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1. Introduction

Anastomotic leakage is one of the most serious complications following surgery of the esophagus. Post-surgical fistula and anastomotic leakage are major causes of morbidity and mortality. The reported incidence of anastomotic leakage after an esophagectomy is between 2.3 % and 5.9 % [1,2]. It is associated with a high rate of mortality. Conservative treatment with nutritional support and antibiotic therapy is usually adopted at first, but this is sometimes insufficient to obliterate leakage or can take 20-30 days, even if it is successful. Anastomotic leakage is usually improved simply by draining the anastomotic site [3], but sometimes an esophago-respiratory fistula occurs due to penetration by the abscess to the trachea or main bronchus [4-6]. This causes a very serious clinical condition, predisposing the patient to life-threatening pneumonia.

If conservative therapy fails, re-surgery remains as a final option. These surgical operations are invasive. The cases in which it is impossible to accomplish primary closure require another operation that is selected on consideration of the patient’s general status and prognosis. There are reports of the use of a muscle flap in the pectoralis major to repair a tracheomediastinal fistula after esophagectomy [3]. Surgical intervention such as suturing and covering with omentum or muscle flap and esophageal bypass is indicated for mediastinitis, widespread graft necrosis and abscesses due to leakage [7] and is thought to be necessary if the fistula leads to a respiratory tract because repetitive pneumonia would result in poor physical condition [8,9]. But occasionally it would have been invasive and then no surgical attempt to treat the fistula was considered.

Currently, there are a various endoscopic techniques for the management of anastomotic leakage. Endoscopic techniques are useful and technically feasible in chronic fistulas. This procedure is a less invasive alternative to traditional surgical revision.
There are reports of closing a gastrointestinal fistula or anastomotic leakage using fibrin glue, but fibrin glue is sometimes insufficient and is used with growth hormone or a clip. Several investigators reported a failure to close the fistula with this technique.

A clip is used firstly for hemostasis and applied for spontaneous closure of a perforation or endoscopic mucosal resection and sub-mucosal dissection. Rodella reported that endoscopic clipping to close an anastomotic leakage after a gastrectomy was effective and required only a short hospital day [10]. There are hardly any reports of endoscopic clipping for anastomotic leakage after an esophagectomy, although this technique has been performed on rare occasions for anastomotic leakage of duodenal stump or colorectal surgery.

Esophageal stenting at the anastomotic site is an effective method for treating anastomotic leakage after an esophagectomy, but when the anastomotic site is not stenotic and located near the neck, so it was predicted that migration and odynophagia would occur after stenting.

In this chapter, the treatment process using endoscopic clipping with fibrin glue after an operation that leads to a favorable outcome in which an esophago-mediastinal fistula is successfully repaired is discussed.

2. The treatment method for esophago-mediastinal fistula and anastomotic leakage

2.1. Conservative management

Conservative treatment excludes surgical treatment.

Leakage and fistula of the esophagus often lead to a localised infection and systemic sepsis. In particular, mediastinitis is a serious complication of esophageal surgery. The use of broad-spectrum antibiotics is initiated.

Total parenteral or enteral nutrition is provided. Leakages and fistula are associated with malnutrition, due to protein loss, lack of food intake and hypercatabolism, often associated with sepsis. Malnutrition causes hypoproteinaemia with an increased risk of wound dehiscence and infection and decreases muscle bulk and function. In this situation fibroblastic activity is reduced and leads to failure of scar contraction, leading to fistula formation with a delayed healing time.

Nasogastric decompression is performed, and the infected area is cleaned by orally administered saline. The region of the leak is drained and perianastomotic drainage is applied to the patients.

Cervical anastomotic leaks are successfully treated with conservative approaches. Thoracic anastomotic leaks, in the past, were related to high mortality rates [11]. When the abscess was limited to the pleural cavity, a chest tube could achieve adequate drainage. However previous studies had revealed that most of the contained leaks were limited to the
mediastinum [4, 5]. It is difficult to deal with this type of leakage because abscess cavities close to the mediastinum are difficult to reach with a conventional chest tube. Thoracic drainage inserted through trans-nasal route may be a helpful treatment for this type of leak. Moreover endoluminal application of a vacuum-assisted wound closure (EVAC) system is reported as an available method for the leak of colon, gastric and esophageal anastomosis.

