Spindle Cell Carcinoma of the Larynx with Rhabdomyoblastic Heterologous Element: A Rare Form of Divergent Differentiation

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Abstract Spindle cell (sarcomatoid) carcinoma of the larynx is a rare subtype of squamous cell carcinoma that shows a prominent spindle cell component with a mesenchymal phenotype. Heterologous elements may be seen in these spindled areas and usually consist of osteosarcomatous or chondrosarcomatous differentiation. We describe an unusual spindle cell carcinoma of the vocal cord in a 68 year old male which demonstrated rhabdomyosarcomatous differentiation as confirmed by desmin and myogenin immunoreactivity. Thus rhabdomyosarcomatous differentiation adds to the phenotypic spectrum of spindle cell carcinomas of the larynx and should be considered before invoking a diagnosis of true rhabdomyosarcoma of the larynx.

Keywords Carcinosarcoma · Spindle · Larynx · Rhabdomyosarcomatous · Differentiation

Introduction

Spindle cell carcinoma (SPC) of the larynx, also known as sarcomatoid carcinoma or carcinosarcoma, is an uncommon tumor characterized morphologically by the presence of a distinct in situ or invasive epithelial component with a malignant spindle cell component. The presence of in situ component is often helpful in establishing the diagnosis in biopsy specimens where the tumor is comprised of spindle cells only [1]. The epithelial component is a squamous cell carcinoma admixed with a malignant sarcomatous

component that is either non-descript or contains heterologous elements (i.e. osteo- or chondrosarcomatous) [1–3]. Although the presence of rhabdomyosarcomatous elements is fairly frequent in carcinosarcomas at other body sites [4–8], it is extremely rare in the larynx [9, 10]. We hereby describe the pathologic and immunohistochemical findings of a laryngeal SPC with rhabdomyosarcomatous differentiation.

Case Report

A 68 year old man presented to the ENT clinic with a 2 week history of hoarseness. He denied throat pain, dysphagia, and lumps in the neck. Physical examination was unrevealing. Laryngoscopic examination demonstrated a nodular mass arising from the right vocal cord. The mass was subsequently resected and submitted for pathologic examination.

Microscopic examination demonstrated an invasive tumor with biphasic morphology. The tumor was comprised of nests of keratinizing squamous cell carcinoma interspersed within a malignant spindled component (Fig. 1a). A surface dysplasia/in situ carcinoma was present as well (Fig. 1b). The sarcomatoid component was comprised of spindle and stellate shaped cells with enlarged, pleomorphic and hyperchromatic nuclei, dispersed in a myxoid to hyalinized stroma. A peculiar cambium-like condensation of the spindle cells was noted around many of the epithelial cell nests (Fig. 1c). Several of these cells showed rhabdomyoblastic features including cells with bright eosinophilic cytoplasm, plasmacytoid morphology as well as elongated cells with cytoplasmic striations (Fig. 1d). Antibodies utilized for immunohistochemistry are listed in Table 1. The squamous component showed strong immunoexpression of cytokeratin 5/6

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(Fig. 2a), p63 (Fig. 2b), AE1/3, 34 β -E12 and epithelial membrane antigen while the spindled component showed rare cells positive for the aforementioned markers. The spindle cells showed diffuse positivity for vimentin and smooth muscle actin and were negative for S-100. Rhabdomyoblastic differentiation was highlighted by desmin (Fig. 2c) and myogenin (Fig. 2d).

Discussion

Biphasic tumors of the head and neck have been described using variety of terminologies; carcinosarcoma, sarcomatoid carcinoma, SPC, metaplastic carcinoma, or pleomorphic carcinoma. In contrast to prior belief, molecular genetic studies have shown evidence of monoclonal origin of both the epithelial and spindle cell component, which then invalidates the usage of terms also used historically for SPC such as ‘collision tumor’ or ‘squamous cell carcinoma with reactive stroma’ [11–13]. Of note, many choose to delineate ‘carcinosarcomas’ as tumors with distinct epithelial and stromal components (without intermingling or transition) and often heterologous elements, such as this case. This

