Clinical Case Report

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Late-onset bronchopleural fistula after lobectomy and adjuvant chemotherapy for lung cancer

A case report and review of the literature

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Abstract

Rationale: Late-onset bronchopleural fistula (BPF) induced by chemotherapy after lobectomy for lung cancer is rarely reported, lacking reliable preventive approaches. A timely identification and individualized treatment is essential for prognosis.

Patient concerns: A 52-year-old female patient complained of fever, productive cough, and fatigue 1 week after adjuvant chemotherapy following right lower lobectomy and systemic mediastinal lymph node dissection. Chest computed tomography (CT) indicated pneumothorax and thick-walled empyema cavity within her right-sided thorax.

Diagnoses: The patient was diagnosed as late-onset BPF based on clinical manifestation and chest radiography.

Interventions: In addition to antibiotics, a chest tube was reinserted under CT guidance, and vacuum suction was utilized for continuous drainage. Next cycle of adjuvant chemotherapy was terminated.

Outcomes: The empyema cavity was gradually closed in 1 month after conservative treatment, and the patient survived with good condition up to now.

Lessons: Late-onset BPF should be kept in mind when the patient suffered from productive cough and chills during postoperative chemotherapy. And a prompt conservative management might be effective.

Abbreviations: 3D-CTBA = three-dimensional-computed tomography bronchography and angiography, BEF = broncho-oesophageal fistula, BPF = bronchopleural fistula, CRT = chemotherapy and radiotherapy, CT = computed tomography, MRSA = methicillin-resistant *Staphylococcus aureus*, NHL = non-Hodgkin lymphoma, NSCLC = nonsmall cell lung cancer, TOF = tracheo-oesophageal fistula, VATS = video-assisted thoracoscopic surgery.

Keywords: 3D-CTBA, bronchopleural fistula (BPF), late-onset, lung cancer, single direction

1. Introduction

Bronchopleural fistula (BPF) after pulmonary resection is not uncommon but challenging to manage, with a incidence of 4% to 20% in patients after pneumonectomy and <1% after lobectomy.[1] It is reported that non-R0 resection, right-sided pneumonectomy, long bronchial stump, diabetes, infection, neoadjuvant therapy, and corticosteroids are independent risk factors of such complication.[2] However, to the best of our knowledge, late-onset BPF following lobectomy (>30 days after surgery) is rare. We herein report an unusual case of delayed BPF after one cycle of adjuvant chemotherapy following lobectomy for nonsmall cell lung cancer (NSCLC). Literatures related to this potentially lethal complication were reviewed.

This report was approved by Institutional Review Board of Xuzhou Central Hospital, and written informed consent was obtained from the patient. The clinical data were treated anonymously for privacy issue.

2. Case presentation

A 52-year-old female nonsmoker was admitted to our hospital because of the chest computed tomography (CT) during health examination indicated an irregular nodule located in the right lower lobe (Fig. 1A), in suspicious of malignancy. Her previous

