

Case Report

Experiences in the diagnosis and treatment of postoperative esophagopleural sac fistula

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Abstract: Esophagopleural sac fistula is a rare complication of esophagectomy associated with a relatively high mortality rate. To examine the diagnosis and treatment of esophago-mediastinal/pleural sac fistulas, 6 cases of esophago-mediastinal/pleural fistula of different etiologies, with a critical appraisal of current domestic and international clinical research, were analyzed. Our six patients were recovered and discharged from the hospital. Although contrast abdominal computed tomography, using a water-soluble contrast medium, and endoscopy can be used for the diagnosis of esophago-mediastinal/pleural sac fistulas in specific patients, observation of clinical symptoms remains the most important criterion for diagnosis. A standardized evaluation of specific issues is recommended for all patients to effectively determine the need for re-thoracotomy. Stent implantation under endoscopy should be avoided unless absolutely necessary. However, vacuum sealing and drainage of a transesophageal anastomotic stoma can facilitate healing of a leak. Pleural lavage can be used, when necessary, to relieve clinical symptoms and, again, facilitate healing of a leak. Moreover, maintaining intact pleura on the pleural cupula can reduce the risk of a cervical anastomotic fistula from spreading into the chest cavity.

Keywords: Esophagectomy, anastomotic fistula, esophageal cancer, esophageal perforation

Introduction

Esophagopleural sac fistulas is a rare complication of esophagectomy associated with a relatively high mortality rate that can result from a range of etiologies, the most common being anastomotic fistulas after esophageal surgery and gastric stump fistulas following replacement of the esophagus. Esophagopleural sac fistulas resulting from idiopathic esophageal rupture and perforation and iatrogenic injury and following interventions for tracheoesophageal fistula are also relatively common. Due to pollution of the thoracic cavity by contents of the gut, the rate of mortality in patients with esophagopleural sac fistulas is substantial, typically resulting from complications, such as shock, respiratory insufficiency and massive hemorrhage. Effective treatment of esophagopleural sac fistulas within a clinical context remains difficult. In our department, we perform approximately 200 operations per year for esophageal diseases, with an observed anastomotic fistula rate of approximately 10%.

Importantly, our rate of mortality for the treatment of anastomotic fistula has significantly decreased. In this paper, we present a detailed summary to the diagnostic procedure and treatment for 6 patients with esophagopleural sac fistula of differing etiologies. Based on our observations and experiences, supported by a critical appraisal of recent domestic and international research literature, we present our clinical guidelines for the treatment of esophagopleural sac fistulas.

Case 1

A 47-year-old female patient was hospitalized due to progressive sensation of choking on food which had persisted for 2 months. On gastroscopy, the cardiac mucosa was found to be congested, edematous and slightly elevated, which are typical indications of a space occupying lesion of the cardia. The patient was treated with radical cardiac carcinoma excision, with end-to-side esophagogastrostomy, below the aortic arch, for gut reconstruction. During the

surgery, 3 tubes were placed and retained *in situ*: a gastric tube, a duodenal nutrition tube and a thoracic drainage tube. Upon noting abdominal discomfort post-surgery, a computed tomography (CT) abdominal examination was performed, with multiple small air-fluid levels identified within the abdominal intestinal structure. Based on this evidence, a diagnosis of ileus was made. Six days later, the patient complained of dyspnea and a chest CT examination was performed (**Figure 1A**), with a number of loculated hydrops and pneumatosis identified in the left thoracic cavity and hydrops in the right thoracic cavity. The left thoracic cavity was punctured and 200 ml of light bloody fluid drained. Subsequently, a thoracic drainage tube was placed in the left thoracic cavity to drain air and approximately 300 ml of sepioid fluid. Nine days later, a gastrointestinal (GI) contrast examination was performed (**Figure 1B**), with a relatively large anastomotic fistula identified. A second surgery was performed three days after the GI examination. On direct visualization, a relatively large anastomotic stoma and proximal anastomotic stoma gastric stump crevasse were observed, with slight edema and red-blood staining of the tissues of the esophageal and gastric wall. An excision was performed, including release of surrounding tissues, and a mutual anastomosis created. The mediastinal drainage tube, thoracic catheter, gastrointestinal decompression tube, and the duodenal nutrition tube were retained *in situ*. Post-operatively, intravenous nutrition was provided, with good patient recovery outcomes observed. Ten days after the secondary surgery, a small amount of taupe fluid was drained from the mediastinal drainage tube, indicative of a potential anastomotic fistula. Approximately 2 weeks later, about 10 ml of fluid was drained via the mediastinal drainage on a daily basis. A second contrast GI examination was performed, with an anastomotic fistula identified (**Figure 1C**). A subsequent contrast GI examination was performed 40 days after the second surgery, with no leakage of the contrast medium identified (**Figure 1D**). Oral feeding was re-introduced at this point. However, 3 days later, fine vegetable matter was drained via the mediastinal drainage tube. Fasting was re-instituted and 58 days after the second surgery, very little fluid was observed from the mediastinal drainage tube and the tube was removed. However, the thoracic drainage tube was retained as

small amounts of purulent fluid were drained on an occasional basis. Oral feeding was re-introduced, again, 70 days after the second surgery, with close monitoring of the patient for the 10 subsequent days. As no adverse outcomes were observed, the thoracic drainage tube was removed and the patient was discharged. A follow-up CT examination was performed 7 months after the second surgery, with no evidence of persisting issues (**Figure 1E**).

Case 2

A 65-year-old male patient was hospitalized following 3-month history of dysphagia. This patient had a history of diabetes. He was treated with trans-l-thoracic radical cardiac carcinoma excision, with end-to-side esophagogastrostomy, below the aortic arch, for gut reconstruction. During the surgery, 4 tubes were placed and retained *in situ*: a gastric tube, a duodenal nutrition tube, a thoracic drainage tube, and a mediastinal drainage tube. After the surgery, intravenous nutrition was implanted, with insulin administered to control blood glucose levels. Seven days after surgery, approximately 700 ml of brown fluid was suddenly drained via the mediastinal drainage tube. This fluid was consistent with the fluid being drained via the gastric tube. Thus, a diagnosis of possible anastomotic fistula or gastric stump fistula was made. Radiography was performed (**Figure 2A**), confirming that the thoracic drainage tube remained in place and was unblocked, and with no obvious hydrops or pneumatosis visible in the chest. Twenty days post-surgery, there was little drainage from either the mediastinal or thoracic drainage tubes. An upper GI contrast examination was performed, with no leakage of the contrast medium identified (**Figure 2B**). One week after the examination, the patient was placed on a liquid diet, with no adverse issues observed. Subsequently, the patient was transitioned to a semi-fluid diet and the gastric tube was closed. However, an orificium fistula was observed. Twenty-five days later, all drainage tubes were removed and the patient was discharged. An abdominal CT examination was performed about 2 weeks after discharge, with no further complications identified (**Figure 2C**).

