CASE REPORT

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Co-occurring *KEAP1* and *TP53* mutations in lung squamous cell carcinoma induced primary resistance to thoracic radiotherapy: A case report

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Abstract

In lung squamous cell carcinoma, KEAP1 mutations frequently coexist with TP53 mutations. A preclinical model showed that mutations leading to the activation of the *KEAP1–NRF2* pathway contribute to clinical radioresistance. However, there have been few clinical reports on the association between the presence of *KEAP1* and *TP53* mutations in patients with lung squamous cell carcinoma. Here, we report the case of a 62-year-old patient with advanced lung squamous cell carcinoma with *KEAP1* and *TP53* mutations who experienced primary resistance to thoracic radiotherapy. She was administered pembrolizumab in combination with cytotoxic agents as the first-line treatment and the best response was a partial response. However, the mediastinal lymph node metastases regrew 11 months after the chemotherapy. Thus, she received thoracic radiation therapy for localized lesions. However, the lesions within the radiation field had apparently progressed. Although she received subsequent chemotherapy, the lesion rapidly progressed. Treatment strategies including radiotherapy based on genetic stratification, such as *KEAP1* and *TP53* mutation status, should be implemented for lung squamous cell carcinoma.

KEYWORDS
KEAP, lung squamous cell carcinoma, next-generation sequencing, thoracic radiotherapy, TP53

INTRODUCTION

KEAP1, a negative regulator of *NFE2L2* (hereafter *NRF2*), is mutated in 20–30% of lung cancers.[1,2] *KEAP1* mutations have been detected along with *TP53*, *KRAS*, and *STK 11* in lung adenocarcinoma.[3] In lung squamous cell carcinoma, *KEAP1* mutations frequently coexist with *TP53* mutations. The *KEAP1/NRF2* axis has been recognized as a central cornerstone for the cross-talk between cellular defense and survival pathways, and is an important step in the initiation and progression of many chronic diseases, including cancer. Additionally, a preclinical model showed that mutations leading to the activation of the *KEAP1–NRF2* pathway contribute to clinical radioresistance.[4] However, there have been few clinical reports on the association between the presence of *KEAP1* and *TP53* mutations in patients with lung squamous cell carcinoma. Here, we report the case of a patient with advanced lung squamous cell carcinoma with *KEAP1* and *TP53* mutations who experienced primary resistance to thoracic radiotherapy.

CASE REPORT

The patient was a 62-year-old woman with a history of 24 pack-years of smoking and clinical stage T3N2M1c stage IV lung squamous cell carcinoma, presenting with chest wall and bone metastases. The tumor proportion score for programmed death ligand 1 expression was 1% (22C3 assay). She was administered pembrolizumab in combination with carboplatin and nab-paclitaxel as the first-line treatment. The mediastinal lymph node metastases (#2R and #4R) had

