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Endoscopic Management of Esophagorespiratory Fistulas

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I. INTRODUCTION

Esophagorespiratory fistulas (ERFs) are pathologic communications between the esophagus and any portion of the respiratory tract. ERFs lead to recurrent aspiration that can cause lethal pulmonary infections and significantly decrease quality of life for patients.[1,2] Treatment of ERFs has been shown to not only improve dysphagia and aspiration, but also lead to increased survival times.[3] While there is limited outcome data to guide clinical decision-making, the purpose of this review is to describe the current literature that supports the various endoscopic techniques utilized to manage ERFs.

II. ETIOLOGY

ERFs are classically divided into two broad categories, acquired and congenital, of which congenital are more common.[4] Acquired ERFs can be further subdivided into benign and malignant. Benign ERFs can be iatrogenic and caused by luminal procedures such as bronchoscopy, endotracheal intubation, gastrointestinal endoscopy, or as a complication of esophageal stent placement.[5,6,7] Esophageal inflammation and diverticulum are other known benign causes of ERF.[4]

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Malignant ERFs are a devastating complication of esophageal, lung cancer, large B-cell lymphoma, neuroendocrine tumors, and other tumors.[8] They are associated with lower patient survival times and clinical success rates when compared to patients with benign fistulas. Balazs described the incidence of fistulas in patients with esophageal cancer to be between 0.9 and 22%, but these may occur more frequently than documented given their difficult diagnosis at the end stage of malignant disease.[1,2] ERFs in malignancy are usually a complication of disease progression and nearly half of patients with ERF have metastatic disease at the time of diagnosis.[9] Palliative oncologic treatments including chemotherapy and radiation are not thought to directly cause ERF. Instead, they lead to ERF formation either by increasing survival times or decreasing tumor burden without leaving necessary tissue to maintain patency of the lumen.[1,2]

ERFs can be located at any point along the esophagus and respiratory tract. ERF in the proximal and mid-esophagus are most common. Fisutlae in the proximal esophagus have been shown to be the most difficult to manage and associated with the most adverse events and shortest survival time, while patients with distal ERF have the longest survival.[8] Patients with mid-esophageal fistulae have intermediate survival. This may reflect the anatomic proximity of the proximal esophagus to the trachea, allowing for widespread contamination of both lung fields on aspiration.

III. NON-ENDOSCOPIC MANAGEMENT OF ERF

A. Operative Management

Operative management such as esophageal bypass with reconstruction, thoracotomy with direct suture closure, and esophageal defect with pedicled soft tissue flap interposition are treatment options in select patients, although these are all major surgical undertakings.[10,11] For patients with acquired, non-malignant ERF, surgical options may provide the best opportunity for full recovery in good operative candidates. The choice of surgical technique is dependent on the etiology, size, and location of the fistula. Pre-operative requirements such as Eastern Cooperative Oncology Group (ECOG) status of 0-2 and lack of metastatic disease make surgery prohibitive for many patients with malignant ERF.[9] Indeed, the vast majority of patients with malignant ERF are poor surgical candidates at the time of presentation and other palliative and therapeutic interventions are typically considered.

B. Concurrent Chemoradiotherapy (CCRT)

Historically, the presence of a malignant ERF was considered a relative contraindication for CCRT, but recent evidence has demonstrated significantly increased survival with CCRT in esophageal squamous cell carcinoma (SCC) complicated by ERF.[12] Koike et al. studied the effect of 5-fluorouracil and cisplatin combined with full dose radiotherapy in patients with esophageal cancer complicated by malignant ERF. They found complete closure of esophago-mediastinal fistulae in 3/3 patients but only 4/13 patients with esophago-respiratory fistula achieved clinical success. A more recent study showed that CCRT combined with enteral nutrition can achieve promising improvement and closure of malignant fistulae.[13]

IV. ENDOSCOPIC MANAGEMENT

A. Bronchoscopy Monotherapy

Some patients may have contraindications to endoscopic management such as non-passable esophageal obstruction by tumor.[14] Several studies have demonstrated successful endotracheal or endobronchial stent placement with improvement in clinical symptoms.[14,15,16] However, the anatomical complexity of the respiratory system makes airway stenting a more challenging procedure compared to esophageal stenting. In addition to multiple branch points, different airway locations vary in their diameter, thickness, and nearby anatomic structures. These factors require that different airway stents are utilized according to the size and location of the malignant ERF.[14]

