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Case report

Small cell lung cancer transformation during immunotherapy with nivolumab: A case report

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ABSTRACT

We report a rare case of transformation of non-small cell lung cancer (NSCLC) to small cell lung cancer (SCLC), without epidermal growth factor receptor (EGFR) gene mutation, during immunotherapy treatment with nivolumab. A 75-year-old man was referred to our hospital following the observation of a 64 mm mass in a chest computed tomography (CT) scan. A transbronchial biopsy of the mass identified the pathological presence of poorly differentiated NSCLC, with no histological signs of SCLC. No mutations were identified in the EGFR gene. A clinical diagnosis of NSCLC (cT3N3M1a, stage IV) was made following a positron emission tomography (PET)–CT scan and enhanced brain magnetic resonance imaging. Docetaxel and bevacizumab were selected as the first-line chemotherapy regimen; however, after two cycles, the patient developed a gastrointestinal perforation, and discontinuation of cytotoxic chemotherapy was recommended. Owing to gradual disease progression, immunotherapy with nivolumab was selected as the second-line regimen. During the immunotherapy, the tumor continued to progress and some subcutaneous tumors emerged. Biopsy of a subcutaneous tumor revealed SCLC, with positive immunostaining for cluster of differentiation 56, synaptophysin, and thyroid transcription factor-1. Serum tumor markers of SCLC were also elevated. Based on these results, we concluded that in this case NSCLC had transformed to SCLC during immunotherapy with nivolumab.

1. Introduction

The immune checkpoint inhibitor nivolumab, an anti-programmed death-1 (PD-1) antibody, causes inhibition of the PD-1/programmed death ligand-1 (PD-L1) pathway. In phase III trials, treatment with nivolumab for both advanced squamous cell lung cancer and non-squamous non-small cell lung cancer (NSCLC), improved the overall survival of patients compared to treatment with docetaxel [1,2]. In December 2015, nivolumab was approved for use in the treatment for patients with advanced or recurrent NSCLC in Japan. Nivolumab is now widely used for NSCLC, but its potential effects are not fully known.

During the treatment of lung cancer, the development of resistance to chemotherapy is inevitable.

Adenocarcinomas with an epidermal growth factor receptor (EGFR) mutation are often treated with EGFR-tyrosine kinase inhibitors (TKIs), as these drugs are most effective for this type of NSCLC. Resistance to EGFR-TKIs frequently occurs within 1–2 years of treatment [3,4], due to the development of a secondary mutation in the EGFR gene (e.g. T790M mutation) in approximately 50–60% of cases [5,6]. Tumor transformation to small cell lung cancer (SCLC) is another treatment resistance mechanism, and occurs in 3–14% of cases [5–7]. As EGFR-TKIs are most commonly used for the treatment of EGFR-mutant adenocarcinoma, most of the reported transformation cases are of adenocarcinoma with EGFR mutation. There are a few cases of transformation from adenocarcinoma with wild-type EGFR, but these cases are seldom reported [8]. To the best of our best knowledge, SCLC transformation during immunotherapy treatment of NSCLC with nivolumab has not previously

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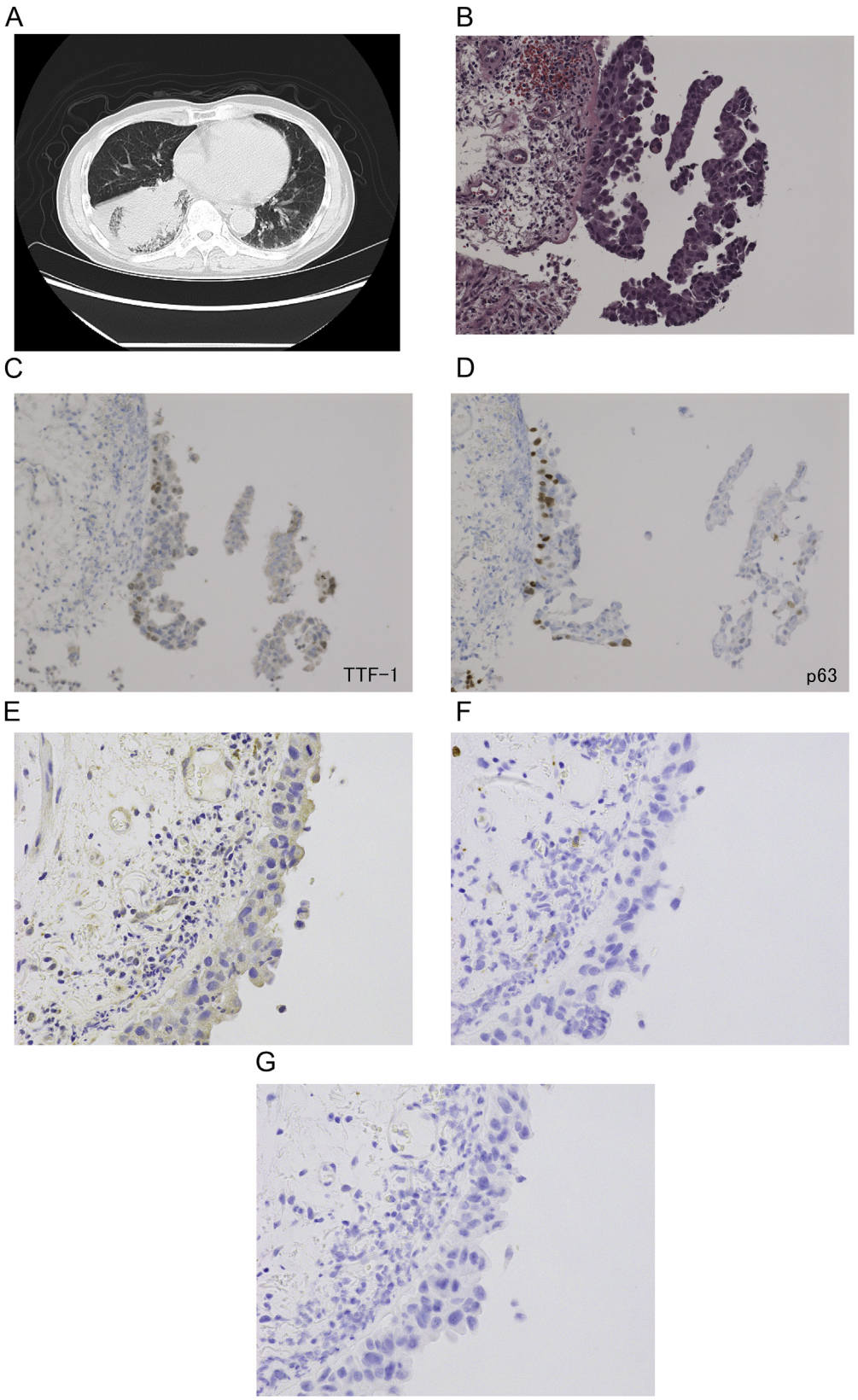

Fig. 1. A: Computed tomography scan shows a mass in the lower lobe of the right lung, accompanied by small subpleural nodules and right pleural effusion. Fig. 1B–D: Initial biopsy specimens showing malignant cells with anisokaryosis and hyper chromatic nuclei (B, hematoxylin and eosin [H&E] staining × 200). Immunohistopathological analysis demonstrated weakly positive staining for thyroid transcription factor 1 (TTF-1) (C, × 200) and p63 (D, × 200), which suggested non-small cell lung cancer with unclear differentiation. Fig. 1E–G: Immunohistopathological analysis demonstrated negative staining for neuron specific enolase (NSE) (E, × 400), CD56 (F, × 400) and synaptophysin (G, × 400).