Case Report: iMDT Corner

Intrapleural minocycline pleurodesis for bilateral pneumothorax due to septic pulmonary embolism: a case report

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Background: Pneumothorax is a rare but serious complication of septic pulmonary embolism (SPE). SPE is a life-threatening disorder wherein infected thrombi bring infarction of the terminal and small caliber parts of the pulmonary vasculature and develop multiple nodular and cavitary lesions. Interventions other than conservative chest tube drainage for pneumothorax due to SPE have rarely been reported. Here, we present a case of bilateral pneumothorax due to SPE treated with intrapleural minocycline pleurodesis.

Case Description: A 72-year-old male patient previously diagnosed as esophageal carcinoma developed metachronous bilateral pneumothorax while treated for brain metastases. Based on blood cultures and chest computed tomography images, he was diagnosed with pneumothorax secondary to SPE due to methicillin-susceptible *Staphylococcus aureus* bacteremia. Bilateral chest tube drainage was instituted. Continuous air leakage was found bilaterally after chest tube placement. He was treated with broad-spectrum antibiotics based on the susceptibility profile and supportive treatment for sepsis. Approximately 3 weeks later, air leakage significantly reduced. We performed intrapleural minocycline pleurodesis bilaterally to prevent the recurrence of pneumothorax; the left side was firstly treated and the right side was treated 2 weeks later. Both chest tubes were successfully removed two days after procedures. Although the patient finally died of brain metastases 1 month after pleurodesis, he never recurred pneumothorax.

Conclusions: Intrapleural minocycline pleurodesis may be one of the useful and efficacious options in terms of treating intractable pneumothorax associated with SPE. Intrapleural minocycline pleurodesis could be a consideration for intractable pneumothorax related to SPE.

Keywords: Minocycline; pleurodesis; pneumothorax; septic pulmonary embolism (SPE); case report

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Introduction

Background

Septic pulmonary embolism (SPE) is a rare life-threatening disorder wherein infected thrombi cause an infarction of pulmonary vasculature and the development of multiple nodular with subsequent cavitary lesions (1). This condition has been associated with infective endocarditis, intravenous drug abuse and septic thrombophlebitis (1).

Rationale and knowledge gap

Pneumothorax is an uncommon and serious complication of SPE because it could affect lungs bilaterally and could easily deteriorate respiratory condition (2-4). Many reports demonstrated successful treatment with chest tube drainage (4). However, interventions other than conservative chest tube drainage have rarely been documented.

Objective

We herein report a case of metachronous bilateral pneumothorax due to SPE treated with intrapleural minocycline pleurodesis. We present this article in accordance with the CARE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1923/rc).

Case presentation

A 72-year-old man presenting with hoarseness was diagnosed with esophageal squamous cell carcinoma with nodal metastases causing left laryngeal nerve palsy. He was treated with thoracoscopic esophagectomy following chemotherapy; eight courses of nivolumab were added after surgery. However, 8 months after esophagectomy, the patient presented with neurological symptoms such as dizziness. Multiple brain metastases were detected by non-contrast brain computed tomography (CT). One of the brain metastases lesions was planned for surgical tumor resection. He underwent craniotomy without any complications. His neurological symptoms gradually improved, thus he was planned to be transferred to a rehabilitation hospital. While he was waiting for being transferred, he suddenly developed fever and hypotension 1 month after the brain surgery. Because there was a clinical suspicion of sepsis, whole-body CT was taken to detect any sources of infection. It revealed multiple ground-glass opacity and nodular shadows accompanying cavitary lesions observed in bilateral lung fields (*Figure 1*). Because the previous chest CT performed 2 weeks before did not show these abnormal nodular shadows, these new lesions seemed to be inflammatory or infectious rather than metastatic nodules. Blood cultures detected methicillin-susceptible *Staphylococcus aureus* (MSSA) growth. Transthoracic echocardiography did not reveal any signs of infective endocarditis. Considering both blood cultures and imaging, he was diagnosed with sepsis caused by MSSA and SPE representing left pneumothorax (*Figure 1*).

