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Pleomorphic carcinoma of the trachea after chemoradiotherapy for laryngeal cancer

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SUMMARY

A 66-year-old male patient who had received chemoradiotherapy (CRT) for laryngeal cancer 2 years ago visited a local doctor complaining of dyspnoea and wheezing. CT scan showed narrowing of the trachea caused by a tumour. We intubated the trachea over the tumour using a bronchoscope. A week later, the truncated tracheal tumour obstructed the tracheal tube, compromising the patient's breathing. We removed the obstructed tube and inserted a new one. We submitted the tissue from the tube to a pathologist. Histopathological diagnosis was pleomorphic carcinoma, a subtype of sarcomatoid carcinoma. The mechanism of epithelial–mesenchymal transition (EMT) occurring after CRT was detected in the tumour. Because he had undergone CRT for laryngeal cancer, surgery was not indicated, and we started radiation therapy. Sarcomatoid carcinomas including pleomorphic carcinoma of the trachea are extremely rare, with few reported cases, and EMT is associated with this histological type and CRT.

BACKGROUND

Primary tracheal tumours are rare. One report found only two primary tracheal tumours detected in 9000 autopsy cases.¹ Pleomorphic carcinoma, a subtype of sarcomatoid carcinoma, is rare in any organ. To date, only three cases of sarcomatoid carcinoma in the trachea have been reported.^{2–4} Epithelial–mesenchymal transition (EMT) is related to metastasis and resistance to therapy.⁵ Generally, surgical resection is considered useful for tracheal tumours. We searched the literature, but did not find any cases of a primary tracheal tumour developing after CRT for a head and neck tumour. We report a case of rare primary tracheal tumour related to EMT.

CASE PRESENTATION

A 66-year-old male patient received chemoradiotherapy (CRT) (intensity modulated radiation therapy: IMRT, 66 Gy/33Fr, and docetaxel) for squamous cell carcinoma of the larynx 2 years before this event. He was a former smoker with a history of two cerebral haemorrhages. He developed dyspnoea and wheezing lasting about a month, and visited a local otolaryngologist. His vital signs were normal. On auscultation, wheezing was heard. The doctor suspected bronchial asthma, and performed blood tests and a CT scan to exclude other diseases. Blood tests showed no significant abnormal findings, including tumour markers. The CT scan showed a tumour causing narrowing of the trachea, so the doctor consulted a respiratory physician in the same facility. The situation was considered

life-threatening and the patient was intubated using a bronchoscope and placed on a mechanical ventilator. The tumour obstructing the trachea was identified using a bronchoscope (figure 1). The large tumour had a stalk and bled easily. The next day, the patient became feverish and developed hypoxaemia. Bilateral consolidations of the base of the lungs were observed by chest X-ray. Blood tests showed elevated inflammatory markers including C-reactive protein. The patient was diagnosed with ventilator-associated pneumonia (VAP) and antibiotic treatment by intravenous drip of tazobactam/piperacillin 13.5 g/day was initiated. Four days later, the patient was sent to our hospital for intensive treatment for VAP and treatment of the tracheal tumour.

INVESTIGATIONS

CT scan showed the tumour obstructing the trachea (figure 2). We initially considered the tumour as a metastasis of laryngeal cancer previously treated, but the location was near the second tracheal cartilage and different from location of the first malignancy. A week later, the truncated part of tracheal tumour had obstructed the tracheal tube, compromising his breathing. We exchanged the tube and submitted the tissue truncated in the tube to a pathologist. We considered the part of tumour was accidentally resected by tracheal tube sliding. Histopathological findings (H&E staining) of the tumour showed both an epithelial and a spindle cell component (mesenchymal component) in the same specimen (figure 3). In immunohistochemical staining, the epithelial component stained epithelial markers such as E-cadherin, and the mesenchymal component stained mesenchymal markers such as Zeb-1 and Twist. In the part of the epithelial component in contact with the mesenchymal component, the transitional component was observed. In the mesenchymal component (spindle cell component), E-cadherin was negative, and Zeb-1, Twist and Snail/Slug were positive, so EMT was suspected (figure 4). Expression of Ki-67, a marker of cell proliferation, was similar in both component. All the results of immunohistochemical staining are shown in table 1.

