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Tracheal small cell carcinoma with RB1 Splice site mutation treated by chemoradiotherapy: A case report

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Introduction

Primary tracheal carcinomas are rare, with a reported incidence of 0.19% among 2004 patients with respiratory tract malignancies (Ampil, 1986). The major pathological types of tracheal carcinomas are squamous cell carcinoma (44.8%) and adenocystic carcinoma (16.3%) (Urdaneta et al., 2011). By contrast, primary tracheal small cell carcinoma (TSCC) accounts for only 4% of primary tracheal malignancies (Qiu et al., 2015). The prognosis of TSCC is worse than that of other tracheal malignancies (Chen et al., 2020), but the specific genomic alterations in TSCC have yet to be identified. The molecular hallmarks of small cell lung carcinoma (SCLC) include inactivating genomic alterations in the retinoblastoma susceptibility gene (RB1), which encodes the tumor suppressor Rb. Using immunohistochemistry (IHC), Mahadevan examined the expression of Rb as well as the RB1 mutation status (Mahadevan and Sholl, 2022) in patients with SCLC and identified an association between the patchy expression of Rb and a splice site mutation in RB1, a rare pattern (Mahadevan and Sholl, 2022). However, whether Rb expression affects the oncogenic status and clinical prognosis of TSCC similarly to SCLC is unknown. Here, we present the first reported case of TSCC with splice site mutation in RB1 in a patient treated with concurrent chemoradiotherapy.

Case and methods

A 55-year-old man was admitted to our hospital for bloody sputum and upper abdominal pain of 9 months duration. He had a significant history of tobacco use (33 pack-years). Laboratory tests showed a high neuron-specific enolase level of 23.9 ng/mL (reference: < 15.0 ng/mL) and a high pro-gastrin-releasing peptide level of 204.7 pg/mL (reference: < 80.9 ng/mL). His-chest X-ray showed the disappearance of the line of the right tracheal wall (Fig. 1A) and, in the lateral radiograph, a narrowing of the tracheal airway at Th2–4 (yellow arrow in Fig. 1B). Chest computed tomography (CT) revealed a tracheal tumor > 7 cm in diameter at C7–Th4 (Fig. 1C–E). A swollen lymph node was found in the right supraclavicular fossa (blue arrow in Fig. 1E). Because of the tumor's growth around the trachea but no disruption of the tracheal structure, lung cancer or a metastatic tumor was probably ruled out. In the CT scan, no tumors were found other than the thoracic region which was suspicious of cancer. The bronchoscopic image showed infiltrative changes with absent delineation of the bronchial cartilages, swelling, and an irregular bronchial mucosa (Fig. 2A). Due to the easy bleeding that occurred during bronchoscopy, the right supraclavicular lymph node was biopsied. Diffuse sheets of small, blue, round tumor cells larger than lymphocytes, indicative of small cell carcinoma, were seen on the hematoxylin- and eosin-stained biopsy sample (Fig. 3A). On IHC, the neoplastic cells were positive for synaptophysin (Fig. 3B), chromogranin, CD56, and thyroid transcription factor 1 (TTF-1). There were 87.5% Ki-67-positive cells per high-power field. Therefore, the patient was histologically and clinically diagnosed with primary TSCC of limited stage.

In accordance with the regimen for limited-stage SCLC, the patient was administered concurrent chemoradiotherapy consisting of cisplatin (130 mg/body) and etoposide (170 mg/body) with 45 Gy irradiation. Tumor reduction was confirmed by bronchoscopy (Fig. 2B). However, 6 months after chemoradiotherapy, the tracheal tumor progressed, and

