Phrenic Nerve Palsy Following Radiation Therapy for Patient With Breast Cancer

Akhil Sharma, DO; Fazal Raziq, MD; Tyler Kemnic, DO; Rohan Prasad, DO

ABSTRACT

Introduction: Breast cancer is the most common malignancy affecting women in US today. Radiotherapy used after breast-conserving surgery has been shown to decrease local recurrence while minimizing side effects. Peripheral neuropathy remains a common and well-known complication of radiotherapy for breast cancer; however, it is rarely associated with phrenic nerve palsy after treatment of breast cancer.

Case presentation: We describe a 66-year-old woman with a significant past medical history of chronic obstructive pulmonary disease and asthma who presented with hypoxia after completing radiotherapy for breast cancer. After ruling out other causes of hypoxemia, the patient was diagnosed with diaphragmatic dysfunction, likely caused by phrenic nerve palsy resulting from radiotherapy-induced neuropathy after treatment of breast cancer.

Conclusion: This is the first reported incidence of phrenic nerve palsy resulting from radiotherapy for breast cancer.

INTRODUCTION

Breast cancer is the most common malignancy among women in the US. The overall incidence of breast cancer has continued to rise over the course of past 4 decades. This rise in incidence is a result, in part, of early detection and improvements in treatment modalities, leading to improved mortality. Currently, several treatment options for breast cancer exist, including surgery, hormonal therapy, chemotherapy, radiation, or some combination thereof.

Radiotherapy is used to achieve local control of malignancy while minimizing systemic side effects. When used as curative treatment, it aids in reducing tumor size, making them more resectable, or by destroying tumors that are too small or widely dispersed to resect. Palliative radiotherapy is use of radiation for symptomatic improvement and is used when mass effect or tumor location results in symptoms that reduce quality of life. A key limitation of radiotherapy is radiation-induced damage to surrounding tissues. Commonly affected tissues after radiation for breast cancer include the heart, ipsilateral lung, and contralateral breast.

Radiation-induced brachial plexus neuropathy is a known complication of radiotherapy for breast cancer. In addition, recent case reports have shown phrenic nerve damage after radiation to the head and neck for mantle cell carcinoma. We present the first case of phrenic nerve palsy resulting from radiotherapy for breast cancer.

CASE PRESENTATION

A 66-year-old woman with a past medical history of chronic obstructive pulmonary disease, asthma, left breast lobular carcinoma with lumpectomy in 2000, left breast ductal carcinoma with lumpectomy and brachytherapy in 2004, presented to radiation oncology with abnormal contouring of the left breast (Table 1). Follow-up ultrasound and mammography with biopsy showed invasive ductal carcinoma stage 1A T1a N0 M0 in the left breast. Given recurrent malignancies, the patient was offered mastectomy, which she declined. She underwent wire localized lumpectomy followed by radiotherapy.

Soon after beginning radiotherapy, the patient reported shortness of breath to her primary care provider. Echocardiography to assess cardiac function was performed and showed mild left ventricular hypertrophy, a left ventricular ejection fraction of 65% to 70%, and normal right ventricular systolic function. Pulmonary function testing completed after finishing radiotherapy showed decreased functional residual capacity, residual volume, and nonspecific ventilatory defect, but no obstructive defect or significant bronchodilator response.

One month after completing radiotherapy, the patient presented to the emergency department for hypoxia (< 85% on home pulse oximetry). Her baseline oxygen requirements were 2 L via nasal canula nightly. However, 2 days prior to admission, she began experiencing fatigue, with no improvement despite home albuterol, tiotropium bromide, and 2.5 L supplemental oxygen continuously. On presentation, she denied fevers, chills, coughing, wheezing, sick contacts, and chest pain. She was vitally stable, saturating at 90% on the 2-nasal cannula, and in no acute distress. On physical examination, there were no signs of peripheral edema, jugular venous distension, or accessory respiratory muscle use. Cardiovascular examination demonstrated regular rate and rhythm, and no appreciable murmurs. Lung auscultation demonstrated decreased breath sounds in the right lung field, but no wheezing, rhonchi, or rales.

