

Chemotherapy-induced Spontaneous Pneumothorax: Case Series

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ABSTRAK

Kami laporkan 2 orang pasien dengan limfoma dan rhabdomyosarkoma dengan metastasis paru yang mengalami pneumotoraks spontan setelah kemoterapi. Kasus 1, seorang pria berusia 43 tahun, datang dengan keluhan sesak napas 10 hari sebelum masuk rumah sakit. Tidak ada riwayat trauma atau terapi tuberkulosis sebelumnya. Tiga minggu sebelumnya pasien mendapat kemoterapi CHOP siklus pertama untuk limfoma non Hodgkin's stadium II BE. Pada foto toraks didapatkan adanya pneumotoraks kanan. Setelah mendapat terapi dengan pemasangan chest tube thoracotomy (CTT) selama 1 bulan, pasien mengalami perbaikan dan kemoterapi dilanjutkan tanpa komplikasi lebih lanjut. Kasus 2, seorang pria 35 tahun datang dengan keluhan sesak napas dan nyeri dada pada hari keempat setelah kemoterapi sistemik siklus kedua untuk rhabdomyosarkoma stadium IV (metastasis paru) dengan doxorubicin, ifosfamid, mesna, dan dacarbazine. Foto toraks memperlihatkan adanya hidropneumotoraks bilateral. Setelah terapi dengan pemasangan CTT selama 2 minggu, pasien mengalami perbaikan dan kemoterapi dilanjutkan tanpa komplikasi lebih lanjut.

Mekanisme pneumotoraks yang terjadi setelah kemoterapi belum jelas diketahui. Terdapat beberapa hipotesis di antaranya: 1). Pecahnya bula subpleura setelah kemoterapi; 2). Pecahnya bula emfisematosa pada bagian paru yang mengembang akibat obstruksi parsial oleh tumor; 3). Tumor lisis atau nekrosis akibat efek sitotoksik kemoterapi yang secara langsung menimbulkan pembentukan fistula. Pada pasien dengan keluhan sesak napas dan nyeri dada mendadak yang terjadi setelah kemoterapi tumor yang bersifat kemosensitif, perlu dipikirkan kemungkinan terjadinya pneumotoraks spontan. Penatalaksanaannya adalah dengan reekspansi paru. Pneumotoraks yang diinduksi kemoterapi seharusnya dikelola sebagai kegawatdaruratan onkologi.

Kata kunci: *pneumotoraks spontan, kemoterapi, tumor kemosensitif, kegawatdaruratan onkologi.*

ABSTRACT

We present 2 patients who developed spontaneous pneumothorax (SP) following rapid regression of lymphoma and rhabdomyosarcoma with lung metastases. Case 1, a 43-year old man was admitted to our hospital with dyspnea 10 days before admission. He denied any recent trauma or previous treatment for lung tuberculosis. Three weeks prior to admission, he received first cycle of CHOP for non-Hodgkin's lymphoma stage II BE. Chest X-ray consistent with right pneumothorax. After treatment with chest tube drainage for about 1 month, the patient recovered and chemotherapy could be continued without further complications. Case 2, a 35-year old man was admitted to other hospital with dyspnea and chest pain on day 4 after second cycle of systemic combined chemotherapy for rhabdomyosarcoma stage IV (lung metastases) with doxorubicin, ifosfamide, mesna, and dacarbazine. Chest X-ray showed hydropneumothorax on right and left lung. After treatment with chest tube drainage about 2 weeks, the patient recovered and chemotherapy could be continued without further complications.

The mechanism of pneumothorax following chemotherapy is not clearly understood yet, however, several

hypotheses have been considered: 1) the rupture of a subpleural bulla after chemotherapy; 2) the rupture of an emphysematous bulla in an over expanded portion of the lung which is partially obstructed by a neoplasm; 3) tumor lyses or necrosis due to cytotoxic chemotherapy directly induces the formation of fistula. Dyspnea and chest pain suddenly appear during successful chemotherapy for metastatic chemosensitive tumors should alert the physician to the possibility of SP. The treatment is directed toward lung re-expansion. Chemotherapy induced pneumothorax should be considered as oncologic emergency.