distinction is not known to be of significance in the larynx. SPCs account for about 2.7 % of all benign and malignant laryngeal tumors and 4.2 % of squamous cell carcinomas of larynx. Patient demographics are fairly similar to those of conventional squamous cell carcinoma. These tumors are most frequently seen in middle aged to elderly males. Tobacco and alcohol abuse is strongly associated with this tumor. Although these tumors have been described in the setting of prior radiation exposure, it has not been shown to be a causal factor [1, 10]. However, SPCs arising in this setting are associated with an aggressive clinical course [1, 10]. SPCs most commonly occur in larynx. Within the larynx, the vast majority arises in the glottis from the true vocal cord and anterior commissure [1, 14]. Oral cavity is the next most frequent site for this tumor affecting the lower lips, tongue and buccal mucosa [15]. Heterologous elements, such as osteocartilagenous elements, in SPCs have been documented in 7–15 % of cases of SPCs depending on the subsite in head and neck [1, 3, 16]. However, rhabdomyosarcomatous differentiation in SPC is exceptionally rare. Table 2 summarizes the findings of prior reports of SPC with rhabdomyosarcomatous components. Srinivasan et al. [9] described an autopsy case of a node negative laryngeal

Fig. 1 **a** SPC demonstrating an invasive carcinomatous component embedded in a cellular stroma (Hematoxylin and Eosin, $\times 40$). **b** The surface epithelium shows severe dysplasia/carcinoma in situ (Hematoxylin and Eosin, $\times 200$). **c** The sarcomatoid component is comprised of primitive appearing stellate to spindle shaped cells with scant to moderate amount of cytoplasm, dispersed in a myxoid background. Note the sharp distinction between the carcinoma and sarcoma

component and concentric condensation of spindle cells around the squamous nests (cambium-like zone) (Hematoxylin and Eosin, $\times 100$). **d** The sarcomatous component shows pleomorphic plasmacytoid to elongated spindle cells with moderate amount of eosinophilic cytoplasm and eccentrically placed nuclei (“fetal-type rhabdomyoblasts”). *Inset* A few cells demonstrate cross striations (*arrow*) (Hematoxylin and Eosin, $\times 400$)

Table 1 List of antibodies for immunohistochemistry

Antibody	Clone	Host	Provider	Strength
34 β -E12	34 β -E12	Monoclonal Mouse	Dako	1:40
Cytokeratin 5/6	D5/16 B4	Monoclonal Mouse	Dako	1:50
Cytokeratin AE1/3	AE1/3	Monoclonal Mouse	Dako	1:100
Desmin	DE-R-11	Monoclonal Mouse	Ventana	Predilute
Epithelial membrane antigen	E29	Monoclonal Mouse	Cell Marque	Predilute
Myogenin	F5D	Monoclonal Mouse	Cell Marque	Predilute
p63	4A4	Monoclonal Mouse	Thermo	1:200
S-100	Z0311	Polyclonal rabbit	Dako	1:500
Smooth muscle actin	IA4	Monoclonal Mouse	Cell Marque	Predilute

carcinosarcoma with rhabdomyosarcomatous differentiation in a 55-year old male. Antemortem biopsy was diagnosed as primary rhabdomyosarcoma. Subsequent autopsy examination of the entire mass revealed prominent in situ and invasive squamous cell carcinoma admixed with a

pleomorphic rhabdomyosarcoma. Goldman et al. [10] described an admixture of squamous cell carcinoma and rhabdomyosarcoma in a cervical node of a patient with primary laryngeal squamous cell carcinoma. There was no evidence of malignant spindle cell component in the primary tumor. Antanova et al. [17] reported a case of rhabdomyosarcoma and squamous cell carcinoma which arose in the larynx of a 55-year old man as 2 topographically distinct tumors. These findings were not that of a SPC.