Case 3

A 65-year-old male patient was hospitalized due to a cough and bloodstained expectoration

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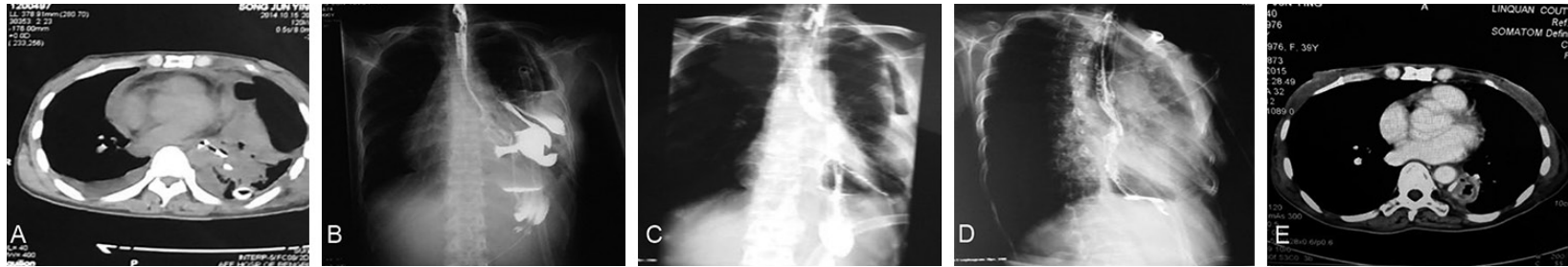


Figure 1. Features of DSA and CT imaging for case 1. (A) Loculated hydrops and pneumatosis identified in the left thoracic cavity and hydrops in the right thoracic cavity; (B) A relatively large anastomotic fistula; (C) A relatively small anastomotic fistula; (D) Absence of contrast medium leakage; and (E) No evidence of persisting issues.



Figure 2. Features of DSA and CT imaging for case 2. (A) Absence of obvious hydrops or pneumatosis in the chest; (B) Absence of contrast medium leakage; and (C) No evidence of further complications.

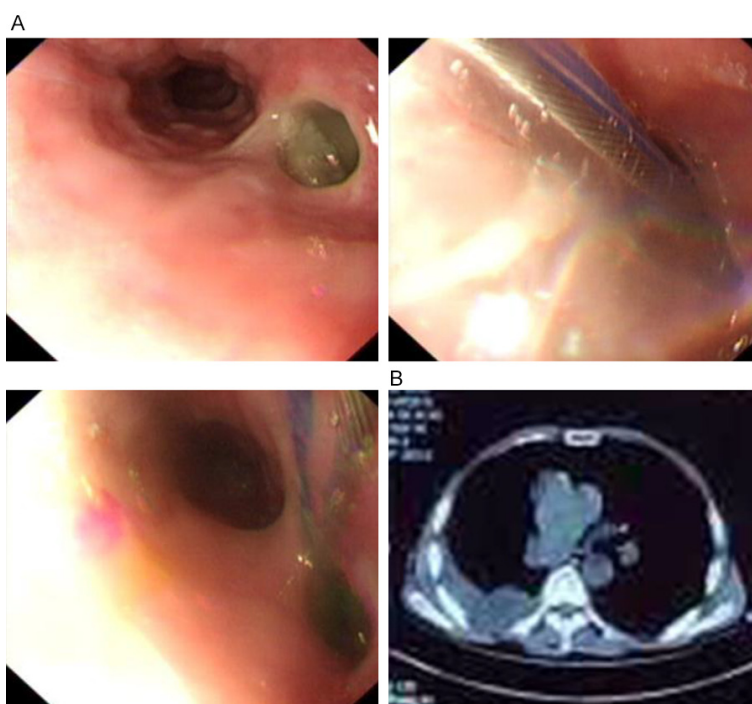


Figure 3. Features of gastroscopy and CT imaging for case 3. (A) A small, round leak, approximately 35 cm from the incisor; and (B) Loculated pleural effusion in the right chest wall, which were deemed to be vomica.

developing 12 years after surgical management of left lung for cancer. A cancer diagnosis of the central lobe of the right lung was made and the patient was treated with radical excision of the central lobe of the right lung. Thick adhesions and atresia of the thoracic cavity were observed during the surgery. Food debris was drained from the thoracic drainage tube at 5 days post-surgery. The gastric tube was maintained *in situ* and nasogastric feeding implemented. A gastroscopy was performed 16 days post-surgery, with a small, round leak identified, approximately 35 cm from the incisor

(Figure 3A). As the walls of the leak were smoothed, a nutrient tube was placed and retained in the chest via the leak, as a means of supporting the leak itself. After 22 days, no drainage fluid was observed in the catheter and the thoracic drainage tube was removed. A fluid diet was implemented 1 week later. However, the patient developed a fever approximately 6 days after the first administration of fluid. A CT scan was performed with loculated pleural effusions identified in the right chest wall, which were deemed to be vomica (Figure 3B). One thoracic drainage tube was placed in the vomica, and fasting re-instated. The patient was able to receive a semi-fluid diet 10 days later, with no adverse issues observed. The thoracic drainage tube was removed 64 days after the orificium fistula

was observed. At the point, the patient was on a regular diet and was discharged 4 days later. The patient returned for drainage of an abscess about 2 weeks after discharge and again, 7 months post-surgery. No further complications were observed.

Case 4

A 48-year-old male was hospitalized for persistent cough and expectoration for over 20 years, recently aggravated by bloodstained sputum. A diagnosis of abscess in the middle and lower

lobes of the right lung was made. During surgery, a closed partial adhesion of the esophagus to the membrane of the inferior lobar bronchus was observed. Following careful separation of the esophagus from the bronchus, a blockage of the bronchus was identified. However, the central and lower lobes of the right lung were excised with no further special treatment performed. One week post-surgery, approximately 300 ml of cloudy liquid was drained via the thoracic drainage tube. Emergency gastroscopy was performed, with an esophageal wall leak identified about 30 cm from the incisor, with a diameter <0.5 cm (**Figure 4A**). The leak exhibited 2 diverticula caused by local stretching of the esophageal wall. One of these fistulas was connected to the thoracic cavity, while the other was normal. A gastric tube and duodenal nutrition tube were placed *in situ*. The patient was discharged 13 days later, with the gastric, duodenal nutrition and thoracic drainage tubes *in situ*. The patient was re-hospitalized about 6 months later, having lost 10 kg. A gastroscopy was performed with an enlargement of the leak identified (**Figure 4B**). A 20 mm stent was customized and the stent graft was implanted in the esophagus by gastroscopy (**Figure 4C**). However, 3 days later, lateral leakage occurred after the intake of food and the patient was observed to be in pain and obvious discomfort. A gastroscopy was performed again 8 days later. The stent was covered by food debris and was displaced (**Figure 4D**). Consequently, the stent was removed and the patient was discharged (**Figure 4E**).

Case 5

A 48-year-old male patient was hospitalized with a 5-year history of stomach discomfort following eating. A gastroscopy was performed, with a squamous cell carcinoma identified, 30-40 cm from the incisor. The patient was treated with trans-r-thoracic 3-incision radical esophageal carcinoma excision in the middle thoracic segment, with end-to-side esophago-gastrostomy, in the cervical region, for gut reconstruction. Immediately after the operation, the patient exhibited good recovery. The patient was administered a liquid diet 8 days post-surgery but developed a fever over the subsequent 2 days. A contrast GI examination was performed (not shown: the film was lost), with no sign of contrast medium leakage.

