Case Report

Primary small-cell carcinoma of the trachea - Uncommon but aggressive

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ABSTRACT

Primary tracheal tumors are rare, and small-cell carcinoma (SCC) of the trachea is an extremely rare and aggressive cancer. Treatment guidelines for tracheal SCC are not available because it is not common. Only a few cases have been reported in the literature to date. We describe the case of a 60-year-old man with a persistent cough. Biopsy and immunohistochemistry tests showed primary tracheal SCC. On imaging, it was confirmed as localized and did not have any distant metastases. The patient received neoadjuvant chemotherapy followed by chemoradiation and maintenance chemotherapy. Even though he responded well at first, he got skeletal metastases within 6 months. Individual case reports and retrospective research contribute to existing treatment options, which include surgical resection, chemoradiation, and chemotherapy alone. Small-cell lung cancer management methods are often used to guide treatment. Care standards need to be improved with the help of more research.

Key words: Case reports, Chemoradiotherapy, Chemotherapy, Small-cell carcinoma, Tracheal neoplasms

Primary tracheal tumors are exceedingly rare, with an estimated annual incidence of 0.142 instances per 100,000 people, or 0.034% of all malignancies [1,2]. Squamous cell carcinoma is the most commonly diagnosed subtype, accounting for around 49% of cases, followed by adenoid cystic carcinoma, which accounts for 20% [3]. Primary small-cell carcinoma (SCC) of the trachea is extremely rare and might be confused with metastatic cancer originating in the lungs, such as small-cell lung carcinoma (SCLC). Due to its rarity, there is little understanding of the clinical behavior and best treatment protocol for primary tracheal SCC. Large population-based databases, such as the surveillance, epidemiology, and end Results (SEER) database, are useful tools for investigating rare entities [4].

We present a very rare case of primary SCC of the trachea.

CASE PRESENTATION

A 60-year-old man presented to our department 1 year ago, complaining of a persistent cough for 1 month. He had previously been evaluated at another hospital, which included laboratory tests, imaging, and a biopsy, and was then referred to us for further management.

The patient was alert, with stable vital signs. No pallor, icterus, lymphadenopathy, or edema was noted. Nutritional status was adequate. Routine blood and urine tests were within normal parameters. Bronchoscopy revealed a growth on the posterolateral wall, partially occluding the endotracheal lumen (Fig. 1a), and a biopsy was taken for histopathological examination.

A positron emission tomography/computed tomography (PET-CT) scan revealed 18F-fluorodeoxyglucose-avid, heterogeneously enhancing endophytic soft-tissue thickening in the trachea on the right side, at the level of the thyroid gland, abutting the right lobe at the C7-D1 vertebral level. The lesion was sized 9 mm × 22 mm × 24 mm and had an SUVmax of 4.41. No substantial cervical lymphadenopathy was observed (Fig. 1b).

The histopathological examination revealed a hypercellular tumor with relatively pleomorphic, tiny, spherical tumor cells organized in sheets. The cells are circular to oval, with hyperchromatic nuclei and a small quantity of eosinophilic to unclear cytoplasm. A few unusual mitoses and nuclear smudging were observed. The adjacent sparse stroma demonstrates minor inflammatory infiltrates with isolated regions of hemorrhage and crushing artifacts, suggesting SCC (Fig. 2a and b). Immunohistochemistry tested positive for cytokeratin, epithelial membrane antigen (few), synaptophysin, chromogranin A, and thyroid transcription factor-1, but negative for leukocyte common antigen, terminal deoxynucleotidyl transferase, CD30, desmin, Mic2, and NKX2.2. There was extensive and robust p53 expression, and the Mib-1 labeling index

