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CASE REPORT

Malignant mesothelioma following thoracic radiotherapy for lung cancer

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Summary As the number of long-term cancer survivors increases, secondary malignancies are becoming a greater clinical issue. Although some of these malignancies may be related to common environmental exposures, a significant number are considered to be therapy-related. Pleural malignant mesothelioma is a neoplasm that may be related to asbestos exposure or radiation exposure. Previous reports of pleural mesothelioma as a second malignancy have tended to follow radiotherapy for extra-thoracic malignancies such as Hodgkin's disease, breast cancer and Wilms' tumor. We report the case of a 66-year-old woman with no prior asbestos exposure who developed pleural mesothelioma 17 years after pneumonectomy and adjuvant radiation therapy for non-small cell lung cancer. Opacification of the lung field from prior therapy made determination of the diagnosis more challenging. Secondary malignancies such as mesothelioma should be considered in patients who develop unexplained symptoms even long after treatment of a primary tumor.

1. Introduction

As the number of cancer survivors increases, the rate of post-cancer and post-therapy complications, including secondary malignancies, is also increasing. In childhood cancer survivors the risk of a second malignancy is five times the risk of malignancy in the general population [1]. In 15 year survivors of Hodgkin's disease in particular, an 18.5-fold increase risk of secondary malignancy has been reported [2].

Although the appearance of a second malignancy may be related to a common environmental exposure or may be coincidental, cancer therapy itself may increase the risk of secondary malignancy. Radiation exposure has long been known to be potentially carcinogenic. Reports of malignancies attributable to radiation therapy first appeared shortly after the initial use of radiation therapy to treat cancer [3]. Observations of skin cancers and leukemias in radiation technicians and radiologists were followed by reports of secondary malignancies in patients treated with radiation. The most common secondary malignancies associated with

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radiation exposure are hematologic, including acute leukemias and myelodysplastic syndrome, which usually occur in the first years after exposure. Solid tumors, including lung cancer and sarcomas, have also been associated with radiation exposure, but occur after a significantly longer latency period and this risk continues for several decades [4].

Malignant mesothelioma is an uncommon neoplasm that has been linked to prior radiation therapy for various tumor types, with Hodgkin's disease being the most common primary malignancy. However, in the setting of a prior lung cancer, distinguishing between recurrence of lung cancer and a secondary pleural mesothelioma could be especially difficult. In the present report, the case of a woman who developed mesothelioma after radiation therapy for lung cancer is described.

2. Case report

In 1988, a 49-year-old woman presented with dyspnea and was found to have a right lung mass. She had a 56 pack-year history of smoking, recently discontinued. Social and occupational history did not reveal evidence of environmental or occupational exposure to asbestos. Pneumonectomy resulted in resection of Stage III adenocarcinoma of the right lung (T2N2M0, apical mass 5.0 cm × 3.9 cm with ipsilateral mediastinal and subcarinal lymphadenopathy). She received adjuvant radiotherapy to the right lung field to a total dose of 6000 rads. A Cobalt 60 therapy unit delivered 24 fractions over 46 days, initially 4000 rads to a 13 cm × 15 cm field, after which the field was narrowed to focus on the bronchial stump for an additional 2000 rads.

Over the next 17 years she developed emphysema but had no evidence of recurrent lung cancer on clinical or radiographic examinations. In August 2005, she noted a mild increase in dyspnea on exertion, and in the fall of 2005 she developed right upper quadrant pain which did not improve with treatment for gastroesophageal reflux disease. In December 2005 she was hospitalized with an exacerbation of abdominal pain. Chest X-ray showed changes of a previous right pneumonectomy with opacification of the right lung field. CT scan of the abdomen and pelvis revealed lymphadenopathy in the retroperitoneum, retrocural area, porta hepatis and right costophrenic angle. However, images of the lower lung also revealed massive right pleural thickening, multiple small pulmonary nodules and a left pleural effusion. CT scan of the chest demonstrated a rind-like, thickened pleura in the right lung field, numerous miliary pulmonary nodules, a small left pleural effusion and extensive mediastinal lymphadenopathy. Neither pleural plaques not interstitial fibrosis were seen.

Needle core biopsy of the thickened right pleura disclosed epithelioid malignant mesothelioma, comprised of sheets and cords of epithelioid cells with moderately abundant eosinophilic cytoplasm and eccentric nuclei with occasional nucleoli infiltrating the chest wall, connective tissue and skeletal muscle. The immunohistochemical staining profile was consistent with mesothelioma. The tumor exhibited diffuse staining for cytokeratins AE1/AE3 and strong nuclear and cytoplasmic staining for calretinin. Patchy positivity was observed for CK 5/6. The tumor was non-immunoreactive for TTF-1. The report of the patient's prior lung carcinoma described a poorly differentiated adenocarcinoma that did not invade the pleura.

The patient was treated with pemetrexed and cisplatin but had a steady downhill course complicated by pulmonary emboli, upper extremity thrombophlebitis, left sided pleural effusion and persistently worsening dyspnea and died in April 2006.

3. Discussion

Malignant mesothelioma is a rare neoplasm, particularly in women. In 2003, 560 cases of malignant mesothelioma of the pleura and peritoneum in women were reported in the SEER database. Unlike men, whose higher incidence of mesothelioma varies with birth cohort and is associated with occupational asbestos exposure, the lifetime probability of mesothelioma in U.S. women is 3.6×10^{-4} [5]. Eighty percent of mesothelioma cases occur 20—50 years following asbestos exposure while the remaining 20% are considered to be non-asbestos-related [6]. It has been suggested that other agents, including non-asbestos fibers and radiation therapy, may play a causative role in these cases.

Radiation treatment for malignant and non-malignant conditions has been associated with the development of pleural, peritoneal and pericardial mesotheliomas. Over the last 25 years, 31 cases of radiation-associated pleural mesotheliomas have been described in the English literature (Table 1) [7—25]. Patients ranged in age from 1 to 63 years at the time of diagnosis of their primary tumor with the onset of mesothelioma occurring after a marked latency period of 7—50 years. The male:female ratio among radiation-associated mesotheliomas was 1:1, unlike the 5:1 male:female ratio of mesotheliomas in the general population. The prognosis of this disease is generally quite poor, although some patients have had extended survival after diagnosis. The longest survivals noted were 8 years in a patient previously treated for ovarian cancer[21] and 6 years in a patient radiated for Hodgkin's disease [25]. Secondary pleural mesotheliomas occurred most commonly in patients radiated for Hodgkin's disease [8,11,16,17,19—21,25], Wilms' tumor [12—14,23] and breast cancer [9,15,18,20,24]. One patient developed mesothelioma 50 years after radiation exposure to the 1945 Nagasaki atomic bomb blast [22]. However, this patient was a former shipyard worker, a well-recognized source of asbestos exposure.

The association between malignant mesothelioma and radiation treatment has primarily been based on case reports. Three retrospective cohort studies have been published with conflicting results. However, these studies have significant methodologic limitations. Using SEER data from 1973 to 1993, Neugut et al. [26] did not find an increased risk of mesothelioma in patients treated with radiation for breast cancer or Hodgkin's disease. Of the 250,000 breast cancer survivors identified, only 6 later developed mesothelioma: 2 in the 25% treated with radiation and 4 in the 75% who were not. None of the 13,734 Hodgkin's disease patients identified developed mesothelioma, irrespective of radiation therapy. The combined relative risk (RR) with radiation was not significant (1.56, 95% confidence interval (CI) 0.18—5.63). Cavazza et al. [20] published a series of 8 iden-