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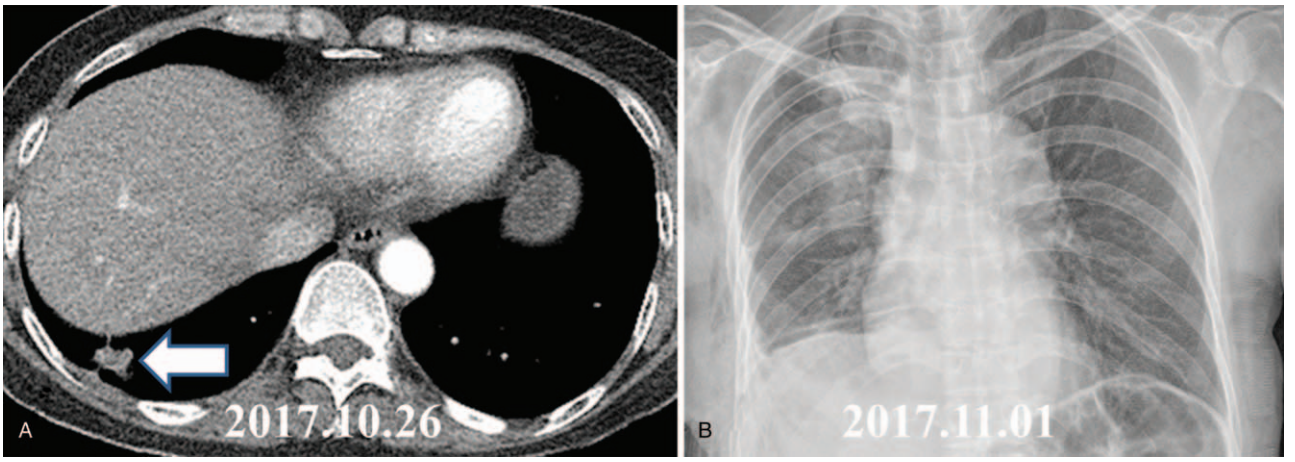

Figure 1. (A) CT scan on the first admission showed pulmonary nodule located in right lower lobe. (B) On the third postoperative day, chest X-ray indicated re-expansion of right upper and middle lobes.

medical history was unremarkable. Tuberculosis, bronchiectasis, and rheumatism were excluded by laboratory tests and radiograph. Further abdomen CT, cranial magnetic resonance, and bone emission CT were carried out. Then this case was initially diagnosed as lung cancer and clinically staged as cT1bN0M0 according to the 8th edition of TNM staging system for NSCLC, and a timely resection was chosen.

Fast-track protocol in thoracic surgery was utilized. To diminish intraoperative injury of the potentially aberrant vessels, her right pulmonary arterial and venous tree was preoperatively analyzed using three-dimensional-computed tomography bronchography and angiography (3D-CTBA) by the free-access software OsiriX. Then uniportal video-assisted thoracoscopic right lower lobectomy in a single direction was performed successfully on October 29, 2017. It followed the sequence of right lower pulmonary vein, lobar bronchus, lower pulmonary artery, and oblique fissure. Systemic mediastinal lymph node dissection was finally manipulated. The bronchial stump was closed using a 45-mm EndoGIA (Covidien, Boulder, CO) stapler. Because there was no sign of air leak after lobectomy, bronchial stump reinforcement and prophylactic mechanical or chemical pleurodesis of right chest cavity were not performed.

The operating time was 85 minutes, with nearly 100 mL of blood loss. Ultrasound-guided serratus anterior plane block was applied for postoperative pain relief. Ambulation out of bed and oral feeding was initiated from the first postoperative day (POD). R0 resection was achieved. Pathological diagnosis was well-differentiated pulmonary adenocarcinoma, with visceral pleura invasion (pT2aN0M0, I B). The postoperative course was uneventful, and the patient was discharged on the fifth POD as a chest X-ray showed satisfactory re-expansion of right upper and middle lobes (Fig. 1B).

On the 24th POD, she was readmitted for adjuvant chemotherapy, without palpitation, dyspnea, or fever, except mild nonproductive cough. Physical examination, laboratory tests, and chest X-ray (Fig. 2A) were unremarkable. Then the first cycle of pemetrexed (500 mg/m^2 of body surface area) and cisplatin (75 mg/m^2 of body surface area) was administered, along with dexamethasone (5 mg daily for 3 days) to diminish cisplatin-related adverse effects.

On the 37th POD (1 week after chemotherapy), she was readmitted and complained of fatigue, productive cough, fever (the body temperature was 38.6°C), and chills. Hemoptysis was not observed. Her right-sided respiratory sound was slightly reduced. She received piperacillin/sulbactam (3.0 g, every 12 hours) intravenously with an empirical diagnosis of pneumonia. However, the symptoms were not alleviated 3 days later. Meanwhile, repeated culture of the sputum was negative of bacteria, fungus, or tuberculosis. Therefore, further tests were carried out for a correct diagnosis. Chest CT indicated pneumothorax and localized pleural effusion with cavity formation in right thorax (Fig. 2B). Based on these findings, a late onset postoperative BPF was strongly suspected. As shown in the CT image, the fistula might be located at the edge of right lower bronchial stump. However, the patient could not endure bronchoscopy exploration.