However, delayed gastric emptying and a left pleural effusion were apparent. One thoracic closed drainage tube was implanted to drain cloudy liquid, with a diagnosis of probable anastomotic stoma or gastric stump fistula made. A gastroscopy was performed again 5 days after placement of the drainage tube, with an anastomotic fistula identified (**Figure 5A**). A duodenal nutrition tube was placed for support, via the leak, using gastroscopy. A CT examination when fever developed again, with an effusion identified on the right anterior upper chest wall. A venipuncture tube was implanted primarily for drainage, but also to drain the flushing fluid used for washing the area. The flushing tube was removed once the fever had resolved. A contrast GI examination was performed 22 days after implantation of the supporting tube, with no evidence of leakage of the contrast medium. Oral feeding was implemented 65 days after the leak was first observed, with the supporting tube removed 74 days after fistulization. The patient fasted for 3 days prior to refeeding, with good subsequent recovery. However, food debris was observed in the thoracic drainage tube 85 days after fistulization, on an occasion when the patient had eaten excessively. No leakage of the contrast medium was identified on radiography (not shown: the film was lost), and gastric emptying was normal. The patient was discharged, with the drainage tube *in situ*, and with recommendation to refrain from excessive eating for 2 months. With normal eating, no drainage was observed, and the drainage tube was removed after 2 months. On follow-up CT examination performed 7 months post-surgery, a local inclusion was identified on the right anterior upper chest wall (**Figure 5B**). Eight months post-surgery, pyogenic fluid flowed out via the original flushing tube which was connected with the thoracic cavity. Chest radiography was performed (**Figure 5C**). Although the anterior film was negative, a partial pneumothorax in the upper part of the right anterior chest was observed on the lateral film. Open drainage of the pleural cavity was performed, with full recovery achieved 4 weeks later.

Case 6

A 67-year-old female patient was hospitalized following a sensation of choking on food, the severity of which had increased over the past 3 weeks. A diagnosis of esophageal cancer in the

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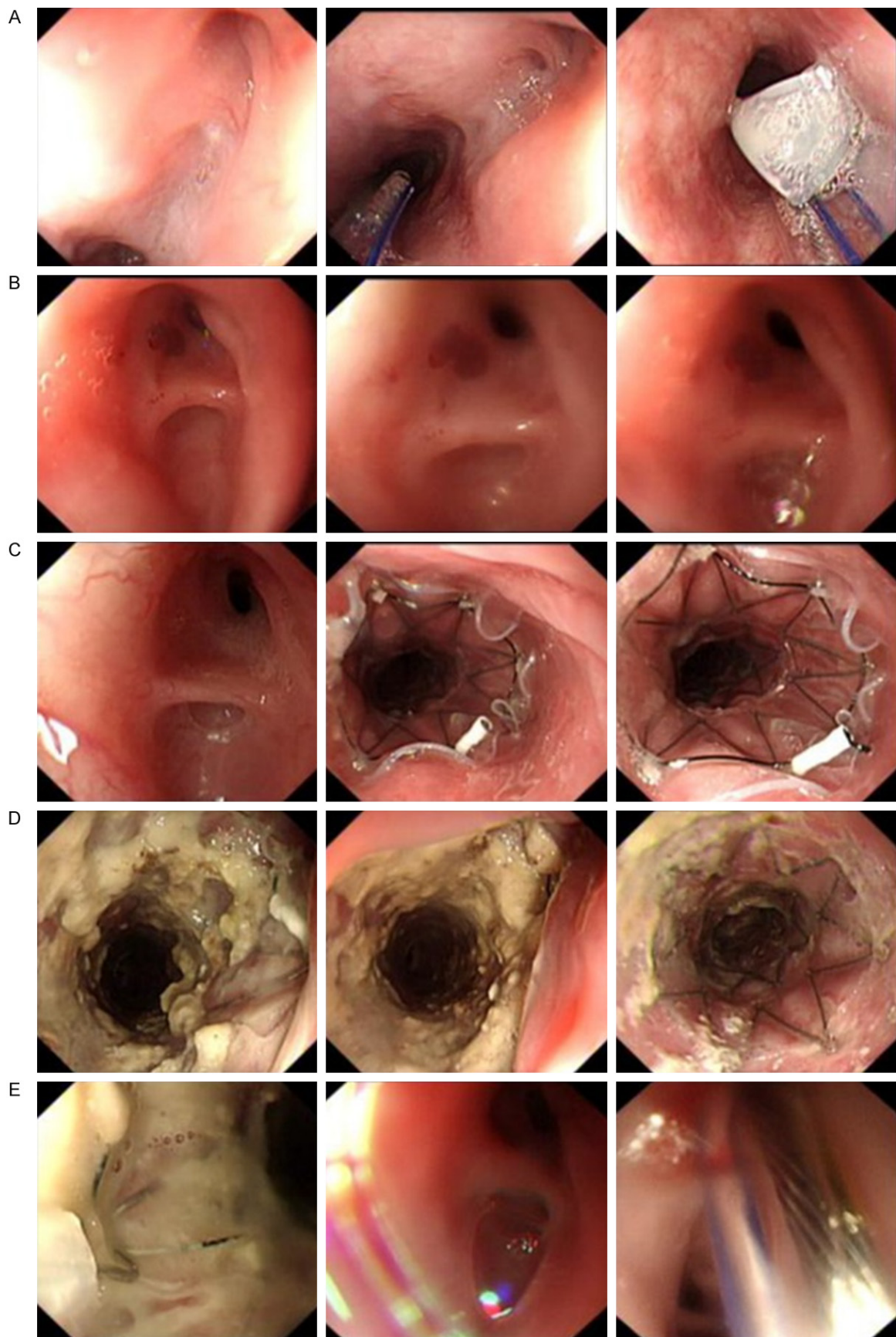


Figure 4. Features of gastroscopy for case 4. (A) Leakage of the esophageal wall, about 30 cm from the incisor, with a diameter <0.5 cm; (B) Enlargement of the leak; (C) A 20 mm stent graft implanted in the esophagus; (D) The stent covered by food debris and displaced; and (E) The stent was removed.

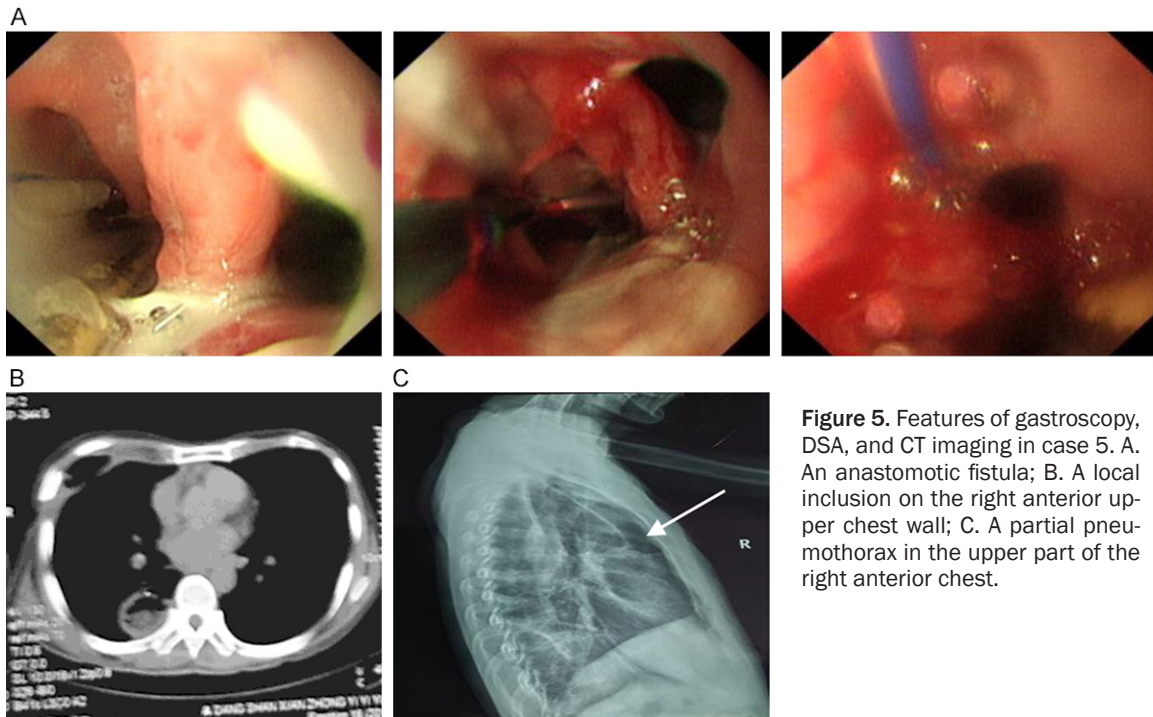


Figure 5. Features of gastroscopy, DSA, and CT imaging in case 5. A. An anastomotic fistula; B. A local inclusion on the right anterior upper chest wall; C. A partial pneumothorax in the upper part of the right anterior chest.