DIFFERENTIAL DIAGNOSIS

At this point, we had considered the tumour to be tracheal recurrence of laryngeal cancer, but the pathological type and location was different. Pathological findings showing the epithelial and spindle cell components were decisive in diagnosis. The spindle cell component was greater than 10%, and from this result we diagnosed the



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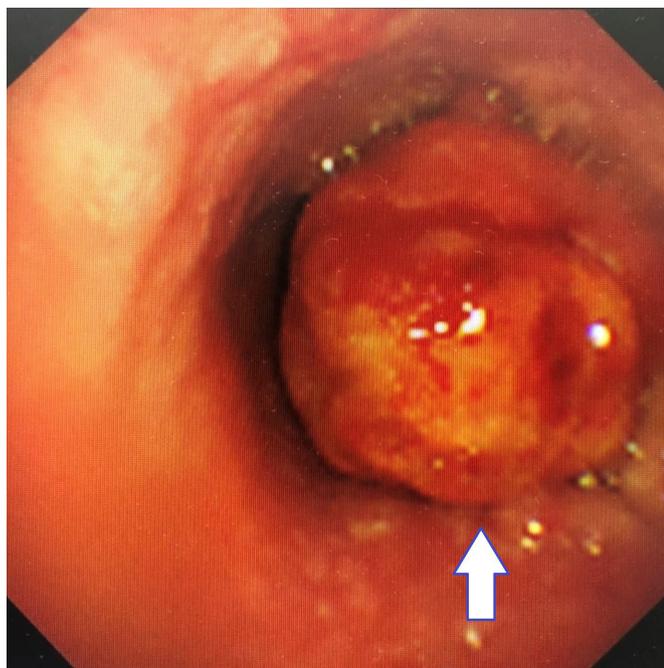


Figure 1 Bronchoscopic findings of the tracheal tumour. The tumour narrowed the trachea and was prone to bleeding.

tumour as pleomorphic carcinoma, a subtype of sarcomatoid carcinoma.

TREATMENT

We continued antibiotic treatment for VAP and performed a tracheostomy 10 days after re-intubation. The tumour was located near the second tracheal cartilage and we made a tracheotomy at the third tracheal cartilage to avoid the tumour. We considered bronchoscopic resection for remaining tracheal tumour, but decided not to do it because the tumour was prone to bleeding and the stem was too large and we understand that bronchoscopic resection of tracheal tumour is at high risk and is generally performed only in the operating room under general anaesthesia for patients in good general condition. Although we considered the option of complete resection of the tumour, we chose RT through the tumour board meeting because surgery after CRT for laryngeal cancer would have entailed an increased risk of complications including necrosis and rupture of previously irradiated structures. RT (IMRT, 60 Gy/30Fr) was

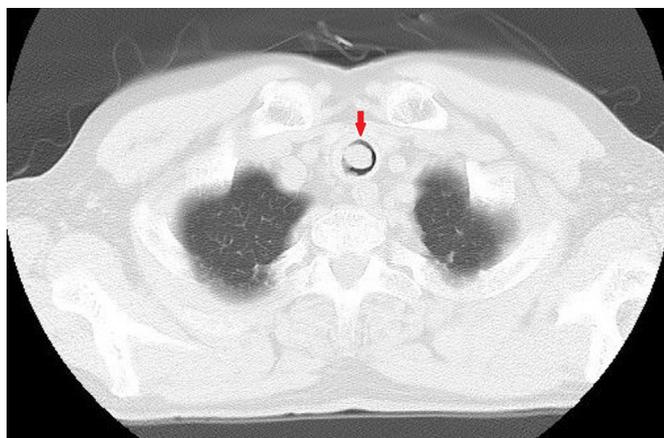


Figure 2 CT scan showing narrowing of the trachea.