Then a 14 French catheter was reinserted into right chest cavity under CT guidance (Fig. 2C). Vacuum suction of the tube was used for continuous chest drainage. Besides, normal saline irrigation into chest cavity was used 3 times daily. Thoracic effusion with active inflammatory signs was cultivated but failed to identify a definite pathogen, although bleeding and chyle leakage could be excluded.

Another chest CT was performed 5 days later, which revealed that pneumothorax was disappeared (Fig. 2D). Thereafter, her clinical condition was gradually improved, and intravenous antibiotics were terminated 10 days later. One month after chest drainage, the patient was discharged when productive cough was stopped and the CT showed shrunken empyema cavity (Fig. 2E). Besides, moxifloxacin tablet was used for another 7 days (0.4 g daily). On the 3-month follow-up, CT images revealed the closure of BPF (Fig. 2F).

3. Discussion

The onset of BPF could be classified as early (1–7 days), intermediate (8–30 days), and late (>30 days).[3] Fistulas almost always occur within 3 months after surgery,[4] especially within 8 to 12 POD.[5] The diagnosis of BPF is made using a combination of clinical, radiographic, and bronchoscopic findings. The initial manifestations include fever, chills, cough with expectoration of

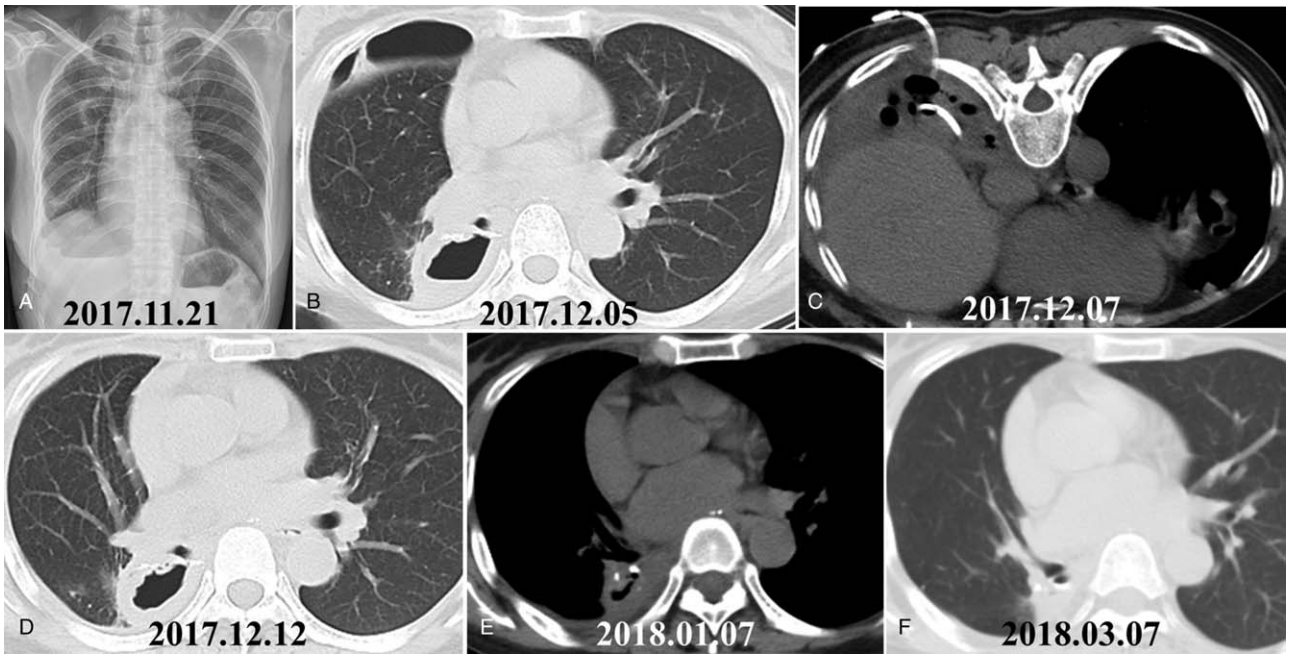

Figure 2. (A) Chest X-ray on the second admission showed generally normal thoracic cavity. (B) CT on 37th POD indicated right-sided pneumothorax and think-walled empyema cavity. (C) A 14 French catheter was reinserted. (D) Pneumothorax was disappeared after chest drainage. (E) The empyema cavity was shrunken 1 month after therapy. (F) On the 3-month follow-up, CT image showed closure of the BPF.

purulent fluid, dyspnea, and newly emerged pleural effusion on the chest radiograph.

The presented case was staged as I B (pT1bN0M0 with visceral pleural involvement) and received adjuvant chemotherapy following right lower lobectomy for lung cancer. The time of chemotherapy initiation was 25 days after surgery. Dexamethasone was used. Then BPF was occurred on 37th POD (1 week after chemotherapy). Surgery-related bronchial injury, early initiation of adjuvant chemotherapy, and glucocorticoid might result in a delayed healing of the bronchial stump. Accordingly, there are several issues that need to be elucidated.

First, the updated NCCN guideline for NSCLC (2019, Version 2) demonstrates that adjuvant chemotherapy is considered for I B lung cancer patients with high-risk factors, which include poorly differentiated tumors (including lung neuroendocrine tumors but excluding well-differentiated neuroendocrine tumors), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and unknown lymph node status.[6] As for the presented patient with R0 resection, the efficacy of postoperative chemotherapy on prognosis necessitates better evidence. This patient did not receive further anticancer therapy after the healing of BPF, and she was survived up to now without tumor recurrence or metastasis.