upper chest segment was made. The patient was treated by trans-r-thoracic 3-incision radical esophageal carcinoma excision in the upper thoracic segment, with end-to-side esophago-gastrostomy, in the cervical region, for gut reconstruction. Chest radiography was performed 6 days post-surgery, with a subcutaneous pneumatosis identified of the right chest wall (**Figure 6A**); otherwise, the radiographs were unremarkable. The thoracic drainage tube was removed 8 days post-surgery. Subsequently, the patient complained of aching in the area of the right chest wall. A contrast GI examination was performed 26 days post-surgery, with a post-esophageal cancer anastomotic fistula identified, with a hydropneumothorax on the right side (**Figure 6B**) and closed chest drainage was performed. A flushing tube was retained via the thoracic drainage tube, with approximately 600 ml of sepia fluid drained (**Figure 6C**). Ten days after drainage, a duodenal nutrition tube was implanted for support, via the leak, using gastroscopy (**Figure 6D**). Radiographic re-examination was performed 16 days later, with no evidence of effusion, although an obvious leak was observed (**Figure**

6E). A follow-up radiographic examination was performed 32 days later, with evidence of the leak being much smaller (**Figure 6F**). During this period, chest CT examination was performed, with a partial anastomotic stoma and connection to the chest cavity identified (**Figure 6G**). A contrast GI re-examination was performed 70 days post-surgery (**Figure 6H**). With no evidence of contrast medium leakage, the fluid diet was replaced by a semi-fluid diet, followed by a normal diet, with no issues observed at any stage. The patient was discharge 80 days post-surgery.

Discussion

Due to a poor blood supply to the esophagus, and the special structure of the chest cavity to maintain a negative pressure, esophagopleural sac fistulas are often difficult to heal, with a series of serious complications often observed. A systematic study from the United States [1] reported a fistula rate, after both manual and mechanical anastomosis, of 0-26%. In an experienced treatment center, the mortality rate associated with esophagectomy ranges be-

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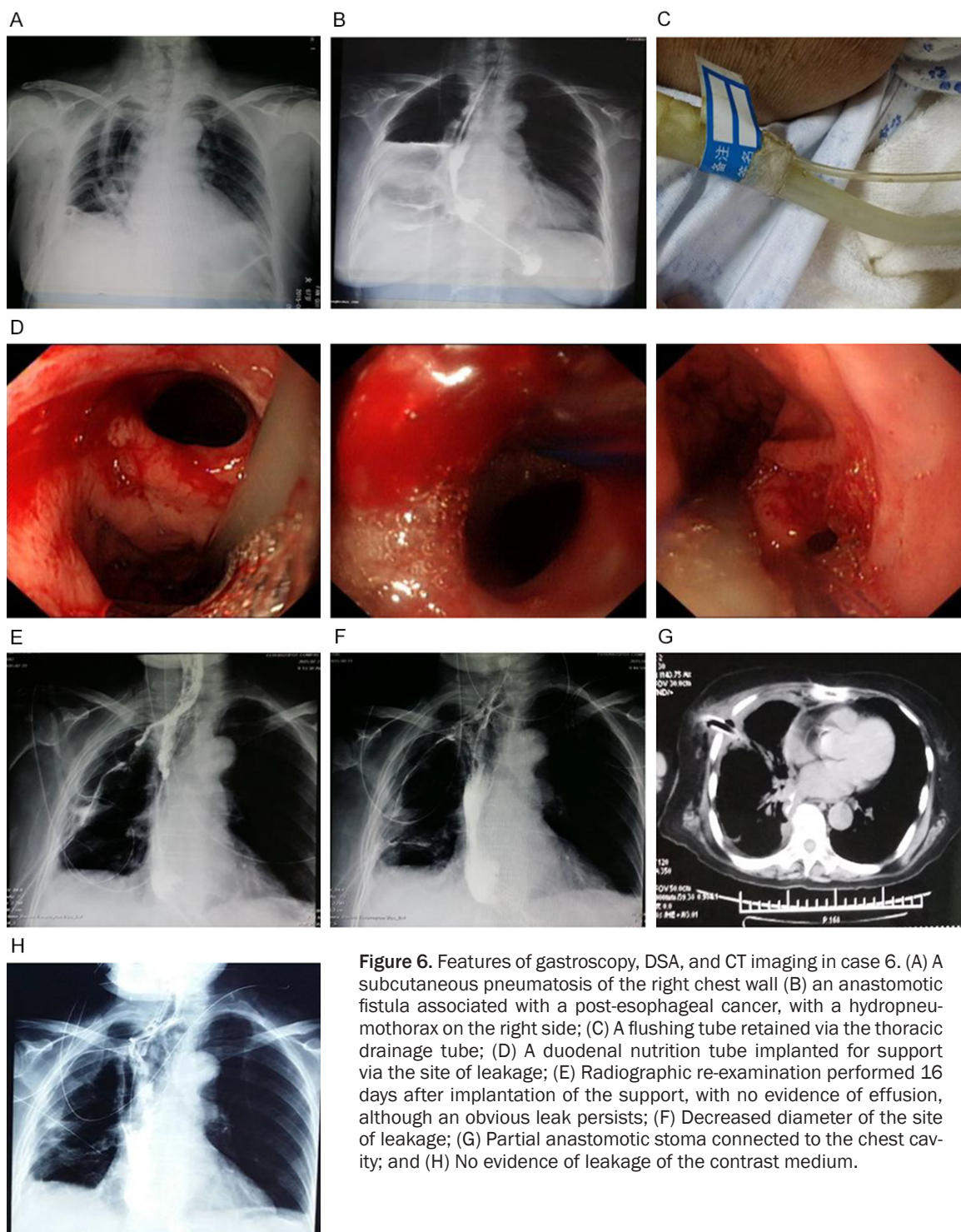


Figure 6. Features of gastroscopy, DSA, and CT imaging in case 6. (A) A subcutaneous pneumatosis of the right chest wall (B) an anastomotic fistula associated with a post-esophageal cancer, with a hydro-pneumothorax on the right side; (C) A flushing tube retained via the thoracic drainage tube; (D) A duodenal nutrition tube implanted for support via the site of leakage; (E) Radiographic re-examination performed 16 days after implantation of the support, with no evidence of effusion, although an obvious leak persists; (F) Decreased diameter of the site of leakage; (G) Partial anastomotic stoma connected to the chest cavity; and (H) No evidence of leakage of the contrast medium.

tween 2% and 5% [2]. In recent years, with improvement in medical technologies and peri-operative management, the rate of anastomotic fistulas has decreased, but still remains as high as 3-5% and associated to a relatively high mortality rate [3]. According to several major international reports, currently, the esophagec-

tomy-specific mortality rate is estimated to be between 2.5% and 2.9% [4-6].

