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Trapped in a Breathless Condition - A Case Report and Discussion of a Malignant Pleural Effusion and Trapped Lung

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Introduction

Malignant pleural effusions (MPE) are a common complication of underlying malignancies, frequently requiring management by specialty practitioners. Although the most common cause of malignant pleural effusions is bronchogenic carcinoma with a frequency of 7-23%, it is also seen with other malignancies [1]. Unfortunately, individuals suffering from MPE have a poor prognosis, in the realm of 3-18 months depending upon functional status and primary malignancy [2,3]. Therefore, with this limited time, relieving symptoms associated with MPE such as dyspnea, chest pain and cough to enhance quality of life is a major goal.

This case represents the challenges associated with the treatment of malignant pleural effusions, and how to approach an "untreatable" effusion. We will present a case report followed by a discussion of identification of MPE, the use of manometry, trapped lung and treatment options with a focus on fibrinolytics and indwelling pleural catheters.

Case Report

A 26-year-old male with no significant past medical history presented in March of 2015 with hematuria found to have bilateral renal masses - large mixed cystic/solid lesions on computerized tomography. He was diagnosed with clear-cell renal cell carcinoma with metastasis to the lymph nodes and pulmonary nodules suspicious of metastasis. Shortly after diagnosis, he completed 3 cycles of chemotherapy (sunitinib) prior to developing a pleural effusion, requiring thoracentesis for symptom relief as an outpatient procedure. With progression of disease, his chemotherapy was switched to temsirolimus, however his condition continued to deteriorate. After multiple emergency room visits, he ultimately required hospitalization for pain management and treatment of his pleural effusion, at which time he had a Karnofsky Performance Status of 70% (he was able to care for himself, but unable to do any active work).

The day after his admission, he underwent his second thoracentesis with 1000 ml of straw colored exudative pleural fluid drained. Unfortunately, the procedure was aborted secondary to chest discomfort, prior to optimal removal of all fluid. In addition, the opening pleural pressure was -5 cm h20 with drop to -30 cm h20, consistent with a trapped lung. His third thoracentesis followed a few days later, yielded 700 ml of fluid, with a decrease in pleural pressure from 0 to - 25 cm h20.

Throughout his admission, the patient became increasingly dyspneic, with increasing oxygen requirements. During his 16-day length of stay, pulmonology, oncology and palliative care were consulted. Upon evaluation by the interventional pulmonologist, after his 3rd thoracentesis, he was found to have formed a complicated hemithorax with multiple small pockets of fluid, dense congealed thickening and entrapment of the lung and thus was no longer a candidate for PleurX indwelling catheter. Cardiothoracic surgery was consulted however given his poor prognosis, they were unable to offer decortication to alleviate his condition. Instead, lysis of adhesions with tPA was recommended, given the formation of dense loculations.

Confined with a pleural effusion that could not be drained and ongoing progression of disease, the patient's goals of care were discussed further. When presented the option of chest tube placement followed by tPA with the hopes of eventual pluerodesis, the patient decided to shift the focus toward quality of life, without further aggressive interventions. He stated, "I never wanted any of this; I just want to go home and breathe". He was subsequently discharged home with hospice with a patient controlled analgesic (PCA) pump for relief of his symptoms of dyspnea and pain. The weekend after discharge home, the family was able to host a barbecue for all of his friends and loved ones. He died comfortably in his hospital bed at home, surrounded by his family, 6 weeks after his discharge.

Diagnosis of malignant pleural effusion

Perhaps the most pivotal factor in the treatment of MPE is the identification of an effusion as malignant. Without proper and timely diagnosis, treatment can be delayed, which can be detrimental to quality of life. Diagnosis can be done via biopsy

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Table 1: Diagnosis of Malignant Pleural Effusion [2,4,7].