Second, the optimal interval between radical surgery and postoperative therapy is still uncertain. Whether a delayed administration of chemotherapy might compromise its efficacy is debatable. It is reported that one-third of NSCLC patients start adjuvant chemotherapy beyond 10 weeks after surgery, and delayed chemotherapy does not appear to be associated with inferior survival in NSCLC patients.[7] Another report indicates that time to initiation of adjuvant chemotherapy ($\leq$35 days vs >35 days after curative resection) does not affect disease-free survival of NSCLC patients.[8]

In addition, adjuvant chemotherapy remains efficacious when started 7 to 18 weeks after pulmonary resection for NSCLC,[9] and patients who recover slowly from thoracic surgery may still benefit from delayed adjuvant chemotherapy (up to 4 months after surgery). Moreover, patients vary considerably in their ability to tolerate adjuvant therapy while recovering from a lung cancer resection.[10] Multiple factors including health status and postoperative complications may affect a patient's tolerance to chemotherapy.[11,12] Therefore, a longer recovery period for the presented case might be reasonable, although BPF lacks reliable preventive approaches.

Third, glucocorticoid used in the first cycle of adjuvant chemotherapy might also contribute to late-onset BPF. Neoadjuvant therapy and a right lower lobe location are risk factors of BPF within 30 days after a lobectomy.[13,14] Diabetes mellitus is another independent risk factor of this complication.[15] Meanwhile, pulmonary cavitation, esophagorespiratory fistula, hemorrhage, bronchial stenosis, esophageal stenosis, and bronchiectasis are associated with high-dose chemoradiotherapy for NSCLC.[16] Furthermore, postoperative mechanical ventilation and preexisting pleuropulmonary infection might be positively correlated with the incidence of BPF following pneumonectomy.[17] Other causes of BPF include but not limited to low nutritional status, a large bronchial stump (>2.5 cm), extensive lymph node dissection, residual tumor in the resection margins, excessive peribronchial dissection, prolonged postoperative mechanical ventilation, bronchoscopy for sputum suctioning, bacterial or fungal infection, and tuberculosis.[5] The incidence of BPF after lung resection for tuberculosis is 0% to 6.6%, partly because of already inflamed bronchi.[18] The most severe BPF-related complications are acute respiratory distress syndrome after aspiration and tension pneumothorax. Thus, the onset of postoperative BPF should always be kept in mind.