Diagnosis of an esophagogastric fistula

The most common examination method is a contrast GI examination using water-soluble

contrast media, while CT imaging and endoscopy are typically less commonly used. Clinicians and researchers [7] have raised some doubt regarding the value of upper GI contrast as a routine examination post-esophagectomy due to its low sensitivity. Indeed, some studies have reported the sensitivity of contrast examination performed with water-soluble media to be only about 40% for anastomotic fistula diagnosis [8], while barium sensitivity can be as high as 80% by comparison [9]. Studies have reported the sensitivity of CT examination to be as high as 73% [10]. However, gastroscopy is an invasive method and, therefore, is not viable as a routine examination method. Upponi et al. [11] compared the accuracy of multi-slice CT scanning and radiography for the diagnosis of post-esophagectomy anastomotic fistula, which indicated that while CT examination provided higher tolerability and sensitivity, its specificity was lower than that of radiography when testing for latent anastomotic fistula. Strauss et al. [10] examined 97 patients after intrathoracic esophagogastronomy for esophagectomy and concluded that, compared to oral administration of contrast medium only, CT imaging, performed 7 days post-surgery, enhanced the sensitivity of testing for anastomotic fistula, as well providing confirmation of a 'true' absence of an anastomotic fistula from a previous negative radiographic examination. Low [12] has previously defined a diagnostic and treatment algorithm for post-esophagectomy anastomotic fistula. According to this algorithm, if clinical symptoms of a patient indicate leak, but the radiographic examination is negative, further examination should be performed with barium meal contrast or CT imaging. A water-soluble contrast medium was considered to be the most common method to identify a post-esophagectomy leak, with CT being able to identify some leaks which were not apparent on radiographic examination. However, it is difficult to determine the significance of intra-mediastinal gas inclusions identified on CT imaging performed 1 week post-surgery. Goense et al. [13] previously examined the diagnosis and treatment of post-esophagectomy cervical anastomotic fistula. Routine contrast-enhanced CT examination was performed on day 6 post-surgery, with endoscopy performed in cases of suspected leaks. Based on findings from the examination and clinical symptoms, cervical fistulas were

classified into 4 categories: class 1 fistulas were defined as asymptomatic (i.e., identifiable only by imaging); class 2 fistulas were associated with local cervical symptoms; class 3 fistulas were associated with respiratory system symptoms due to pleural or mediastinal spread; and class 4 fistulas were associated with systematic dysfunction due to gastric necrosis. Jones et al. [14] previously used radiographic evaluation of the *intactness* of cervical anastomotic stomas and found that contrast radiography was not applicable for anastomotic fistula screening due to the risk of aspiration and its low diagnostic sensitivity. However, because of its high specificity for diagnosis of anastomotic stomas, they concluded that contrast radiography was valuable for screening of patients with clinically suspected leaks. DeArmond et al. [15] developed an electrolyte-gated leak detection device, based on a rat model, demonstrating that both sensitivity and specificity of their device (100%, 80%, respectively) were higher than that of barium contrast medium.

Of importance were reported findings [16, 17] that an anastomotic fistula can still be present when pneumatic cavities and/or loculated effusion around an anastomotic stoma are identified on a chest CT, even though chest drainage liquid is not cloudy, the methylene blue test result is negative and no medium leakage is identified on esophageal contrast radiography. This CT evidence would specifically indicate a latent leak, especially when both pneumatic cavities and loculated effusion are present. Any patients with such symptoms should be diagnosed as having an esophagopleural sac fistula. Shuxin et al. [18] performed contrast radiography in the Trendelenburg position for 21 patients with post-gastroesophageal anastomosis, all of whom exhibited some symptoms of anastomotic fistula. They concluded that this method could greatly enhance the detection rate of clinically suspected anastomotic fistula, and provide a basis for subsequent clinical treatment. Therefore, based on current research and clinical evidence, oral administration of water-soluble contrast material is not sufficiently sensitive for the diagnosis of anastomotic fistulas, with the test being associated with a relatively high false negative rate. However, water-soluble contrast remains irreplaceable simply due to its high diagnostic specificity. CT scan can provide indirect evidence of an

anastomotic fistula via observation of close or distant pneumatic cavities and transudation of contrast medium from the anastomotic stoma. However, CT has a low diagnostic specificity and a relatively high false positive rate. As well, given its invasive nature, endoscopy also remains unsuitable as a screening method for anastomotic fistula, and should only be used for highly suspected fistulas that cannot be conclusively identified with other examination methods.

The false negative rate of gastrointestinal contrast with oral administration of diatrizoate in patients with anastomotic fistulas in our study was very high, similar to that reported in other study [19]. The risk for false negative identification could perhaps be mitigated, to some degree, by the use of imaging in the Trendelenburg position. However, many of our patients were in a poor state of health and, therefore, unable to be placed in this position. Consequently, oral feeding was implemented in some patients prior to full healing of the fistula, which aggravated infection of the chest cavity. Unfortunately, our institution lacks sufficient experience in the diagnosis of anastomotic fistula using CT examination and endoscopy. Therefore, a treatment course is pursued and clinical confirmation of a fistula obtained prior to selecting further examination by CT and endoscopy. In our experience, appropriate positioning of drainage tubes around the anastomotic stoma during surgery, combined with close observation of symptoms post-surgery, are crucial for early identification of anastomotic fistula. When treating patients described in cases 1-4, observation of abnormal drainage fluid in the thoracic drainage tube was indicative of a clinical diagnosis of esophagopleural sac fistula, with confirmation by further examination. For patients with cervical anastomosis, described in cases 5 and 6, the main presenting symptoms of a possible fistula were fever (case 5) and chest pain (case 6). CT examination identified local effusion which confirmed extension of the fistulas into the chest during drainage. At present, in our department, we regularly administer oral contrast medium for upper GI contrast examination, 7-8 days post-surgery as a means of judging the status of the anastomotic stoma and efficacy of gastric emptying. This upper GI examination is consistently performed prior to allowing the consumption of

solid food. The majority of patients presented in our case series developed symptoms prior to post-operative day 8. Abnormalities of the drainage fluid and respiratory insufficiency, as well as a high rate of pulmonary wheezing in patients with otherwise normal respiratory function, were common presenting symptoms. Prior to digestive juices being drained, the majority of these respiratory symptoms result from irritation of the chest cavity by digestive juices. According to our experiences, anastomotic fistulas occurring 2 to 3 days after anastomosis are typically large and, therefore, can be discovered by observing the drainage fluid, provided that the drainage tube has been placed appropriately. The majority of leaks that occurs 4 to 8 days post-surgery typically result from ischemia and, therefore, can be diagnosed by careful observation of specific clinical symptoms, with subsequent confirmation using appropriate examination. To confirm the diagnosis, the first choice should be the use of an oral, diatrizoate-based, GI contrast medium, with CT imaging performed to confirm the location of drainage tubes. CT imaging is further used to confirm the presence of chest inclusions and, thereby, determine the appropriate course of treatment, whether conservative or operative.

If an esophagopleural sac fistula is discovered post-surgery, which patients require surgical intervention?

Treatment methodologies for esophagopleural sac fistulas may be divided into 2 categories: either conservative or operative. However, the literature remains divided on which of these treatments is more effective [20-22]. Conservative treatment includes fasting, intravenous administration of antibiotics, enteral nutrition or parenteral nutrition, and smooth drainage via the thoracic drainage tube. Operative treatment includes mediastinal washing, clearance of necrotic tissues, drainage tube relocation, and/or anastomotic stoma detection without repair. Furthermore, tissues at the site of leakage can be reinforced, and the leak filled, depending on the experience of the surgeon. If appropriate, re-anastomosis may be performed.