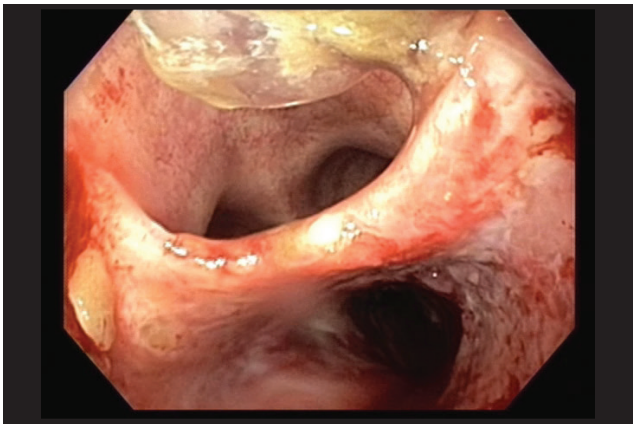

Figure 1a. Endoscopic image of a large tracheoesophageal fistula believed to be secondary to radiation therapy. Note airway lumen at top of image (tip of endotracheal tube is visible in the airway) and esophageal lumen visible at the bottom of the image

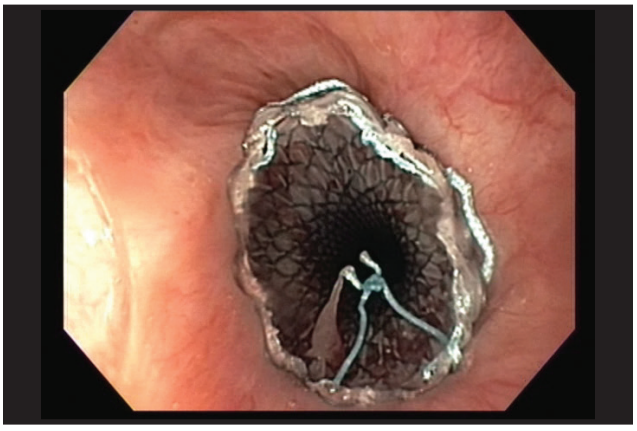

Figure 1b. Same patient as in Figure 1a after placement of an esophageal stent.

B. Esophageal Monotherapy

a. Esophageal Stents

The first stents to treat ERFs were rigid plastic tubes and were associated with a variety of complications and these older stents are now obsolete.[17] Esophageal intubation in the form of self-expanding metal stents (SEMS) was first introduced in the 1980s for palliation of esophageal stenosis, and is currently the gold

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standard for endoscopic management of malignant ERFs.[18] Advantages of SEMS include their ability to be constrained to small diameters on a delivery catheter, thus largely eliminating the need for pre-insertion dilatation.[19] (Figure 1)

SEMS may be or fully covered or partially covered. Partially covered stents have the advantage of anchoring and embedding into the esophageal wall making them less prone to migration, but are susceptible to tumor ingrowth.[20] In contrast, covered stents have higher rates of migration, but have been shown to have better palliation because of decreased need for re-intervention secondary to recurrent dysphagia.[21] Covered stents are more easily retrieved. Thus, stent choice depends on the expected risks of stent migration or tumor overgrowth for the particular patient.

The literature reports high technical success rates defined by complete ERF closure following esophageal stent placement of nearly 100%.[17] Adverse events have been reported in as many as 40% of patients but are generally minor.[8] Complications of stent placement in ERF include aspiration, malposition, migration, ERF progression, and perforation.[22] Stent migration is a common complication with a rate of 25 to 32% and may be secondary to insufficient expansion, tumor shrinkage due to chemo or radiation therapy, lack of a stenosis to help anchor the stent, or stent malposition.[23]

b. Over-the-Scope Clips

Endoscopically placed clips are an established method of sealing ERF. Through-the-scope clip (TTS) technology has been available for over 10 years and most endoscopists now have access to over-the-scope clips (OTSC), which are much larger than TTS clips.[24] The OTSC system consists of a nitinol alloy clip that is equipped with teeth. The clip is preloaded on an applicator cap and mounted on the endoscope tip. The OTSC devices are available in several different sizes and configurations. OTSC have been used to treat ERFs due to their ability to grasp more tissue and provide greater compressive force.[25,26] They have been generally used for treatment of small defects.[27] Large ERF may be difficult to close by any method, including OTSC devices.

