, low grade dysplasia, high grade dysplasia, adenocarcinoma) determines recommendations for surveillance intervals and the need for endoscopic eradication therapy (EET) (42,43,45). Endoscopy is regarded as the gold standard for screening and is optimally performed utilizing high-resolution/high definition white light endoscopy to visualize mucosal detail (42,43,45). Advanced imaging technologies for endoscopic surveillance have been developed in an attempt to improve detection. These include dye-based chromoendoscopy, electronic chromoendoscopy such as narrow-band imaging, volumetric laser endomicroscopy and confocal laser endomicroscopy (43,50).

Less invasive diagnostic methods have been studied in BE, including the uTNE and the Cytosponge Cell Collection Device. uTNE can be considered as an alternative method to conventional upper endoscopy for BE screening with comparable performance characteristics compared to endoscopy (sensitivity 98% and specificity 100%) (42,45,51). The Cytosponge is a well-tolerated device that obtains esophageal tissue samples for testing of protein biomarkers and has a 73% sensitivity and 94% specificity for the diagnosis of BE (42). The EsoCheck Cell Collection Device, a retractable balloon attached to a string that, when swallowed, gathers cell from the distal esophagus that can be used to detect DNA markers of BE (45). Another novel device is the wide-area transepithelial sampling with three-dimensional computer-assisted analysis (WATS-3D). WATS-3D utilizes a brush to sample layers

of the esophageal epithelium. When used in addition to endoscopic forceps biopsy, WATS-3D increased the overall detection of BE in adults (52).

Treatment and management

Among patients with BE, symptoms of GER should be managed with use of daily PPI therapy to maximize acid suppression and treat esophagitis, unless symptoms require twice daily dosing for reflux symptom control (42,43,45). Moreover, studies have shown that use of PPI therapy decreased the risk of neoplastic progression in patients with BE (25,53). Long-term exposure (>3 years) of PPI therapy was associated with a lower risk of EAC and/or BE with high grade dysplasia (53). While it has been proposed that long term PPI use can potentially lead to the development of gastric adenocarcinoma or gastric neuroendocrine tumors through mechanisms that promote pan-colonization of *H. pylori* or hypergastrinemia, respectively, current studies have not supported an association of long term PPI use with gastric cancers, neuroendocrine tumors, or premalignant changes (54-57). In a randomized, double blind placebo controlled trial that followed participants over a medium 3-year period, it was found that pantoprazole was not associated with long-term harmful outcomes with the exception of enteric infections (58). Thus, in cases where PPI use is clinically needed, the benefits outweigh the risks.

EET plays an important role in the management of BE, dysplasia, and early EAC. Patients with evidence of nodularity or visible abnormalities in the BE segment

should undergo endoscopic mucosal resection (EMR) of the lesion as both a diagnostic and therapeutic maneuver (42,43). Endoscopic ablative therapies are not recommended in patients with nondysplastic BE due to the low risk of progression to EAC (42,43). However, ablative therapies are considered the preferred treatment strategy for patients with confirmed low grade dysplasia or high grade dysplasia (42). Radiofrequency ablation (RFA) is the most commonly used ablative modality, with high rates of complete eradication of intestinal metaplasia (CEIM) and dysplasia (42,44,59). Cryotherapy involves rapid freezing and slow thawing of tissue resulting in cellular injury through the use of various cryogens and can be used in BE refractory to RFA (60). These endoscopic eradication therapies have not been described for the use of BE in pediatric patients.