2.1.1. Thoracic drainage inserted using interventional radiology (CT-guided)

Anastomotic leakage and a thoracic abscess are sometimes detected after the esophagectomy. Established options for sealing intrathoracic anastomotic leaks after esophagectomy include surgical revision and conservative treatments, such as percutaneous chest tube drainage (the traditional “three-tube method”). The traditional “three-tube method” was the most widely applied method. However, it is difficult to insert a drain into a cavity that is very close to the trachea or aorta. (Fig.1. A) Percutaneous CT-guided abscess drainage is associated with high technical and clinical success rates. This minimally invasive form of therapy may have a role in the management of patients with potentially life-threatening mediastinal abscesses [12].
**Figure 1.** A. The esophagomediastinal fistula had not closed after surgery. B. The abscess is located in the site surrounding lung tissue and close to the trachea and inferior subclavian artery and then thoracic drainage is difficult. C. A trans-nasal-gastric tube is inserted into the esophagomediastinal fistula.
2.1.2. Thoracic drainage inserted through trans-nasal route

Thoracic drainage through the trans-nasal route is performed, when it is difficult to insert a drain into the cavity. This technique appears to be an effective, technically feasible, and minimally invasive treatment option for intrathoracic esophagogastric anastomotic leak [13]. We performed trans-nasal drainage at the site of intrathoracic esophagogastric anastomotic leak. (Fig.1. A,B,C) Recently, the endoluminal application of a vacuum-assisted wound closure (EVAC) system for the closure of esophagogastric anastomotic fistulas has been reported [14]. The sponge results in formation of granulation tissue, and the vacuum removes wound secretions, reduces edema, and improves blood flow, leading to wound closure. EVAC is available and recommended for cases refractory to established endoscopic treatment options [15].

2.2. Endoscopic management

A leakage or fistula will close with basic conservative treatment and local irrigation of between 50 and 80%. The rate of spontaneous closure diminishes rapidly. Fistulae or leakages of anastomotic junctions of the gastrointestinal tract used to be an indication for surgery. However, patients are often severely ill and endoscopic therapeutic options have been suggested to avoid surgical intervention. When it fails to close the cavity of the esophago-mediastinal fistula (Fig.2. A), additional treatment is necessary, so endoscopic techniques are performed. The aim of the endoscopic treatment is also to shorten the closure time of the leakage.
Endoscopic Clipping and Application of Fibrin Glue for an Esophago-Mediastinal Fistula
Figure 2. A. The drain is inserted into the mediastinal fistula and abscess cavity after operation showed by X-ray film. B. CT detects anastomotic leakage and a thoracic abscess cavity. C. An endoscopy reveals that the fistula has failed to close after the operation. D. Endoscopic clipping with fibrin glue. E. An endoscopy indicates that we succeeded in closing the fistula. F. CT revealed no cavity or fistula.

2.2.1. Endoscopic management of anastomotic leakage using fibrin glue

Fibrin glue is used to support the growth of fibroblasts, stimulated from fibrin, thrombin and factor XIII. The Basic principle of sealing a fistula with fibrin is that the mixture of the two components (fibrinogen and thrombin) simulates the coagulation cascade in the fistulous tract while forming a matrix of fibrin. The scar formation process is stimulated and in the process the fibrin will be replaced slowly by collagen. Fibrin glue application has become an alternative and relatively novel method in clinical practice to avoid surgery after different kinds of leakages within the last few years. In 36.5% of cases, treatment success was reached with fibrin glue application as the sole endoscopic therapy [16]. Endoscopic fibrin glue-based interventions are a valuable option in the treatment of leakages or fistulae of the gastrointestinal tract [17]. The endoscopist can perform this treatment easily and safely; and it is not necessary to be very experienced in this technique because it is based on the use of the needle injector [18]. H. Messmann reported that 1–4 ml of fibrin sealant is applied per session and performed an additional sub-mucosal injection of fibrin near the orifice after filling the fistula tract with fibrin if the orifice was small because the swelling induced by the sub-mucosal depot may contribute an additional closure effect. They also mentioned that this additional fluid volume may lead to washing part of the sealant into the gastrointestinal-tract. After application of the fibrin the endoscopist should refrain from using the suction system of the scope. Endoscopic sealing has to be repeated, in most cases, in intervals of a few days until closure achieved.
However, severe infection complications are associated with a poor success rate. Moreover, the cost of fibrin glue is high but the advantage of a shorter hospital stay is significant in reducing global costs [17]. Treatment success with further endoscopic procedures was seen. Vicryl plug or clipping are reported as additional endoscopic procedures because endoscopic treatment failure with consecutive surgical intervention became necessary [15,19-22].