A left sided percutaneous small caliber (16 Fr) chest tube drainage was placed for left pneumothorax. One week after the left pneumothorax occurred, he also developed right pneumothorax (*Figure 2*). Right chest tube drainage with 16-Fr chest tube was initiated as well. Continuous and large volume air leakage was observed in both chest tubes. He was treated with appropriate broad spectrum antibiotics (piperacillin/tazobactam and vancomycin later switched to cefazolin) and supportive treatment such as adequate volume resuscitation and vasopressor therapy for sepsis shock. Surgery for pneumothorax was not indicated because of his poor general condition. The negative pleural fluid culture was found (*Figure 2*).

While chest tube drainage was continued bilaterally, the respiratory status deteriorated due to severe pneumonia (*Figure 3A*). The patient underwent tracheostomy for better suction clearance and rehabilitation 1 week after initiation of right chest tube drainage. His respiratory condition did not require mechanical ventilation and thus the patient was not intubated before and after the development of pneumothorax.

Highlight box

Key findings

- Intrapleural minocycline pleurodesis may be used for pneumothorax associated with septic pulmonary emboli.

What is known and what is new?

- Intrapleural minocycline pleurodesis is one of the therapeutic options for intractable pneumothorax.
- Intrapleural minocycline pleurodesis may be effective for pneumothorax associated with septic pulmonary emboli.

What is the implication, and what should change now?

- Intrapleural minocycline pleurodesis could be considered as a treatment option for intractable pneumothorax related to septic pulmonary embolism.

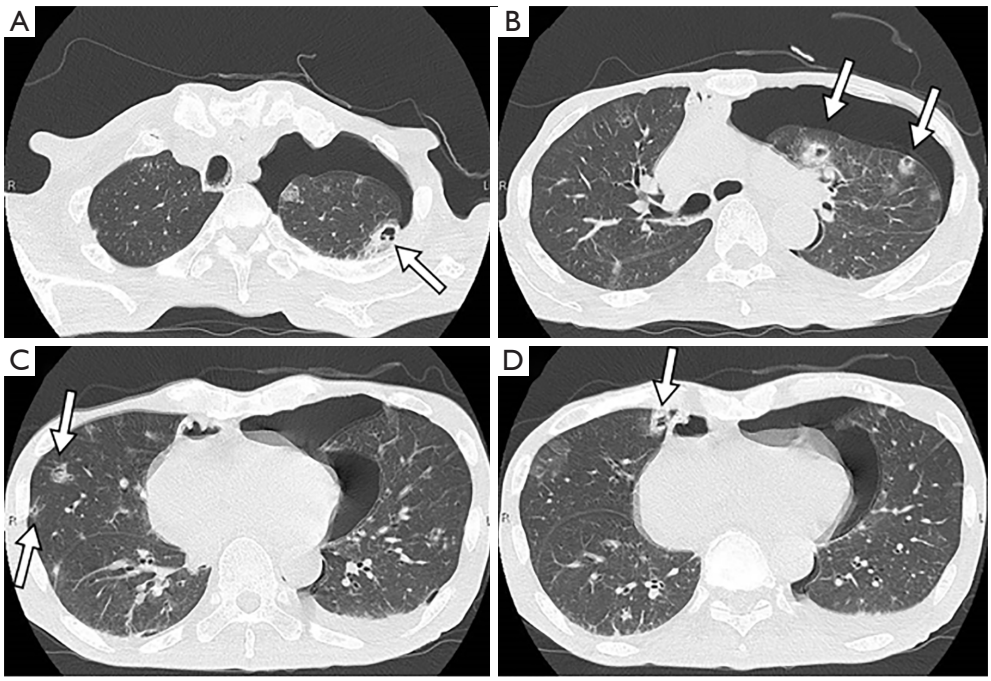

Figure 1 Computed tomography findings. Left pneumothorax was detected in the left lung (A,B). Septic emboli were observed in the left lung (A,B; white arrows) as well as in the right lung (C,D; white arrows).

