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Rapid Sarcomatoid Transformation of Lung Squamous Cell Carcinoma After Neoadjuvant Therapy: A Case Report

JUWAIRIYA ARSHI[1], MADELINE SAUER[2] and FENG YIN[1]

[1]*Department of Pathology and Anatomical Sciences, University of Missouri at Columbia, Columbia, MO, U.S.A.;*
[2]*School of Medicine, University of Missouri at Columbia, Columbia, MO, U.S.A.*

Abstract. *Pulmonary sarcomatoid carcinoma is a rare variant of non-small cell lung cancer. Here, we report on the case of a 67-year-old male with a diagnosis of biopsy-proven moderately differentiated squamous cell carcinoma of the left lower lobe of the lung. The tumor cells on biopsy had epithelioid morphology with strong immunoreactivity for CK7 and p40. The mass was surgically removed one year later due to its poor response to stereotactic radiotherapy and chemotherapy. The lobectomy specimen revealed pleomorphic mitotically active spindle cell neoplasm with scattered foci of epithelial component. The tumor cells showed diffuse immunopositivity for vimentin, as well as focal immunoreactivity for CK7, p40 and S100 in the epithelial component. To the best of our knowledge, this is the first documented case of histopathologic sarcomatoid transformation of lung squamous cell carcinoma after neoadjuvant therapy. The clinical course, diagnosis and a review of literature are presented*

Non-small cell lung cancer is the leading cause of cancer mortality worldwide (1, 2). As a rare variant of non-small cell lung cancer composing less than 1% of lung carcinoma cases (3), sarcomatoid carcinoma is a poorly differentiated tumor and carries grave prognosis. Epithelial to mesenchymal transition (EMT), a process that epithelial cells acquire a spindle cell morphology because they lose their cell-cell adhesion and polarity, is considered as one of the underlying mechanisms (4).

Currently rare cases with sarcomatoid transformation have been reported in pulmonary adenocarcinoma patients who had acquired resistance to tyrosine kinase inhibitors (TKI) (5, 6). There is no published report on sarcomatoid transformation in squamous cell carcinoma (SCC) of the lung. Here, we present the first documented case of histopathologic sarcomatoid transformation of lung squamous cell carcinoma after neoadjuvant therapy. The clinical course, diagnosis and a review of the literature are present.

Correspondence to: Feng Yin, MD, Ph.D., Department of Pathology and Anatomical Sciences, University of Missouri, Columbia, MO 65212, U.S.A. Tel: +1 5738826687, e-mail: fengyin@health.missouri.edu

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Case Report

A 67-year-old male presented with a left lower lobe lung mass in October 2018. Patient had a history of extensive tobacco use and a head and neck squamous cell carcinoma status post total laryngectomy and chemoradiation therapy, completed in July 1997. The patient reported one episode of hemoptysis but denied fevers, chills, vomiting or difficulty breathing. This lung nodule has been followed up by serial imaging since 2014, and originally it measured 0.9 cm in greatest dimension. Computed tomography (CT) and positron emission tomography – computed tomography (PET/CT) scans showed enlargement of the lung nodule in April 2018 (Figure 1A and B). A follow up CT and PET/CT scan performed in September 2018 showed rapid enlargement of the pulmonary nodule measuring 2.5 cm (Figure 1C and D), suggesting progression of malignancy.
A CT-guided left lower lobe lung nodule biopsy showed medium sized tumor cells with epithelial morphology and nested/trabecular growth pattern, consistent with a non-small cell carcinoma of the lung. Immunohistochemical stains showed that the tumor cells were strongly positive for p40 and CK7, and negative for CK20 and TTF-1, supporting the diagnosis of a squamous cell carcinoma (Figure 2).

The patient elected to have Stereotactic body radiation therapy (SBRT), which he completed in February 2019. Follow-up CT scan in September 2019 showed marked enlargement of the left lower lobe lung mass (5.5 cm). There was also an adjacent 1.0 cm non-FDG avid pulmonary nodule. With a concern for progression of malignancy, patient underwent left thoracotomy with left lower lobectomy.

