Chemotherapy-Associated Recurrent Pneumothoraces in Lymphangioleiomyomatosis

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Lymphangioleiomyomatosis is a rare cause of pneumothorax in women. We present the case of a 48-year-old woman with lymphangioleiomyomatosis, who had never had a pneumothorax prior to commencing chemotherapy for breast cancer. During chemotherapy she developed 3 pneumothoraces and 2 episodes of pneumomediastinum. We suggest that the pneumothoraces were caused by the chemotherapy. To our knowledge, this is the first reported case of chemotherapy triggering pneumothoraces in a woman with lymphangioleiomyomatosis. *Key words: lymphangioleiomyomatosis; lymphangiomyomatosis; pneumothorax; chemotherapy; pneumomediastinum.* [Respir Care 2010; 55(11):1491–1494. © 2010 Daedalus Enterprises]

Introduction

Pulmonary lymphangioleiomyomatosis (LAM) is a rare cause of pneumothorax in women. The diagnosis is usually made between the ages of 30 and 50 years. LAM is associated with dyspnea and a mixed obstructive/restrictive pattern on pulmonary function testing. Extensive research has been carried out on LAM, but the trigger for the proliferation of LAM cells that eventually infiltrate the lungs and contribute to the cystic destruction remains unknown. Effective therapy remains elusive.

We present the case of a 48-year-old woman who was diagnosed with LAM and subsequently with metastatic breast cancer. She had not had a pneumothorax previously, but within 4 months of starting chemotherapy she had 3 pneumothoraces and 2 episodes of pneumomediastinum. We suggest that the chemotherapy caused the pneumothoraces.

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Case Report

A 48-year-old woman initially presented with increasing shortness of breath on exertion. She was dyspneic on walking 600 feet or ascending one flight of stairs. She had a 30-pack-year history of smoking but had quit 3 years previously. Pulmonary function tests showed an FEV_1 of 0.81 L (28% of predicted), forced vital capacity of 2.31 L (68% of predicted), and a diffusion capacity of 37% of predicted, which is consistent with a severe obstructive defect. High-resolution computed tomography (CT) showed diffuse cystic changes consistent with either severe emphysema or LAM. A 6-min-walk test showed desaturation to 81% from walking 600 feet. The diagnosis of LAM was confirmed via biopsy of a right kidney mass (an incidental finding on ultrasound) that was found to be an angiomyolipoma. She was prescribed domiciliary oxygen and followed up in the clinic.

A year and a half after her initial presentation she was diagnosed with breast cancer, with a single metastasis in the liver. She was started on chemotherapy with docetaxel, trastuzumab, and lapatinib. Each cycle of therapy commenced with docetaxel given on day 1. Trastuzumab was given once weekly for the 3-week cycle and lapatinib was given orally daily. Chemotherapy began within 2 weeks of this diagnosis. Prior to commencing chemotherapy she had no history of pneumothorax.

Shortly after starting chemotherapy she developed new-onset shortness of breath and oxygen saturation of 80% on room air. Arterial blood gas analysis found pH 7.36, P_{aCO_2}

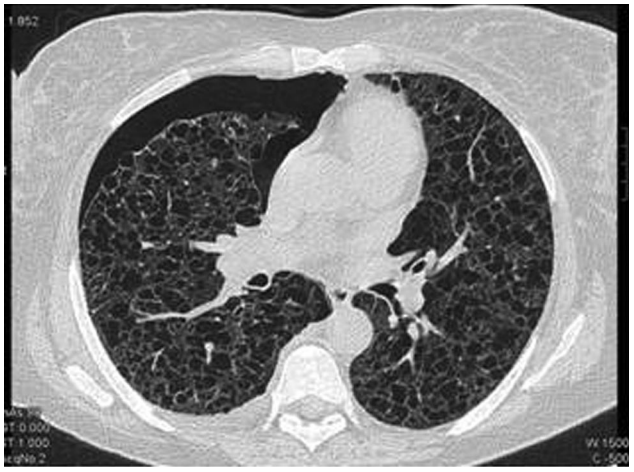

Fig. 1. Computed tomography shows diffuse cystic change consistent with lymphangioleiomyomatosis. A left-sided pneumothorax is evident.

55 mm Hg, P_{O_2} 41 mm Hg, and HCO_3^- 30.4 mEq/L. CT showed no evidence of pulmonary embolism, pneumothorax, or new infiltrates, but demonstrated multiple cysts consistent with LAM. Following clinical improvement she was discharged home and advised to continue her prescribed oxygen.

