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Radiotherapy-induced secondary lung cancer: a medical case report

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Introduction

Lung cancer is the second most commonly diagnosed cancer. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for about 80% of all lung cancer diagnoses.[1] Pancoast tumors are a clinically distinctive and aggressive subtype of lung cancer and consist of tumors invading the apical chest wall in the superior sulcus/apex of the lung. Although Pancoast tumors account for only 3%-5% of lung cancers, NSCLC accounts for over 95% of Pancoast tumors, and the prognosis of patients diagnosed with this disease is poor.[2]

Treatment of NSCLC Pancoast tumor usually involves a tri-modal approach with chemotherapy-radiotherapy followed by surgical resection. Radiotherapy combined with chemotherapy can successfully treat a small number of patients and can provide palliation in most patients with an advanced-stage tumor. Surgery often requires a thoracic surgeon to remove the lung component, a spinal surgeon to resect the spinal component, and a plastic surgeon to perform a large graft to cover the defected area. Postoperative chemotherapy may offer additional benefits to patients with resected NSCLC.[3]

Although the prognosis of patients with NSCLC Pancoast tumor has traditionally been poor, recent technological advancements have led to significant improvements in the prognosis of these patients. According to a recent clinical trial, the 5-year survival rate of patients treated with tri-modal therapy was about 50%.[4] There are also published data on patients with Pancoast tumors treated with high-dose radiotherapy. The results demonstrate that selected patients with Pancoast tumors treated with high-dose intensity-modulated radiotherapy (IMRT) concurrent with chemotherapy may have long-term disease-free survival.[5,6] Still, most of these patients have low overall survival and very often the late toxicities of treatment cannot be assessed. One of the late side effects of radiotherapy is secondary cancer, which may occur in 17%-19% of patients. The use of radiotherapy increases a patient's risk of developing secondary cancer during their lifetime.[7] Preston et al.,[8] have shown that the lungs are more susceptible to develop radiation-induced cancers compared with other organs. Thus, the risk of secondary cancer in patients with lung cancer is highly correlated with radiotherapy and deserves further investigation.[7] As young patients are likely to survive for a longer duration after radiotherapy, they are at a greater risk of developing secondary cancers.[9] Moreover, secondary radiotherapy-related cancer is often a concern in patients treated with radiotherapy for cancers with a better prognosis, such as Hodgkin lymphoma, breast, testicular, cervical, and thyroid cancer.[10]

In this paper, we discuss a possible case of secondary cancer in a patient with a stage 4 NSCLC Pancoast tumor that was treated with radical dose lung radiotherapy.

Case presentation

A 59-year-old woman presented with left eye ptosis in the winter of 2009. She described her symptom as a drooping eye lid when she was trying to apply make up to the area around her eye. When asked more detailed questions by her family doctor, she reported occasional episodes of coughing, which she thought were related to seasonal allergies. She had mild exertional shortness of breath but was able to manage all her daily activities. She had a few episodes of transient pain in the left shoulder that she attributed to sleeping on her shoulder. The pain was effectively treated with ibuprofen. She had paresthesia in her 4th and 5th left digits, as well as left-hand weakness (difficulty gripping). She had a history of occasional night sweats but no change in appetite or weight loss.

After reviewing her past medical history (Table 1), it was noted that she had had asthma for about 12 years and had been on prednisone for the past 5 years. Other than mild osteoarthritis and a remote history of pneumonia, she did not have any other health issues. She did report a history of smoking 1.5 packs of cigarettes per day for about 35 years, and that warranted a chest X-ray, which showed a 5 cm mass in the left apical lung. A computed tomography (CT) scan performed in November 2009 showed a 4.7 × 6.2 × 5.2 cm mass in the left upper lobe (Figure 1). A few lymph nodes (LNs) were noted in the superior mediastinum and the left hilum. A second pulmonary nodule measuring 1.4 × 2.7 cm was noted inferior to the predominant one. Both the pulmonary nodule and mediastinal/hilar LNs were suspicious for malignancy. Magnetic resonance imaging (MRI) done in January

2010 (Figure 2) showed a 5 cm left apical mass with direct invasion of the left innominate and subclavian vein. There was thrombosis of the left internal jugular vein, and a diffusely abnormal signal was noted within the T2 vertebral body. The rest of the staging investigation, including brain MRI and an abdominal pelvic CT scan, came back negative for the metastatic spot.

