A Review of Primary Osteosarcoma of the Larynx and Case Report

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Abstract Sarcomas of the larynx are exceedingly uncommon, of which primary laryngeal osteosarcomas are the rarest. To date, 25 cases of primary laryngeal osteosarcomas have been reported in the literature. Laryngeal osteosarcomas may closely simulate sarcomatoid carcinomas, since both entities share clinical, histological and immunohistochemical features. Herein, we report a case of primary laryngeal osteosarcoma in a 55 year old male, focusing on the importance of light microscopic, immunohistochemical and ultrastructural features in accurately establishing the diagnosis. In addition, the current paper provides a review of the English language literature on the subject. Laryngeal osteosarcomas usually carry a dismal prognosis with no general consensus on the most effective mode of therapy. Similarly, the current patient developed bilateral lung metastases 8 months after the initial surgery.

Keywords Laryngeal osteosarcoma · Sarcomatoid carcinoma · Immunohistochemistry · Electron microscopy

Case Report

A 55 year old male presented at the Division of Otorhinolaryngology, Tygerberg Hospital, Cape Town, South Africa, with a 4 months history of dysphonia and mild dyspnoea on exertion. He elicited a smoking history of 2 years, a habit that ceased 28 years ago. His medical history was otherwise unremarkable and no palpable cervical lymph nodes were detected on clinical examination. Direct laryngoscopy demonstrated a solid ulcerating polypoid lesion at the level of the right vocal cord (Fig. 1). Computerized tomography (CT) scans revealed an ovoid soft tissue mass of the right glottis with increased peripheral density. The lesion occupied the laryngeal vestibule with supraglottic extension (Fig. 2a, b).

Histological examination of an incisional biopsy performed at direct laryngoscopy revealed a malignant neoplasm composed predominantly of atypical spindled cells and osteoid. Due to the small size of the biopsy, it was not possible to offer an exact diagnosis. The microscopic features and the macroscopic finding of a polypoid glottic lesion were nevertheless highly suggestive of a sarcomatoid (spindle cell squamous cell) carcinoma; however, due to the lack of a squamous component, a primary laryngeal osteosarcoma could not be excluded. A chest radiograph was taken which showed no abnormalities. The patient was subsequently lost to follow up for several months. Eventually, 7 months after the initial laryngoscopy, the patient underwent a total laryngectomy with wide surgical margins.

Macroscopic examination of the resected specimen disclosed a 60 × 45 × 45 mm ulcerating polypoid lesion

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with a gritty consistency and a solid white-haemorrhagic cut surface. The lesion was loosely attached to the anterior part of the thyroid cartilage (Fig. 3).

Histological assessment of representative sections from the resected larynx showed a malignant spindle cell neoplasm with significant osteoid production and varying degrees of calcification (Fig. 4a). Focally, the pleomorphic spindled tumour cells occurred in a fascicular arrangement and showed marked cellular atypia with anaplastic tumour giant cells, abnormal mitotic figures, apoptotic bodies and necrosis (Fig. 4b). Cartilaginous invasion was absent, but the tumour cells were intimately associated with the perichondrium at the inferior aspect of the thyroid cartilage

Fig. 1 A solid ulcerating polypoid lesion is seen at the level of the right vocal cord

(Fig. 4c, d). The atrophic and ulcerated surface epithelium did not show evidence of dysplasia or carcinoma-in situ. Numerous sections from the tumour were analyzed, however lymphovascular invasion, squamous or cartilaginous differentiation could not be found. Immunohistochemical staining was done on representative tumour sections using standardised techniques, commercially available antibodies and antigen retrieval as recommended by the manufacturers of the antibodies. The tumour cells were negative for cytokeratins (AE1/AE3, MNF-116, CK5/6, CK7, CK8, CK19, CK20), epithelial membrane antigen (EMA), P63, desmin, and S100 protein. The tumour cells were diffusely immunoreactive for vimentin, but only weakly and focally positive for smooth muscle actin (SMA).

Formalin-fixed tissue was processed for electron microscopy according to standardised protocol. Ultrastructural examination showed spindled cells with abundant rough endoplasmic reticulum and extracellular matrix, compatible with osteoid and immature bone (Fig. 5a, b, c). Desmosomes, tonofilaments or actin myofilaments were absent. The absence of demonstrable epithelial origin and/or differentiation by light microscopy, immunohistochemistry and electron microscopy supported the diagnosis of a conventional primary osteosarcoma (osteoblastic type), possibly arising from the perichondrium of the thyroid cartilage.