Thus this case serves to expand the morphologic diversity in laryngeal SPC. The major differential diagnosis is a true laryngeal rhabdomyosarcoma. The demographic features of true rhabdomyosarcoma in the larynx are somewhat different however. Overall, primary sarcomas of the larynx are rare tumors, representing 0.3–1 % of all laryngeal malignancies. Primary rhabdomyosarcoma is a tumor of pediatric population and is exceedingly rare in adults greater than 30 years of age in contrast to SPC which predominate in the 5th to 6th decades. Histologically, with adequate sampling demonstrating epithelial and spindled components, this differential diagnosis can be readily resolved. In our case both the malignant epithelial (including in situ) and rhabdomyosarcomatous components were clearly identified on the hematoxylin and eosin stained sections. However, small biopsies may occasionally

Fig. 2 a, b The SPC demonstrates strong cytoplasmic staining with cytokeratin 5/6 (2a, $\times 400$) and strong nuclear staining with p63 (2b, $\times 400$) in the carcinomatous component. The sarcomatoid component immediately adjacent to the carcinomatous nests shows

scattered cytokeratin 5/6 and p63 positive cells. c, d Some of the malignant spindle cells demonstrate strong cytoplasmic staining with desmin (2c, $\times 400$) and strong nuclear staining with myogenin (2d, $\times 400$)

Table 2 Carcinosarcoma with rhabdomyoblastic differentiation—Larynx

References	Age	Sex	Clinical presentation	Histology	Outcome
Srinivasan et al. [9]	55 years	M	Heavy smoker with hoarseness, dysphagia and burning sensation in the throat for 2 months. Bulky polypoid mass in left glottis and supraglottis	Initial biopsy showed rhabdomyosarcomatous elements. Autopsy examination revealed admixed invasive squamous cell carcinoma	Died of disease
Goldman et al. [10]	73 years	M	Hoarseness for 4 months. Tumor mass in the epiglottis. History of radiation followed by multiple recurrences; primary and metastatic cervical nodes	Primary site—squamous cell carcinoma. Metastatic site (post radiation)—admixture of squamous cell carcinoma and rhabdomyosarcoma	Died of disease after 3 years and 10 months from diagnosis

sample only the spindled component making diagnosis challenging [1, 9, 14]. Thus this case reaffirms the need to have a high index of suspicion for SPC when encountering a spindle cell malignancy in the larynx, even with a distinct mesenchymal line of differentiation. Primary sarcomas may show some overlapping immunohistochemical features with SPC, including keratin reactivity in some cases. However, unlike SPC in which stromal cells express p63 in about 63 % of the cases, most rhabdomyosarcomas are typically negative [14]. In a collision tumor, another differential diagnostic consideration in this case, two clonally distinct neoplasms are found adjacent to one another and intermingle as the term would suggest. This is in contrast to the monoclonal origin of both components in SPC [11–13]. A collision tumor is acceptable if there is proof that both tumors are clonally distinct. To this end, morphologic and immunoexpression profiles can be used as surrogates for molecular phenotype if sufficiently divergent. However, in this case, the shared expression of p63 and cytokeratin in both components argues against a collision tumor.

SPC of the larynx are associated with a favorable outcome in contrast to other sites in the upper aerodigestive tract. A number of factors determine the prognosis of laryngeal SPC; tumor location (glottis vs non-glottic), T stage, vocal cord mobility, prior radiation exposure, presence of necrosis and lack of immunoexpression of epithelial markers. Clinical course of laryngeal conventional squamous cell carcinomas and SPCs have been reported to be similar. From treatment standpoint, SPC are considered as carcinomas and treated similar to conventional squamous cell carcinomas with initial excision, especially if the tumor has a predominantly exophytic growth [1, 3, 16]. Radiation therapy is indicated in recurrent tumors or tumors with extensive stromal invasion. Presence of heterologous elements is not associated with significant difference in prognosis of SPC [1].

In summary, it is important to consider the various entities described above in the differential diagnosis when confronted with a biphasic tumor in the larynx. Although rare at this site, pathologists should be aware of the possibility of rhabdomyosarcomatous heterologous differentiation

in a SPC. Thorough histological examination of small biopsies is important to look for an epithelial/in situ carcinoma component when the initial impression is that of a pure sarcoma in the larynx.

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