Table 1 Past medical history and comorbidities

1. Asthma
2. Chronic obstructive pulmonary disease
3. Gastroesophageal reflux disease
4. Fibromyalgia
5. Hypertension
6. Hypothyroidism
7. Left leg deep vein thrombosis in 2016
8. Osteoarthritis
10. Atrial fibrillation

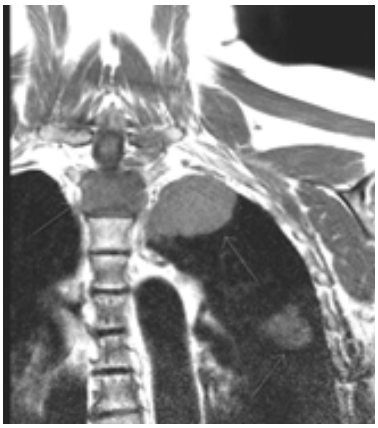

Figure 1 Pre-treatment chest computed tomography scan (November 27, 2009).

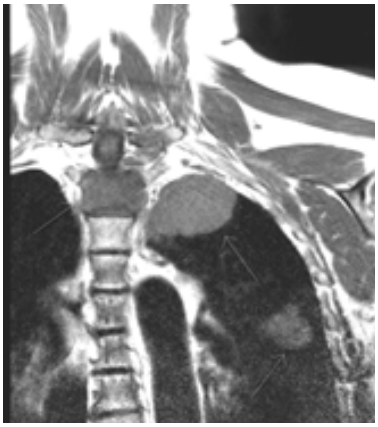

Figure 2 Pre-treatment chest magnetic resonance imaging (January 8, 2010).

Her case was discussed at the University Health Network (UHN) thoracic rounds, and given the suspicious T2 bone marrow involvement, she was thought to have at least a locally advanced but most likely stage 4 Pancoast tumor. Therefore, surgical resection was not recommended, and the patient received radical radiotherapy with a total dose of 6600 cGy in 33 fractions concurrent with two cycles of cisplatin and etoposide. She then received two more cycles of cisplatin-etoposide adjuvant to her radical treatment. She completed the entire course of treatment in April 2010.

The radiotherapy field covered the primary tumor, the vertebral body, the secondary tumor, and mediastinal-hilar LNs (Figure 3). She responded very well to her treatment and, apart from a transient episode of radiation pneumonitis, had no other side effects. Her tumor was successfully ablated and left a small area of fibrotic post radiotherapy change in the left upper lung (Figure 4).