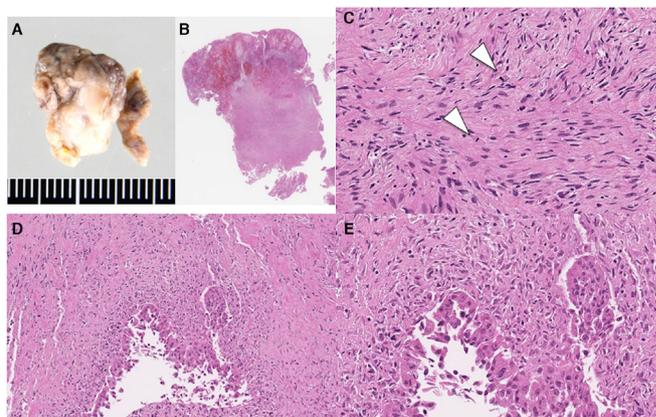


Figure 3 Macroscopic findings (a) showed a tumour 13 mm × 10 mm in size. Histopathological findings (H&E staining) of the tumour at lower magnification (b) show the upper level of the figure filled with the necrotic component. In the spindle cell component (c), arrows indicate typical spindle cells. The transitional component (d and e) shows the epithelial component in contact with the mesenchymal component.

performed and avoided damage of normal tissues around the tumour as much as possible.

OUTCOME AND FOLLOW-UP

Two months have passed since he received RT and the patient is alive. However, we cannot yet evaluate the outcome of treatment because there was no evaluable lesion. In the future, we will evaluate the outcome based on recurrence and metastasis of the tumour, and survival.

DISCUSSION

Tracheal tumours cause varying degrees of dyspnoea depending on tumour size, and are often misdiagnosed as bronchial asthma or chronic obstructive pulmonary disease.⁶ In this case, because the patient received CRT for laryngeal cancer 2 years before

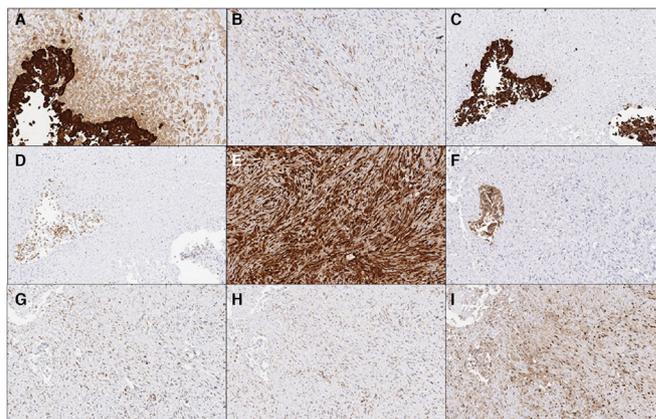


Figure 4 Immunohistochemical staining showed that the epithelial component was positive for CK AE1/AE3 but the mesenchymal component was negative (a). The spindle cell component (b) was negative for CK AE1/AE3. The epithelial component was positive for CK 5/6 but the mesenchymal component was negative (c). The epithelial component was positive for p40 but the mesenchymal component was negative (d). The spindle cell component (e) was positive for vimentin (e). The epithelial component was positive for E-cadherin but the mesenchymal component was negative. Zeb-1 (g), Twist (h) and Snail/Slug (i) were positive in only the mesenchymal component.

Table 1 Immunohistochemical staining findings

Antibody	Clone	Source	Dilution	Pretreatment	Result of Epithelial component	Result of Spindle cell component
CK AE1/AE3	AE1/AE3	Dako	1:200	MW	positive	weak positive
EMA	E29	Dako	1:100	None	positive	negative
CK5/6	D5/16B4	Dako	1:100	MW	positive	negative
E-cadherin	4A2C7	Zymed Laboratory	1:5	MW	positive	negative
p40	BC28	Bio Care Medical	1:80	None	positive	negative
p63	4A4	Nichilei	1:2	MW	positive	negative
Vimentin	Vim3B4	Dako	1:200	MW	negative	positive
Desmin	D33	Dako	1:100	None	negative	negative
S-100	polyclonal	Dako	Ready to use	MW	negative	negative
Muscle actin	HHF35	Enzo Diagnostics	1:100	None	negative	negative
alfa-SMA	1A4	Dako	1:100	None	negative	positive
CD34	NU-4A1	Nichilei	1:100	MW	negative	negative
KIT	polyclonal	Dako	1:100	MW	negative	negative
Bcl-2	124	Dako	1:10	MW	negative	negative
Zeb-1	polyclonal	SIGMA	1:50	MW	negative	positive
Twist	Twiat2C1a	Abcam	1:50	MW	negative	positive
Snail/Slug	polyclonal	Cell Signalling	1:80	MW	negative	positive
Ki-67	MIB-1	Dako	1:50	MW	22.60%	24.00%
TP53	DO-7	Novocastra	1:100	MW	negative	negative