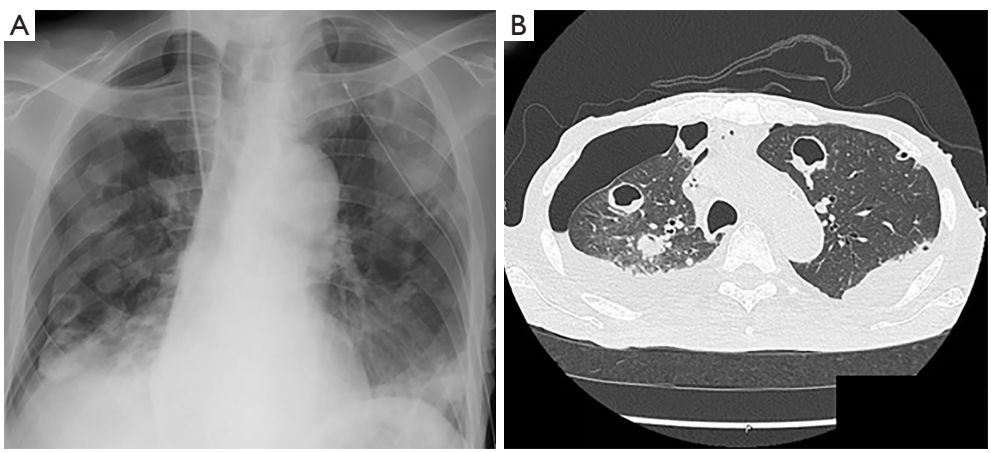

Figure 2 Images of right pneumothorax. (A) Chest radiograph revealed right pneumothorax and bilateral cavitary lesions. (B) Computed tomography showed right pneumothorax and bilateral septic emboli.

Seventeen days after the initiation of left chest tube drainage, air leakage was successfully controlled in left chest tube. Chest X-ray revealed that the left pneumothorax had disappeared. In order to prevent recurrence of the left pneumothorax, we decided to perform intrapleural minocycline pleurodesis. Sasaki *et al.* reported that approximately 32% of patients with secondary pneumothorax experienced recurrence in 3 months without pleurodesis (5). In addition, another article reported that patients with bilateral pneumothorax had a fourfold recurrence rate compared to those with unilateral pneumothorax (6). Based on these reports, we assumed that the patient would develop recurrent pneumothorax in a short term. Medical pleurodesis was indicated in the

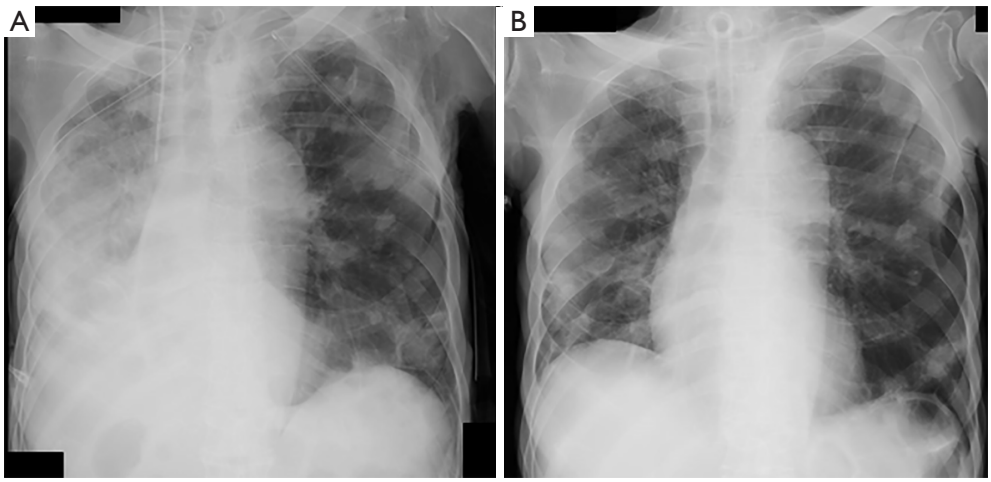

Figure 3 Chest radiograph findings. (A) One week after right chest tube drainage, the patient developed right-sided pneumonia. (B) One week after removal of chest tubes, no pneumothorax was observed.