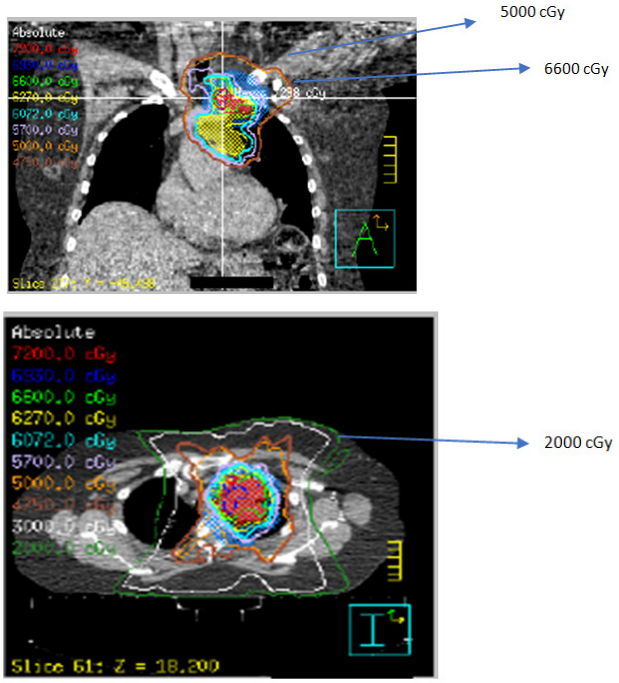

Figure 3 Radiotherapy dosimetry (February 2010).

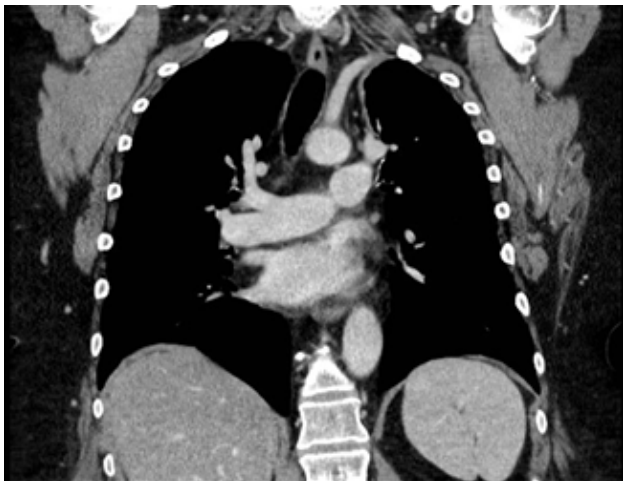

Figure 4 Follow-up chest computed tomography scan (August 24, 2017).

In 2017, as there was no sign of recurrent or metastatic disease (Figure 4), she was given the option of being discharged from the routine follow-up appointment versus getting another CT scan in 2 years. She chose the latter option; therefore, a CT scan was repeated in December 2019, and the result showed new development of a round mass measuring 4.9 × 4.2 × 4.5 cm (Figure 5). A positron emission tomography (PET) scan showed significant fluorodeoxyglucose (FDG) avidity in the mass with a max standardized uptake value (SUV) of 5. There were no FDG-avid mediastinal or hilar LNs, and the rest of the staging investigation (abdominopelvic CT scan and brain MRI) showed no metastasis. The patient remained quite asymptomatic. A biopsy was done, which showed a spindle cell tumor with a sarcomatoid transformation.

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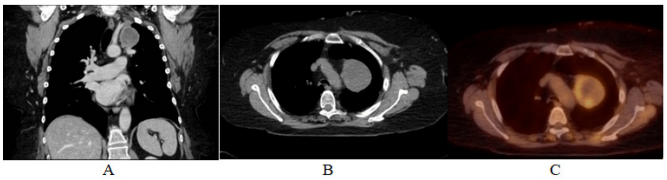

Figure 5 Follow-up scan in December 2019 showing the development of a left upper lobe mass (red arrow). (A) Left upper lobe mass (computed tomography [CT] image, coronal view). (B) Left upper lobe mass (CT image, axial view). (C) Left upper lobe mass (positron emission tomography image, axial view).

The patient's case was discussed at the thoracic rounds as well as the sarcoma meeting. The recommendation was to proceed with surgical resection. The patient underwent surgical resection in February 2020, and a portion of the superior segment of the left upper lobe of the lung with a portion of the first rib were removed. An 8.6 cm, well-circumscribed, poorly differentiated pleomorphic spindle cell sarcomatoid carcinoma was identified and staged as pT4N0. All surgical margins were negative for malignant cells, and the closest surgical margin to the malignant cell was 1 cm. There was no lymphovascular invasion, and 3/3 resected peribronchial LNs were negative for malignancy. The final pathology reported the tumor as a pulmonary sarcomatoid pleomorphic carcinoma. The pathologist did not detect any MET variants in the sample. The sequencing was done with a capture reagent that targeted MET in such a way that it would detect about 50% of the DNA sequence variants that would lead to MET exon 14 skipping. Therefore, the result was not conclusively negative for MET exon 14 skipping.

