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Case Report

CASE REPORT

Histological conversion from adenocarcinoma to small cell carcinoma of the lung after treatment with an immune checkpoint inhibitor: a case report

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Abstract

The transformation of adenocarcinoma to small cell lung cancer has been reported as acquisition of resistance to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors. We here report a patient who presented histologically confirmed transformation of adenocarcinoma to small cell lung cancer after treatment with immune checkpoint inhibitor. A 65-year-old man was treated with pembrolizumab as first-line therapy and achieved temporarily a stable disease with progression after six cycles of this agent. At that stage, a transbronchial biopsy showed small cell lung cancer, and he was found to have high serum concentrations of neuron-specific enolase despite concentrations of numerous tumor markers, including neuron-specific enolase, having been within normal limits at the time of presentation. The patient thereafter was treated as a small cell carcinoma patient using cisplatin plus irinotecan and amrubicin.

INTRODUCTION

Histologically confirmed transformation of adenocarcinoma to small cell lung cancer (SCLC) has been reported after treatment with immune checkpoint inhibitors as a component of first-line therapy or as sole agents in second- or later-line therapy [1–3]. Such transformation has been accompanied by acquisition of resistance to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors [4].

We report a case of a patient who presented histological transformation after the first-line monotherapy with an immune checkpoint inhibitor.

CASE REPORT

A 65-year-old man with smoking history of 34 pack-years was admitted to our hospital with chest X-ray abnormalities (Fig. 1A). Computed tomography (CT) revealed a mass in the right upper lobe. CT-guided biopsy of the lung was performed. Histologically, the tumor cells grow invasively, forming irregular glandular structures, positive for thyroid transcription factor-1 (TTF-1), cytokeratin 7 and synaptophysin, resulting in a diagnosis of adenocarcinoma (Fig. 1B). CT, ^{18}F-fluorodeoxyglucose positron emission tomography CT and magnetic resonance imaging revealed the right hilar lymph node metastasis and left adrenal

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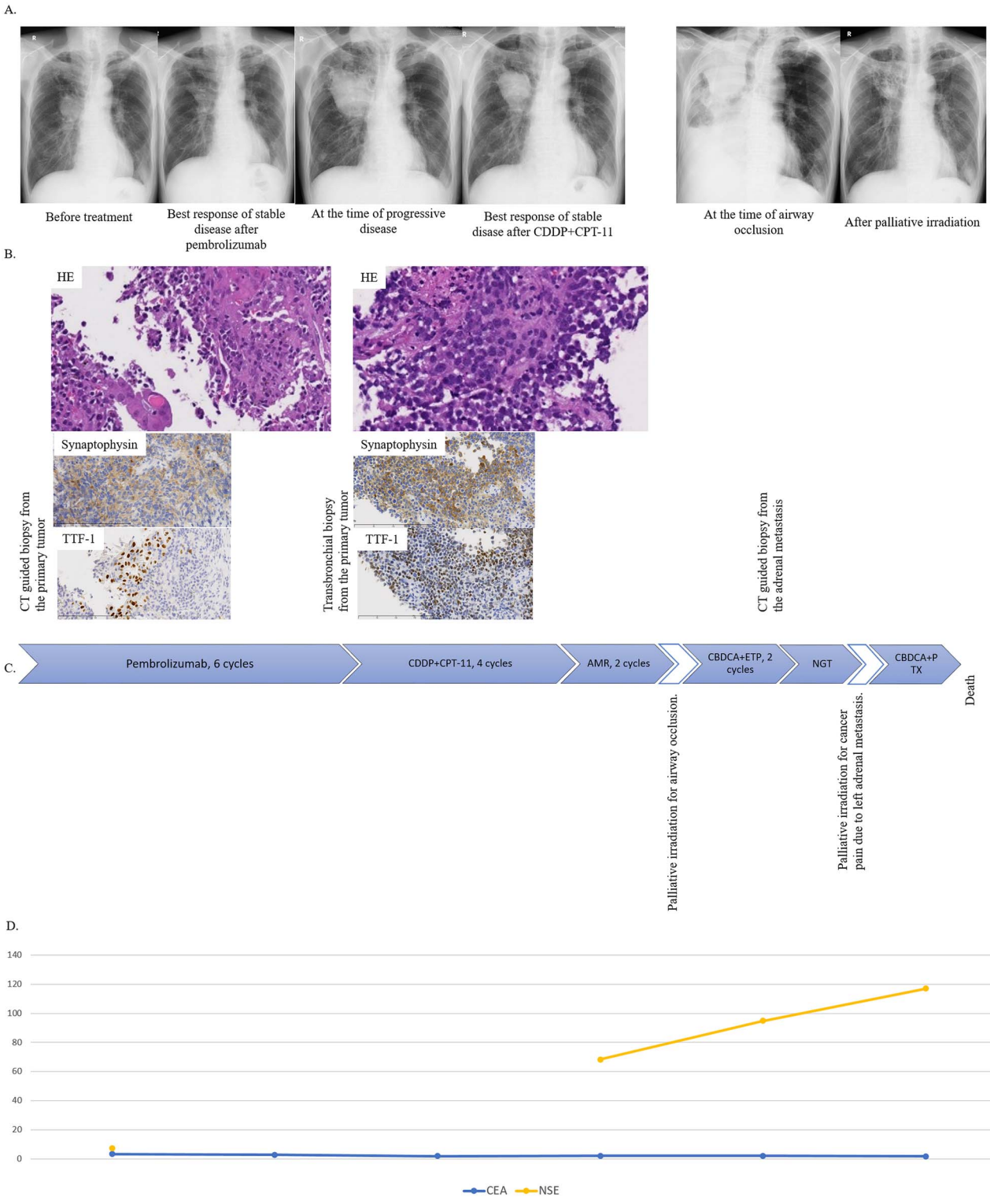