this episode, we suspected a metastatic tumour originating from laryngeal cancer. However, the pathological type of the tracheal tumour was different from that of the previous laryngeal cancer. The tracheal tumour was diagnosed as pleomorphic carcinoma, a subtype of sarcomatoid carcinoma. Furthermore, tracheal metastasis of laryngeal cancer is extremely rare, and metastatic tracheal tumours generally originate from breast cancer, colorectal cancer or renal cancer.⁷ Histopathological findings in this case demonstrated the transitional component (the epithelial and mesenchymal component), and we concluded that EMT had developed in this tumour. EMT has been studied extensively relating to mechanisms of cancer metastasis and recurrence.^{8,9} At the transcriptional level, E-cadherin is repressed by a number of E-cadherin transcriptional repressors (EcTRs), including Zeb-1, Zeb-2, Snail/Slug, E12/E47 and Twist. Expression of these EcTRs in tumour epithelial cells is inversely correlated with E-cadherin expression and associated with increased invasiveness/metastasis and poorer clinical prognosis.¹⁰ The expression of EcTRs results in repression of the epithelial phenotype and promotion of EMT.¹¹ EcTRs are present in mesenchyme and repress transcription of E-cadherin and induce to mesenchymal feature. One report studied the relationship between sarcomatoid carcinoma and EMT, and this case showed one of the typical patterns of EMT.¹² However, no study has found a relationship between tracheal sarcomatoid carcinoma and EMT. It has been reported that sarcomas were seen in just 3.8% of tracheal tumours.¹³ Only three cases of tracheal sarcomatoid carcinoma have been reported.²⁻⁴ The higher value of Ki-67, the more the cell proliferation and tumour invasion ability. In this case, 22.4% of Ki-67 expression in epithelial component and 24.0% in spindle cell component were low compared with median 62% (range, 20% to 87%) expression in pulmonary pleomorphic carcinoma of 17 patients reported in Japan.¹⁴ Pleomorphic carcinoma is a subtype of sarcomatoid carcinoma, and is defined as an epithelial tumour including more than 10% spindle and/or giant cells.¹⁵ This case was compatible with the characteristics of pleomorphic carcinoma. Several reports identify complete resection as the first choice for treatment of primary tracheal tumours.¹⁶

However, as the patient had undergone CRT for laryngeal cancer, we considered surgical resection to have a higher risk of complications including necrosis of the trachea and ruptured suture. We thus selected RT for this patient. However, the effect of RT can be considered to be limited. The Netherlands Cancer Registry reports median survival of 91 months in cases of resection without RT, 82 months in cases of resection with RT, 11 months for patients who underwent only RT and 3 months for patients who did not receive either therapy.¹⁷ We should note that this result included cases of palliative RT, but it is clear that RT is inferior to resection. We should consider other treatment

Patient's perspective

I only remember the moment before I was connected to the ventilator. I will do what I can to ensure the success of my treatment and rehabilitation.

Learning points

- ▶ We should consider tracheal tumour as a differential diagnosis in patients with symptoms such as shortness of breath and wheezing similar to bronchial asthma or chronic obstructive pulmonary disease.
- ▶ We should add tracheal tumours in the list of differential diagnosis in post-irradiated cases with tumour of larynx, hypopharynx, and supraglottic region.
- ▶ We should treat cases of such difficult malignant tumour with specialists through tumour board meeting.
- ▶ There have been few reports of primary tracheal tumours related to epithelial–mesenchymal transition, and we need to investigate further.
- ▶ We need to develop effective treatments for tracheal tumours that are difficult to resect.

options for unresectable tracheal tumours, and we need to follow-up this case carefully.

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