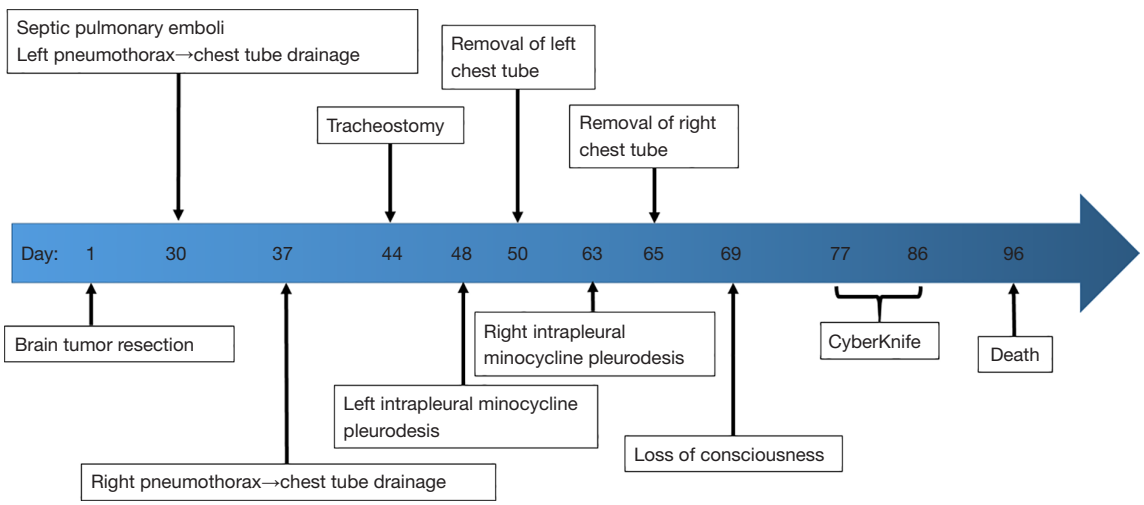

Figure 4 Description of performed procedures and the progress of the patient's condition.

present case, especially for patient's critical condition. The next day, the patient underwent intrapleural injection of 300 mg of minocycline hydrochloride via the chest tube into his left thoracic cavity. Before pleurodesis, 100 mg lidocaine was administered via chest tube for pain relief. Air leakage remained undetected after left minocycline pleurodesis. The left chest tube was removed in 2 days.

Twenty-five days after initiation of right chest tube drainage, air leakage was successfully controlled. After confirmation on chest X-ray we performed intrapleural minocycline pleurodesis in the same way as the left pleurodesis. The right chest tube was also removed in 2 days.

Although pneumothorax never recurred after pleurodesis (*Figure 3B*), the man suddenly manifested loss of consciousness due to recurrence of the brain tumor with multiple lesions 4 days after removal of the right chest tube. CyberKnife® radiosurgery was performed to treat the recurrence. However, his level of consciousness never improved again and his general condition deteriorated. The patient finally passed away 1 month after loss of consciousness. His clinical course is summarized in *Figure 4*. All procedures performed in this study were in accordance with the ethical standards of the institutional committee and with the Helsinki Declaration (as revised in 2013). Written