2.2.2. Endoscopic management of anastomotic leakage using clipping

The use of metallic clips has been reported for hemostasis and closure of a perforation caused by various matter. Endoscopic closure by clipping was found to be effective for idiopathic or iatrogenic esophageal perforation.

Application of an endoclip is a relatively simple procedure and recently reported as a method for closing anastomotic leakage of gastrointestinal tract [10,23-28] (Table 1.). The clip fixing device with a loaded clip can be passed through the forceps channel of a standard endoscope. As soon as the Teflon coating is in endoscopic sight the clip can be pushed forward out of the coating. Stepwise pulling on the handle of the fixing device leads to opening of the prongs. Through manipulation of the tip of the endoscope the clip can be brought into position to grasp the tissue flanks of the leakage. It may be helpful to apply suction during this manoeuvre so that leaks that have a larger diameter than the total span of the clip can be treated. A further pull on the handle mechanism closes the endoclip and detaches the whole clip from the fixing device. Usually several clips are applied, positioning the first clips to the extremities of the leak or even outside the leakage borders to obtain a kind of ‘zipper’ effect while grabbing tissue step by step from the outside to the centre of the defect. With this method leaks up to 2 cm in diameter can be closed; larger leaks need more than one session. Exact data on clipping for therapy of post-surgical leakage are rare; most articles relate to endoscopic clipping of perforations following endoscopic procedures.

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Table 1. Endoscopic clipping to close the anastomotic leakage of gastrointestinal tract
2.2.3. **Endoscopic clipping with fibrin glue**

A contrast instillation and radiological visualisation of the fistula system or cavity was performed during the endoscopic procedure of every therapeutic closure, both with fibrin and clips. H. Messmann reported that a double-lumen catheter can be placed over the guide wire into the fistula [18]. If a single-lumen catheter is used instead of a double-lumen probe for sealing, the catheter lumen has to be flushed between the instillation of fibrinogen and thrombin. The sealing of the fistula begins as far as possible away from the orifice; thus the risk of fluid retention can be minimised.

Metallic endoclips were applied, controlling the closure of the leakage by endoscopy.

A combination of clipping and fibrin sealing is probably more effective, especially in treatment of larger leakages [10,28,29]. H. Messmann et al. applied several careful injections into the tissue using a double-lumen needle between the placed clips and also mentioned that their own experience with clips alone is not as positive as it is mentioned. Clips are used to close the fistula while suction is applied to reduce the size of the fistula hole after filling the fistula with fibrin glue. Application only of synthetic glues via endoscopy or clipping is not available.

2.2.4. **Endoscopic stenting**

Esophageal stenting at the anastomotic site is reported as an effective method for treating anastomotic leakage after an esophagectomy and is one of the most popular endoscopic treatments. The use of a removable covered stent in the setting of anastomotic leak or spontaneous perforation, alone or as an adjunct to conventional surgical management, is feasible in sealing the leak, resolving sepsis, and expediting return to enteral nutrition [30]. Stent migration is a commonly observed complication in other reported series occurring in up to 50% of patients and frequently requires restenting to regain control of a leak [31]. We had a case of stent migration after leak closure. (Fig.3.A,B) The rate of distal stent migration is possibly even higher following stenting of malignant stenoses due to the lack of a stricture. The patients who had the stent sutured, all required operative intervention for debridement of the necrotic and contaminated tissue so the stent and suture were placed at the time of this surgery. It is also predicted that odynophagia would occur after stenting if the anastomotic site is close to the neck. However new plastic stents are easy to remove, very effective and might have therapeutic potential to replace fibrin glue application and clipping.

2.2.5. **Other endoscopic therapy**

To reduce the necessity of another surgical intervention and enhance natural healing other endoscopy-based therapeutic options are available.