FIGURE 1 Computed tomography findings of the right supraclavicular lymph node (#1R) and mediastinal lymph node (#4R) metastases (a) before initiation of radiation therapy, (b) 3 months after radiation therapy, and (c) 9 months after radiation therapy
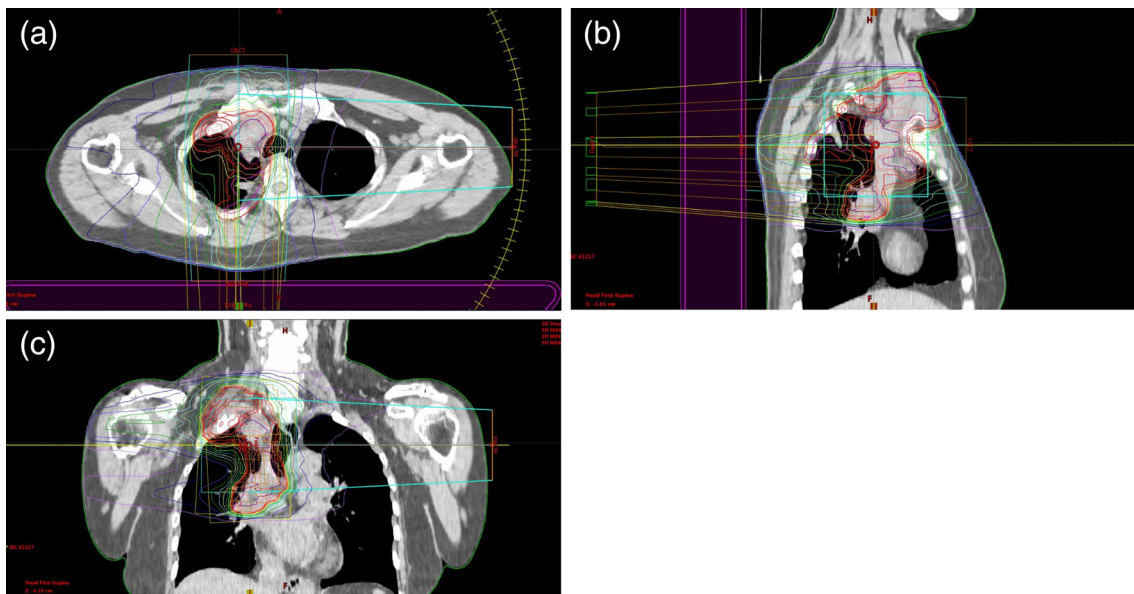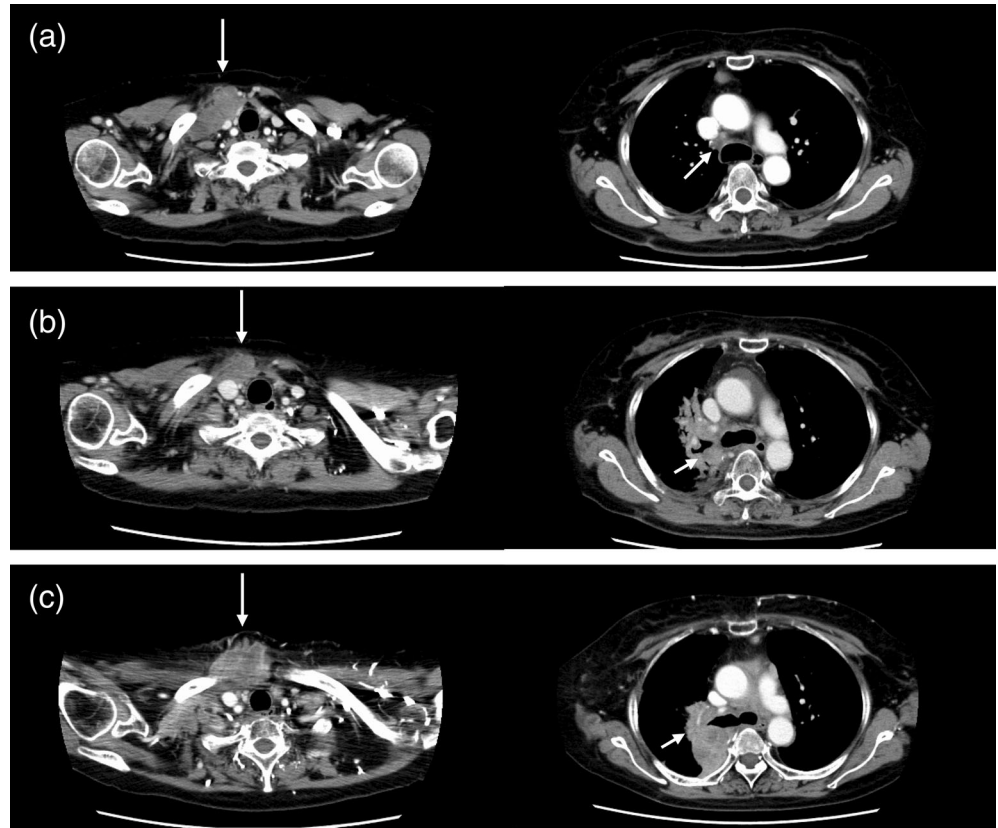