The patient had an uneventful post-surgical recovery. However, 8 months after surgery, he presented with significant weight loss and increasing lassitude. Upon clinical examination, there was no evidence of recurrence of the primary lesion, nor any cervical lymphadenopathy. A chest radiograph revealed bilateral calcific radiopacities

Fig. 2 Coronal (a) and axial (b) CT reformatted images demonstrating an ovoid soft tissue mass in the right glottic area with increased peripheral density. The lesion occupies the laryngeal vestibule with supraglottic extension. (c) Posterior-anterior chest radiograph

demonstrating bilateral pulmonary cannonball metastases of osteogenic sarcoma. This radiograph was taken 8 months after surgery. The initial radiograph did not show these changes

Fig. 3 Fungating exophytic mass with an ulcerated surface is attached to the perichondrium of the thyroid cartilage on the right side

consistent with lung metastases (Fig. 2c). Given the earlier diagnosis of primary laryngeal osteosarcoma, the lung metastases were considered to be osteosarcomatous in nature and no further clinical procedures (e.g. CT guided FNAB) were deemed necessary to confirm the nature of the metastases.

Literature Review and Discussion

Sarcomas of the larynx are very rare, accounting for 0.3–1 % of all laryngeal neoplasms. The most common sarcomas of the larynx are chondrosarcomas and fibrosarcomas. Primary laryngeal osteosarcoma is the rarest of all laryngeal sarcomas [1–5].

It usually involves the vocal cords, anterior commissure and soft tissues of the larynx. In contrast to skeletal osteosarcomas, laryngeal osteosarcomas have a striking predilection for elderly males [2, 3].

Jackson and Jackson [6] described laryngeal osteosarcoma for the first time in 1942. An extensive Pubmed search resulted in only 25 published cases of primary laryngeal osteosarcoma. The mean age at presentation was 63.5 years, with an age range of 51–80 years (Table 1) [1, 5–7, 9–26]. In the reported cases (including the present case), only two cases occurred in females, with a male:female ratio of 13:1 (Table 1). Four cases were associated with history of previous radiotherapy and one case with a

history of skeletal Paget's disease. Hoarseness and dyspnoea were the most common presenting clinical symptoms. Other symptoms included dysphonia, odynophagia, haemoptysis, odontalgia and loss of consciousness. Seven cases involved the right vocal cord only or in association with the left vocal cord, anterior commissure and thyroid cartilage. Only three cases involved the cricoid cartilage. Radiographically, most cases presented as destructive infiltrative lesions of the thyroid cartilage, cricoid cartilage or the vocal cords with transglottic involvement. Few cases have reported a polypoid lesion compromising the airway (Table 1). In the present case, the lesion was loosely attached to the perichondrium of the thyroid cartilage with no signs of invasion of the cartilage by the tumour. In the current case, it is highly likely that the lesion originated from the perichondrium of the thyroid cartilage since this was the focal site of attachment and histologically there is continuity between the tumour and the perichondrium of the thyroid cartilage (Fig. 4c, d). Alternate but less likely origins include the soft tissues of the anterior commissure with secondary involvement of the thyroid cartilage.

The aetiological factors involved in the development of laryngeal osteosarcoma are yet to be elucidated. No direct association between tobacco and alcohol consumption has been reported [1]. Kassir et al. in 1997 proposed previous history of radiation, skeletal Paget's disease, fibrous dysplasia or retinoblastoma as possible aetiological factors [4, 7]. Laryngeal framework ossification was also entertained as one of the risk factors [5]. The current patient had none of the above mentioned risk factors, apart from smoking for 2 years only. The patient ceased the habit 28 years ago, which makes it highly unlikely to be an aetiological factor in causation of the current lesion. Tobacco and alcohol consumption on the other hand are well established factors associated with carcinosarcoma/sarcomatoid carcinoma [30, 33]. A few reported cases of laryngeal osteosarcoma arose from dedifferentiated chondrosarcomas of the larynx [5, 7, 9, 17]. Carcinosarcomas/spindle cell squamous cell carcinomas show divergent differentiation and probably derive from a common precursor cell as suggested by ploidy and immunohistochemical analysis of the spindled and the epithelial cells [27, 28]. Ultrastructural studies of carcinosarcomas also support epithelial differentiation in the form of tonofilaments and desmosomes being present in both cell types [7, 29].

Cytokeratin expression decreases and may even be absent in sarcomatoid carcinomas as the degree of epithelial differentiation decreases [28, 30] and tumour cells acquire more mesenchymal characteristics [29]. Many technical factors such as fixation, characteristics of antibodies and antigen retrieval may also influence potential false negative or positive immunohistochemical findings [30].