Table 1 Case reports of bilateral pneumothorax due to septic pulmonary embolism

Author	Year	Age (years)/sex	Underlying disease	Pathogen	Source of infection	Treatment	Outcome
Aguado *et al.* (2)	1990	19/M	Intravenous drug abuser	MSSA	Tricuspid valve endocarditis	Chest tube drainage	Survive
Corzo *et al.* (3)	1992	23/M	Intravenous drug abuser	MSSA	Tricuspid valve endocarditis	Chest tube drainage	Survive
Kato *et al.* (7)	2013	66/M	Type 2 diabetes mellitus	MSSA	Prostatic abscess	Chest tube drainage	Dead
Galili *et al.* (8)	2018	39/M	Intravenous drug abuser	MSSA	Tricuspid valve endocarditis	Chest tube drainage	Dead
Kapoor *et al.* (9)	2018	33/F	Intravenous drug abuser	MSSA	Tricuspid valve endocarditis	Chest tube drainage	Dead
Ikejiri *et al.* (10)	2022	73/F	Head angiosarcoma	MSSA	Central port venous infection	Chest tube drainage	Dead
Dashtkoohi *et al.* (11)	2022	15/F	None	MSSA	Tricuspid valve endocarditis	Chest tube drainage + VATS decortication	Survive
The present case	2023	72/M	Esophageal carcinoma with brain metastases	MSSA	Unknown	Chest tube drainage + pleurodesis	Dead

M, male; F, female; MSSA, methicillin-susceptible *Staphylococcus aureus*; VATS, video-assisted thoracoscopic surgery.

informed consent was obtained from the guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

International multidisciplinary team (iMDT) discussion

Here, we performed intrapleural minocycline pleurodesis for a case of bilateral pneumothorax due to SPE. Bilateral pneumothorax due to SPE has been described by a limited number of case reports (2,3,7-11). We reviewed the literature and summarized the cases of bilateral pneumothorax secondary to SPE in *Table 1*. Most of the cases were treated with chest tube drainage (*Table 1*). Only one case underwent video-assisted thoracic surgery decortication for infectious hydropneumothorax (11). Our case would be unique in terms of intrapleural minocycline pleurodesis.

Intrapleural minocycline pleurodesis could be efficacious against secondary pneumothorax, especially in terms of prevention of recurrence of the pneumothorax (12-14). Previous reports have already demonstrated the efficacy and safety of minocycline pleurodesis (12-14). Minocycline inflames the pleural surface and induces dense adhesion, which can prevent recurrence of pneumothorax (12,15). Although talc would be one of the most commonly used agents for chemical pleurodesis to treat intractable pneumothorax and usage of talc against pneumothorax is covered by national health insurance in Japan, talc pleurodesis could develop adult respiratory distress syndrome or empyema as complications (14). Unlike talc, major complications have been rarely reported regarding minocycline (14). Autologous blood patch could be another optional agent to prevent pneumothorax (14). However, autologous blood patch pleurodesis could cause empyema, especially in patients who have concurrent bloodstream infection (14). According to previous studies, successful rate of minocycline pleurodesis, talc pleurodesis and autologous blood patch pleurodesis was 79%, 94% and 72% respectively (16-18). Considering the patient's general condition, we decided to use minocycline as an agent for pleurodesis in order to prevent recurrence of pneumothorax. Indeed, we did not observe recurrence of pneumothorax after pleurodesis. Intrapleural minocycline pleurodesis could be a promising method to treat a severely-ill patient with pneumothorax and it needs to be studied prospectively in an experimental fashion.

The etiology of SPE has not clearly been understood in the present case. The transthoracic echocardiography did not show any signs of endocarditis. As shown in *Table 1*, right-sided endocarditis, central venous catheter-related infection, and abscess of another tissue are the sources of SPE causing bilateral pneumothorax. In the current case, the patient had no evidence of such conditions but did have a blood stream infection with MSSA. One possible source would be peripheral venous catheter-related infection. Catheter-related bloodstream infection is a notorious condition mostly caused by central venous line (19). However, catheter-related bloodstream infection could

occur due to peripheral venous line (20). Indeed, the patient received peripheral parental nutrition. Moreover, this patient received immune checkpoint inhibitor, which has a certain level of risk for developing infection as reported previously (21). These factors might have triggered his severe condition.