FIGURE 2 Radiation treatment plan. Dose distribution of a volumetric modulated arc therapy plan in an axial (a), sagittal (b), and coronary (c) scan images

shrunk, and the best response was a partial response. However, these lymph node metastases regrew, and a new right supraclavicular lymph node metastasis (#1R) developed 11 months after the initiation of first-line treatment (Figure 1a). Since these were localized disease, she suspended the systemic therapy and initiated thoracic radiation

therapy for localized lesions (volumetric modulated therapy: 60 Gray/30 Fractions [Figure 2]). However, computed tomography (CT) performed 3 months after radiation showed that the lesions within the radiation field had apparently progressed (Figure 1b). Next-generation sequencing (OncoGuideTM NCC Oncopanel System[5]) using the tissue

obtained from mediastinal lymph node (#2R) metastasis before the initiation of radiotherapy revealed a *KEAP1* Y525C mutation, estimated as a loss-of-function mutation, wild-type *NRF2*, and a *TP53* R306* (c. 916C>T) mutation, a truncating mutation. She received subsequent chemotherapy (docetaxel as second-line therapy and S-1 as third-line), but the lesions inside and outside the radiation field (multiple lung metastases and pleural dissemination) rapidly progressed (Figure 1C), and a thrombus in the superior vena cava was observed. Owing to the worsening of her general condition, she died 2 years after the initial treatment.

DISCUSSION

This patient showed primary resistance to thoracic radiotherapy in lung squamous cell carcinoma with *KEAP1* and truncating *TP53* mutations.

The *KEAP1-NRF2* pathway protects cells from oxidative and toxic stresses. In response to oxidative stress, *NRF2* is released from *KEAP1*, translocates into the nucleus, and promotes the transcription of genes involved in defense against reactive oxygen species.[6] Jeong et al. reported that constitutive *NRF2* activation and reactive oxygen species suppression by *KEAP1* deletion promoted tumor aggressiveness, metastasis, and resistance to oxidative stress and radiotherapy in a preclinical model.[4] Additionally, Binkley et al. retrospectively evaluated 232 patients with localized non-small-cell lung cancer (NSCLC) and found that *KEAP1* and *NRF2* mutations were significantly associated with local recurrence within the radiation field after radiotherapy.[7] The presence of loss-of-function or gain-of-function mutations for *KEAP1* and *NRF2*, respectively, affects the clinical outcome of radiotherapy in patients with NSCLC.

TP53 is the most commonly altered gene in cancer, and mutations confer cell growth and survival advantages through a combination of loss of tumor suppressor functions and gain of oncogenic activity. The p53 pathway also plays an important role in radiation-induced DNA repair and the cell cycle.[8,9] Defective p53 has been associated in vitro with radioresistance in various cell lines.[10–12] TP53 mutations have been associated with clinical radioresistance in patients with solid tumors such as endometrial cancer and head and neck cancer.[13,14] Additionally, *TP53* is mutated in over 80% of human lung squamous cell carcinomas harboring *KEAP1* mutations.[1] Saleh et al. showed that *KEAP1* mutations co-occurring with truncating *TP53* mutations were negative prognostic factors in a retrospective cohort study including 1518 patients with localized NSCLC.[15] Furthermore, advanced NSCLC patients with *KEAP1*-mutations with wild-type or truncating *TP53* mutations in advanced-stage tumors had shorter overall survival than those with *KEAP1* mutations co-occurring *with TP53* missense mutations. Indeed, this patient with co-occurring mutations in *TP53* and *KEAP1* achieved a response to initial chemotherapy in combination with an immune checkpoint inhibitor, but progressed rapidly and experienced primary resistance to thoracic radiotherapy. Further investigation on how the co-occurrence of *KEAP1* and *TP53* leads to primary resistance to radiotherapy in NSCLC, especially in lung squamous cell carcinoma, and the development of treatment strategy to overcome the resistance is needed.

In conclusion, we presented a case of primary resistance to radiotherapy in lung squamous cell carcinoma harboring *KEAP1* and *TP53* mutations. Treatment strategies, including radiotherapy based on genetic stratification, such as *KEAP1* and *TP53* mutation status, should be implemented for NSCLC, especially lung squamous cell carcinoma.

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