Table 1 Reported cases of primary laryngeal osteosarcoma

No	Reference	Age (years)/gender	Site	Clinical features	Radiological features	Follow up
1	Jackson and Jackson [6]	51/M	CC	Hoarseness, dyspnoea and dysphagia	NA	Local recurrence after 3 month. DOD after 6 month with mediastinal metastasis
2	Clerf [25]	51/M	Larynx NOS	Hoarseness and dyspnoea	N/A	DOD 14 month later with local recurrence and lung metastasis
3	Sprinkle [24]	71/M	Posterior surface of RVC	Hoarseness	N/A	FOD 24 month later
4	Morley et al. [23]	62/M	RVC, LVC	Hoarseness, dyspnoea, Acute respiratory obstruction, Occasions of consciousness loss	Polypoid lesion of RVC, LVC with supra-glottic extension	DOD after 3 months
5	Dahm et al. [22]	79/M	RVC and anterior commissure	Hoarseness and difficulty in breathing	Polypoid mass occupying the airway	DOD with multiple lung metastasis
6	Haar et al. [21]	66/M	CC	Hoarseness	Mass posterior wall of the proximal trachea mass displacing the oesophagus anteriorly	DOD with lung metastasis 21 month later
7	Gorenstein [20]	75/M	RVC and ventricle	Hoarseness	N/A	DOD/14 month with local and distant metastasis
8	Suchatlampong et al. [19]	67/M	LVC, anterior and posterior commissure and supraglottis	Hoarseness and dyspnoea	Mass involving the glottis region with supraglottic extension	DOD after 6 months
9	Remagen et al. [18]	65/M	Article in German	Article in German	Article in German	Recurrence after 1 year. DOD in 24 months
10	Laskin et al. [17] ^a	56/M	Larynx NOS	NA	NA	unknown
11	van Laer et al. [16]	75/M	LVC and L pyriform fossa	Dysphagia, discomfort in the throat	Amorphous mass of calcification between the	Recurrence 13 month later
12	Pinsole et al. [14] ^b	65/M	RVC and anterior commissure	Dyspnoea and dysphonia	1.5 cm polypoid tumour involving the RVC and anterior commissure	Recurrence after 1 month, resected with pectoralis flap, FOD 60 month later
13	Sheen et al. [9] ^a	56/M	Left neck and anterior TC	Hoarseness	Hyperdense mass in the left upper neck	Died 1 year and 9 month with extensive disease
14	Myssiorek et al. [13]	47/M	TC	Hoarseness, dyspnoea, otalgia, haemoptysis	Destructive lesion of TC with extension into soft tissues	DOD/12 months with bone metastasis
15	Berge et al. [10]	60/F	CC	Dysphonia, dysphagia and weight loss	Expansion of the medullary portion of the cricoid cartilage with encroachment on the airway	FOD/44 months
16	Marginal et al. [15]	50/M	RVC, LVC	Hoarseness	NA	FOD/24 months
17	Marginal et al. [15]	59/M	TC	Hoarseness	Destructive lesion of the TC extending to para-pharyngeal soft tissue	DOD/18 month after surgery with multiple lung metastases
18	Marginal et al. [15]	60/M	RVC and anterior commissure	Dyspnoea	Polypoid mass of the right VC with extension into anterior commissure	FOD 60 months after surgery
19	Marginal et al. [15]	69/M	True vocal cord	Dyspnoea, dysphonia and cough	Two metastatic nodules in the lung	Lost follow up

Table 1 continued

No	Reference	Age (years)/gender	Site	Clinical features	Radiological features	Follow up
20	Topaloglu et al. [12]	80/M	RVC, LVC and ventricular bands	Hoarseness, progressive dyspnoea	Soft tissue mass narrowing the airway	FOD/15 month after operation
21	Athré et al. [5] ^a	69/F	Larynx, strap muscles and thyroid gland	Progressive dyspnoea	Dystrophic calcification outside the confines of the larynx	DOD with lung metastasis/10 months
22	Arslan et al. [26]	69/M	Larynx NOS	Persistent hoarseness	Lung metastasis	DOD/lung and neck metastasis
23	Mottola et al. [11]	56/M	TC, CC and Para-tracheal space	Dyspnoea, dysphagia and dysphonia	Tumour mass affecting the glottis and supra-glottis	DOD/3 month from surgery
24	Sanaat et al. [1]	71/M	True and false cords	Dyspnoea, dysphagia and odynophagia	Solid mass destroying both cords with supra and infra-glottic extension	DOD/after 1 year. Bone and lung metastases
25	Ulusan et al. [7] ^a	59/M	Anterior commissure	Hoarseness and dyspnoea	Normal chest, abdominal and bone radiographs	Disease free/8 years
26	Current case 2013	55/M	Perichondrium of the RTC	Dysphonia and dyspnoea on excretion	Soft tissue mass in the right glottis area with increased peripheral density	Bilateral lung metastases 8 month after surgery

DOD died of disease, *FOD* free of disease, *TC* thyroid cartilage, *CC* cricoid cartilage, *RVC* right vocal cord, *LVC* left vocal cord, *RTC* right thyroid cartilage, *NA* not available

^a Post radiation laryngeal osteosarcoma

^b History of Paget's disease

The presence of extensive ulceration may furthermore prevent the histological detection of dysplasia or squamous cell carcinoma in situ in the overlying epithelium. Sampling errors and technical factors may also confound the pathologist's ability to detect epithelial differentiation [30, 31].