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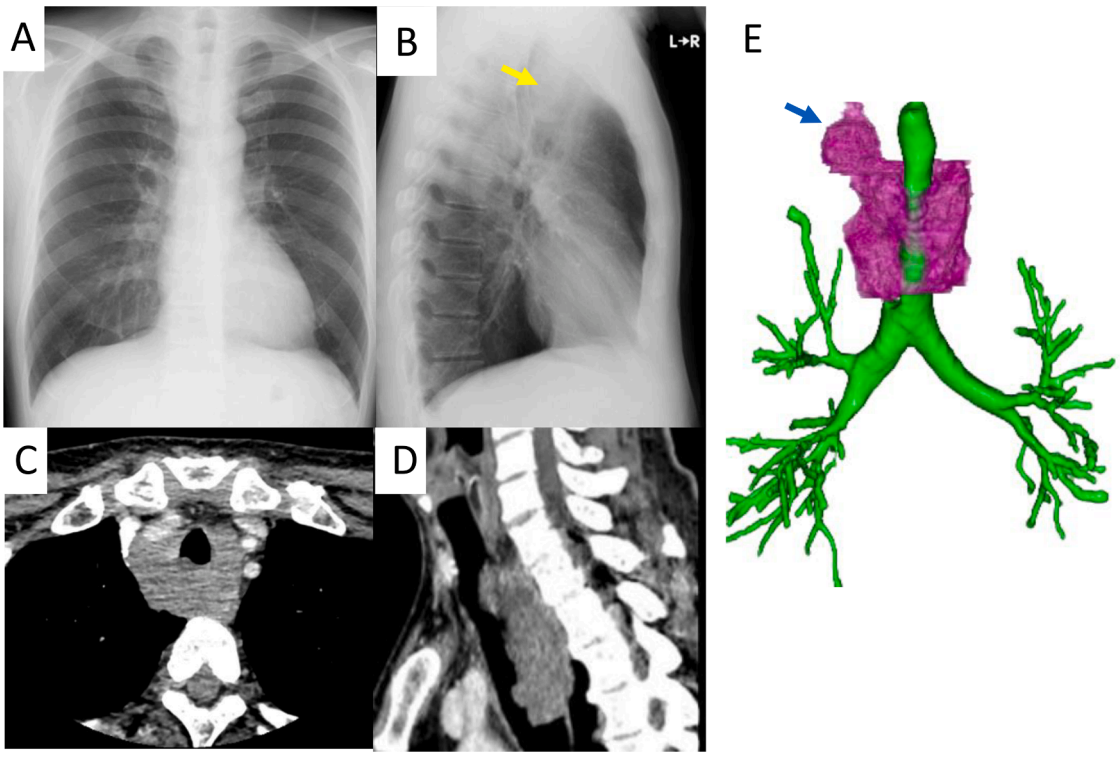

Fig. 1. Frontal (A) and lateral (B) chest X-ray. Contrast-enhanced axial (C), sagittal (D), and three-dimensional (E) computed tomography.

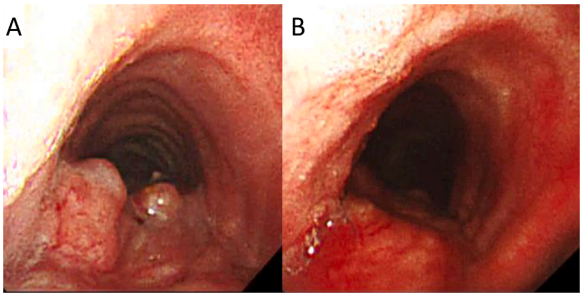

Fig. 2. A bronchoscopic image obtained before concurrent chemoradiotherapy (A). After 1 cycle of chemotherapy and irradiation with 45 Gy, airway stenosis was improved remarkably (B).

pancreatic metastasis was detected. He was therefore treated with amurubicin (65 mg/body) for 5 months but subsequently died due to a severe systemic infection associated with the progression of the pancreatic metastasis. A detailed postmortem IHC analysis of the lymph node was performed. the examinations of IHC were analyzed for conventional neuroendocrine markers synaptophysin, chromogranin A, CD56, thyroid transcription factor-1(TTF-1), Ki-67, tumor protein 53 (TP53), Rb/RB1, and cyclin D1. Rb IHC was performed using a rabbit anti-Rb protein (clone EPR17512, Abcam). Marker expression was evaluated by a semiquantitative H-scoring method. H-scores were derived by multiplying the percentage of positive tumor cells (0–100%) by staining intensity ordinal values yielding a range of possible H-scores from 0 to 300. The analysis revealed patchy Rb expression and the absence of cyclin D1 expression (Fig. 3C, D), which indicated RB1 splice site variants. Negativity for TP53 was also determined.

Discussion

To our knowledge, this is the first reported case of TSCC associated with RB1 splice site mutation in a patient administered by chemoradiotherapy.

TSCC is generally classified together with extrapulmonary neuroendocrine carcinoma (EPNEC). Previous studies showed that the frequencies of gene mutations, including TP53 and RB1, differed in EPNEC