Table 1

Previously reported cases of late-onset bronchial fistula.

Author	Number of the cases	Age, y	Type	Etiology	Time interval*	Diagnostic methods
Lazo Ramos et al[19]	Not available	Not available	BPF	Collapse therapy for pulmonary tuberculosis	Not available	Chest radiograph
Rajesh et al[20]	1	39	TOF	Foreign body	18 mo	Barium swallow
Weber et al[21]	1	42	TOF	Blunt chest trauma and thoracotomy	20 y	Chest radiograph and bronchoscopy
Ahmad et al[22]	1	67	TOF	MRSA infection and chemotherapy for NHL	Not available	Flexible endoscopy
Giovanni Leuzzi et al[23]	1	54	BPF	Right lower lobectomy for NSCLC	2 mo	Expectoration of staple line, fiber-optic bronchoscopy
Takagi et al[24]	8	Not available	Pulmonary fistula	Pulmonary segmentectomy	Not available	Not available
Sharma et al[25]	1	42	BEF	Tuberculosis, parietal lobe abscess	15 y	Chest radiograph
Noh et al[26]	1	69	BPF	Pneumonectomy for lung cancer	4 y	Chest radiograph
Kanzaki et al[27]	2	Not available	Pulmonary fistula	Pulmonary resection, chemotherapy with bevacizumab	Nearly 3 mo	Not available
Abugroun et al[28]	1	72	TOF	CRT for squamous lung cancer	1 y	Barium swallow
Yang et al[29]	1	3	TOF	Foreign body aspiration	3 mo	Rigid bronchoscopy

BEF = broncho-oesophageal fistula, BPF = bronchopleural fistula, CRT = chemotherapy and radiotherapy, MRSA = methicillin-resistant Staphylococcus aureus, NHL = non-Hodgkin lymphoma, NSCLC = nonsmall cell lung cancer, TOF = tracheo-oesophageal fistula.

* Time interval between the surgery, injury or treatment and the onset of bronchial fistula of the patients.

On the contrary, the incidence of delayed/late-onset BPF following lobectomy is rare. Similar reported cases are tabulated in Table 1. The causes of late-onset bronchial fistula include collapse therapy for pulmonary tuberculosis, foreign body aspiration, blunt chest trauma, refractory infection, chemotherapy and radiotherapy, with a time interval of 2 months to 20 years between the surgery, injury, or therapy and the onset of bronchial fistula.

The management of BPF includes conservative and surgical interventions, which focuses on chest drainage, control of the pleural infection, and obliteration of the residual pleural cavity.[30] Surgical intervention should be cautious because of promised performance status of the patients. Endobronchial naso-bronchial lavage is useful for BPF >5 mm.[31] Besides, endobronchial valves are well tolerated and effective for patients with BPF,[32] which facilitate administration of intrapleural fibrinolytics and antibiotics for definitive treatment of empyema.[33] A multimodal approach including insertion of tracheobronchial conical stent, open pleural packing, and closure of bronchial stump with omentoplasty is particularly effective for BPF with empyema.[34] Finally, evidence for bronchial stump reinforcement leading to a reductive incidence of BPF is conflicting.[5,35] However, coverage of the stump with vascularized intercostal flaps could be considered for pneumonectomy or sleeve lobectomy with bronchoplasty.

In summary, late-onset BPF during postoperative chemotherapy following lobectomy for lung cancer should be kept in mind. A short interval between surgery and adjuvant therapy or glucocorticoid administration might be risk factors of BPF. High-quality evidence is necessary to confirm our findings.