Keywords: *spontaneous pneumothorax, chemotherapy, chemosensitive tumors, oncologic emergency.*

INTRODUCTION

Chemotherapy is one of the modalities of cancer treatments. The principal obstacles to the clinical efficacy of chemotherapy has been toxicity to the normal tissue of the body especially rapidly growing cells.¹ Many side effects of chemotherapy are predictable, depending on the drugs in the regimen, and can be prevented or easily diagnosed and managed effectively without causing substantial morbidity. Many of these can cause unpredictable and rare side-effects, occurring in fewer than 1% of patients, which can develop as immediate life-threatening illnesses.² Nowadays, spontaneous pneumothorax (SP) caused by chemotherapy has been reported sporadically.

SP is generally observed in healthy young men, as a result of rupture of apical and/or subpleural blebs. Pneumothorax can also occur secondary to a variety of pulmonary disorders such as chronic obstructive pulmonary disease (COPD), pneumoconiosis, diffuse interstitial fibrosis, and infection diseases. Iatrogenic factors are continuous positive pressure ventilation, closed-chest cardiac massage, and tracheostomy.³ Although SP is a well known complication of primary lung cancer and metastatic lung disease, it is a rare complication of chemotherapy, with a reported incidence of less than 1%, and is commonly associated with chemosensitive tumours such as germ-cell tumours, lymphomas, and sarcomas and rarely with lung and gynaecological malignant disease.^{4,5} Pneumothorax seems to occur 2–7 days after chemotherapy treatment and can be unilateral or bilateral.²

These complications should be kept in mind in order to avoid further sequelae. A search for the presence of intrapleural pathology by a thorough

clinical and radiological evaluation should be made in all patients with unexplained dyspnea and chest pain after received chemotherapy. Clinicians should be aware that spontaneous pneumothorax may be one of the manifestation of chemotherapy's side effect.

CASE ILLUSTRATION

Herein, we present 2 patients who developed SP following rapid regression of lymphoma and rhabdomyosarcoma with lung metastasis.

Case 1: A 43-year old man was admitted to our hospital with complaints of dyspnea and productive cough 10 days before admission. There were no history of fever, nor recent trauma or previous treatment for lung tuberculosis. Three weeks prior to admission, he received first cycle of CHOP for non-Hodgkin's lymphoma stage II BE.

He had tachypnea and tachycardia. On physical examination, we found left tracheal deviation, pulmonary examination revealed right sided hypersonor percussion notes and diminished breath sound on auscultation. His chest X-ray was consistent with right pneumothorax (**Figure 1**). Chest X-ray before chemotherapy was within normal limit (**Figure 2**). Mycobacterium tuberculosis was not detected in his sputum. We did not perform a chest computed tomography (CT) scan for evaluated lung involvement from lymphoma due to financial problem.

According to British Thoracic Society (BTS) pleural disease guideline 2010, patients with primary SP or secondary SP and significant breathlessness associated with any size of pneumothorax should undergo active intervention.⁶ In this patient, we inserted chest tube thoracotomy (CTT) in emergency room.

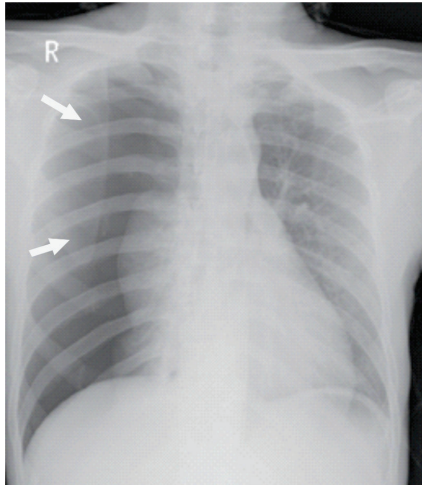


Figure 1. Chest X-ray consistent with right pneumothorax.