1	Chest X-ray - identification of effusion
2	CT scan - can identify parenchymal disease, metastasis, LN involvement
3	Ultrasound - can identify pleural lesions and adhesions, assist with thoracentesis
4	MRI - limited benefit, evaluate for chest wall involvement
5	Diagnostic thoracentesis- nucleated cell count and differential, total protein, lactate dehydrogenase, glucose, pH, amylase and cytology. a) Complications: pneumothorax, bleeding, infection, spleen or liver laceration. b) Relative contraindications: minimal effusion (less than 1 cm in thickness from fluid level to chest wall), bleeding diathesis, anticoagulation and mechanical ventilation.
6	Closed pleural biopsy - less sensitive than pleural fluid cytology a) Low yield: Distribution of tumor in areas not sampled by blind biopsy, operator inexperience, early stage disease with minimal pleural involvement. b) Contraindication: bleeding diathesis, anticoagulation, chest wall infection, lack of patient cooperation. c) Complications: pneumothorax, hemothorax, vasovagal reaction.
7	Medical Thoracoscopy - direct visual control with thoracosope or indirectly by video. a) Indication: evaluation of exudative effusion of unknown cause, staging, biopsy, treatment with pleurodesis.
8	Bronchoscopy - low yield. Used to exclude endo-bronchial obstruction, especially before pleurodesis if lung does not re-expand after thoracentesis.
9	Surgical Biopsy a) Video Assisted Thoracic Surgery • Contraindication: mechanical ventilation, prior contralateral pneumonectomy, operator inexperience, pleural space adhesions b) Open biopsy

or with radiographic evidence of a pleural tumor, however is most commonly diagnosed following a diagnostic thoracentesis, definitively with cytology. (Table 1) [4] There are a few criteria included to classify an effusion as malignant; exudative (with a fluid protein > 3 g/dl, pleural fluid-serum protein ratio > 0.5, lactate dehydrogenase level > 200 IU and pleural fluid-serum LDH ratio > 0.6), although a minority of malignant effusions can be transudative. Cytology obtained from pleural fluid can also assist in diagnosing an effusion as malignant. Malignant Pleural effusions occur as a consequence of inflammation, vascular leakage and enhanced angiogenesis. This complication can arise in lung adenocarcinoma, malignant pleural mesothelioma, lymphoma, breast, colon, gastric and ovarian adenocarcinoma [5,6].

Trapped lung

Another complication of metastatic disease involving the pleura is a phenomenon known as trapped lung. This occurs when a dense layer of malignant tissue encases the visceral pleura resulting in incomplete lung re-expansion after pleural fluid drainage. As the peel restricts expansion of the lung parenchyma, a high negative pleural pressure develops with in the pleural space. This will result in increased pleural fluid formation and a chronic pleural effusion.

Trapped lung can be diagnosed via manometry during thoracentesis; pleural space elastance (change in pleural pressure/amount of pleural fluid removed) more than 14.5 cm h20/L. Pleural pressure is the result of inward and outward forces changing during inspiration and expiration. During inspiration, there is expansion of the lungs due to increase in the negative pleural pressure of the thoracic cavity. Any pathology affecting lung expansion will result in abnormalities of pleural pressure during respiration.

Currently, manometry is not routinely used during thoracentesis; perhaps, as it is time consuming, requires additional training, and can lead to inappropriate decisions if not coupled with clinical presentations. However, it can help guide management and identify pathophysiology of pleural effusion. As pleural elastance can change throughout the procedure, especially with large-volume thoracentesis, it can be beneficial to calculate it during thoracentesis for identification of unexpandable lung. It can also be used as a predictor of successful pleurodesis, in measuring the absolute closing pressure and overall elastance. The higher the elastance, the probability of the pleural layers being pulled apart is increased which can interfere with pleurodesis. A high index of suspicion should be maintained in the diagnosis and management of trapped lung in the setting of malignant pleural effusions so to prevent repeated thoracentesis; which, will result in more problems and complications such as chest pain, formation of loculations and recurrent effusions [8].

In addition to pleural pressure changes, measured by manometry, the pleural rind (thickening) can also be seen via direct visualization with air contrast computed tomography or video-assisted thoracoscopy [9]. In the aforementioned case, a diagnosis of trapped lung was made after the second thoracentesis which was complicated by severe chest pain, resulting in aborted procedure. In cases of trapped lung, patients are less likely to benefit from pleurodesis, a procedure in which adhesions are formed between the visceral and parietal pleura, to prevent the reaccumulation of fluid within the pleural space [10]. Similar to malignant pleural effusions, trapped lung will result in shortness of breath. Dyspnea due to trapped lung can be due to many physiological and pathological responses (Table 2).