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A workup for infectious causes, including influenza A/B, respiratory syncytial virus (via polymerase chain reaction), a pediatric respiratory panel, urinalysis, and COVID-19 were negative. A chest x-ray demonstrated new-onset right-side diaphragmatic paralysis not seen on prior chest x-rays (Figure 1). The patient was given 125 mg solumedrol in the emergency department and was continued on 40 mg prednisone for 4 days, with improvement in symptoms. Given chest x-ray findings, she was ultimately diagnosed with hypoxia secondary to diaphragmatic weakness. Once stable, the patient was discharged home on room air with instructions to follow up with the pulmonology outpatient service.

**DISCUSSION**

Treatment of breast cancer requires a multidisciplinary approach. The decision regarding treatment is based on multiple factors, including cytogenetics, staging, and individual risk factors. Treatment of stage I or stage II breast cancer often involves breast-conserving surgery followed by radiotherapy. The purpose of radiotherapy is to achieve greater local control of the malignancy and to decrease the rates of local recurrence. However, earlier data have shown no improvement in mortality when comparing groups that received radiotherapy with those that did not. The lack of survival benefit was determined to be the result of increased cardiovascular mortality in patients receiving radiotherapy. This was the result of increased radiation delivery to the heart, particularly the left anterior descending artery, during treatment. Since this initial determination, greater effort has been placed on decreasing the amount of radiation delivery to the heart, which has been achieved by several means, including more specific mapping of the tumor, intensity-modulated radiation therapy, and hypofractionated delivery of the radiation. Follow-up studies since applying these techniques have shown improving survival rates in patients, while maintaining decreased recurrence rates. However, a drawback of these changes has been increased radiation delivery to surrounding tissues, including the lungs, the contralateral breast, and the entire heart. As this technology continues to change, an assessment of its complications is vital to improve morbidity in patients.

Peripheral neuropathy is a known complication of radiation. Pathogenesis surrounding radiation-induced neuropathy is poorly understood. Current hypotheses suggest possible causes, including metabolic abnormalities associated with diabetes mellitus and, less commonly, hereditary neuropathy with liability to pressure palsy or familial amyloidosis.

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**Table 1. Timeline**

<table>
<thead>
<tr>
<th>Date</th>
<th>Primary concern of patient</th>
<th>Diagnostic testing/intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/20</td>
<td>Patient presents for unspecified asthma.</td>
<td>Chest x-ray shows encroachment at C4 and C5.</td>
</tr>
<tr>
<td>12/19</td>
<td>Patient presents to radiation oncology with abnormal contouring of left breast.</td>
<td>Left mammogram shows scattered fibroglandular density and benign-appearing calcifications. Left breast ultrasound shows left breast nodule and abnormal lymph nodes in left axilla with thickened cortex. Core biopsy of left breast shows grade 1 invasive ductal carcinoma with negative left axillary lymph nodes.</td>
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<tr>
<td>2/20</td>
<td>Patient has surgery for grade 1 invasive ductal carcinoma.</td>
<td>Patient undergoes breast lumpectomy with wire localization and axillary sentinel node biopsy.</td>
</tr>
<tr>
<td>3/20</td>
<td>Patient has follow-up with radiation oncology.</td>
<td>Patient undergoes breast lumpectomy with wire localization and axillary sentinel node biopsy.</td>
</tr>
<tr>
<td>4/20</td>
<td>Patient undergoes head and neck imaging to rule out metastatic disease.</td>
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</tr>
<tr>
<td>5/20</td>
<td>Undergoes scheduled pulmonary function testing.</td>
<td>Results show FVC of 2.31 (110% of predicted), FEV1 of 2.73 (109% of predicted) and FEV1/FVC ratio of 0.84. Post bronchodilator FVC, 2.8 L (111% of predicted); FEV1, 2.38 L (113% of predicted); FEV1/FVC ratio, 0.85; and normal-appearing flow volume loop. Functional residual capacity, 1.95 L (73% of predicted); residual volume, 1.1 L (57% of predicted); total lung capacity, 3.94 L (82% of predicted); diffusion capacity of lungs to carbon monoxide, 85% of predicted. Other results show no obstructive defect, no significant bronchodilator response, nonspecific ventilatory defects, a total lung capacity within normal limits, and a diffusion capacity within normal limits.</td>
</tr>
<tr>
<td>7/20</td>
<td>Patient presents to the hospital with shortness of breath and hypoxemia. Oxygen saturation is &lt; 85% despite a 2 L nasal canula.</td>
<td>Infectious causes investigated, including influenza A/B, respiratory syncytial virus (via polymerase chain reaction), pediatric respiratory panel, urinalysis, and COVID-19 (twice), were negative. The patient was given 125 mg solumedrol in the emergency department and was continued on 40 mg prednisone for 4 days. A chest x-ray showed right-side diaphragmatic paralysis.</td>
</tr>
<tr>
<td>3/21</td>
<td>Patient undergoes head and neck imaging to rule out metastatic disease.</td>
<td>Brain CT without contrast shows stable microvascular ischemic changes. CT angiogram of the neck and brain shows no significant intracranial or extracranial stenosis.</td>
</tr>
</tbody>
</table>