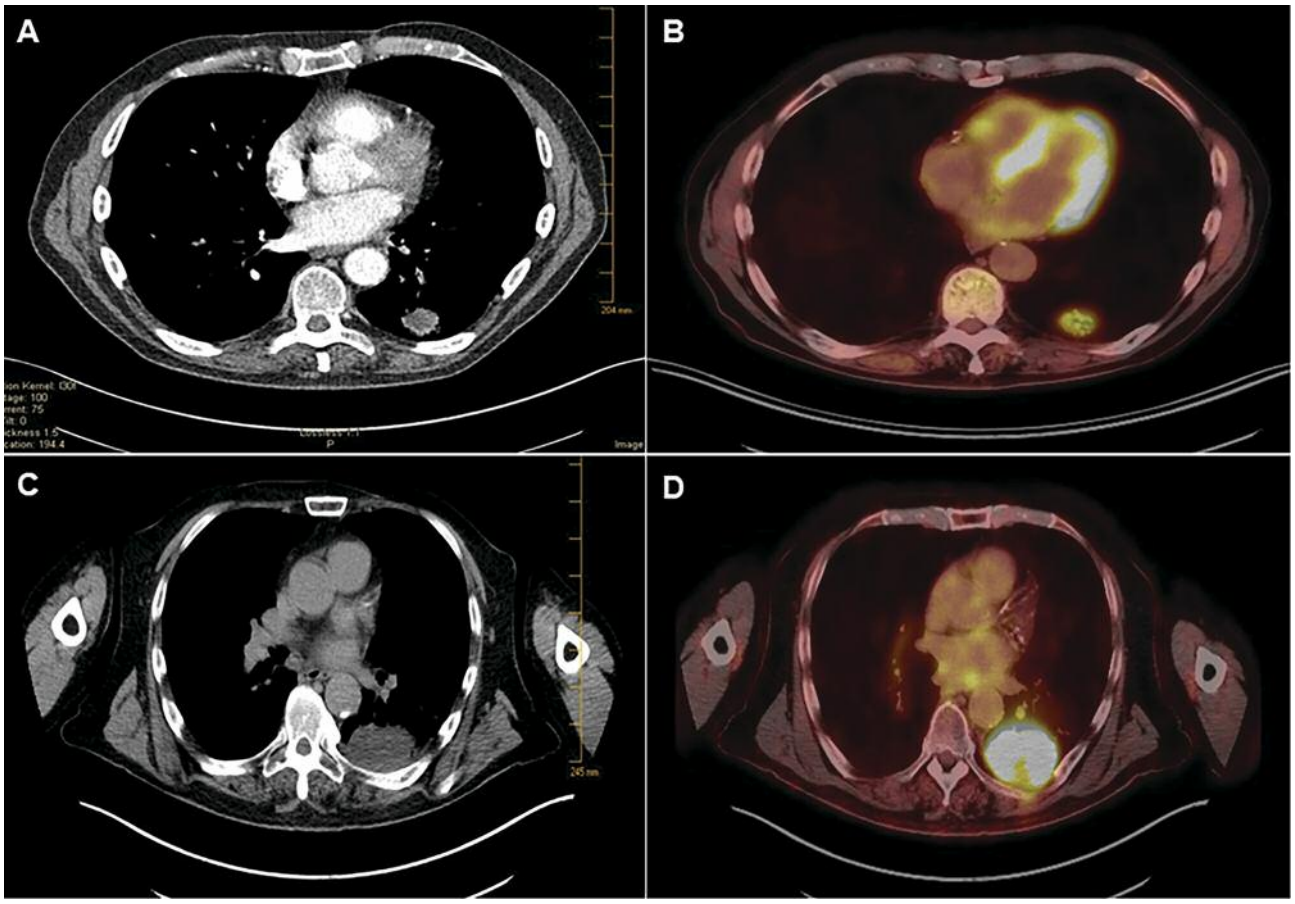

Figure 1. *Radiographic findings of the lung mass. (A) CT scan performed in April 2018 in a 67-year-old man. A 1.2 cm left lower lobe pulmonary mass was seen; (B) PET/CT scan done in April 2018 showing the FDG avid mass; (C) CT scan and (D) PET/CT scan performed in September 2019 showed enlargement of the mass suggesting progression of malignancy. A 2.5 cm left lower lobe pulmonary mass was seen.*