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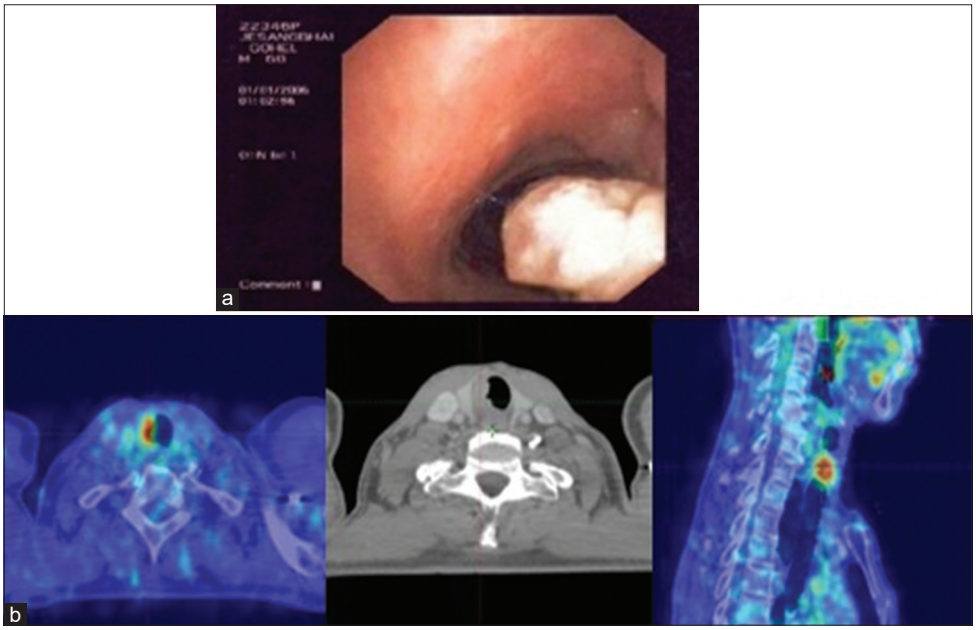

Figure 1: Bronchoscopy (a) shows growth on the posterolateral wall that partially occludes the endotracheal lumen. Positron emission tomography/computed tomography images (b) showing 18F-fluorodeoxyglucose-avid tracheal growth on the right side, abutting the right lobe of the thyroid gland at the level of C7-D1 vertebral level

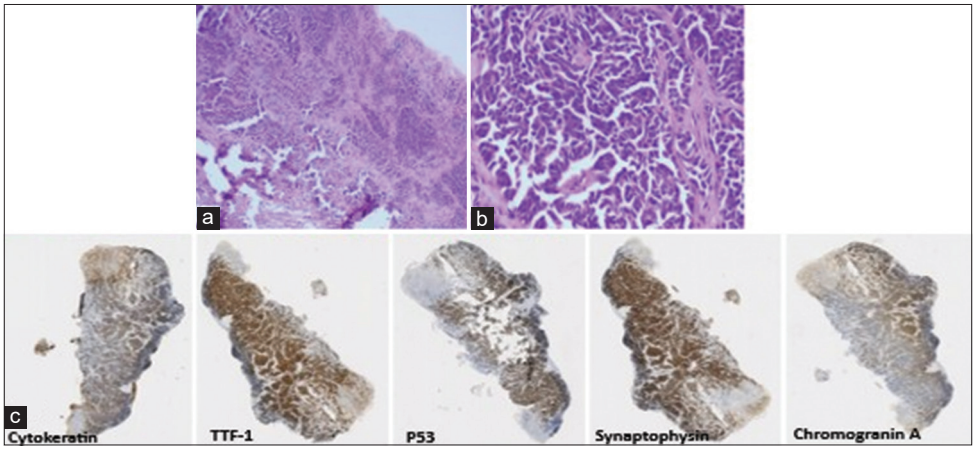

Figure 2: The sections (Hematoxylin and Eosin stain; (a ×10 and b ×40) depict a hypercellular tumor with pleomorphic, tiny, spherical tumor cells in sheets. The cells are circular to oval, with hyperchromatic nuclei and a small quantity of eosinophilic to unclear cytoplasm. Few unusual mitoses and nuclear smudging were seen. Immunohistochemistry (c) shows positivity for cytokeratin, thyroid transcription factor-1, P53, synaptophysin, and chromogranin A

was approximately 50%, confirming the diagnosis of SCC (Fig. 2c).

Following the completion of baseline tests, this case was considered in a multidisciplinary tumor board, and due to its aggressive nature and risk of early systemic spread, it was decided to start neoadjuvant chemotherapy (NACT), followed by concomitant chemoradiation and maintenance chemotherapy. The patient received the first cycle of NACT with cisplatin and etoposide, followed by concurrent chemoradiation utilizing the volumetric modulated arc therapy technique, which delivered a total dose of 60 Gy in 30 fractions (60 Gy/30#). He then received two cycles of maintenance chemotherapy, which were completed by December 2024.