A previous study [23] supported the use of operative treatment for patients with early-

stage solitary anastomotic fistulas occurring after esophagectomy or resection of a cardiac carcinoma, with a conservative course treatment being preferable for patients with advanced-stage anastomotic fistulas. Kulshrestha et al. [24] proposed that anastomotic fistulas with minor leaks occurring can be treated conservatively, provided that they are locally observed and discovered prior to intake of food. The fistula in our patient described in case 1 was discovered on post-operative day 6. As the radiographic examination identified that the leak was large, in combination with the strong belief by one of the patient's family member of operative treatment providing the most appropriate treatment course, surgery was performed 12 days after the leak was discovered, despite concerns regarding the difficulty of treating the leak in the context of serious infection-related tissue edema. During the surgery, we did identify a crevasse in the anastomotic stoma, and we were unable to repair its adnexa. Indeed, because of the magnitude of the leak, conservative treatment would have been ineffective. The tissues of the gastric and esophageal walls were red, although with only edema. The anastomotic stoma and the tissues of the gastric wall were well-vascularized and the intra-thoracic length of the stomach was appropriate. Therefore, we resected 2 cm of the esophagus and a small part of the gastric wall at the anastomotic stoma, and subsequently performed a manual gastric stump-esophagus side-to-end anastomosis, using a full-thickness interrupted suture. Prior to closing, good form and structure of the suture was confirmed. At the same time, we placed and retained a mediastinal drainage tube on the esophageal bed, along with a routine thoracic catheter. Based on our experience with this patient, we propose that discovery of a leak, providing full drainage for 1 week, until no obvious edema exists, following by operative treatment, including re-anastomosis, is a suitable treatment approach. For patients with early post-anastomosis leaks (i.e., developing 2-3 days after anastomosis), we recommend immediate re-anastomosis as these leaks always involve tissues local to the anastomosis. Indeed, in our case series, 1 case of unexpected digestive juice drainage the day following anastomosis was treated with emergency re-anastomosis, with positive recovery outcomes. When considering treatment for the patient

described in case 5, we had concerns regarding the viability of an operative treatment, and were unsure of the most appropriate method to proceed with the surgery. Therefore, we selected a conservative course of treatment, with good recovery outcomes observed, but that extended over a long time course which was unsatisfactory. Moreover, approximately 8 months post-surgery, pyogenic fluid was drained from the chest wall and it resulted in a deep, blind fistula. It is possible that selection of an operative treatment approach would have shortened the healing period, and the development of a post-operative purulent fistula might have been avoided.

The treatment of benign and tardive esophageal perforation, discovered 24 h after the onset of leakage, has been reviewed by Okonta and Kesieme [25] who summarized findings from 147 previously published cases. Based on their appraisal of available evidence, Okonta and Kesieme concluded that esophagectomy can not only clear the focus of an infection in the chest cavity, but can simultaneously eliminate peroral and transgastric infections. For tardive esophageal perforation that cannot be repaired, operative treatment is safer and more effective than conservative treatment. When treating our patient described in case 3, we performed resection of the primary lung cancer, and subsequently resected the middle lobe of the same lung for secondary lung cancer. During separation, the esophagus was damaged, which resulted in post-operative esophageal perforation. Although conservative treatment was successful, a chest wall abscess developed post-operatively. If the inclusions in the chest cavity had been identified during CT examination, we would have proceeded with clearance of these inclusions during the surgery and provided more effective draining of fluid from the chest which would have prevented the abscess from forming. For the patient described in case 4, although the post-operative gastroscopy identified only a small leak, the stretching of the associated diverticulum, which was completely different from the anastomotic fistula, resulted in a significant increase in the size of the leak, with possible perforation, despite a 6-month course of conservative treatment. Outcomes would likely have been improved in this case with the use of an esophagectomy for gut reconstruction.

Based on our critical appraisal of available clinical and research evidence and on our experience, we propose that conservative treatment should be considered in the following patients: (1) those with identified small leaks; (2) those in whom the disease is localized to the mediastinum or the effusion in the chest cavity can be drained smoothly; and (3) in patients with no obvious clinical symptoms. Operative treatment is recommended for the following patients: (1) those with substantial leaks; (2) those with effusion in the chest cavity that cannot be drained and, therefore, with a likelihood of subsequent localized inclusions developing; (3) those with obvious clinical symptoms, such as recurrent fever and substantial leukocyte increase; and (4) those with gastric stump fistulas. Operative procedures are primarily aimed at clearing vomica, allowing pulmonary re-expansion, providing drainage and removing an obstruction, repairing and embedding of a leak, or implantation of a nutrient tube, via the leak, for support. Operative procedures can also be used for secondary resection and reconstruction in specific cases.

Discussion on stent implantation for esophagopleural sac fistulas

Due to obstruction, hemorrhage, esophageal perforation, hyperplasia of granular tissue, tumor recurrence, and other complications, early literature [4, 26-28] discouraged stent implantation under endoscopy for the treatment of esophagopleural sac fistulas. In 2010, Sharma et al. [29] suggested that a review of the literature provided evidence of the possible usefulness of self-expanding stents for the treatment of anastomotic fistulas and esophageal perforation. At that time, however, Sharma et al. suggested that a bio-absorbable stent should be used for benign esophageal diseases. Subsequent research to evaluate the feasibility of stent implantation for the treatment of esophagopleural fistulas reported a success rate more than 90% [30-33]. In 2013, Dray et al. [34] reviewed evidence for the application of endoscopy in the management of complications associated with surgery of the digestive system, reporting that there is sufficient evidence to support a role of endoscopy in the treatment of esophagogastric anastomotic fistulas. They suggested that stent implantation, under endoscopy, could be performed for

patients with a leak smaller than 70% of the tube diameter, with smaller leaks being treatable with other materials, such as clamps and glue. Endoscopy alone should not be performed for post-esophagectomy anastomotic fistulas, but should be combined with drainage, anti-infection treatment, nutrition support, and surgical treatment. Very few studies have been able to prove the efficacy of endoscopy for esophageal fistula treatment.

Although a few studies have used prospective and retrospective designs to quantify the efficacy of endoscopy in the treatment of an esophageal fistula, these studies were not sufficiently powered to draw firm conclusions. Thus, the use of retrievable self-expanding metal stent remains controversial, despite evidence of satisfactory clinical effects, especially for the treatment of esophagogastric surgical fistulas. In 2014, Schweigert et al. [35] compared clinical outcomes of 49 patients who developed post-esophagectomy anastomotic fistula, 29 of whom had undergone stent implantation and 20 with standard operative treatments. The incidence rate of infection and acute renal insufficiency was higher in the operative group. Although not statistically different, the mortality rate was 24.1% among patients with stent implantation and 45% among patients treated operatively. In the stent implantation group, 3 patients sustained stent-related complications, including aortic erosion and acute massive hemorrhage. Consequently, Schweigert et al. suggested that only 60% of anastomotic fistula patients are suitable for stent implantation, and treatment should be performed according to the specific conditions of each individual. In treating our patient described in case 4, the size of the leak increased despite a 6-month course of conservative treatment. Stent implantation was performed in this patient. However, 3 days post-implantation, a lateral wall leak developed after food intake, with gastroscopy used to confirm displacement of the stent. A previously published study described the need to repeat stent implantation using a larger size stent due to displacement of the initial stent in a patient who had sustained an iatrogenic esophageal perforation [36]. In this case report, the stent ultimately had to be removed after the patient complained of pain of sufficient severity to prevent food intake. These unsatisfactory out-

comes of stent implantation may have resulted from the stent model, fixation technique or patient-specific characteristics. In fact, Schweigert et al. suggested that stent implantation should be considered only for a subcategory of patients. A large, multicenter, cooperative study should be conducted to establish evidence-based guidelines regarding patient selection for stent implantation, as well as guidelines on preferred stent model, location and technique for implantation. Such guidelines would substantially improve treatment of esophagopleural sac fistulas.