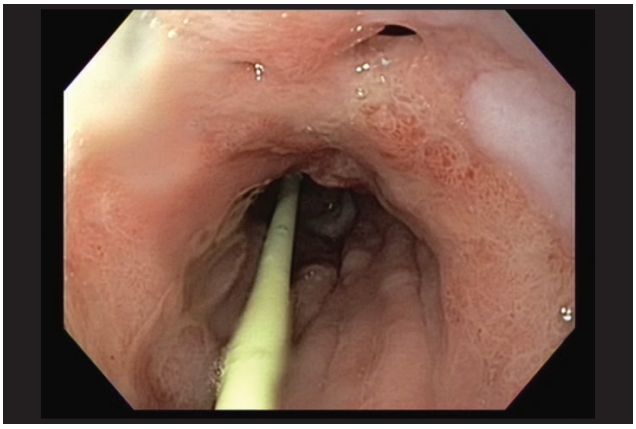

Figure 2a. Multifocal tracheoesophageal fistulas in a patient following esophagectomy for esophageal cancer.

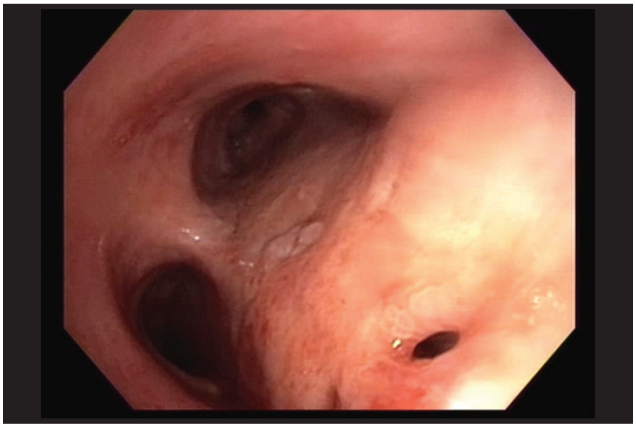

Figure 2b. Bronchoscopic view of the same fistulas shown in Figure 2a.

The OTSC method has lower therapeutic efficacy for closing fistulae when compared to esophageal perforations and leaks.[27,28] The main barrier for successful sealing of ERF with OTSC is the ability to completely approximate the borders of the defect and suction damaged tissue inside the cap because ERF often have fibrotic and retracted rims. However, there are studies showing promise for treating ERFs with OTSC in conjunction with other interventions. A recent multicentre retrospective study examined 5 patients with OTSClips alone or in combination with esophageal stents, airway stents, or with stents and endoscopic sutures.[8] One patient in this study had OTSC monotherapy and did not achieve clinical success. The remaining four patients with combination therapy achieved technical and clinical success in 4/4 patients. Additionally, evolving OTSC technology such as the Padlock Clip show promise for improved efficacy of these devices to treat ERFs.[26,28]

c. Atrial Septal Defect (ASD) and Ventricular Septal Defect (VSD) Occluders

A novel method for endoscopic closure of ERF is the use of ASD and VSD occlusion devices. These devices have been used for percutaneous closure of cardiac septal defects since the 1970s with a goal of inducing an endothelial response and closure of the defect.[29] The device typically consists of two nitinol, self-expanadable, polyester coated discs connected by a thin waist that is compressed inside a loaded catheter. The two discs have different diameters after deployment.

The first reported successful closure of an ERF with a VSD occluder device was performed in 2006 after a patient with non-malignant ERF had failed other endoscopic options.[30] Since then, ASD occluder devices have also been utilized with varying clinical success.[31,32] The device is placed by maneuvering a guide wire endoscopically with fluoroscopic assistance into the fistula orifice from the esophageal side, and threading the wire through the hypopharynx such that both ends come out of the mouth. The occluder is then threaded through either orifice and deployed with one disc on either side of the fistula.