The lobectomy specimen showed a well circumscribed yellow-tan mass measuring 6.7×6.5×4.5 cm and appeared to be involving the pleura. Sections of the lobectomy specimen showed a predominantly spindle cell neoplasm with approximately 30% of tumor necrosis and frequent mitosis (mitotic rate 46/10 high power fields) (Figure 3). The spindle cells were diffusely positive for vimentin. Rare foci of epithelial components were noted, which were focally positive for p40, CK7, cytokeratin AE1/AE3, and S100, negative for SOX10, Napsin A, TTF-1 and EMA. These findings are most compatible with a sarcomatoid transformation from the original squamous cell carcinoma of the lung.

In addition, there was a subpleural well circumscribed nodule within the inferior aspect of the lower lobe, which was histologically consistent with a hamartoma corresponding to the non-FDG avid pulmonary nodule on PET/CT.

Patient's postoperative recovery was uneventful. At post-operative follow-up, the patient was doing well with no new complaints. However, PET/CT performed at 2 months after surgery showed a small concerning focus at the tumor resection site.

Discussion

Sarcomatoid carcinoma, which has sometimes been referred to as metaplastic sarcoma or pseudosarcoma, is an aggressive variant that is notorious for its association with metastases, recurrence and poor survival rate. It is a biphasic high-grade tumor with an epithelial and spindle cell component, and represents about 0.5-0.8% of all pulmonary malignant tumors (3). Frequently, these tumors show poor response to chemoradiotherapy and surgical removal remains the mainstay of treatment approach.

Our case is unique. Sarcomatoid transformation has not been described in a squamous cell carcinoma of the lung. In our case, the original biopsy was typical for a moderately differentiated squamous cell carcinoma of the lung. After