Author contributions

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Formal analysis: Rui-Mei Zhang, Miao Zhang.
Funding acquisition: Miao Zhang.
Investigation: Miao Zhang.
Methodology: Dong Liu.
Resources: Chu Zhang.
Software: Yong Pan.
Visualization: Dong Liu.
Writing – original draft: Chu Zhang, Yong Pan, Wen-Bin Wu, Miao Zhang.
Writing – review and editing: Chu Zhang, Rui-Mei Zhang, Wen-Bin Wu, Miao Zhang.

References

[1] Cooper WA, Miller JIJr. Management of bronchopleural fistula after lobectomy. Semin Thorac Cardiovasc Surg 2001;13:8–12.
[2] Sirbu H, Busch T, Aleksic I, et al. Bronchopleural fistula in the surgery of non-small cell lung cancer: incidence, risk factors, and management. Ann Thorac Cardiovasc Surg 2001;7:330–6.
[3] Varoli F, Roviaro G, Grignani F, et al. Endoscopic treatment of bronchopleural fistulas. Ann Thorac Surg 1998;65:807–9.
[4] Gaur P, Dunne R, Colson YL, et al. Bronchopleural fistula and the role of contemporary imaging. J Thorac Cardiovasc Surg 2014;148:341–7.
[5] Salik I, Abramowicz AE. Bronchopleural Fistula. SourceStatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019.
[6] National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Small Cell Lung Cancer, Version 2. 2019. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx#site. Accessed January 15, 2019.
[7] Booth CM, Shepherd FA, Peng Y, et al. Time to adjuvant chemotherapy and survival in non-small cell lung cancer: a population-based study. Cancer 2013;119:1243–50.
[8] Liu Y, Zhai X, Li J, et al. Is there an optimal time to initiate adjuvant chemotherapy to predict benefit of survival in non-small cell lung cancer? Chin J Cancer Res 2017;29:263–71.
[9] Salazar MC, Rosen JE, Wang Z, et al. Association of delayed adjuvant chemotherapy with survival after lung cancer surgery. JAMA Oncol 2017;3:610–9.
[10] Kozower BD, Sheng S, O'Brien SM, et al. STS database risk models: predictors of mortality and major morbidity for lung cancer resection. Ann Thorac Surg 2010;90:875–81.
[11] Teh E, Abah U, Church D, et al. What is the extent of the advantage of video-assisted thoracoscopic surgical resection over thoracotomy in terms of delivery of adjuvant chemotherapy following non-small-cell lung cancer resection? Interact Cardiovasc Thorac Surg 2014;19:656–60.
[12] Jiang G, Yang F, Li X, et al. Video-assisted thoracoscopic surgery is more favorable than thoracotomy for administration of adjuvant chemotherapy after lobectomy for non-small cell lung cancer. World J Surg Oncol 2011;9:170.
[13] Okuda M, Go T, Yokomise H. Risk factor of bronchopleural fistula after general thoracic surgery: review article. Gen Thorac Cardiovasc Surg 2017;65:679–85.