One month after commencing chemotherapy she was admitted with a 2-day history of worsening shortness of breath. A right-sided pneumothorax was found on chest radiograph and further evaluated via CT (Fig. 1). A chest drain was inserted, and the pneumothorax resolved.

Chemotherapy continued (Fig. 2). Two weeks later she was again admitted with a right-sided pneumothorax. A chest drain was inserted. As this was the second right-sided pneumothorax, we conducted a video-assisted thoracoscopic surgical pleurodesis. Her postoperative course was complicated by hypercapnic respiratory failure, which responded to noninvasive ventilation.

On the day of her planned discharge, 1 month later, she suddenly became unwell. She had chest pain and increased dyspnea. A left-sided pneumothorax was diagnosed, a chest drain was inserted, and she underwent another left-sided video-assisted thoracoscopic surgical pleurodesis.

Once again, she had a complicated postoperative course, with type-2 respiratory failure that required noninvasive ventilation and a left-lower-lobe collapse/consolidation that required intensive physiotherapy and antibiotics. She required continuous noninvasive ventilation.

She subsequently developed 2 episodes of pneumomediastinum, both within 48 h of trastuzumab administration (Figs. 3 and 4). The pneumomediastinums were treated with CT-guided insertion of chest drains, and resolved on subsequent chest radiographs.

Unfortunately, she continued to deteriorate and finally succumbed to nosocomial pneumonia 4 months after she was diagnosed with breast cancer.

Discussion

LAM is an uncommon disease that occurs predominantly in women. It is characterized by smooth muscle cell infiltration and cystic destruction of the lung.[1] Clinically, LAM is characterized by progressive dyspnea on exertion, recurrent pneumothoraces, abdominal and thoracic lymphadenopathy, and abdominal tumors, including angiomyolipomas and lymphangiomyomas. LAM occurs in approximately 30% of women with the tuberous sclerosis complex, a genetic disorder associated with seizure, brain tumors, and cognitive impairment. It also occurs in women who do not have tuberous sclerosis complex (ie, sporadic LAM).

Women with LAM have symptoms for an average of 3–5 years and experience an average of 2.2 pneumothoraces before the disease is diagnosed.[2] Diagnosis of LAM requires a high-resolution CT that demonstrates thin-walled cystic change, and either a positive tissue biopsy or a compatible clinical context, such as clinically confirmed tuberous sclerosis, angiomyolipomata, or chylothorax. The diagnosis of LAM in our patient was confirmed via characteristic CT findings and a biopsy-proven renal angiomyolipoma. Approximately 93% of patients with tuberous sclerosis complex LAM, and 30–50% of patients with sporadic LAM, have renal angiomyolipomas, which are benign renal tumors composed of dysplastic blood vessels, smooth muscle, and variable amounts of fat.[1]

The average age at diagnosis of LAM in multiple series has been approximately 35 years.[1] Classically, LAM presents with a mixed ventilatory defect on pulmonary function testing. The National Heart, Lung, and Blood Institute's LAM registry reported that, in their large cohort of 230 patients, 57% exhibited an obstructive pattern, the average FEV_1 was 70% of predicted,[3] and the mean rate of FEV_1 decline was 75 ± 9 mL/y. LAM mortality is approximately 10–20% at 10 years after the onset of symptoms,[4,5] and 30% at 10 years after lung biopsy,[6] but the time to death ranges widely.

Pneumothoraces occur in approximately 60–70% of patients with LAM, and the rate of recurrence is $> 70\%$, which is the highest among all chronic lung diseases.[1] Although pneumothoraces are common in LAM, we suggest that the pneumothoraces in our patient were triggered by the chemotherapy, which was effectively controlling the breast cancer. Our patient had never had a pneumothorax prior to chemotherapy, and the pneumothoraces had an immediate temporal relationship to the chemotherapy.

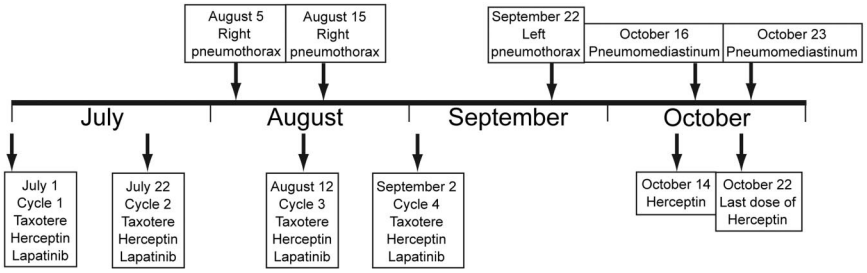

Fig. 2. Timeline of the 4 months from the start of chemotherapy to death.