After that, the patient was lost to follow-up for 3 months. He returned in March 2025, complaining of lower back pain that had persisted for several days. A repeat PET-CT scan revealed skeletal metastases in the bilateral femora, several pelvic bones, the sacrum, and several dorso-lumbar vertebrae (Fig. 3). He was then scheduled for palliative radiation to painful skeletal metastatic sites (30 Gy in 10 fractions). After the completion of palliative radiation, the patient was lost to follow-up again. The patient's death was confirmed through telephonic communication with his son.

DISCUSSION

Primary tracheal tumors are infrequent, accounting for only 0.2% of all respiratory tract cancers, while adenoid cystic carcinoma, squamous cell carcinoma, and SCC (SCC) account for around 34%, 31%, and 2% of cases, respectively [5-7]. To the best of our knowledge and English literature search, <100 cases have been reported to date (Table 1). Primary tracheal SCCs are distinct clinical entities from tracheal metastases of SCLC. Patients commonly present with symptoms such as cough, breathing difficulties, chest discomfort, hemoptysis,

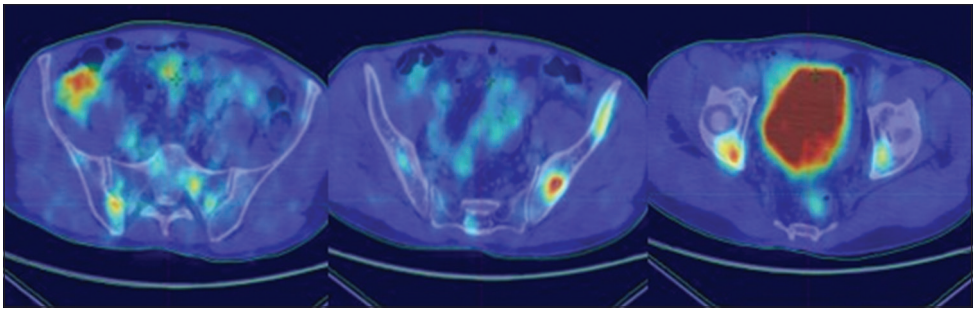

Figure 3: Positron emission tomography/computed tomography images showing 18F-fluorodeoxyglucose-avid skeletal metastases in pelvic bones

Table 1: Literature review concerning treatment and outcome

S. No.	Study	Year	No. of cases	Treatment	Outcome
1.	Qiu *et al*. [5]	2015	1	CCRT	Died
2.	Ahn *et al*. [11]	2016	1	NACT (EP) → 30 Gy/10# RT → EP	Disease free at 12 months followup
3.	Hetnał *et al*. [16]	2010	4	Surgery+RT; RT alone; CCRT; palliative	5-yr OS: Surgery+RT 66%; RT 16%; CRT/palliative 0%
4.	Chao *et al*. [19]	1998	2	Radiotherapy (RT)	Not specified
5.	Mornex *et al*. [20]	1998	2	Radiotherapy (RT)	Not specified
6.	Thotathil *et al*. [21]	2004	1	EP+50 Gy RT	Died 28 months post-treatment
7.	Lan *et al*. [22]	2010	1	Electrocautry followed by EP+60 Gy/30# RT	Disease-free at 12 months' follow-up
8.	Luo *et al*. [23]	2014	1	Concurrent CCRT (tracheal+synchronous esophagus SCC)	Disease-free at 12 months' follow-up
9.	Chen *et al*. [24]	2024	1	EP+adebrelimab (immuno-chemotherapy)	Ongoing treatment, response observed
10.	Honings *et al*. [26]	2009	1	Not detailed	Not specified
11.	Xie *et al*. [27]	2011	7	RT (SEER-based cohort)	Suggested benefit; specifics not detailed
12.	Heikal [28]	2012	71	Surgery, CCRT, Palliative (SEER-based cohort)	Not specified
13.	Piórek *et al*. [29]	2022	1	Not detailed	Not specified
14.	Sakamoto *et al*. [30]	2023	1	CCRT (EP+45 Gy RT)	Died 11 months later due to pancreatic metastasis
15.	Salimi *et al*. [31]	2023	1	CCRT	Died 8 months later
16.	de la Sota-Montero *et al*. [32]	2023	1	CCRT with Cisplatin	Not specified
17.	Sugimoto *et al*. [33]	2023	1	NACT (EP) → 45 Gy/30# RT → 25 Gy/10# PCI	Disease-free at 5 months' follow-up
18.	Present case	2025	1	NACT (EP) → CCRT 60 Gy/30# → EP → Palliative RT	Progression and died after 12 months

RT: Radiation, EP: Etoposide and Platinum-based chemotherapy, CCRT: Chemoradiation, NACT: Neoadjuvant chemotherapy, PCI: Prophylactic cranial irradiation

and dyspnea. As a result, these tumors are frequently misdiagnosed as bronchial asthma or obstructive lung illness, which causes delays in proper treatment [8].