Figure 1: (**A**) Chest X-ray films in time sequence. (**B**) Photomicrographs of hematoxylin and eosin (HE)-stained sections and sections stained for thyroid transcription factor-1 (TTF-1) and synaptophysin in the primary tumor resulted in diagnosis of adenocarcinoma at the time of initial presentation (left) and of small cell carcinoma after six courses of pembrolizumab (right). All the photomicrographs are shown at 40x magnification. (**C**) Treatment course of the patient. AMR, amrubicin; CBDCA, carboplatin; CDDP, cisplatin; CPT-11, irinotecan; ETP, etoposide; NGT, nogitecan; PTX, paclitaxel. (**D**) Changes in tumor marker concentrations over time. CEA, carcinoembryonic antigen; NSE, neuron-specific enolase.

metastasis; the clinical stage was T3N1M1b (ADR), Stage IVB. Serum concentrations of relevant tumor markers were within normal limits. The tumor was negative for both EGFR mutation and EML4-ALK gene translocation and strongly positive for programmed death-ligand 1 (PD-L1). The patient was therefore treated with pembrolizumab as first-line therapy (Fig. 1C). The best response was stable disease (SD); the primary tumor progressed after six cycles of pembrolizumab.

At this stage, a transbronchial biopsy was performed. Small tumor cells with high nuclear-cytoplasmic ratio proliferate in sheet pattern and revealed the primary tumor was small cell lung cancer (Fig. 1B). NSE concentration was high at 68.3 ng/ml (Fig. 1D). Regimens for SCLC, including four cycles of cisplatin plus irinotecan (best response SD) and two cycles of amrubicin, were administered (Fig. 1C). Immediately prior to the third course of amrubicin, he became febrile and developed severe acute respiratory failure because of occlusive pneumonia associated with the primary tumor. Palliative irradiation achieved rapid shrinkage of the tumor and prompt resolution of his respiratory condition (Fig. 1A). Systemic therapy was then begun. However, progressive disease with increasing adrenal metastases was diagnosed. A CT-guided biopsy of the adrenal revealed SCLC. During the course, no brain metastases were detected. The patient died 17 months after SCLC transformation. During disease progression, NSE increased, whereas CEA remained normal (Fig. 1D).

DISCUSSION

SCLC is morphologically defined as carcinoma with cells that have a small size, an irregular round shape, scant cytoplasm, finely granular nuclear chromatin and absent or inconspicuous nucleoli, while adenocarcinoma is defined as carcinoma with an acinar/tubular structure or mucin production [5, 6]. Though immunohistochemistry is important for differential diagnosis, TTF-1, one of the adenocarcinoma markers, is present in 70–90% of SCLCs, while up to two-thirds of SCLC is negative for synaptophysin. So, the morphology of the tumor with hematoxylin and eosin stain is important [5].

Several studies have reported histologically documented transformation of adenocarcinoma to SCLC with acquisition of resistance to EGFR-tyrosine kinase inhibitors [4]. Four cases of histological transformation during treatment with immune checkpoint inhibitors (ICIs) have been reported. In three of these, this transformation occurred when ICIs were being used as a single agent during second- or later-line therapy [1–3]. In the remaining case, ICI was used as first-line therapy in combination with cytotoxic agents [2]. Therefore, this is the first report of transformation from adenocarcinoma to SCLC possibly mediated by resistance to first-line ICI monotherapy.

There are several possible biological explanations for SCLC transformation, including intratumoral heterogeneity, RB1 inactivation occurring due to treatment of adenocarcinoma and type II alveolar cells having the potential to develop into both SCLC and adenocarcinoma [7]. The current patient had a high NSE concentration at the time of diagnosis of SCLC and a marked response to irradiation and responded to a degree to cisplatin plus irinotecan, all of which is consistent with SCLC. Because only a biopsy was examined histologically and not the whole tumor, it is very possible that the described clinical course was attributable to heterogeneity of the tumor; however, the fact that SCLC was diagnosed in both the primary lung tumor and adrenal metastasis supports the possibility of 'transformation' in our patient.

In conclusion, this is the first report of SCLC transformation after treatment with pembrolizumab as first-line therapy. SCLC transformation after ICIs should be considered. Thus, repeat biopsy may be useful in determining the optimal treatment strategy following ICIs.

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CONFLICT OF INTEREST STATEMENT

None.

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None.

ETHICAL APPROVAL

Our institutional review board waived the requirement of ethical approval for this case report.

CONSENT

Comprehensive, written informed consent was obtained from the patient for the publication of this case report.

GUARANTOR

N.M. is the guarantor.

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