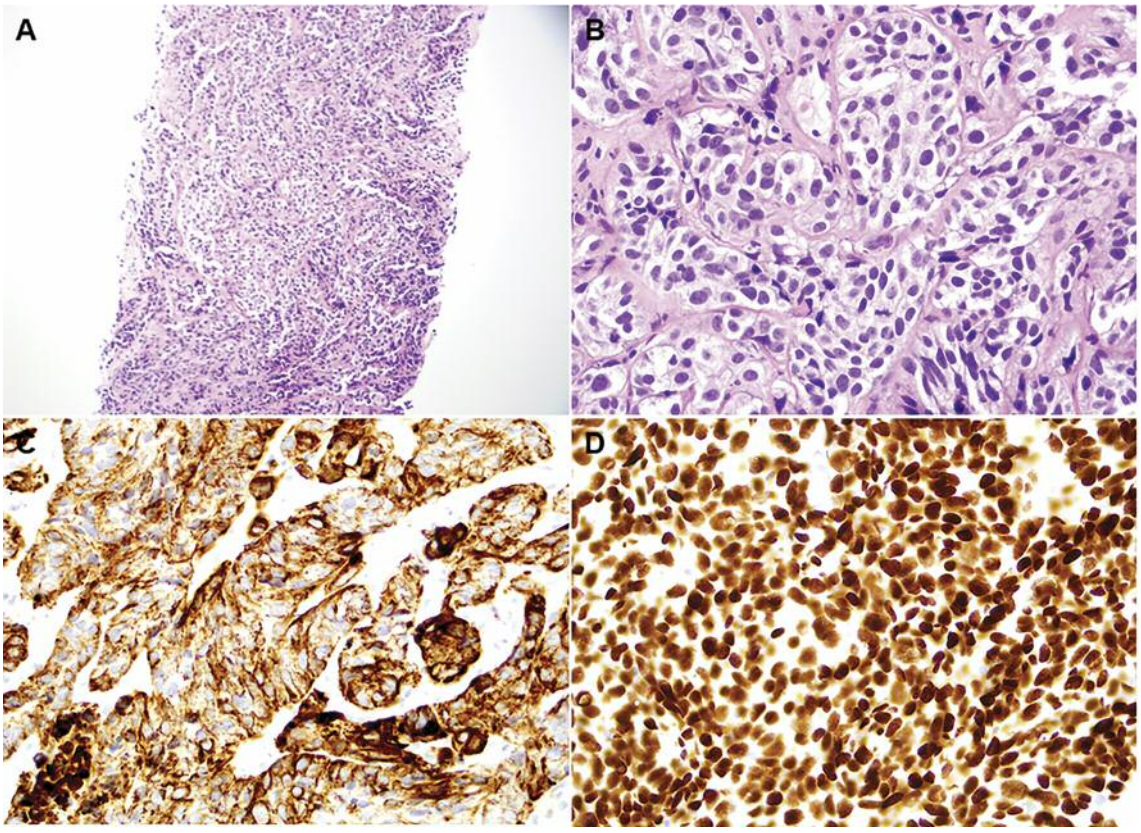

Figure 2. *Histochemical analysis and immunohistochemistry of the lung mass biopsy (September 2018). (A-B) Epithelial neoplasm with nested and trabecular growth pattern. (A) H&E satin, 40×; (B) H&E satin, 200×; (C-D) Immunohistochemistry showing that the tumor cells are positive for CK7 (C) and p40 (D) (C and D, 400×).*

