Surg Today (2000) 30:469–472

SURGERY TODAY

Bilateral Recurrent Pneumothorax Complicating Chemotherapy for Pulmonary Metastatic Breast Ductal Carcinoma: Report of a Case

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Abstract: Secondary spontaneous pneumothorax (SSP) is a rare complication of chemotherapy for pulmonary metastases and to the best of our knowledge, only 28 cases have been described, most of which occurred in patients with osteosarcoma or germ cell tumors. We present herein the case of a 56-year-old woman in whom bilateral and recurrent SSP was caused by the rupture of pulmonary lacunae induced by chemotherapy, given for bilateral lung metastases secondary to breast carcinoma. Our experience of this case led us to conclude that: patients with pulmonary metastases may develop bilateral and/or recurrent pneumothoraces following chemotherapy; computed tomography scan is essential for defining the cause of SSP; and closed chest tube drainage remains the therapy of choice, while chemical pleurodesis may also be used to prevent recidivant SSP.

Key Words: chemotherapy, secondary spontaneous pneumothorax, pulmonary lacunae, pulmonary metastasis, breast cancer

Introduction

Primary spontaneous pneumothorax is generally observed in healthy young men, as a result of the rupture of apical and/or subpleural blebs. Spontaneous pneumothorax can also occur secondary to a variety of pulmonary disorders such as chronic obstructive pulmonary disease, pneumoconioses, diffuse interstitial fibrosis, and infectious or neoplastic diseases.[1] However, secondary spontaneous pneumothorax (SSP) is rarely associated with primary lung cancer,[2] although it has been documented as a complication of pulmonary metastases, either before or after chemotherapy and radiotherapy.[3]

Reprint requests to: A. Bini
(Received for publication on Feb. 8, 1999; accepted on Nov. 11, 1999)

We report herein an unusual case of bilateral recurrent pneumothorax occurring in a woman in whom lung metastases from a breast ductal carcinoma were being treated with combination chemotherapy. A thorough review of the literature revealed only one other such case.[4]

Case Report

A previously healthy 51-year-old woman who was a nonsmoker underwent a right mastectomy with radical axillary lymph node dissection in January 1993 for an infiltrating ductal carcinoma, 4 cm in diameter, with microscopic lymphatic vessel infiltration. The cancer was classified as grade II, sec. AJCC, with 10% positivity for estrogenic and 20% positivity for progestinic receptors. At the time of surgery there was no evidence of metastatic disease (T2, N0, M0: stage IIA) and she was administered eight adjuvant cycles of cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and 5-fluorouracil 600 mg/m^2 (CMF), on days 1 and 8 in a series of 28 days.

The patient remained well for 44 months after surgery, but in October 1996, a regular follow-up examination revealed an increase in carbohydrate antigen 15-3, and a chest X-ray showed multiple bilateral pulmonary nodules consistent with metastases (Fig. 1). She was immediately commenced on chemotherapy with mitomycin C (10 mg/m^2), methotrexate (35 mg/m^2), and mitoxantrone (10 mg/m^2) (MMM) on day 1 in a series of 28 days, and tamoxifen 20 mg daily, which achieved good radiologic response of the pulmonary metastases. The day after the administration of the fourth cycle of MMM, on March 3, 1997, the patient complained of a sudden cough and left pleuritic pain. A chest radiograph showed a left spontaneous pneumothorax and a chest tube was inserted, after which the lung reexpanded spontaneously. The drain was removed and the patient was discharged home on day 10 following chemo-

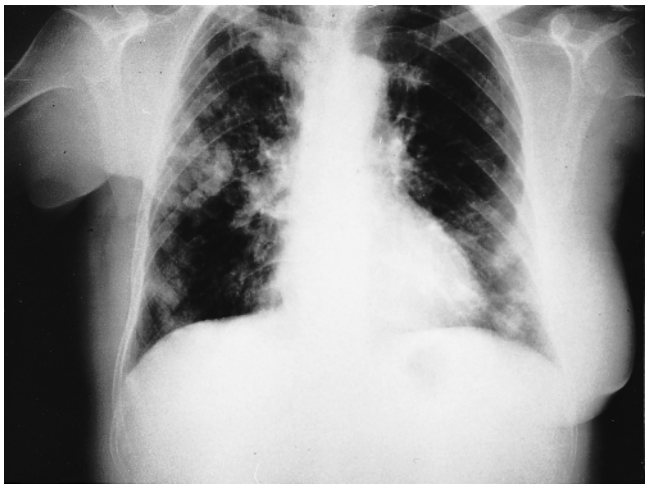

Fig. 1. Standard chest X-ray performed 44 months after right mastectomy shows multiple noncalcified nodules suggestive of hematogenous metastases. No cysts or bullae were visible