Endoscopic suturing seems to be a promising new treatment.
Figure 3. A. Endoscopy indicated distal covered metallic stent migrated to the stomach. B. A fistula is observed in the non-covered part of a migrated metallic stent.
Pross et al. presented a successful closure method with a resorbable vicryl cylinder used as a plug [21]. The plug was inserted into the defect after repeated fibrin therapy. Little data has been published regarding these methods and is still lacking.

2.3. The treatment process

2.3.1. Thoracic drainage inserted using interventional radiology or through trans-nasal route

A chest X-P revealed pneumothorax, and anastomotic leakage and a thoracic abscess were detected after the operation via CT (Fig. 2B). For approximately one month, thoracic drainages, and the nasogastric placement of sump tube through the leak were performed and conservative therapy with total enteral nutrition was continued. The cavity of the thoracic abscess caused by the leakage reduced in size, but the esophago-mediastinal fistula and the air cavity were still present 33 days after the operation. An additional thin drain was inserted using interventional radiology, but it failed to close the fistula 68 days after the operation (Fig. 2C).

Additional treatment to the thoracic drainages was necessary, so we decided to perform other endoscopic techniques.

2.3.2. Endoscopic clipping with fibrin glue

First we applied synthetic glues via endoscopy. The nasogastric placement of tube through the leak is already performed. We flushed the fistula system with physiological sodium chloride solution. And then fibrin was applied through the nasogastric tube located at the lowest position of the anastomosis. In the next step we usually insert a standard sump tube and apply thrombin into the fistula; a guide wire can be helpful to advance the probe to the distal end of the fistula with complicated or very long fistulae. A contrast medium was used through the endoscope we could confirm no leakage after filling with fibrin glues. However, an X-P taken three days after this technique indicated air leakage. Next we applied clipping to close the fistula twice, but within one week after clipping a clip had dropped out. We use metallic endoclips (MD 850,Olympus Corp., Tokyo, Japan) which have a fully opened distance between the clip prongs of 12 mm long and 6 mm wide. In our case a clip dropped out a few days after clipping at the first and second sessions, and we expected that a single clip would not allow a successful closure. Esophageal pressure in swallowing at the neck site is high and the movement of air entering a gap in the fistula appeared to dislodge the clip. Finally, we succeeded in closing the fistula using three clips with fibrin glue because we eliminated the gap in the fistula (Fig. 2D). It was important to apply suction by endoscope when we attempted to close the fistula by clipping as the suction reduced the size of the fistula and facilitated the clipping. At the third treatment, we also filled with fibrin glue at the right lateral position where the fistula was located at the lowest position of the anastomosis and then followed this with endoscopic closure. An endoscopy indicated that we had succeeded in closing the fistula (Fig. 2E). A gastrographin swallow showed no
leakage (data not shown) and CT revealed no cavity or fistula 7-10 days after clipping (Fig. 2F). We had succeeded in closing the fistula with clip and fibrin glue in our case [29].

3. Conclusion

Several investigators reported a failure to close a fistula with only fibrin glue. Rodella reported that endoscopic clipping to close an anastomotic leakage after a gastrectomy was effective [10]. Endoscopic closure by clipping was found to be effective for idiopathic or iatrogenic esophageal perforation. Clipping alone also sometimes fails to close an anastomotic leak or fistula. Esophageal pressure in swallowing at the neck site is high and the movement of air entering a gap in the fistula appeared to dislodge the clip. It is important to apply suction by endoscope when we attempt to close the fistula by clipping as the suction reduced the size of the fistula and facilitated the clipping. Endoscopic clipping is recommended by Rodella et al. to treat leakages less than 2 cm in diameter.

The endoscopic clipping with fibrin glue treatment is effective and not invasive. Fibrin sealant and clipping are effective and probably established methods. It results in a steady improvement of the patient’s condition and minimized surgical stress, so it should be started earlier.

Furthermore a reduced hospital stay will obviously decrease the costs of treatment. The cost of fibrin glue is high but the advantage of a shorter hospital stay is significant in reducing global costs. In conclusion, the endoscopic use of fibrin glue and clip are easy, safe and can shorten the time of closure of fistula, in selected cases, with an apparent reduction of global costs.

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