Drainage for esophagopleural sac fistulas

Uncontrolled infections of the mediastinum and chest cavity are the leading cause of mortality in patients with esophagopleural sac fistulas. Complete drainage is the key to treating such infections [37-39]. Currently, placement of a gastric tube and thoracic catheter is the standard of practice following all esophagectomy surgeries. An additional drainage tube should be placed at the mediastinum or around the anastomotic stoma. Retaining a drainage tube *in situ* around the anastomotic stoma during the anastomosis can reveal the presence of a fistula and can also drain fluid smoothly without further invasive drainage technique being required. In the absence of a drainage tube around the anastomotic stoma and mediastinum, a leak could remain undiscovered and, consequently, development of inclusions in the chest and mediastinum are difficult to prevent. This would require drainage tubes to be inserted under CT- or ultrasound-guidance. Of clinical importance, if the thoracic drainage tube can drain effusion, the drainage tube around the anastomotic stoma can also be used as a flushing tube. With respect to the duration of time required for healing of the leak, patients with a drainage tube placed in the immediate area of the anastomotic stoma typically exhibit a much shorter healing time [40]. In patients who develop post-anastomosis fistulas, the digestive juice around the anastomotic stoma and the loculated effusion and empyema in the chest cavity should be drained. Price et al. [41] recommended placing a drainage tube at the site of leakage through the skin under video-assisted thoracoscopy. However, in our view, effective placement of the drainage tube under video-assisted thoracoscopy is difficult in the presence of chest inclusions, as well as increas-

ing the difficulty of opening all vomicae for drainage. In this case, although a smooth drainage of leaked fluid is possible, the tissues with infections cannot be completely drained if existing vomicae cannot be thoroughly cleared. Therefore, we suggest that this video-assisted method may be effective in the early-stage of a leak, in the absence of chest inclusions. If inclusions have formed, we recommend clearing all vomicae operatively, with placement of a drainage tube near the leak and another in the chest cavity. If necessary, a flushing tube may also be included, requiring a drainage tube to be placed around the anastomotic stoma as well.

In recent years, internal drainage has been increasingly used, where a drainage tube is placed in the chest around the leak, either directly by endoscopy or under radiographic-guidance, and then connected to a tube with a vacuum aspiration device via the nose. Liu et al. [42] reported on their placement of a silicone tube into the chest around the leak via the nose to perform continuous vacuum aspiration. In this case, food intake was implemented immediately after closure of the leak, with good outcomes identified on esophagography. Other case studies have also reported positive effects for continuous vacuum aspiration [43, 44]. Similarly, vacuum assisted closure (VAC), as described in a number of previous international studies [30, 45-49], has been successfully used for the treatment of intra-thoracic anastomotic fistulas. Specifically, VAC consists of placing a metal sponge in the necrotic cavities around the leak, with attached tubes led out via the nose to connect with the vacuum aspiration device (100-125 mmHg). This treatment has been shown to have good efficacy, and is potentially even better than those observed with stent implantation [30].

When treating our patients described in cases 1 and 2, mediastinal drainage was placed during the secondary operation. In both cases, drainage effects were very good: all fluid from early-stage fistulas could be drained; fistulas were revealed in timely; and a series of complications related to fistula effusion were avoided. Under the premise that nutrient supplementation was sufficient, leaks healed in both of these patients without the need for further treatment. For patients described in cases 3-6, a duodenal nutrition tube was placed in the chest via the leak, without connection to a vac-

uum aspiration device. Among these 4 cases, 3 patients healed fully and were discharged, while 1 patient required further nutritional support therapy after discharge. Healing time was faster for patients with placement of a drainage tube around the leak than in patients in whom such a tube was not inserted. Therefore, placement of a drainage tube via the leak does not only drain effusion around the leak, but also facilitates expansion of the tissues around the leak and eventual closure. Normally, when an esophagopleural sac fistula is discovered, pus exists around the leak and cannot be cleared thoroughly by aspiration. Therefore, we believe that the primary purpose of the drainage tube is to support and facilitate healing of hyperplastic tissues, as well as to drain chest effusion from the digestive tract via the leak.

A drainage/support tube should routinely be placed at the anastomotic stoma or the mediastinum during esophagectomy. For post-esophagectomy patients or those with an esophageal perforation treated conservatively, the drainage/support tube should be routinely placed via the leak. For patients with loculated effusion, the effusion and inclusions should be cleared via thoracoscopy, and the thoracic drainage tube unblocked. If this is not possible, a thoracotomy should be performed to clear the infection and ensure that the thoracic drainage tube is functioning effectively, with replacement of the tube, or placement of an additional drainage tube, considered when necessary.

Cervical anastomotic stoma-mediastinum/pleural sac fistula

Two patients in our case series received tardive treatment as their symptoms developed a number of days after the surgery. One of these patients was a female whose early symptoms consisted mainly of chest pain and fever which we attributed to malnutrition and hypoproteinemia. The other patient was a male whose primary symptoms were fever which we attributed to incomplete gastric emptying, post-operatively. These two patients had the following characteristics in common: (1) routine 3-incision thoracotomy with open pleura; (2) cervical anastomotic stomas that were not fixed to the surrounding tissues; (3) cervical anastomotic fistulas directly spreading into the chest cavity without any obvious symptoms at the neck; and (4) localized inclusions on the anterior chest

wall. With respect to prevention, the following measures may prevent the post-operative formation of cervical anastomotic stoma-mediastinum/pleural sac fistulas. (1) The general health of the patient should be improved, including correction of hypoproteinemia prior to surgery. (2) Contrast-enhanced CT should be routinely used to clearly identify the distribution of the mediastinal lymph nodes. (3) When separating the thoracic apex esophagus and clearing the superior mediastinal lymph nodes during surgery, care should be taken to ensure that the pleural apex remains intact as far as possible, desirably as per pre-operative contrast-enhanced CT scanning results. If this is not possible, a THO may be performed under the premise that the intrathoracic lymph nodes can be cleared as per the applicable requirements. (4) During reconstruction of a tubular stomach, the gastric tube should either have an even or slightly large diameter than the esophagus to facilitate tissue adhesion on the gastric wall and thoracic opening before the formation of an early fistula. (5) The remnant cervical esophagus should be 2-3 cm, and not too long, otherwise the anastomotic stoma may fall directly into the mediastinum or chest cavity. (6) The cervical anastomotic stoma can be sutured to the fascia of the cervical long muscles but should not be sutured to the prevertebral fascia to prevent the development of centrum osteomyelitis and extradural abscess from an anastomotic fistula. (7) Ensure that the cervical vacuum sealing drainage is unblocked, and retain the cervical drainage tube for an appropriate time in patients with poor health status or anastomosis. (8) If fever, cervical pain or other similar symptoms occurs in the absence of a clear cause, the cervical wound should be re-opened for open drainage, even in the absence of redness, swelling or fluid discharge at the site of the wound. (9) A GI contrast examination should be performed prior to the intake of food to observe the status of healing of the anastomotic stoma and gastric emptying in order to avoid fistulas resulting from an increase in anastomotic stoma tension. From the perspective of treatment, once a cervical anastomotic stoma-mediastinum/pleural sac fistula occurs, a CT examination should be performed to confirm whether loculated effusion exists in the chest cavity or mediastinum, and the fluid of any vomicae must be drained completely. In cases with multiple vomicae, operative intervention should be performed as necessary to

clear all vomicae and ensure thorough drainage. At the same time, a thoracic/mediastinal drainage tube can be placed via the leak to facilitate the healing of the anastomotic stoma. Other treatments, including nutritional support and anti-infective therapy, should be performed as per standard routine treatment for thoracic anastomotic fistulas.