CT = computed tomography; FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy.
compression of nerves from radiation-induced fibrosis, direct axonal damage, and demyelination, among other factors.10 Furthermore, presentation of radiation-induced neuropathy can be delayed by a decade after the initial dose, resulting in neuropathic complications in the distant future.10

Treatment of breast cancer with radiotherapy has been associated with brachial plexus neuropathy and upper extremity weakness.7 Phrenic nerve palsy has never been linked to radiotherapy to the chest wall for breast cancer treatment. Instead, it has been linked to radiotherapy to the supravacular and axillary regions for treatment of Hodgkin’s lymphoma13 and mantle cell lymphoma.8 In each of these cases, the patient presented with bilateral diaphragmatic paralysis resulting from phrenic nerve injury from radiotherapy.

Our patient had right-side diaphragmatic paralysis diagnosed by chest x-ray (Figure 1). There are many causes of diaphragmatic paralysis, including traumatic injury to the phrenic nerve, demyelinating diseases, infections such as Lyme disease, or inflammatory conditions such as sarcoidosis. Our patient underwent an extensive infectious workup, which was negative; had negative antineutrophilic antibodies; and negative cyclic citrullinated peptide antibodies. Her clinical picture was also inconsistent with systemic demyelinating diseases. Given her unilateral diaphragmatic paralysis, Lyme disease was thought to be unlikely because it traditionally presents with bilateral diaphragmatic paralysis.

The patient also underwent imaging of the head and neck as part of routine screening, which showed cervical spinal fusion hardware at C5 and C6, with minimal degenerative changes and no metastatic disease to the vertebrae (Figure 2). Although previous imaging had shown osteophytic encroachment at the level of C5, this is unlikely to be the cause of the patient’s diaphragmatic paralysis. If phrenic nerve palsy was a result of compression at the spinal level, the patient would also have upper extremity neuropathy in a C5 dermatomal distribution, with resulting weakness and neuropathic pain, which she did not. Furthermore, compression at the level of C5 results in clinically significant diaphragmatic paralysis in only 15% of cases.

In contrast, our patient was treated initially with brachytherapy in 2004 for her initial breast cancer; she was then treated with tangent radiation therapy (a total of 4500 cGy) for her recurrent breast cancer in 2020. After the completion of this second treatment, the patient was diagnosed with right-side diaphragmatic paralysis. Given the course of the right phrenic nerve over the pericardium of the right atrium, and repeated exposure to radiotherapy, there is a greater likelihood that the patient developed phrenic nerve palsy as a result.

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Figure 1. Chest x-ray on day of admission shows right-side diaphragmatic paralysis.

Figure 2. Neck and brain computed tomographic angiogram shows no osteolytic lesions and minimal degenerative changes at the level of C5 and C6.
of radiation-induced injury. Taking these observations into account, we conclude that the phrenic nerve injury was a result of repeated exposure to therapeutic radiation to the chest wall.

**CONCLUSION**

Although complications of radiation therapy are thought to be predictable, changes in the angles at which radiation is delivered may lead to new set of complications. Changes in radiation delivery have been made to decrease radiation dose delivered incidentally to the heart, particularly to the left anterior descending artery, resulting in an improvement in mortality outcomes. However, it has come at a cost of radiation to the whole heart and surrounding structures. Given these changes are recent, patients treated with this new methodology may present with atypical complications. This case demonstrates the first reported incidence of phrenic nerve palsy occurring as a result of radiation therapy to the chest wall for breast cancer.

**Disclosure Statement**

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