Esophageal neoplasms

Epidemiology and clinical presentation

Esophageal neoplasms are extremely rare in children. EAC and esophageal squamous cell carcinoma (ESCC) comprise the majority of childhood esophageal malignant neoplasms, however several benign neoplasms have been reported. Esophageal neoplasms in children are summarized in *Table 1* (61-75). Caustic ingestion, tobacco use, and history of esophageal atresia repair are considered risk factors for both EAC and ESCC (61,62). Both EAC and ESCC, found near or at an anastomotic site, are seen as long-term sequela (>30 years) after reconstruction of esophageal atresia (76-78). It is speculated that after repair, long-standing GERD, esophageal stasis, and mucosal damage lead to the development of these malignancies (76). GER and BE are considered risk factors for EAC (61,79). Approximately 60% of pediatric patients with EAC have pre-existing conditions associated with GER, such as hiatal hernia, esophageal atresia repair, and obesity (62). In a case series of fourteen pediatric patients with EAC, 78% of cases were associated with BE, suggesting that, similar to adults, BE is a strong risk factor for the development of EAC (61).

The most common presenting symptoms of esophageal carcinomas and other neoplasms in children are progressive dysphagia and weight loss (*Table 1*) (61-75). In adults, EAC predominantly develops in the lower one-third of the esophagus. However, in approximately 40% of pediatric EAC cases, the lesion can be found above the distal esophagus (61,63).

Diagnosis

Survival is dependent on various factors including disease stage, prompt diagnosis, growth pattern, tumor location, and rate of growth (62,64). Better outcomes for EAC are seen with surveillance endoscopy and early detection of the disease (45). In a study examining adult patients with BE that developed EAC, 49.3% of patients were in BE surveillance programs and diagnosed by endoscopy. These patients were more likely to be diagnosed at an early stage, have longer survival and have lower cancer-related mortality (80).

Pediatric diagnostic and treatment guidelines for esophageal cancer are not well established due to the rarity of esophageal neoplasms in childhood, thus we focus on review of adult literature and studies. In patients with suspected esophageal neoplasms, diagnosis typically combines information from imaging of the thorax, upper endoscopy or other procedural intervention to obtain histology, and a multidisciplinary evaluation by surgery and oncology specialties. Diagnosis is confirmed by histological review of biopsy tissue (61).

Treatment and management

Surgical esophagectomy is considered the treatment of choice for submucosal cancers, poorly differentiated cancers, or cancers with a high risk of lymph node metastasis (42,81). Less invasive surgical resection techniques can be considered. In a retrospective study comparing conventional open esophagectomy (OE), minimally invasive esophagectomy (MIE), and Hybrid esophagectomy, there was no significant difference between the three techniques for the outcomes of lymph nodes retrieved, resection margin-positive disease, and tumor recurrence (82).

Other treatment options in adults include adjuvant chemotherapy and EET (81). EET, which includes EMR and endoscopic ablative techniques such as RFA and cryotherapy, has demonstrated safety and efficacy for eradication of IM and disease remission with few adverse effects (59,81,83,84). Early data in adults suggests the use of immunotherapies as possible treatment options for advanced gastrointestinal (GI) cancers, although there are limited approvals to date (85-87). These types of therapeutics include immune checkpoint inhibitors such as ipilimumab (CTLA-4 inhibitors), nivolumab and pembrolizumab (PD-1/PD-L1 inhibitor), and tyrosine kinase inhibitors targeting human epidermal growth factor

