Primary Laryngeal Clear Cell Chondrosarcoma: Report of a Case and Literature Review

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Abstract We present an example of clear cell chondrosarcoma (CCC) arising in the thyroid cartilage, and review the literature regarding this neoplasm in the larynx. This patient has no evidence of disease 3 years post hemilaryngectomy. Although rare and morphologically distinct, CCC follows the same benign clinical course as conventional laryngeal chondrosarcoma.

Keywords Clear cell chondrosarcoma · Larynx · Chondrosarcoma

Introduction

Chondrosarcoma arising in the larynx is uncommon, comprising approximately 1 % of laryngeal tumors [1]. In this anatomic site, chondrosarcoma is typically a slow-growing, low-grade neoplasm that affects patients in the sixth decade of life, and is complicated by late recurrence and metastasis [1–3]. Regardless of anatomic location, the clear cell variant is the least common subtype of chondrosarcoma, and its presence in the head and neck is exceedingly rare. We present the histopathologic and immunohistochemical findings of an example of clear cell chondrosarcoma (CCC) arising in thyroid cartilage of the larynx to alert pathologists to the possibility of its occurrence in this location.

Case history

A 48-year old Caucasian male with a 30-pack year smoking history was seen by his otolaryngologist because of hoarseness, gradually increasing neck mass, and 30-lb weight loss over the past 1 year. He had been experiencing intermittent dysphagia to liquids with associated cough and episodes of choking. CT scan from the outside hospital (with contrast) demonstrated a $2.5 \times 2.4 \times 2.4$ cm expansile, ovoid expansile mass limited to the left thyroid cartilage. The mass was described as having radiologic features exhibiting marked chondroid matrix deposition. The radiologic impression was chondrosarcoma versus chondroma. No significant soft tissue component was seen with imaging, but the mass caused forward displacement and 75 % narrowing of his airway. The right thyroid cartilage and cricoid cartilage were radiologically unremarkable. He had no evidence of metastatic disease. Fiberoptic laryngoscopy revealed a left supraglottic submucosal mass that extended from the epiglottis to the arytenoid. Endoscopic examination demonstrated impaired movement of the left vocal fold only. Subsequent resection via a vertical hemilaryngectomy and left thyroplasty with tracheotomy was performed. Follow-up CT imaging and flexible fiberoptic laryngoscopy revealed an intact larynx with normal true vocal cord mobility bilaterally and no signs of recurrent disease. He is without signs or symptoms of recurrence 3 years later.

Pathology

The resected specimen consisted of a left partial laryngectomy containing a 1.7 cm tan-brown, friable mass without the translucent off-white appearance typical of conventional chondrosarcoma. Microscopic examination

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Fig. 1 **a** A sharp transition exists separating foci of conventional chondrosarcoma with its hyalinizing matrix and lacunae (*right*) from areas of clear cell chondrosarcoma (*left*). H&E stain. **b**. A monotonous solid population of large cells with sharp, clearly visible cell borders fills the pre-existing marrow space separated only by short trabeculae of woven bone. Note the absence of dense chondroid matrix in this field. H&E stain. **c** Tumor cells contain an enormous amount of clear to partly eosinophilic cytoplasm. Enlarged nuclei have irregular contours and an occasional cytoplasmic pseudoinclusion (*left center*). H&E stain. **d** PAS-positive cytoplasmic droplets are present in most cells. **e** S-100 stain. Positive nuclear and cytoplasmic staining is seen in every cell. Membranous staining is exaggerated in some cells

showed small foci of conventional grade I chondrosarcoma with partly calcified chondroid matrix mixed with clear cell areas. This transition from conventional ChS to CCC was often abrupt (Fig. 1a). Most tissue sections contained a tightly-packed proliferation of large polygonal tumor cells closely mixed with trabeculae of woven bone. These areas showed a complete replacement of the bone marrow by tumor cells that displayed sharply defined cell borders, and voluminous amounts of balloon-like cytoplasm that varied from optically clear to partly eosinophilic (Fig. 1b). Relatively monotonous, rounded, but slightly irregular nuclei were centrally located within cells. Inconspicuous nucleoli were noted in some, and nuclear cytoplasmic pseudo-inclusions were not infrequent (Fig. 1c). Occasional cells were binucleated. Little to no matrix was present in these areas of clear cell proliferation. Necrosis was absent. Mitotic activity was assessed using a 40× objective (Olympus BX-50), and counting 50 high-power fields. No mitotic figures were found. Clear cells were PAS-positive, diastase sensitive, and expressed diffuse, strong S-100

staining of cell nuclei and cytoplasm (Fig. 1d, e). Inked margins were negative for tumor.