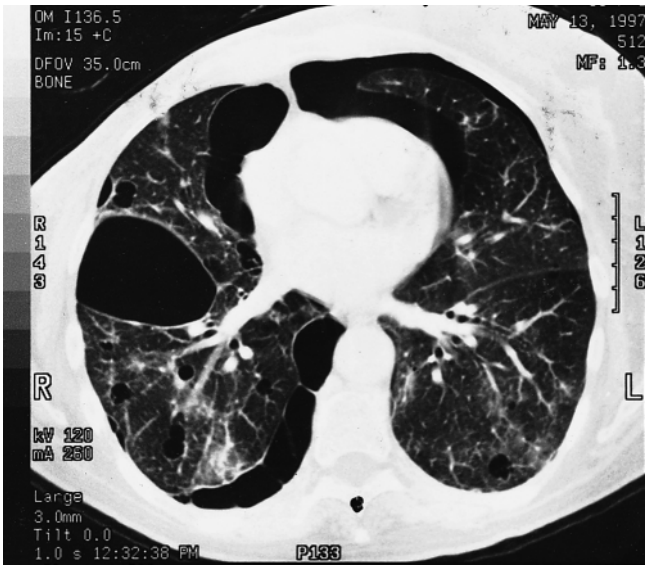

Fig. 2. High-resolution computed tomography scan at the level of the lower lobe pulmonary veins demonstrated bilateral pneumothoraces and multiple pulmonary cysts of varying size with slight diffuse thickening of the visceral pleura. Note the absence of pulmonary nodules or masses

therapy. In April 1997, 1 month later, the patient became acutely dyspneic and re-presented to the hospital with signs of acute respiratory insufficiency: a chest X-ray revealed a bilateral spontaneous pneumothorax, 90% in the left side and 60% in the right side. Immediate intercostal chest drain insertion in the left side reexpanded the left lung spontaneously. The chest tube was removed 20 days later.

Due to the persistence of the right pneumothorax and middle grade dyspnea, the patient was referred to our institution in May 1997. A thoracic computed tomography (CT) scan was performed that showed the persistence of bilateral pneumothoraces, the left one at the apex and the right one complete, as well as multiple bilateral pulmonary lacunae (Fig. 2). A fibrobronchoscopic examination with bronchoalveolar lavage (BAL) was also carried out, and cytological examination revealed the presence of malignant adenocarcinomatous cells that were positive for estrogenic and progestinic receptors. A chest drain with suction was inserted into the right hemithorax which achieved complete reexpansion of the right lung. After 10 days the chest drain was removed and the right lung remained fully expanded. The patient was discharged.

Only 15 days later, in June 1997, she presented again with acute dyspnea and left pleuritic chest pain. A chest X-ray showed partial collapse of the left lung, and a chest tube was inserted with negative pressure. The lung was fully reexpanded in 2 days, but the suction drainage was continued for 6 weeks due to a persistent air leak. Thereafter, the lung was finally stabilized and the drain was removed.

In August 1997, 5 days later, the patient redeveloped tachypnea and pleuritic pain in the chest with tachycardia. A total pneumothorax of the left lung was confirmed and drainage of the left pleural space had to be re-established to achieve the full reexpansion of the left lung. In the following 7 weeks the drain continued to show persistent air leakage and partial left lung collapse with each attempt to suspend suction. Chemical pleurodesis was also attempted, in October 1997, using a talc suspension form of 2 g talc diluted in 50 ml normal saline instilled into the left pleural cavity via the chest tube. The drain was removed 1 week later after complete expansion of the left lung had been achieved.

Unfortunately, the patient developed liver and bone metastases 1 month later, in November 1997, followed by cerebral metastases in January 1998. She died from disseminated cancer in March 1998 without any recurrence of a pneumothorax. The clinical course of our patient is represented chronologically in Table 1.

Discussion

Cancer-related SSP is a rare event, accounting for just 0.05% of all pneumothoraces.[2] Although most tumors may be associated with a risk of SSP, this complication seems to arise most frequently in patients with pulmonary metastatic osteogenic sarcomas and germ cell tumors.[3]

Table 1. Chronology of the clinical course of our patient

Jan. 1993	A 51-year-old woman underwent a right mastectomy with radical axillary lymph node dissection for an infiltrating ductal carcinoma (T2, N0, M0: stage IIA)
Feb.–Jul. 1993	Eight adjuvant cycles of CMF were given
Oct. 1996	Multiple bilateral pulmonary metastases were detected
Nov. 1996–Mar. 1997	Four cycles of MMM and tamoxifen daily were given, achieving good radiologic response of the pulmonary metastases. The fourth cycle of MMM was administered on March 2, 1997
3 Mar. 1997	Left spontaneous pneumothorax occurred, necessitating chest tube insertion, resulting in lung expansion. The drain was removed 10 days later
11 Apr. 1997	Bilateral spontaneous pneumothorax occurred. A chest drain was inserted in the left side with expansion of the left lung. The chest tube was removed 20 days later
13 May 1997	Due to the persistent right pneumothorax the patient was referred to our institution for the first time. A chest drain was inserted with suction in the right hemithorax, achieving complete reexpansion of the right lung. The chest drain was removed 10 days later
17 Jun. 1997	Left spontaneous pneumothorax occurred, necessitating insertion of a chest tube with negative pressure. An air leak persisted for 6 weeks, before the lung was finally stabilized and the drain removed
7 Aug. 1997	Left spontaneous pneumothorax occurred, necessitating chest drainage. In the following 7 weeks the drain continued to show persistent air leakage and partial left lung collapse with each attempt to suspend suction
1 Oct. 1997	Talc chemical pleurodesis was performed and the drain was able to be removed 1 week later after complete expansion of the left lung
Nov. 1997	Detection of liver and bone metastases
Jan. 1998	Detection of cerebral metastases
Mar. 1998	Death from disseminated cancer, without recurrence of pneumothorax