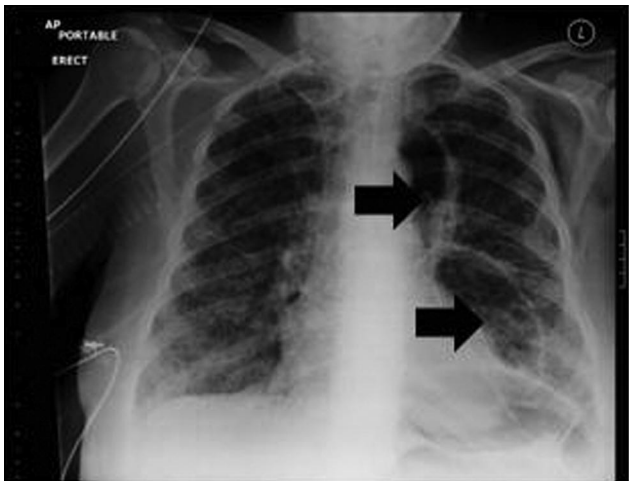

Fig. 3. Chest radiograph shows a left-sided loculated pneumomediastinum. There is a chest drain in situ.

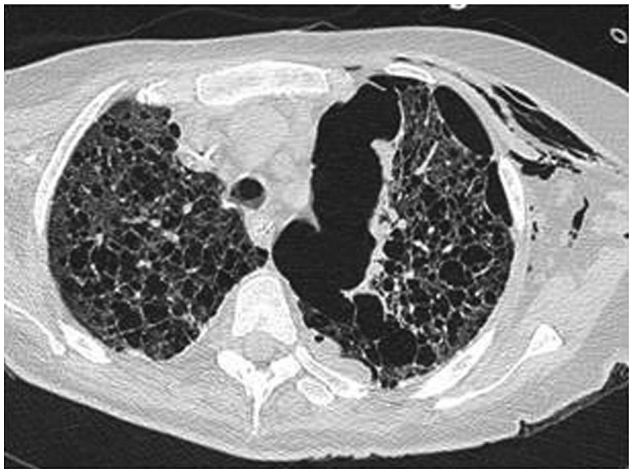

Fig. 4. Computed tomography shows a left-sided pneumomediastinum.

The current treatments for LAM are primarily based on the antagonism of estrogen, and remain experimental.[1] Lung transplantation is an option in patients with marked dyspnea, hypoxemia, and deteriorating pulmonary function. Lung transplantation may have been an option for our patient except that it was prohibited by the diagnosis of metastatic breast cancer.

The chemotherapy may have caused the pneumothorax by its action on rapidly dividing cells. There is evidence to suggest that LAM may be the simplest form of human cancer. Biallelic mutations at a single genetic locus give a histologically innocent-appearing cell all the elements required for unregulated growth, lymphatic or vascular spread, and tissue destruction.[1,7] The finding of recurrent LAM lesions in donor lungs after transplant suggests that LAM can metastasize.[8,9] Perhaps the chemotherapy affects the abnormal cells associated with the condition.

Chemotherapy can cause pneumothorax in patients with pulmonary metastases. These were reported in cases of sarcoma,[10] breast cancer,[11] and lymphoma,[12] among others. Those reports concluded that pneumothorax could be attributed to the anti-tumor effect of cytotoxic agents on underlying lung lesions.

Pneumothorax is a common complication of LAM and can occur in the absence of any known triggers. Our patient, however, never had a pneumothorax prior to her chemotherapy. The pneumothoraces were bilateral and, when pleurodesis had been performed on both sides, pneumomediastinum occurred.

Determining if an adverse event is related to a drug can be problematic. We calculated the Naranjo score[13] to assess the relationship between the chemotherapy and the subsequent pneumothoraces, and the score (5) indicates probable causation. The Naranjo algorithm uses previous data on causation of drug and effect. However, the data about LAM are sparse to nonexistent, given the rarity of LAM.

In addition to being an interesting clinical case, this case highlights an important complication of chemotherapy. Although LAM is uncommon, it affects a similar demographic to breast cancer, a condition treated with an expanding array of chemotherapies. The concept of chemotherapy triggering pneumothorax in LAM is important information for those treating these patients. To our knowledge, this is the first reported case of chemotherapy triggering pneumothoraces in a woman with lymphangioleiomyomatosis.

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