Table 2: Etiology of dyspnea [11].

1	Physiological response of pleural effusion
2	Decreased lung compliance
3	Atelectasis
4	Diaphragmatic dysfunction
5	Restrictive ventilator dysfunction
6	Ventilation-perfusion mismatch

Treatment options

There are a variety of treatment options for malignant pleural effusions including repeated thoracentesis, pleurodesis, pleuroperitoneal shunt, long term thoracostomy tube, implantable pleural catheter, video-assisted thoracoscopic surgery (VATS)/decortication. Symptoms and performance status of the patient, tumor type, and degree of lung re-expansion after removal of fluid are some factors to take into consideration prior to choosing treatment option.

Repeated thoracentesis

Repeated thoracentesis was the initial treatment plan for the gentleman discussed above, as it provides transient symptom relief. Although he was hospitalized during his thoracentesis, this can be offered as an outpatient. Perhaps if manometry was used in the first thoracentesis, and malignant pleural effusion diagnosed early, the patient could have benefitted from pleurodesis prior to the development of complications.

Repeated thoracentesis provides immediate symptom relief but rapid re-accumulation can occur, requiring multiple visits. Practicioners should be cautious when removing more than 1.5 L during any single drainage. It is offered to patients with a short expected survival with a poor prognosis as it is the least invasive of the procedures available. Complications include infection, pneumothorax, bleeding and trapped lung [2,12].

Pleurodesis

Pleurodesis, as defined above, can be achieved with chemically or

mechanically. Chemical pleurodesis is preferred over mechanical as it is better tolerated and minimally invasive. Chemical Pleurodesis is achieved using sclerosing agents, dissolved in 50 ml of normal saline introduced via small bore intercostal catheter. These agents include but are not limited tobleomycin (60,000 units), talc (5 gm of asbestos free, sterilized large particle talc), doxycycline (500 mg), iodine and quinacrine. The ideal agent should have a high molecular weight and chemical polarity, rapid systemic clearance, well tolerated, with a steep dose-response curve. The choice of which sclerosing agent to use can vary, but can be determined by efficacy, success rate, accessibility, ease of administration, safety and cost.It is recommended to use lidocaine 3 mg/kg intrapleurally prior to administering sclerosing agents into pleural space as the procedure can be quite painful.

It can be performed via surgical approach with thoracoscopy or video assisted thoracic surgery, via medical thoracoscopy, or via small bore chest tube at the bedside. The addition of these agents into the pleural space will result in inflammation and fibrosis, thus obliterating the pleural space [4].

Unfortunately, given that the case above was complicated by a trapped lung, pleurodesis was not the management of choice as it would not allow for re-expansion. Other contraindications include airway obstruction secondary to endobronchial tumors, multiple pleural locations and extensive intrapleural tumors. Complications include infection, empyema, fever, pain, hypotension, acute respiratory distress syndrome and acute pneumonitis [4,9,13,14].

Pleuroperitoneal shunt

Pleuroperitoneal shunt can transport up to 1.5 L of pleural fluid into the abdominal cavity with each compression. It was first proposed in 1982 by Weese and Schouten. It can be placed under local anesthesia and has the advantage of early hospital discharge [15] with the advances in the field, pleuroperitoneal shunts have fallen out of favor and are rarely used.

Implantable pleural catheter

Long-term thoracostomy drainage has fallen out of favor with the invent of an implantable pleural catheter (IPC), manufactured and trademarked as PleurX. They have been approved by the Food and Drug Administration since the late 1990s [16]. This is small bore catheter 66 cm long, 15 F silicone rubber catheter with fenestrations along the distal 24 cm, placed within the pleural space.