The most significant complication reported from use of ASD and VSD occluders is device migration to the airway, which may occur from incorrectly sized devices, physiologic esophageal peristalsis, extrusion by external source, or enlargement of the fistula.[33,34] These patients often present with severe cough from bronchial obstruction by the device or pneumonia. Jiang describes a theoretical solution to this problem by using an endotracheal approach and placing the larger, distal disc in the esophagus.[35] The structural design of the device favors its permanence. As it anchors into the fistula, it stimulates an inflammatory response and promotes granulation tissue and re-epithelialization over the device.

d. Parallel Airway and Esophageal Stenting

Combined placement of stents in both the esophagus and the tracheobronchial tree is another endoscopic method that has been utilized for treatment of benign and malignant ERF.[36,37,38] (Figure 2) This method may be advantageous in circumstances in which there is concern for airway compression by an expanding esophageal stent, or in patients with combined symptoms of dysphagia, aspiration, and dyspnea. The stents are similar to those for monotherapy and include SEMs and airway Y stents or self-expanding metallic airway

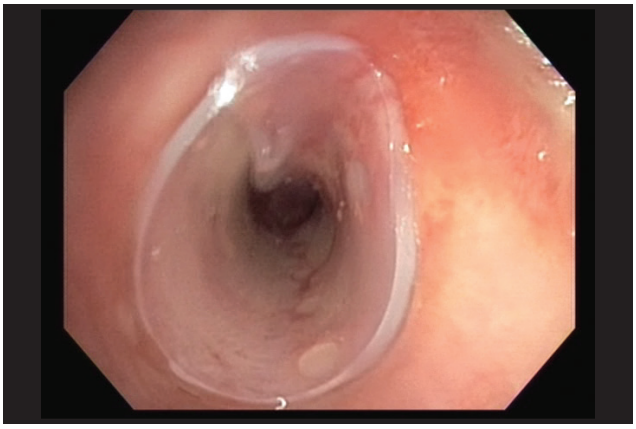

Figure 2c. Bronchoscopic view after placement of a Y-stent in the airway

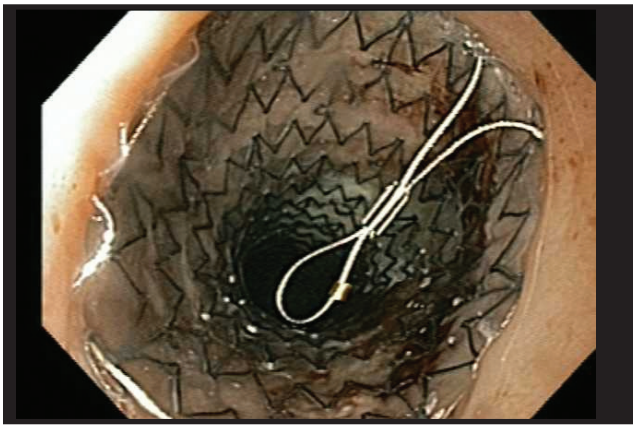

Figure 2d. Endoscopic view after placement of an esophageal stent immediately after airway stent placement.

stents.[38] The procedure is typically performed under general anesthesia, with airway stenting often performed first due to the small risk of airway compression by the expanding esophageal stent.[39] A retrospective analysis by Schweigert demonstrated complete seal of malignant ERF in 9/9 patients using the parallel stent technique without anesthesia related complications.[36] Five out of nine were able to have additional chemo or radiation therapy and 7/9 were able to return home. A more recent, larger study by Wlodarczyk examined 31 patients with malignant ERF and documented technical success in 100% of patients.[39] Only 4 patients required re-intervention because of fistula recurrence, and nearly all patients achieved improvement in degree of dyspnea and dysphagia.

The most feared complications of dual stenting for ERFs are massive bleeding and respiratory

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compromise.[38,39,40] The close proximity of the parallel stents may lead to pressure necrosis causing bleeding and, in rare cases, death. Binkert reported pressure necrosis when Gianturco-Rösch Z stents were used, as a result of tissue erosion at sites where stent struts were in direct opposition causing bleeding from the esophageal venous plexus. Wlodarczyk reported bleeding events in 7/31 patients with malignant ERF.[39] A more recent study of 8 patients treated with dual stent placement, however, demonstrated similar adverse events to esophageal monotherapy without any major complications.[8]

The American College of Chest Physician Guidelines reports a grade C recommendation for stenting of both the esophagus and tracheobronchial tree to achieve the best results for symptom relief.[41] Increased survival time in patients that received dual stenting for malignant ERF compared to airway stenting alone has been demonstrated in a larger, prospective study.[36]

e. Other Methods

Other methods that have been utilized for closure of ERF include fibrin glue, sutures, polyglycolic acid sheets, and argon plasma coagulation. Typically, these methods are used in conjunction with the aforementioned endoscopic techniques to promote direct closure of the fistula. Evidence for their use alone is limited but encouraging.