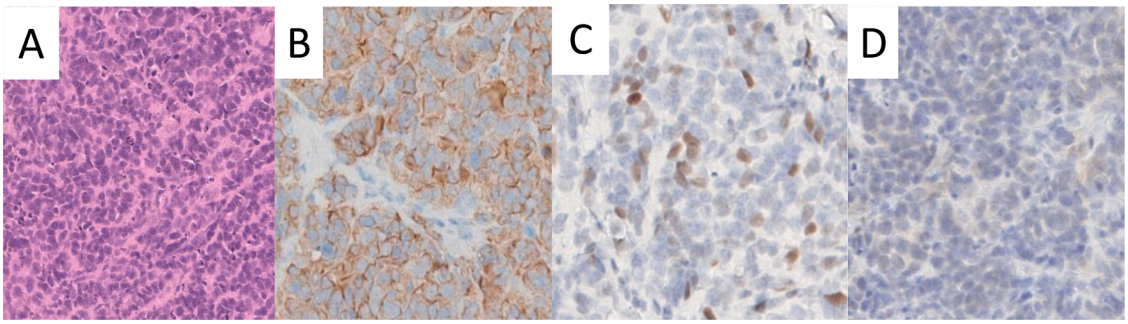

Fig. 3. Pathological images of the biopsy specimen from the right supraclavicular lymph node. H&E staining and low-power field microscopy revealed a small cell carcinoma (A). Immunohistochemical staining of synaptophysin (B), RB-1/Rb (C), and cyclin D1(D). Heterozygous positivity for Rb protein (C) and the absence of cyclin D1 expression (D) indicated the presence of the RB1 splice site mutation.

and SCLC compared with other tumors (Zheng et al., 2015). Therefore, whether TSCC and SCLC are biologically equivalent is unclear, although the clinical prognosis of TSCC is generally worse. Chen et al. (2020) reported a median survival of ~10 months in patients with TSCC and regional lymph node involvement. In our patient, survival was short due to progression of the pancreatic metastasis, despite significant tumor reduction following chemoradiotherapy, as seen on the bronchoscopic images (Fig. 2A, B). In a series of patients with limited-stage SCLC evaluated by Turrisi et al. (1999), the median survival after chemoradiotherapy was 23 months. In another study, the average survival of patients with limited-stage extrapulmonary small-cell carcinomas was 17 months (Soto et al., 2007). Therefore, the genetic features of TSCC may have a greater impact on the course of chemoradiotherapy resistance compared with those of SCLC and other EPNECs. Although little is known about the specific mutations in TSCC, several genomic rearrangements have been identified in genes involved in inactivated regulatory pathways, including SOX2, FGFR1, MYC family, TP53, and RB1, in SCLC (Rudin et al., 2012; George et al., 2015).

RB1 is a tumor suppressor gene that is mutated at variable frequencies in a variety of human cancers. Although its encoded protein, the Rb protein, is a negative regulator of cell proliferation, its actual role as a determinant of oncogenic status is still unclear (Peifer et al., 2012). The Rb protein can be investigated by IHC to indirectly determine the mutations in the RB1 gene. In patients with an Rb positive, the cyclin D1 status is evaluated as well (Febres-Aldana et al., 2022). The most frequent type of RB1 mutation is known to be RB1 loss, which was reported to be 75% of 208 SCLC cases (Febres-Aldana et al., 2022). In contrast, a splice site mutation in RB1 is rare, reported in only 5% (Febres-Aldana et al., 2022). Previous studies of the association of RB1 mutations with therapeutic efficacy in patients with SCLC showed better progression-free survival, overall survival, and sensitivity to chemotherapy in patients with a mutated RB1 gene (McColl et al., 2017; Dowlati et al., 2016; Udagawa et al., 2018). Udagawa et al. (2018) also reported an association between RB1 mutations and radiotherapy sensitivity, based on the improved progression-free survival of patients with SCLC with an RB1 mutation, although this was the case only in patients with limited-stage, not extensive-stage, SCLC.

Cyclin D1 is encoded in the gene CCND1, which is one of the upstream regulators of Rb. In addition, mutationally-inactivated Rb is invariably associated with low or absent expression of cyclin D1 with the mutual exclusivity of Rb loss and cyclin D1 upregulation (Mahadevan and Sholl, 2022). Mahadevan mentioned that the clinicopathologic and genomic features with the combination of the Rb splice pattern and the negative cyclinD1 were comparable to that of Rb-deficient SCLC (Mahadevan and Sholl, 2022). Therefore, the combination is indicated to be the unfunctional status of Rb. These may be related to the sensitivity of chemoradiotherapy in SCLC with RB1 splice site mutation as with RB1 loss.

In our patient, the histological findings in the lymph node showed that the tumor cells were Rb positive and cyclin D1 negative (Fig. 3C, D). Febres-Aldana et al. (2022) demonstrated that Rb positivity could be divided into the splice site mutation or Rb-proficient type, and that over 90% of the cases with the loss of cyclin D1 and the expression of Rb determined the presence of RB1 gene mutations (Febres-Aldana et al., 2022). Accordingly, our patient was diagnosed with TSCC with RB1 splice site mutation. The response of his tumor to chemoradiotherapy was significant (Fig. 2A, B), which may have been related to the RB1 mutation. Therefore, better sensitivity to chemoradiotherapy of TSCC with the RB1 mutation, as previously reported in SCLC, is possible.

Conclusion

This was the first reported case of a primary TSCC with RB1 splice site mutation, as identified by IHC. The presence of the mutation may, at least in part, have accounted for the good response of the tumor to chemoradiotherapy.

Patient consent statement

Informed consent has been obtained from all individuals included in this study.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

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