As shown in *Table 1*, the pathogen causing SPE with bilateral pneumothorax has reportedly been MSSA in all cases. As reported previously, staphylococcus species could cause pulmonary inflammation with consolidation, peripheral necrosis, empyema and multiple small cavities (22,23). In the current case, lesions of SPE were observed bilaterally (*Figure 2B*). Peripheral pulmonary bullae developed by SPE would be the sources of pneumothorax.

Although the patient had never experienced recurrence of pneumothorax after intrapleural minocycline pleurodesis, he finally died due to his worsening condition. The mortality rate of SPE is reportedly about 10–20% (1,24). Moreover, according to *Table 1*, patients with bilateral pneumothorax due to SPE would have a poor prognosis, especially elderly ones.

Question 1: *How do you treat a patient with pneumothorax due to septic pulmonary emboli?*

Expert opinion 1: Dr. Shun-Mao Yang

I would recommend maintaining chest tube drainage until the systemic bloodstream infection is effectively controlled. Following the resolution of the infection, a repeat chest CT should be undertaken to assess alterations in lung parenchyma and known lesions. Given the dynamic nature of pulmonary infections and their severity often linked to the extent of air leak, particularly in cases involving cavitation or abscess formation, monitoring through imaging becomes crucial. Pleurodesis may be considered as an option after discontinuation of the air leak, and it is advisable to conduct a chest CT for a comprehensive reassessment of lung condition before proceeding with pleurodesis.

Expert opinion 2: Dr. Amos Lal

Treatment strategies for pneumothorax secondary to septic emboli

The advances in the field of interventional pulmonology and pleural disease management have made significant strides in recent years, providing a range of treatment options for conditions such as primary and secondary pneumothorax. This condition (pneumothorax), is characterized by the presence of air in the pleural space. When the cause is unknown or if it happens spontaneously, it is referred to as a spontaneous or primary pneumothorax. Similarly, if it is caused due to septic emboli, as described in the case above, it is considered as secondary pneumothorax and is a serious medical emergency. The treatment strategy usually involves a combination of managing the pneumothorax, controlling the infection, and treating the underlying cause. Overall guidance on the management of these patients is guided by the clinical picture based on a case-to-case basis. The general overview is as follows:

(I) Management of pneumothorax: the primary goal is to remove the air from the pleural space and allow the lung to re-expand. This can be achieved through:
   (i) Needle aspiration: this is often the first-line treatment, especially for small pneumothoraxes. A needle is inserted into the pleural space to aspirate the air.
   (ii) Chest tube thoracostomy: for larger pneumothoraces or pneumomediastinum, a chest tube is typically inserted to drain the air (25,26). The tube may need to remain in place for several days until the lung has fully re-expanded and there is no additional air leak from the chest tubes. For uncomplicated pneumothoraces, hydropneumothorax and simple pleural effusions, a small caliber percutaneous tube thoracostomy is preferred.
   (iii) Surgery: in recurrent or persistent cases, surgical intervention may be necessary. Video-assisted thoracoscopic surgery (VATS) is frequently used, which involves the placement of small cameras into the chest to guide the surgery.
   (iv) Pleurodesis: this is a process of intrapleural instillation of a chemical irritant (chemical pleurodesis) which in theory effectively reduces reappearance of spontaneous pneumothorax in patients. The procedure is typically performed in patients who already have a chest tube in place or during thoracoscopy, and often hospital admission is necessary for monitoring and also due to the painful nature of the process (15,27,28). It is beneficial in case the patient has a higher risk from a morbid surgical procedure or when the patient is unwilling to have surgery (29). Use of chemical

pleurodesis for outpatient treatment of primary spontaneous pneumothorax after simple aspiration with or without drainage through an intravenous needle and small-bore pigtail catheter is rare.

(II) Infection control: septic emboli indicate an ongoing infection, which needs to be controlled to prevent further complications.
   (i) Antibiotics: broad-spectrum antibiotics are typically initiated to control the infection, with adjustments made based on culture results due to sometime uncommon pathogens that could result in empyema along with parenchymal infection (23).
   (ii) Optimal source control: source control is the cornerstone to prevent new septic emboli that could worsen the clinical condition, for example in case of an abscess it may need to be drained, either percutaneously or surgically or in case of infective endocarditis, an extended antibiotic course is warranted unless there are fragments of vegetations embolizing that would require the removal of vegetations (most commonly done surgically).