The patient was to receive adjuvant platinum-based chemotherapy; however, her performance status deteriorated after surgery. She was admitted to the hospital in early May 2020 with increasing shortness of breath and a declining performance status. The chest CT angiography did not show any evidence of pulmonary emboli but, unfortunately, revealed tumor recurrence in the left lung apex, pleura, and left-sided pericardium with additional pathological mediastinal LNs. Her clinical picture deteriorated rapidly shortly thereafter, and she passed away in May 2020.

Discussion

Pulmonary sarcomatoid carcinomatosis (PSC) is defined by the World Health Organization as poorly differentiated NSCLC that contains a component of sarcoma or sarcoma-like elements. These cancers often have a poor prognosis, with a commonly reported 5-year overall survival of about 10%; however, some studies have reported higher 5-year overall survival of 30%-80%.[11,12]

These carcinomas are a rare group of tumors accounting for less than 1% of NSCLC.[13] Five subtypes have been described, including pleomorphic carcinoma, spindle cell carcinoma, carcinosarcoma, giant cell carcinoma, and pulmonary blastoma. In a 2019 study, Smadhi et al.,[14] found 43 of 1582 surgically treated patients with lung cancer had PSC. The median survival for these patients was only 8 months. The authors defined the tumor size and a negative surgical margin as important prognostic factors. In 2021, Iijima et al.,[15] reported the outcome of 17 patients with pulmonary pleomorphic carcinoma treated with surgical resection. The 5-year overall survival and disease-free survival rates were 27.2% and 51.0%, respectively. Poor prognostic factors included disease-free survival < 1 year, ipsilateral mediastinal involvement of N2, and the presence of an adenocarcinoma component.

Although the published data on PSC is spare, most studies have concluded that completely resected small tumors carry a favorable prognosis. Our patient had an 8.6 cm tumor that was completely resected with a clear surgical margin of at least 1 cm. Furthermore, there was no LN involvement or lymphovascular invasion. However, this patient progressed rapidly within a month of surgical resection. We believe her prognosis was adversely affected by her previous chest radiotherapy and, most likely, this was a case of radiotherapy-induced secondary cancer.

Radiation-induced secondary malignancy is known as one of the late side effects of radiotherapy. About 17%-19% of patients with cancer who survive may develop a second malignancy. There are multiple factors related to secondary malignancies, including lifestyle, genetic factors, chemotherapy, and radiotherapy.

Follow-up data from the Childhood Cancer Survivor Study have shown that over time, mortality increases due to secondary malignancy compared with other causes.[16,17] Higher death rates due to subsequent malignancy were seen in patients diagnosed between 0 and 4 years. The risk factors in this group included radiotherapy exposure, alkylator therapy, or exposure to the highest dose of epipodophyllotoxin. Khan et al.,[18] reported a high-grade undifferentiated spindle cell sarcoma of the left maxilla in a 24-year-old man with a history of bilateral retinoblastoma treated with radiotherapy at the age of 3 years.

There is limited published literature on secondary malignancy in adult patients treated with radiotherapy. These patients often have cancers with higher overall survival rates, such as breast and prostate.[19,20] To the best of our knowledge, this is the first reported suspected case of radiotherapy-induced malignancy as a form of pulmonary pleomorphic sarcomatoid carcinoma in an adult patient treated with chemotherapy-radiotherapy for lung cancer.

Conclusion

With the advance in lung cancer diagnosis and treatment options, patients may live longer and thus have the possibility of developing late treatment-related side effects. This justifies the longer follow-up duration in this patient population. The data on late radiotherapy effects on treated adult patients with lung cancer is spare, and more reports are needed to understand them better.

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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