[14] Li S, Fan J, Liu J, et al. Neoadjuvant therapy and risk of bronchopleural fistula after lung cancer surgery: a systematic meta-analysis of 14 912 patients. Jpn J Clin Oncol 2016;46:534–46.
[15] Li SJ, Fan J, Zhou J, et al. Diabetes mellitus and risk of bronchopleural fistula after pulmonary resections: a meta-analysis. Ann Thorac Surg 2016;102:328–39.
[16] Dickhoff C, Dahele M, Hashemi SM, et al. Surgical treatment of complications after high-dose chemoradiotherapy for lung cancer. Ann Thorac Surg 2017;104:436–42.
[17] Toufektzian L, Patris V, Sepsas E, et al. Does postoperative mechanical ventilation predispose to bronchopleural fistula formation in patients undergoing pneumonectomy? Interact Cardiovasc Thorac Surg 2015; 21:379–82.
[18] Egyud M, Suzuki K. Post-resection complications: abscesses, empyemas, bronchopleural fistulas. J Thorac Dis 2018;10(Suppl. 28): S3408–18.
[19] Lazo Ramos A, Munoz Gutierrez FJ, Acevedo Thomas C, et al. [Bronchopleural fistula: a late complication of collapse therapy in pulmonary tuberculosis]. Atencion Primaria 1989;6:323–5.
[20] Rajesh PB, Goiti JJ. Late onset tracheo-oesophageal fistula following a swallowed dental plate. Eur J Cardiothorac Surg 1993;7:661–2.
[21] Weber SM, Schurr MJ, Pellett JR. Delayed presentation of a tracheoesophageal fistula after blunt chest trauma. Ann Thorac Surg 1996;62:1850–2.
[22] Ahmad I, Lee WC. Methicillin-resistant Staphylococcus aureus neck infections resulting in a delayed abscess and a tracheo-oesophageal fistula. ORL J Otorhinolaryngol Relat Spec 1999;61:45–7.
[23] Leuzzi G, Alessandrini G, Forcella D, et al. Expectoration of the staple line: a delayed complication after previous lobectomy. Interact Cardiovasc Thorac Surg 2015;20:672–4.
[24] Takagi K, Hata Y, Sasamoto S, et al. Late onset postoperative pulmonary fistula following a pulmonary segmentectomy using electrocautery or a harmonic scalpel. Ann Thorac Cardiovasc Surg 2010;16:21–5.
[25] Sharma P, Kumar A. Delayed presentation of post tuberculous broncho oesophageal fistula in an adult: perioperative anaesthetic management. Indian J Anaesth 2015;59:459–60.
[26] Noh D, Park CK. The management of delayed post-pneumonectomy broncho-pleural fistula and esophago-pleural fistula. Korean J Thorac Cardiovasc Surg 2016;49:138–40.
[27] Kanzaki R, Shintani Y, Inoue M, et al. Late-onset pulmonary fistula after resection of pulmonary metastasis from colorectal cancer following perioperative chemotherapy with bevacizumab. Ann Thorac Cardiovasc Surg 2017;23:149–52.
[28] Abugroun A, Ahmed F, Singh N, et al. Late onset chemo/radiation induced tracheoesophageal fistula in squamous cell cancer of the lung. World J Oncol 2017;8:171–3.
[29] Yang W, Jones M, Mallick S. Tracheo-oesophageal fistula: a delayed complication of missed inhaled magnetic toys. J Surg Case Rep 2018;2018:rjy022.
[30] Bribriesco A, Patterson GA. Management of postpneumonectomy bronchopleural fistula: from thoracoplasty to transsternal closure. Thorac Surg Clin 2018;28:323–35.
[31] Ning Y, Huang H, Xue L, et al. Endobronchial naso-bronchial lavage: an alternative interventional treatment for post-lobectomy bronchopleural fistula. World J Surg 2017;41:785–9.
[32] Giddings O, Kuhn J, Akulian J. Endobronchial valve placement for the treatment of bronchopleural fistula: a review of the current literature. Curr Opin Pulm Med 2014;20:347–51.
[33] Leiter N, Pickering EM, Sangwan YS, et al. Intrapleural Therapy for Empyema in the Setting of a Bronchopleural Fistula: A Novel Use of an Intrabronchial Valve. Ann Thorac Surg 2018;106:e111–3.
[34] Andreetti C, Menna C, D'Andrilli A, et al. Multimodal treatment for post-pneumonectomy bronchopleural fistula associated with empyema. Ann Thorac Surg 2018;106:e337–9.
[35] Pomerantz BJ, Cleveland JCJr, Olson HK, et al. Pulmonary resection for multi-drug resistant tuberculosis. J Thorac Cardiovasc Surg 2001;121:448–53.