Discussion

Chondrosarcoma (ChS) of the entire head and neck region is exceedingly uncommon. For the larynx in particular, evaluation of the NCI's SEER registry over the past 38 years (ending 2010) uncovered only 143 examples of laryngeal ChS representing 0.2 % of all laryngeal tumors [4]. Yet, ChS ranked only third behind squamous carcinoma (representing 95 % of cases) and adenocarcinoma as primary laryngeal malignancies in this study. SEER registry data found a predilection for laryngeal ChS to arise in Caucasians, males (3:1, M:F), and to only rarely develop regional or distant metastases even with T4 neoplasms [4].

Although Travers described ChS of the larynx as early as 1816 [5] and the term ChS was first used in this site by New in 1935 [6] it was not until 1999 that Obenauer et al. [7]

Table 1 Reported cases of laryngeal clear cell chondrosarcoma

Reference	Age (years)/sex	Location	Treatment	Follow-up
1. Kleist et al. [9]	57/M	L cricoid cartilage	3 Local recurrences followed by total laryngectomy	NED, 5 years
2. Said et al. [8]	56/M	L thyroid cartilage	Local resection	NED, 4 years
3. Obenauer et al. [7]	61/M	Cricoid/thyroid cartilages	Multiple local recurrences over 22 years followed by total laryngectomy	NED, 22 years
4. Kollert et al. [10]	46/M	Subglottic larynx	Total laryngectomy	NED, 6 months
5. Current case	48/M	L thyroid cartilage	Hemilaryngectomy	NED, 3 years

described the initial example of CCC of the larynx. Since then, three additional examples have been reported to our knowledge (Table 1) [8–10]. The clear cell type of ChS of bone was initially described by Unni et al. [11]. It is the rarest histologic form of ChS, and though it has been reported in multiple bony sites, its prime location is the epiphysis of long bones particularly the neck and head of the femur, and head of the humerus. The development of CCC in the head and neck is exceedingly rare. In addition to the larynx, head and neck examples of CCC include the maxilla and nasal septum [12–14]. In a recent MEDLINE search for CCC of the head and neck, Mokharti et al. [15] found only nine examples of this rare mesenchymal neoplasm in the head and neck including one in the skull, and the four aforementioned laryngeal examples. As seen in our patient and typical for CCC in general (regardless of anatomic location), all patients with head and neck CCC experienced a prolonged duration of symptoms ranging from 6 months to 2 years prior to seeking medical treatment.

Though rare, the pathologic diagnosis of CCC is not particularly challenging due to its location within bone, its large cells containing an enormous amount of completely or partially clear cytoplasm, sharply defined cell borders, extremely low mitotic rate, focal calcification and woven bone. Since most examples of CCC also contain foci of conventional matrix-producing ChS, it is possible with a small biopsy specimen that only the conventional chondrosarcomatous portion of a mass may be sampled, and thus be misdiagnosed. If one focused only on the clear cells without recognizing foci of chondroid matrix, one could potentially mistake CCC for a metastatic or locally invasive carcinoma having predominantly clear cell histology. Renal cell carcinoma, clear cell type may metastasize to bone with a clinically silent primary tumor. In addition, hyalinizing clear cell carcinoma of the head and neck may extend focally into underlying bone. The former malignancy typically has greater vascularity than CCC, while the latter is a soft tissue, not an osseous-based lesion, and is S-100 negative. Intraosseous mucoepidermoid carcinoma (MucoEp CA) may exhibit clear cell change, which is typically focal in its

distribution. MucoEp CA is also often cystic rather than completely solid, and contains scattered mucin-containing goblet cells. Unlike CCC, these previously mentioned neoplasms are mainly S-100 negative, but will express pan-keratin markers. Kleist et al. [9] however, caution that some cases of CCC may be positive for cytokeratins, and using collagen type II as a confirmatory positive immunohistochemical marker can be helpful. Caution should always be exercised when using epithelial markers in any osseous clear cell neoplasm since these can function as diagnostic traps if positive. For example, Matsuura et al. [16] recently described positive pan-keratin AE1/3 staining in the clear cell component of three of five cases of CCC from the long bones, with variable expression of cytokeratins 7, 8, 18, and 20, but negative staining for other epithelial markers such as epithelial membrane antigen (EMA), and CAM 5.2. In addition to S-100, SOX-9, a marker of chondrogenic differentiation, can be useful also in confirming the diagnosis of CCC, as it was positive in all examples from this series [16].

A recently published array-CGH analysis of twelve cases of CCC showed numerous gains and losses, but none were specific or recurrent [17]. High expression of the p16 downstream target CCND1 was observed in 41 % of their cases of CCC, supporting loss of the inhibitory effect of p16. According to the authors, this high incidence suggests that loss of p16 protein might be a crucial factor for cellular transformation in CCC.

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