Histologic Transformation in a Patient with Lung Cancer Treated with Chemotherapy and Pembrolizumab

To the Editor:

We report a patient with NSCLC with histologic evolution from adenocarcinoma to adenocarcinoma with sarcomatoid changes, squamous cell carcinoma with sarcomatoid changes, and squamous cell carcinoma after chemotherapy and immunotherapy.

A 69-year-old man who had never smoked presented with a dry cough in April 2012. Chest computed tomography showed a 7.2-cm right upper lobe (RUL) tumor with bilateral mediastinal and supraclavicular lymphadenopathy. A biopsy demonstrated adenocarcinoma harboring neither *EGFR* mutations nor anaplastic lymphoma receptor tyrosine kinase gene (*ALK*) translocation. He received palliative radiotherapy of 5000 cGy for dyspnea and six cycles of pemetrexed plus platinum. The RUL tumor became smaller; however, the patient was lost follow-up.

In June 2015, he presented again with progressive left shoulder and arm swelling. Chest computed tomography revealed that the RUL tumor was 2.5 cm in size, with new metastatic lesions on the left chest wall and axillary lymph nodes and left pleural effusion. A pathologic examination of the chest wall tumor revealed adenocarcinoma with sarcomatoid changes (positive staining for thyroid transcription factor 1, cytokeratin 7 [CK7], and vimentin). He received single-agent chemotherapy, including docetaxel and oral vinorelbine, and palliative radiotherapy of 3000 cGy for the chest wall tumor. However, the disease still progressed.

The patient then received pembrolizumab, 2 mg/kg every 3 weeks from October 2015, and the chest wall tumors and left axillary lymph nodes became smaller (Fig. 1*A* and *B*). Massive bilateral pleural effusion subsequently developed; it decreased gradually after oral steroid therapy (Fig. 1*C*). The results of cytologic examination of the pleural effusion were negative for malignancy. The patient discontinued pembrolizumab after four cycles of treatment at his request. His disease status remained as a partial response for 6 months, until one subcutaneous nodule was found in his left chest wall. An excisional biopsy showed squamous cell carcinoma with sarcomatoid changes (immunoreactive to CK7, P40, and focal vimentin). The results of testing for expression of programmed death-ligand 1 (PD-L1) were positive in the three tumor specimens (Fig. 2*A*–*C*). The patient has been kept under observation without cancer treatment since January 2016. A new subcutaneous nodule over the left axillary region was noted in October 2016. Another excisional biopsy was performed, and the pathologic examination revealed squamous cell carcinoma (immunoreactive to CK7 and P40) with no PD-L1 expression. A recurrent palpable subcutaneous nodule over the left axillary area was noted again 2 months after operation. The patient refused further tissue biopsy, and pembrolizumab therapy was restarted in December 2016.

Histologic transformation has been reported in patients with lung cancer who are receiving EGFR tyrosine kinase inhibitors (TKIs).[1–3] Small cell carcinoma evolution from lung adenocarcinoma is one of the mechanisms for resistance to EGFR TKIs, reportedly accounting for 14% of such cases.[1] Recent case reports have also shown that squamous cell carcinoma transformation is a possible mechanism of resistance to EGFR TKIs.[2,3] However, little is known

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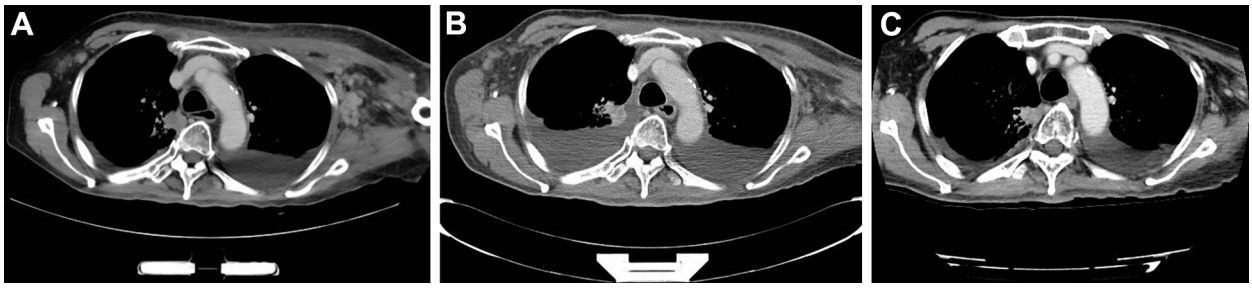

Figure 1. Chest computed tomography. Before pembrolizumab treatment (*A*), after pembrolizumab treatment (*B*), and after steroid therapy (*C*).

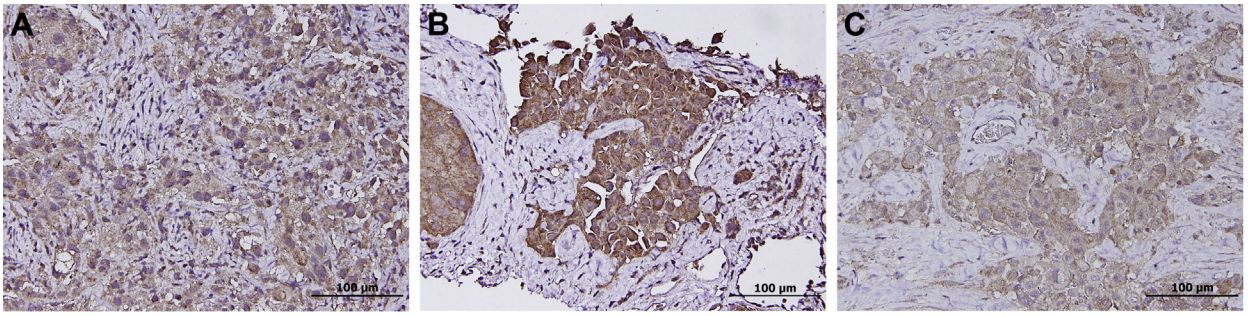

Figure 2. Positive programmed death ligand 1 staining. (*A*) Prechemotherapy biopsy sample. (*B*) Postchemotherapy biopsy sample. (*C*) Postimmunotherapy excisional biopsy sample.

about the histologic evolution after treatment other than with EGFR TKIs, such as chemotherapy or immunotherapy. In this letter, we present a case of lung adenocarcinoma with histologic transformation after chemotherapy and immunotherapy.

Our case demonstrates histologic evolution from adenocarcinoma to adenocarcinoma with sarcomatoid changes, squamous cell carcinoma with sarcomatoid changes, and squamous cell carcinoma after chemotherapy and immunotherapy. In patients with histologic changes after EGFR TKI therapy, the original *EGFR* mutation remains after histologic transformation.[1–3] In our patient, we found that the expression of PD-L1 persisted during initial histologic transformation after chemotherapy and immunotherapy but the PD-L1 expression disappeared subsequently after discontinuation of anti–programmed cell death 1 therapy. To the best of our knowledge, ours is the first report to demonstrate this phenomenon.

Possible mechanisms for histologic transformation have been suggested, including pluripotent cancer stem cell differentiation and intratumor heterogeneity.[4,5] Although the initial biopsy showed pure adenocarcinoma in our patient, a mixed type of tumor cannot be excluded owing to a limited amount of specimen obtained.

In our case, repeated biopsies demonstrated histologic transformation with dynamic PD-L1 expression after chemotherapy and pembrolizumab therapy. This finding showed the importance of repeated biopsies in progressive disease, which may provide useful information when selecting combinations of drugs.

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