This would have been the treatment option of choice for above mentioned case, if not for the development of dense loculations found on ultrasound prior to the procedure. This enforces the importance of timely diagnosis and approach of malignant pleural effusions are essential in the successful palliation of symptoms, such as dyspnea. Implantable pleural catheters can be advantageous for malignant pleural effusions as well as in select cases for symptomatic treatment of trapped lung, in that it can aid in partial lung expansion and therefore improve symptoms.

Among the many advantages of implantable pleural catheters (Table 3), the ability to intermittently drain the pleural fluid to alleviate symptoms and the avoidance of hospitalization are perhaps the most meaningful advantage for the patient [10,17-19].

Video Assisted Thoracoscopic Surgery (VATS)

VATS and decortication is an inpatient procedure which can be offered for a select group of patients. Given the invasiveness of the procedure, requiring general anesthesia and single lung ventilation, along with post-operative chest tubes, patients must have a relatively good prognosis to be offered this treatment option. Although the management of choice in a symptomatic patient with trapped lung, the setting of malignant pleural effusion and associated poor prognosis, will be a relative contraindication for surgical approach in the aforementioned case.

Fibrinolytics

In this case, given the development of loculations due to recurrent thoracentesis resulting in fibrin strands and multiseptation, there were discussions of intrapleural fibrinolytic therapy. As a result of loculations, drainage and therefore palliation of symptoms associated with effusions becomes difficult to control. Fibrinolytics such as tissue plasminogen activator, urokinase or streptokinase can be introduced into the pleural space to break down fibrin adhesions and promote drainage. Although not a feasible option for our patientgiven his goals of care as he developed multiple dense loculations, lytics can be given along with chest tubes or tunneled pleural catheters. Given the risk of allergic reaction, streptokinase is not favored. Usually, 10 mg of tPA can be mixed with 50 ml of normal saline, however dose can range from 2-25 mg of tPA. This is instilled into the chest tube and clamped for 2 hours after which it is unclamped and fluid drains into a drainage unit. This process is repeated twice a day for 3 days followed by repeat imaging. If repeat imaging shows resolution of loculations, pleurodesis may be an option [2,4].

Some cases will arise in which a patient will not be a candidate for the aforementioned interventions. Due to the development of trapped lung and multiple dense loculations, along with a poor prognosis with progression of disease, the patient was no longer a candidate for PleurX indwelling catheter, chest tube with lyticsor pleurodesis. In those situations, what is the best management option?

All of these interventions are in essence palliative. Patients should be informed of their prognosis and options early in the disease process. Advanced directives and goals of care should be discussed by all involved, however are commonly addressed by the interdisciplinary palliative care team. Services offered by palliative care in MPE can include emotional and spiritual support with chaplaincy along with symptom management such as relief of dyspnea and/or chest pain. Opioids can be used to minimize symptoms of dyspnea by decreasing work of breathing and therefor decrease anxiety associated with breathlessness. Palliative care is able to form a bridge to hospice care for these patients, in focusing on the quality of life left to live [20].

In hindsight, it is easy to say the patient in this case should have been offered pleurodesis after the first thoracentesis or an indwelling catheter placed after the second. Regardless of the palliative treatment of the underlying effusion, patients with MPE are known to have a poor prognosis. We must focus on providing treatments to enhance patients' quality of life when such time is limited. We learn through experiences, with an understanding of the crucial timing of the management of a complication such as a malignant pleural effusion and trapped lung; and, in providing symptomatic relief consistent with improving quality of life.

Table 3: [4,16-18].

	Indications	Advantage	Contraindications	Complications
1	Advanced, unresectable pleural malignancy	Cost - effective, well tolerated	Loculations in pleural space	Catheter occlusion, rupture, dislocation
2	Chest x-ray: trapped lung	Patient controlled	Previously failed attempt	Infection, empyema, cellulitis
3	Relief of dyspnea and symptoms with thoracentesis	Minimally invasive, relief of dyspnea	Limited life expectancy	Bleeding
4	Predicted life expectancy > 3mo	User-friendly, safe	Inability to care for drain	Tumor seeding/mets
5		Outpatient procedure	Incomplete evacuation of effusion	Pain, pneumothorax

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