Fibrin glue is made of thombin and fibrinogen. With the addition of calcium and factor XIII, thrombin converts fibrinogen to fibrin and stimulates scar formation at the fistula site.[42] Most of the literature on the use of fibrin glue for ERF comes from the pediatric population, where it is used for endoscopic management of congenital ERF. In select pediatric patients it has been shown to reduce morbidity and recurrence when compared to open approaches or alternative endoscopic techniques.[42] Data is more sparse in the literature with regards to adult patients, however a study by Lippert et al identified 26 patients with fistulas in the esophagus treated with fibrin glue.[43] Nine of these patients achieved success with fibrin glue alone, while the remaining 17 patients required either additional endoscopic therapy with stents or surgical intervention. A case report of a patient with a small, benign ERF secondary to mechanical ventilation demonstrated complete healing of the fistula after bronchoscopic administration of fibrin glue.[44]

Figure 3a. An over-the-scope clip after placement across a small tracheoesophageal fistula.

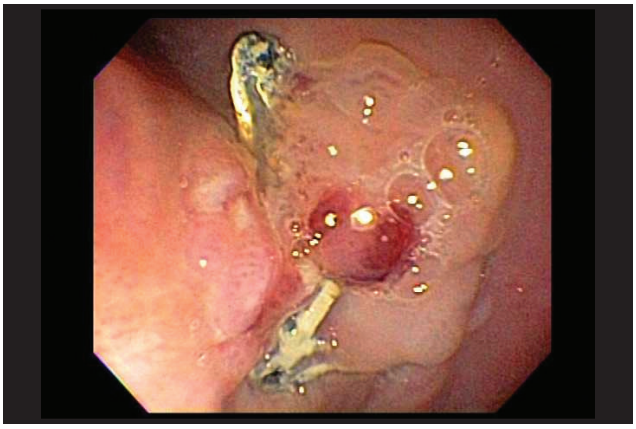

Figure 3b. Same clip seen several months later on follow up exam, still in place.

Argon plasma coagulation (APC) functions by creating coagulation-induced inflammation/granulation along the fistula. Again, this method has been used in conjunction with other endoscopic methods to promote fistula closure. A case report from 2001 demonstrated complete closure of a benign ERF using APC with the addition of endoscopic sutures.[45]

The use of polyglycolic acid (PGA) sheets is another novel technique that has been described in recent case reports to promote complete closure of ERF. PGA sheets are bio-absorble synthetic polymers that are typically used to enhance the strength of sutures during surgical procedures and to prevent delayed perforation.[46] A case report by Han describes complete closure of a post-operative fistula by endoscopically placing PGA sheets over the lesion and securing with endoclips and fibrin glue.[47] The use of PGA sheets in this case increased the area of healthy mucosa available, thereby avoiding the need to clip inflamed tissue. Another case report

by Tsujii describes utilizing PGA sheets as a scaffold inserted within an esophago-mediastinal fistula, then securing with fibrin glue.[46] On re-imaging, the fistula was replaced by granulation tissue. A case report by Matsuura describes complete closure a large, post-esophagectomy ERF after repeated interventions with PGA sheets and fibrin glue.[48] A report by Kinoshita demonstrated complete closure of an ERF secondary to Bechet's disease with 10 repeated applications of PGA sheets combined with fibrin glue and endoclips. None of the above case reports described serious adverse events.[49] Although based on limited data and requiring repeated applications, PGA sheets present a promising method to completely close benign or malignant ERF.

V. CONCLUSION

Benign and malignant ERFs pose both a technical and clinical challenge to today's practitioners. Advances in endoscopic technique have broadened the tools available to allow for improved quality of life for patients suffering from the devastating effects of ERFs. Although the various endoscopic techniques pose different adverse events, an experienced clinician may select the appropriate intervention to maximize the risks/benefits of the procedure based on the size, location, and etiology of the fistula. ■

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