Application of washing

In China, a number of medical practitioners have attempted to wash various areas in patients with esophagopleural sac fistula, using different techniques. The clinical application of washing has not been extensively addressed in research to date. The gastric and chest cavities are commonly included in the washing, with the latter also including the anastomotic stoma (using a transthoracic and transwound approach), as well as pleural lavage, either in the presence or absence of localized inclusions. Different techniques used for washing are summarized below.

Stomach tube washing

Post-operatively, it is not uncommon for some degree of blood clot to remain in the stomach. It is crucial to wash the stomach tube of patients with poor gastric emptying. Patients with esophagopleural sac fistula consistently exhibit serious halitosis and infections of the chest cavity, with a number of these patients also suffering from complicated anaerobic infections of the gastric cavity. Ensuring thorough washing of the stomach tube in these patients is crucial. Flushing fluids commonly used include normal saline, metronidazole, and sodium bicarbonate.

Pleural lavage

Pleural lavage without localized inclusions: Li et al. [50] placed an aseptic inhaling phlegm pipe 0.5-1 cm away from the upper anastomotic stoma via the skin or thoracic drainage tube, and washed the stomach with normal saline continuously for 24 h, until the liquid was clear. Subsequently, they retracted the pipe 0.5 cm every day, and ceased washing after radiographic confirmation of leak closure. Compared to conventional drainage without washing, patient prognosis was much improved. Wang et al. [51] placed a double balloon-catheter, via

the 2nd intercostal space, at the midclavicular line as a flushing tube, and washed the chest cavity using approximately 1500 ml of normal saline combined with a sensitive antibiotic. They reported complete healing achieved in 13 of the 16 patients in their case series. Niu et al. [52] evaluated the effectiveness of chest washing by a direct comparison of washing with an oral administration of 0.1% chloramphenicol saline and washing with normal saline containing gentamicin. Their results showed that chest washing in combination with oral administration of 0.1% chloramphenicol saline was more effective than using normal saline with gentamicin.

Pleural lavage with localized inclusions: For patients with esophagopleural sac fistulas and complicated localized chest inclusions, Li [53] performed CT examination to accurately confirm the location of inclusions, placed and retained fine silicon drainage tubes under CT-guidance and subsequently repeatedly washed the chest cavity using normal saline, after draining all pyogenic fluid, with the washing continued until a clear fluid was obtained. Subsequently, Li performed chest washing in an interrupted manner, using saline in combination with a solution comprised of a sensitive antibiotic, sodium bicarbonate, and hydrogen peroxide. Li removed the washing catheter when the daily drainage of pyogenic fluid was <10 ml and clear. Li reported good recovery outcomes using this technique. Xia et al. [54] reported curing 8 patients who had developed serious intra-thoracic anastomotic fistulas post-esophagectomy using esophageal suture with pleural lavage drainage. Due to the presence of serious inclusions in the chest cavity of these patients, secondary operative treatment was performed to clear all inclusions and to place a flushing tube near the anastomotic stoma. Post-surgery, continuous washing was performed with normal saline. All patients exhibited positive recovery outcomes.

Several issues related to washing in patients with an esophagopleural sac fistula remain to be determined, including: what patients require or can benefit, from washing; how the flushing tube should be placed; what flushing fluid is most appropriate; when washing should be discontinued; and when to remove the flushing tube. Establishing widespread, validated guide-

lines would aid in optimizing this treatment on an individual-patient basis.

In three of our cases, we used washing as an adjunctive therapy: 1 high-position silicon drainage tube was retained *in situ* for the patient in case 1 as a flushing tube during the secondary operation; a venipuncture catheter for fluid drainage and washing was placed and retained in the patient in case 5 when loculated effusion localized to the chest wall was identified; and, a thoracic drainage tube with an aseptic inhaling phlegm pipe was placed directly at the inclusion for washing with a solution of normal saline, sodium bicarbonate and metronidazole in case 6. In case 1, the flushing catheter was removed after 1 week of treatment, with the patient recovering from a persistent fever. For patients in cases 5 and 6, fever persisted and a CT examination was performed; in both cases, with loculated effusion identified, and drainage tubes and flushing catheters were placed. These were removed when fever was no longer apparent, and good lung inflation and absence of inclusions had been confirmed. For the remaining 3 patients in our case series, no flushing catheter was required, due to smooth drainage, normal body temperatures and no obvious loculated effusion.

According to our experience, in cases of smooth drainage, normal body temperature and absence of loculated effusion or pneumatoxis on chest CT, flushing is not required. For patients with smooth drainage and without thoracic inclusions, but with fever, a flushing tube should be placed via the original thoracic catheter for washing. Typically, the fever resolved over a short period of time with washing performed twice per day, as necessary, primarily using sodium bicarbonate, metronidazole and normal saline. For patients with loculated effusion and pneumatoxis, the location of effusion and pneumatoxis should be accurately confirmed by CT to achieve optimal drainage. Drainage of a light yellow fluid is indicative of normal chest effusion, with no washing required. Otherwise, a silicon flushing catheter should be placed via the skin or drainage tube. For patients who underwent secondary operative treatment, irrespective of the degree of re-section or empyema clearance, inclusions should be cleared intra-operatively and a silicon flushing catheter was placed using a high transthoracic approach. Routine post-surgical washing should be performed for 1 week. For

patients with esophagopleural sac fistulas, oral administration of gentamicin during early washing of the leak should provide reasonably efficacy, provided that the drainage is smooth.

In summary, based on our experiences in treating patients with esophago-mediastinal/pleural sac fistulas, as well as our critical appraisal of current domestic and international research evidence, we propose the following. (1) Water-soluble contrast material should be used of contrast GI, CT and endoscopic examinations for diagnosis of esophago-mediastinal/pleural sac fistulas, with evaluation of clinical symptoms being the most important component of the diagnosis. (2) Characteristics of individual patients should be considered when determining the necessity for re-thoracotomy. For patients with localized inclusions, we recommend opening all vomicae for thorough drainage to reduce the risk of empyema, provided that the general condition of the patient is conducive to further operative treatment. (3) At present time, although self-expanding retrievable metal stent implantation has widely been adopted, there is no systematic evidence regarding the negative effects of stent implantation. Thus, we suggest that stent implantation be adopted according to specific patient criteria, rather than adopting a blind application of the technique for all patients. (4) Transesophageal anastomotic stoma vacuum sealing drainage and fine support for the leak can facilitate leak healing. (5) Pleural lavage can relieve clinical symptoms and facilitate leak healing. (6) Intactness of the cupula pleura can significantly reduce the risk of chest cavity involvement in patients with cervical anastomotic fistulas.

Disclosure of conflict of interest

None.

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