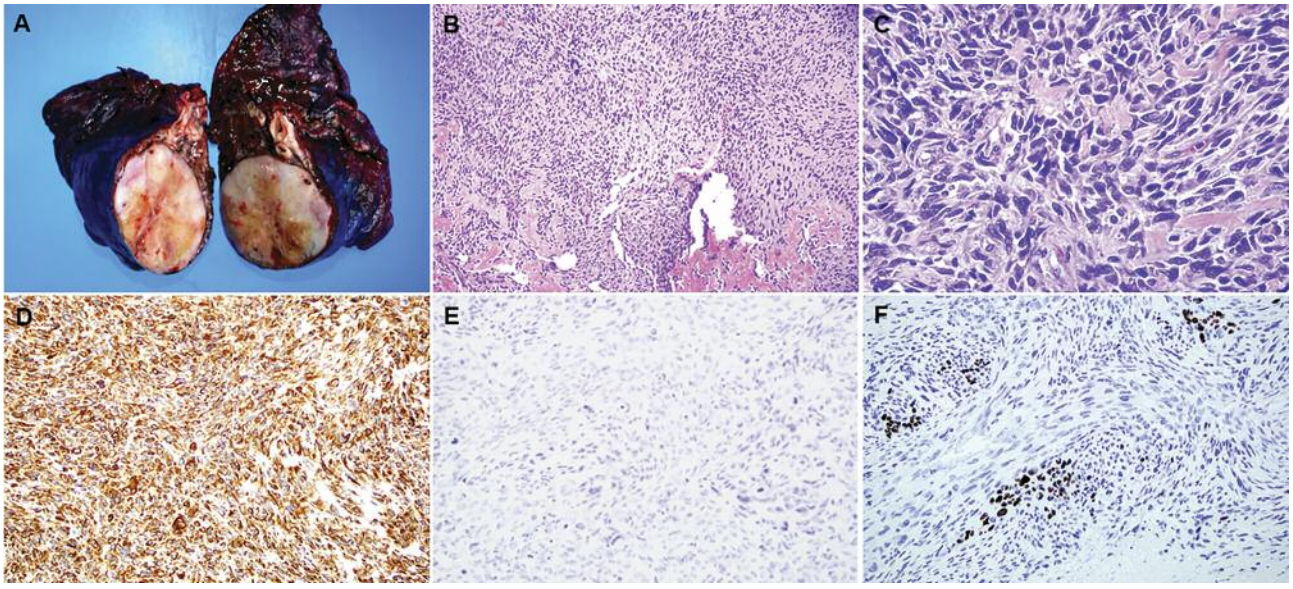

Figure 3. *Gross photograph, histochemical analysis, and immunohistochemistry of the lobectomy specimen (October 2019). (A) Gross Photograph showing large well-circumscribed tumor with homogeneous cutting surface. The tumor grossly involves pleura; (B-C) pleomorphic spindle cell neoplasm. (B) H&E stain, 100×, (C) H&E satin, 400×; (D-F) Immunohistochemistry showing that the spindle cells are positive for vimentin (D), and negative for CK7 (E) and p40 (F). Notably the rare foci of epithelial component are focally positive for p40 (F) (D-F, 200×).*

one-year SBRT, the lobectomy specimen consisted of predominantly spindle cell component with high number of mitotic figures, marked pleomorphism, and areas of necrosis. Immunohistochemical studies demonstrated that the spindle component was negative for CK7 and p40, both of which were strongly positive in the prior tumor biopsy. Small foci of epithelial component were noted, which had partially retained the morphologic and histochemical features of the original squamous cell carcinoma.

It is known that radiation can act as a mutagen that induces genetic alterations such as cytogenetic rearrangements, mutations, gene deletion and amplification. These genetic alterations could lead to unregulated growth, altered cell function, or apoptosis (7, 8). Allan *et al*. have proposed that radiation-associated tumorigenesis is likely caused by the failure of DNA repair mechanisms and apoptotic machinery (7). In fact, the number of microsatellite alterations, loss of heterozygosity and genetic instability occur more frequently in cancers that developed after radiation exposure (9). Our report suggests that sarcomatoid transformation is another potential complication of prolonged radiotherapy in patients with pulmonary squamous cell carcinoma.

Sarcomatoid transformation is a known phenomenon that occurs most commonly in head and neck cancers post radiation therapy (10, 11). A commonly accepted explanation is that this biphasic tumor likely arises from either a single tumor progenitor cell, which undergoes EMT, or alternatively from two different populations of tumor stem cells. EMT can be induced by various growth factors and signaling pathways. Activation of Src oncogene and downregulation of E-cadherin may play important roles in the sarcomatoid transformation of head and neck squamous cell carcinoma, which is associated with aggressive clinicopathologic features (11). Multiple oncogenes and tumor suppressors, including *FGFR1, PIK3CA, DDR2, MET, SOX2, PTEN, TP53* and *CDKN2A*, are implicated in the development of squamous cell carcinomas of the lung (12). It would be of interest to understand whether deregulation of these tumor genes could also lead to sarcomatoid transformation upon exposure to ionizing radiation.

Notably, sarcomatoid transformation can also lead to drug resistance (5). The transformed lung cancer becomes more aggressive, with significantly increased mitotic activity, cytological pleomorphism, tumor necrosis, as well as lymphovascular, perineural and pleural invasion. The prognosis is usually quite dismal. In the reported 6 cases of lung adenocarcinoma with sarcomatoid transformation after treatment, the median survival time from the diagnosis of sarcomatoid transformation was about 2.5 months (6).

In summary, we reported a case of rapid sarcomatoid transformation of pulmonary squamous cell carcinoma one-year after neoadjuvant therapy. The major histopathological alterations included a pleomorphic spindle cell morphology, frequent mitosis, tumor necrosis, and lost p40 and CK7 staining. This case report highlights an unrecognized complication among patients with lung cancer undergoing chemoradiotherapy.

Conflicts of Interest

The Authors declare that there are no conflicts of interest.

Authors' Contributions

JA and FY performed the histological examination, researched the literature, and wrote the manuscript. MS researched the literature and edited the manuscript. All Authors read and approved the final manuscript.

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