(III) Management of underlying cause: the source of the septic emboli must be identified and treated to prevent recurrence.
   (i) Anticoagulation: if the source of emboli is a deep vein thrombosis (DVT), anticoagulation therapy will be initiated.
   (ii) Surgery: if the source is an infected heart valve or other cardiac structure, surgical intervention may be necessary.

(IV) Supportive care: this includes oxygen therapy to alleviate hypoxia, analgesia for pain, and possibly mechanical ventilation in severe cases.

More recently, there has been emerging evidence that a primary spontaneous pneumothoraces could be managed conservatively with reasonably good outcomes (30). However, the specific question of pneumothorax secondary to septic emboli has not been studied in a large randomized controlled trial.

Expert opinion 3: Dr. Debora Russo

I would have treated SPE in a similar way; it is essential to primary treat the infection and the pneumothorax; also, it is important the management of the underlying cause.

I would have repeated the chest CT, to evaluate the progression of lung lesions and the extension of pneumothorax.

In this setting the multidisciplinary team plays a key role to provide the adequate treatment and to improve outcome, especially for complex and rare conditions like SPE.

Expert opinion 4: Dr. Satoshi Watanabe

Antibiotics against the bacteria causing sepsis is given. Pneumothorax should be treated with thoracic drainage according to the severity of the disease, and surgery should be considered if there is no improvement.

Question 2*: *If you would perform pleurodesis for pneumothorax due to septic pulmonary emboli*, *what agent would you use?

Expert opinion 1: Dr. Shun-Mao Yang

I would use OK-432 (Picibanil). In our institute, National Taiwan University Hospital, minocycline has been the predominant pleurodesis drug for the past two decades. The most extensively researched paper on pleurodesis for pneumothorax in our institution also focused on minocycline. However, since the early 2010s, our experience with OK-432 for pleurodesis has led to the observation of a higher primary success rate compared to minocycline (31). Consequently, over the last decade, there has been a shift in the most commonly used chemical agent for pleurodesis in our institute from minocycline to OK-432.

Expert opinion 2: Dr. Amos Lal

The exact treatment strategy will depend on the individual patient's condition and the clinical judgment of the treating physician. It is crucial to monitor the patient closely for signs of improvement or deterioration and adjust the treatment plan as necessary.

Pneumothorax management strategy for patients with prolonged air leaks while on mechanical ventilation is conservative, including drainage of air via one or more small caliber chest tubes, optimal positive end-expiratory pressure and lung protective ventilation strategy (10). In terms of chemical pleurodesis (which should be followed by evacuation of the air from the pleural space for maximum apposition of the pleural surfaces), both talc slurry and minocycline have been studied for the management of spontaneous pneumothoraces with comparable efficacy (12,15,16,28). Unfortunately, to the best of our knowledge, there is no head-to-head comparison when it comes to secondary pneumothorax management, especially secondary

to septic emboli. The option of autologous blood patch would be risky considering the possibility of further spread of infection in the pleural space leading to empyema.

Expert opinion 3: Dr. Debora Russo
I think I would use talc pleurodesis, but minocycline may be an effective alternative therapy.

Expert opinion 4: Dr. Satoshi Watanabe
I would consider to use medical talc first. However, as noted in the manuscript, tetracycline is a reasonable choice.

Conclusions

In summary, we experienced a case with bilateral pneumothorax due to SPE. Intrapleural minocycline pleurodesis was attempted successfully in this case and may be useful in treating pneumothorax associated with SPE. Intrapleural minocycline pleurodesis as a treatment option should be further studied prospectively in an experimental fashion to demonstrate its safety and efficacy in the management of secondary pneumothorax related to SPE.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1923/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional committee and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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