Extrapulmonary SCC (EPSCC) is a rare, aggressive malignancy with biological behavior similar to SCLC. EPSCCs are most commonly seen in the gastrointestinal, genitourinary, and head-and-neck regions. Primary tracheal SCC is a subtype of EPSCCs, which are very rare and thought to arise from multipotent stem cells seen in many tissues [9,10]. These studies highlight the importance of recognizing EPSCC as a distinct but aggressive entity.

Individuals with primary tracheal SCC should undergo a thorough examination of the primary tumor, as well as regional lymph nodes, to determine the locoregional extent of the disease. A chest CT scan is required to rule out pulmonary primary. Bronchoscopy is required for diagnosis and staging, based on visual appearance and histological confirmation. PET-CT is a valuable tool for disease staging and also for response assessment of the treatment. Patients having neurological symptoms should be evaluated with a brain magnetic resonance imaging [9,11].

Currently, there is no universally accepted staging system for primary tracheal tumors. Some authors have used different staging systems based on a limited number of patient records. Licht *et al*. [12] used a staging system based on tumor size, local extension, nodal status, and distant metastasis. Using the T, N, and M criteria, they identified four stages (I-IV), demonstrating that earlier stages were associated with higher survival. Bhattacharyya [13] presented another

staging system. Stages I-IV were defined based on tumor size and extension (T1-T4), as well as nodal status (N0/N1). Significant survival differences were seen between the early and advanced stages. Macchiarini [14] proposed a staging system similar to that used for head-and-neck malignancies. Webb *et al*. [15] improved Bhattacharyya's approach by including the M category. Polish Krakow's [16] staging was location based (trachea alone, chest extension, regional or supraclavicular nodes, distant metastases). Wen *et al*. [17] used SEER data to combine tumor size, nodal involvement, metastasis, and local invasion details.

Due to the rarity of EPSCC and its various primary sites, no randomized clinical trials have been conducted to guide treatment. Individual case reports and retrospective research contribute to existing treatment options, which include surgical resection, chemoradiation, and chemotherapy alone [18]. Chao *et al*. [19] and Mornex *et al*. [20] have demonstrated the role of radiation (RT), but radical RT alone is often associated with poor survival outcomes. Hetnał *et al*. found that local resection followed by adjuvant radiation resulted in better survival rates as compared to radical RT alone [16]. However, surgical outcomes depend on the position of the tumor in the airway, its local expansion, and the patient's comorbidities. Recent studies have shown that high-dose conformal radiation therapy can improve local control, but monotherapy is still not enough because the tumor is very likely to spread.

Some researchers suggest that therapy options for small cell lung carcinoma (SCLC) could potentially be applied to tracheal SCC. Even with aggressive locoregional treatment, recurrence is common. Systemic chemotherapy is an essential part of tracheal SCC management. Platinum-based regimens, primarily cisplatin or carboplatin mixed with etoposide, have been shown to improve survival when used concurrently with RT [21]. After concurrent chemoradiotherapy (CCRT), Lan *et al*. [22] and Luo *et al*. [23] reported disease-free survival for over a year. In some circumstances, including immunotherapy in the EP regimen may increase survival chances. Chen *et al*. opted for a similar treatment protocol of immunotherapy with chemotherapy (Adebrelimab + Carboplatin + Etoposide) from the CAPSTONE-1 study, and it showed superior efficacy with fewer side effects [24]. The risk of brain metastases is very low in primary tracheal SCC, hence prophylactic cranial irradiation is not recommended [9,25].

Based on the published literature, we administered NACT to our patient, followed by CCRT and maintenance chemotherapy. However, the recurrence of distant metastases in this patient showed its aggressive nature. Table 1 shows a review of the literature regarding the treatment and outcomes [5,11,16,19-24,26-33].

CONCLUSION

Primary tracheal SCC is a very rare tumor with a poor prognosis. In the absence of clear clinical recommendations, platinum-based chemotherapy (cisplatin/carboplatin) and etoposide are employed as a neoadjuvant treatment, followed by concurrent chemoradiation, as we did in our instance. Until more cases are documented and better data are available, treatment must rely on extrapolation from other conditions, such as small-cell lung cancer.

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