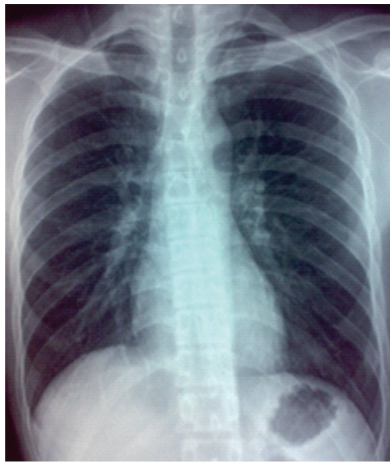


Figure 2. Chest X-ray before chemotherapy

Second cycle of chemotherapy was postponed. After treatment with chest tube drainage about 1 month and chemical pleurodesis was attempted using tetracycline, the patient recovered and chemotherapy could be continued without further complications.

Case 2 : A 35- year old man was admitted to other hospital with dyspnea and chest pain on day 4 after second cycle of systemic combined chemotherapy for rhabdomyosarcoma of the upper left thigh stage IV (lung metastases) with doxorubicin, ifosfamide, mesna, and dacarbazine. There was no history of fever and no reducing dyspnea at rest.

He had tachypnea and tachycardia. On physical examination, we found hyperresonance on percussion and reduced vesicular breath sound on the both chest walls, without tracheal deviation.

His chest X-ray showed hydropneumothorax on right and left lung (**Figure 3**).

Based on BTS pleural disease guideline 2010,⁶ we inserted CTT on bilateral hemithorax in emergency room. Chest X-ray 24 hours after CTT insertion showed complete lung re-expansion (**Figure 4**). After treatment with a chest tube drainage for about 2 weeks and chemical pleurodesis was attempted using tetracycline, the patient recovered and chemotherapy could be continued without further complications.

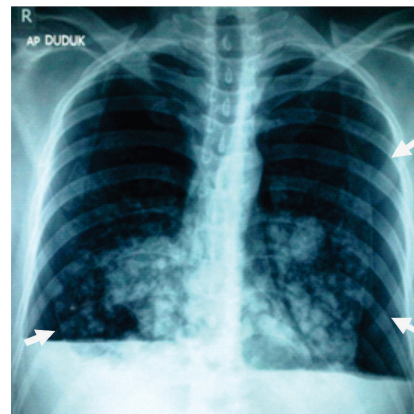


Figure 3. Chest X-ray on admission



Figure 4. Chest X-ray performed 24 hours after insertion chest tube

DISCUSSION

SP in primary pulmonary neoplasm or lung metastases is very rare. However, SP seems to occur more often in patients with metastases from sarcomas, especially osteogenic sarcoma, than in patients with primary lung carcinoma.⁷

Conversely, sporadic case reports describe SP due to lung metastases from teratomas, Wilms' tumors, melanomas, carcinomas of the kidney and pancreas, gynecologic malignancies, lymphomas, choriocarcinomas, and lymphangiomas.^{5,7}

The mechanism of pneumothorax following chemotherapy is not clearly understood yet, however, several hypotheses have been considered:^{4-5,7-10} 1) the rupture of a subpleural bulla after chemotherapy; or growing nodules can cause a check-valve effect, with subsequent overdistension of the alveoli, leading to the release of air into the interstitial tissues and eventual rupture of a subpleural bleb 2) the rupture of an emphysematous bulla in an over expanded portion of the lung which is partially obstructed by a neoplasm; 3) tumor lyses or necrosis due to cytotoxic chemotherapy directly induces the formation of fistula.