Table 1 Esophageal neoplasms in childrens

Type of esophageal neoplasm	Incidence and prognosis	Tumor characteristics	Clinical symptoms	Treatment	Reference
Esophageal adenocarcinoma (EAC)	High frequency of metastasis; 19 pediatric cases reported; Male predominance	32% cases had BE in surrounding areas; Commonly found in the distal esophagus and GEJ	Most common is dysphagia (83%); Weight loss (55%), anemia, dehydration, nausea	Resection (total esophagectomy, partial esophagectomy, esophagogastrectomy); Radiotherapy; Chemotherapy	(61-63)
Esophageal squamous cell carcinoma (ESCC)	23 pediatric cases reported; No gender predominance	Occurrence is evenly distributed within esophagus	Most common is dysphagia; Weight loss, anemia, dehydration, nausea	Resection (total esophagectomy, partial esophagectomy, partial esophagogastrectomy); Radiotherapy; Chemotherapy	(61,62)
Esophageal sarcomas	0.1–1.5% of all esophageal tumors	Most frequently occur as polypoid intraluminal masses; CT/MRI imaging shows enhancing intramural mass	Most common is dysphagia; Weight loss, regurgitation, chest discomfort, respiratory distress	Resection (endoscopic resection, esophagotomy with local excision); Chemotherapy; Radiotherapy	(64-66)
Esophageal leiomyoma	2.6% of cases occurred in children; 22% cases are associated with a familial syndrome (familial leiomyoma and Alport's syndrome); Female predominance	Predominantly diffuse form (91%) as opposed to localized lesions (9%)	Most common is dysphagia; Dyspnea, vomiting, coughing, retrosternal pain	Resection (esophagogastrectomy, esophagectomy, enucleation)	(67,68)
Granular cell tumor (GCT)	Most cases of esophageal GCT have a benign course	The esophagus is the most common site of GCT in the digestive tract; Most cases are solitary lesions; Endoscopic features: yellow, firm, polypoid submucosal mass	Most cases are asymptomatic and found incidentally; Cases with tumor size >1–2 cm may report dysphagia	Resection (EMR, surgical excision)	(69,70)

Table 1 (*continued*)

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Table 1 (*continued*)

Type of esophageal neoplasm	Incidence and prognosis	Tumor characteristics	Clinical symptoms	Treatment	Reference
Infantile myofibroma	Benign neoplasm	One-third of myofibromas are found in the region of the head and neck	1 case presenting as proximal GI obstruction	Surgical resection	(71)
		Occur as solitary, multicentric or multicentric with visceral involvement		Chemotherapy	
		Histologic features: proliferation of fibroblasts, myofibroblasts or both with intravascular growth		Radiotherapy	
Inflammatory myofibroblastic tumor (IMT)	Low-grade neoplasm with potential for local invasion	Occurs in soft tissue and viscera, with esophageal location considered rare	Dysphagia, chest pain, globus sensation, emesis, weight loss, cough, fever	Resection (esophagectomy)	(72)
	6 pediatric cases reported				
Plexiform fibromyxoma (PF)	Follows a benign course after resection	More commonly occurs in the stomach, with preference for the gastric antrum	–	Resection (local excision, thorascopic resection)	(73)
	1 pediatric case reported	Endoscopic features: lobulated intramural/ submucosal pale, pink-tan or red colored, firm mass			
	Male = female				
Plexiform schwannoma (PS)	Benign neoplasm originating from peripheral nerve sheath	Rarely found in the GI tract	–	Resection (local excision)	(74,75)
		Histologic features: tumors with cellular growth pattern			

GEJ, gastroesophageal junction; EMR, endoscopic mucosal resection; GI, gastrointestinal.

receptor 2 (HER2) (85-87). There is an active phase1 study being conducted at the University of Oxford evaluating the combination of an ATR inhibitor with chemoradiotherapy in esophageal cancers in patients 16 years of age or older (ClinicalTrials.gov. NCT03641547). *Table 1* lists the treatment strategies that have been reported in prior case reports, however no common treatment strategies are established in children.

Although esophageal neoplasms in childhood are rare, they should be considered in the assessment of pediatric patients presenting with symptoms of progressive dysphagia and weight loss or with underlying risk factors.

Conclusions

EoE is the most common pediatric esophageal inflammatory condition, second to GERD. The EoE field is rapidly evolving as the incidence and prevalence continue to rise. Since EoE often starts in childhood and progresses to adulthood, new studies and clinical guidelines involve joint effort from pediatric and adult specialists. In contrast, BE and esophageal neoplasms rarely occur in childhood. The relationship between a chronic inflammatory condition like EoE to BE and/or esophageal neoplasms is uncharted. However, increased awareness of and diagnostic screening for EoE in the pediatric population, might have some indirect effect on detecting BE and incipient esophageal neoplasms. Thus, future observational studies will be essential to exploring the relationships between these diseases.

Acknowledgments

Footnote

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