While it is known that epithelial differentiation may be difficult to demonstrate in sarcomatoid carcinoma, the complete lack of any evidence of epithelial differentiation in this case favours the likelihood of a primary sarcoma despite the fact that derivation from a preceding carcinosarcoma cannot be excluded with certainty [30, 31]. Despite careful attention to the mentioned challenges that may prevent detection of preceding carcinosarcoma or epithelial differentiation, the complete lack of such evidence in the current tumour supports the diagnosis of primary osteosarcoma of the larynx.

The correct identification of primary laryngeal osteosarcoma requires careful clinical, radiological and histological correlation. The differential diagnosis of primary laryngeal osteosarcoma includes other malignant spindle cell neoplasms with osteoid production.

The presence of malignant osteoid production and careful exclusion of epithelial differentiation distinguishes primary osteosarcoma from carcinosarcoma/sarcomatoid carcinoma, some of which are well known to contain osteoid [8, 27–33]. Thompson et al. [30] and Viswanathan

et al. [31] described the largest series of laryngeal spindle cell (sarcomatoid) carcinoma, of 187 and 103 cases respectively. As shown in the present case, laryngeal osteosarcomas may clinically, radiologically and histologically resemble sarcomatoid carcinomas (involvement of the glottis, polypoid appearance with surface ulceration, early stage of presentation). There is striking predilection of both tumours to males in the seventh decade, usual clinical presentation with hoarseness of voice and airway obstruction [30–33]. Both lesions may present with severe airways obstructive symptoms. Squamous differentiation or surface dysplasia/carcinoma in situ should lead to a diagnosis of sarcomatoid carcinoma.

SMA positivity has been demonstrated in osteosarcoma and does not imply leiomyosarcomatous differentiation [34]. Sarcomatoid carcinoma may also show fascicular growth pattern and SMA positivity [30, 31]. However its presence does not exclude the diagnosis of osteosarcoma in the presence of osteoid production by tumour cells and lack of other evidence of epithelial differentiation.

Spindle cell melanomas can show osteoid production [35]. Careful histological examination for cytoplasmic melanin or a junctional melanocytic lesion may aid in the distinction of these lesions. Lack of cytokeratin immunoreactivity and positive staining for HMB45, S100, Melan A, MITF, Mart1, and Tyrosinase are diagnostic of

Fig. 4 **a** The osteosarcoma (*left*) is attached to the perichondrium of the thyroid cartilage (*right*). Original magnification $\times 4$. **b** Original magnification $\times 20$. **c** Malignant spindle cells and osteoid production.

Original magnification $\times 10$. **d** Fascicular arrangement of the tumour cells. Original magnification $\times 10$

Fig. 5 **a, b** Abundant extracellular material. **c** Some tumour cells are rich in rough endoplasmic reticulum

malignant melanomas. At the ultra-structural level, demonstration of melanosomes and premelanosomes can further confirm and consolidate the diagnosis.

Metastatic osteosarcoma and osteoblastoma must also be investigated clinically before making the diagnosis of primary laryngeal osteosarcoma [36, 37].

Laryngeal osteosarcoma carries a dismal prognosis with frequent local recurrence and distant metastases, especially to the lung [2, 12, 30]. The review of the English language literature on laryngeal osteosarcoma shows a mean survival

of 12.6 months (± 3.64 ; 95 % CI) with only 23.5 % 2 year survival rate. This patient developed multiple bilateral lung metastases 8 months after surgery.

As yet there is no consensus regarding the management of primary laryngeal osteosarcoma; however the most widely accepted treatment is radical surgical extirpation with wide margins [5]. The use of radiotherapy has been shown to be ineffective [3, 4]. Adjuvant chemotherapy has been suggested in view of its use in the analogous skeletal counterpart to increase survival rates [13].

In essence, the authors submit that the diagnosis of primary laryngeal osteosarcoma in this case is justified by the meticulous morphological, immunohistochemical and ultrastructural exclusion of epithelial differentiation. The presence of lung metastases in the absence of neck node involvement is not typical for a squamous cell carcinoma. The lesion is also unusual due to its polypoid appearance and focal attachment to the perichondrium of the thyroid cartilage at the anterior commissure, without invasion of the cartilage or extension to the vocal cords. It is also very plausible in the authors' opinion that the lesion actually arises from the perichondrium of the thyroid cartilage.

Conflict of interest The authors declare that they have no conflict of interest.

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