When small airways are narrowed by cancer invasion they act as a check valve, causing air trapping and dilation of distal alveolar spaces and eventual rupture. Bronchopleural fistula can be caused by either direct tumor invasion or develop secondary to necrosis of a peripheral tumor from effective chemotherapy, or spontaneous vascular occlusion within the tumor itself. Direct invasion of the pleura by tumor is also a possible mechanism though relatively uncommon.¹¹ Pneumothorax following radiation therapy and following bleomycin lung have been described. It is also possible that tumour invasion and disruption of the visceral pleura and of peripheral bronchioles might produce slow air leakage resulting in small clinically silent pneumothorax.⁴ Lee proposed the temporal relationship between the use of combination chemotherapy and the development of pneumothorax as a consideration of chemotherapeutic's side effects. For example, doxorubicin was the chemotherapeutic agent most likely to impair the wound healing with tissue repair, and may consequently predispose patients with pulmonary metastasis or underlying lung lesions to pneumothorax.¹²⁻¹³

In case 1, the pathogenesis of the SP may have involved the rupture of an emphysematous bulla in an over expanded portion of the lung which is partially obstructed by a neoplasm or tumor lyses or necrosis due to cytotoxic

chemotherapy directly induces the formation of fistula. The mechanism of rupture of a subpleural bulla after chemotherapy is ruled out because patient is no-affected by COPD according his medical history and he denied any recent trauma or previous treatment for lung tuberculosis. The rupture of an emphysematous bulla in an over expanded portion of the lung which is partially obstructed by a neoplasm mechanism is likely but CT scan and bronchoscopy not be done. The likelihood of tumor lyses or necrosis due to cytotoxic chemotherapy directly induces the formation of fistula mechanism is strengthened by responsiveness of the tumor to cytotoxic chemotherapy. This type of complication is not unique, as rapid shrinkage of abdominal lymphoma which is known to lead to perforation of the bowel in some patients.⁵ Based on the mechanisms of the SP, it was always associated with lung involvement,⁸ but in present case, lung involvement not be evaluated.

In case 2, the pathogenesis of the SP may have involved in the rupture of an emphysematous bulla in an over expanded portion of the lung which is partially obstructed by a neoplasm mechanism. Our patient is a non smoker, has no previous history of SP and is not manipulated in any way, so attachment of the rupture of a subpleural bulla after chemotherapy mechanism is ruled out. The tumor lyses or necrosis due to directly induced formation of fistula mechanism of cytotoxic chemotherapy is unlikely, because chest X-ray showed no improvement of lung metastases after chemotherapy. The possibility mechanism of rupture of an emphysematous bulla in an over expanded portion of the lung which is partially obstructed by a neoplasm is more likely. However, we did not performed chest CT scan and bronchoscopy to confirm this.

In both cases, doxorubicin was included in the cytotoxic regimen, however it is difficult to relate its direct effect on pneumothorax.¹² We assumed that pneumothorax in our patients were triggered by the chemotherapy.

The treatment of SP secondary to chemotherapy is directed toward lung re-expansion. A closed chest tube is usually unable to prevent recurrence of pneumothorax in such patient and CTT alone results on only partial

re-expansion of the lung.^{5,14} If an experienced thoracic surgeon is not available or in case patient refuses an operation or the operative risk is too high, chemical pleurodesis by instillation of a pleural irritant into the thoracic drain or by under local anaesthesia is an alternative to invasive surgical treatment.^{3,6} The report of the effectiveness of chemical pleurodesis in primary SP is well documented. In both our cases, chemical pleurodesis with tetracycline successfully results in lung re-expansion. This treatment was effective and at three months follow-up, both the patients have no recurrence of pneumothorax.

CONCLUSION

Sudden dyspnea and chest pain appearing during chemotherapy for metastatic chemosensitive tumors should alert the physician to the possibility of SP. The treatment is directed toward lung re-expansion. Chemical pleurodesis via chest tube may be an effective treatment strategy of pneumothorax. We suggest that chemotherapy-induced SP should be included in oncologic emergencies and require our awareness.

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