CMF, cyclophosphamide/methotrexate/fluorouracil; MMM, mitomycin C/methotrexate/mitoxantrone

SSP is a well known, but rare complication of chemotherapy for pulmonary metastatic cancer. In fact, only 28 cases of SSP occurring as a direct effect of chemotherapy have been documented in the literature. These included 7 patients with osteogenic sarcoma, 7 with germinal tumors, 3 with uterine leiomyosarcoma, 2 with endometrial carcinoma, 2 with synovial cell sarcoma, 2 with lymphoma, and 1 each with Wilm's tumor, thymoma, small cell lung cancer, adenocarcinoma from an unknown primary, and breast cancer.[3–8]

The actual mechanism of the complicating pneumothorax in primary and metastatic lung cancer is not completely understood, but the pathophysiology would depend on the particular tumor involved. For example, in primary lung cancer the SSP may be produced either by the pathological lung abnormalities that occur secondary to smoking, or by progression of the tumor, causing rupture of an ischemic primary lesion into the pleural space.[2] On the other hand, in sarcomas and germ cell cancers, SSP is more likely to be related to tumor necrosis or spontaneous hemorrhages. A similar mechanism proposed to explain chemotherapy-induced SSP involving the spontaneous rupture of chemosensitive peripheral, subpleural nodules or a rapid tumor cell lysis with tumor tissue necrosis has become generally accepted. Other speculative contributing mechanisms include increased intrathoracic pressure following emetogenic chemotherapy, especially cisplatin, and the defective repair process induced by adriamycin.[3,8]

Our patient was a nonsmoker who had no previous history of spontaneous pneumothorax and, although proof of the relationship between the pneumothorax and the effect of chemotherapy is not conclusive, the lack of any other known case or pertinent history, and the temporal relationship to chemotherapy and to its response make this etiology likely. In fact, the occurrence of recidivant SSP in our patient is strongly considered to be related to the radiologic regression of the metastases resulting from chemotherapy. The rapid lysis of the tumor highly responsive to cytotoxic chemotherapy may have caused necrosis of the tumor metastases, leading to the formation of pulmonary lacunae, a term defining thin-walled cystic lesions of the lung. Hence, the pneumothoraces may have occurred secondary to the recidivant ruptures of these lacunae in the pleural space.

The occurrence of cavitation within lung tumors, either spontaneously or secondary to chemotherapy, has been documented by several reviews and case reports; however, only two previous reports have presented a collective eight cases in which cavitation following chemotherapy resulted in cavities with walls so thin that they were usually invisible on chest radiographs and could only be detected by computed tomography. The neoplasms in these eight cases included six with germ cell malignancies, one lymphoma, and one metastatic bladder cancer.[9]

Godwin and colleagues, in their extensive classification of multiple, thin-walled cystic lesions of the lung caused by neoplastic diseases,[10] mentioned the spontaneous cavitation of hematogenous metastases, the pulmonary spread of laryngeal papillomatosis, and

Hodgkin's and non-Hodgkin's lymphomas. We suggest that the pulmonary lacunae and bullae induced by chemotherapy for metastatic lung cancer should be added to this classification.

It must also be pointed out that the SSP related to chemotherapy in pulmonary metastatic cancers may be frequently bilateral, as seen in our patient. It has been estimated that spontaneous pneumothorax occurs bilaterally, either simultaneously or sequentially, in 1% of cases;[1] however, among the 29 cases of SSP associated with chemotherapy, including ours, 9 (31%) were bilateral, 6 occurring simultaneously and 3, sequentially.

Although closed chest tube drainage may be ineffective for preventing recurrent SSP associated with chemotherapy, it remains the treatment of choice considering the high risk of performing surgical treatment in these neoplastic patients whose general condition is usually poor. Moreover, such surgery is technically difficult and rarely indicated unless conservative procedures fail.[7] Chemical pleurodesis should also be strongly considered for patients with recurrent and/or bilateral SSP related to chemotherapy.[1]

Our experience of this case led us to conclude that: cancer patients with pulmonary metastases may develop bilateral and/or recurrent pneumothoraces following chemotherapy; CT scan is essential for defining the cause of SSP; and although not always completely effective for preventing recurrence, closed chest tube drainage is the therapy of choice, surgery is rarely indicated, and chemical pleurodesis may also be used to prevent recidivant SSP.

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