

Dedifferentiated Chondrosarcomas of the Larynx: A Report of Two Cases and Review of the Literature

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Objective: To analyze the long-term clinical outcome of dedifferentiated chondrosarcoma or chondrosarcoma with additional malignant mesenchymal component (CAMMC) of the larynx and compare the results with those of axial chondrosarcomas. **Study Design/Methods:** Two patients with CAMMC of the larynx (0.03%) were retrospectively identified within the archives of the Armed Forces Institute of Pathology between 1970 and 2001. We compared the clinical and histologic features of these two cases with those reported in the English literature (Medline 1966–2001) (Table I). **Results:** Patient no. 1 was a 67-year-old man who presented with a 12-month history of hoarseness and was found to have a 4-cm mass involving the cricoid cartilage. Enucleation was performed and histologically demonstrated a dedifferentiated chondrosarcoma. Without additional intervention, the patient died after 136 months without evidence of disease. Patient no. 2 was a 41-year-old man who also presented with a 12-month history of hoarseness and dysphagia and was found to have a 5-cm mass involving the cricoid cartilage. A total laryngectomy was performed for the dedifferentiated chondrosarcoma. He is alive without evidence of disease at last contact (91 mo). **Conclusion:** CAMMC of the larynx are rare tumors but have a better prognosis than their axial counterparts (mean, 6 mo). Initial voice-sparing surgery can be followed with more aggressive surgery if recurrences develop. **Key Words:** Larynx, chondrosarcoma, dedifferentiated, management, outcome.

Laryngoscope, 112:1015–1018, 2002

Presented at the 105th Annual meeting of the Triological Society, Boca Raton Resort and Club, FL, May 12–14, 2002.

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Editor's Note: This Manuscript was accepted for publication March 7, 2002.

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INTRODUCTION

Chondrosarcomas of the larynx are an uncommon neoplasm comprising 0.1% to 2.0% of all laryngeal neoplasms, whereas “dedifferentiated” or “chondrosarcoma with additional malignant mesenchymal component” (CAMMC) are rare.¹ There have been several published series of laryngeal chondrosarcomas,² but only eight documented cases of CAMMC have, to the best of our knowledge, been reported in the English literature (MEDLINE 1966–2001) (Table I). After the first description of laryngeal chondrosarcoma in 1935,³ a standardized grading system was suggested by Lichtenstein et al.⁴ This grading system is based on a continuum of histologic features from grade 1 to grade 3, with grade 3 tumors demonstrating remarkable pleomorphism, hypercellularity, necrosis, and mitotic figures.^{5,6} Furthermore, it was determined that grade was correlated with long-term clinical outcome.⁷ The term “dedifferentiated” was applied to axial skeleton chondrosarcomas when a chondrosarcoma had areas composed of a malignant mesenchymal component and generally accounts for between 6% to 10% of axial chondrosarcomas, most often involving the proximal femur and pelvis.^{8–12} To date, there is no comparison of the histologic features and clinical outcome of laryngeal CAMMC with axial skeleton CAMMC. We report two additional cases and summarize the cases reported in the literature.

MATERIALS AND METHODS

The records of 161 patients with tumors diagnosed as chondrosarcoma of the larynx were identified in the files of the Otorhinolaryngic-Head & Neck Registry at the Armed Forces Institute of Pathology from 1970 to 1997. After review of the histologic features, only 2 patients had tumors diagnosed as dedifferentiated (CAMMC) chondrosarcoma. These 2 patients represented 0.03% of the 6939 patients with benign and malignant primary laryngeal neoplasms who were seen in consultation during this same time period and 1.2% of all laryngeal chondrosarcomas. Materials within the Institute's files were supplemented by a review of the patient's demographics (gender, age); symptoms at presentation (including duration); and history of radiation exposure. In addition, we reviewed surgical pathology and operative reports and obtained follow-up information from oncology data services by written questionnaires or direct communication with the treating physician or the patient. Follow-up data included

TABLE I.
Clinicopathologic Table of Patients With CAMMC.

Author/year	Age (y)	Sex	Presenting Symptoms; size (cm)	Primary Site	Original Therapy	Recurrence/Metastasis	Follow-up (mo)
Al-Saleem/1970 ²³	71	F	Hoarseness, dyspnea; NR	Cricoid	TL	Soft tissues	D, DD (12)
Bleiweiss/1988 ¹⁵	58	M	Hoarseness; 3	Cricoid	TL	None	A, NED (60)
Hakky/1989 ¹⁷	67	M	Hoarseness, dyspnea; 2.5	Cricoid	Laryngofissure, TL 3 yrs later	None	D, NED (years)
Ferlito/1990 ¹²	74	M	Dyspnea; NR	Cricoid	TL, XRT	Lung	D, DD (30)
Brandwein/1992 ¹	69	M	Dyspnea; >12	Cricoid	Eventual TL	LR	D, NED (216)
Nakayama/1993 ¹¹	58	F	Hoarseness, dyspnea; 3.5	Cricoid	TL	Stomal & regional	D, NED (168)
Nakayama/1993 ¹¹	62	M	Dyspnea, dysphagia; NR	Cricoid	Laryngofissure in 1983, TL in 1991	Clavicle, lung, neck	A, DD, (36)
Faquin/2001 ¹⁰	65	M	Neck mass; 4.5	Thyroid	PL; XRT; TL	LR	NR
Present series	67	M	Hoarseness; 4	Cricoid	Wide resection	None	D, NED (136)
Present series	41	M	Hoarseness, dysphagia; 5	Cricoid	TL	None	A, NED (91)

CAMMC = chondrosarcoma with additional malignant mesenchymal component; TL = total laryngectomy; LR = local recurrence; XRT = external beam radiation therapy; A = alive; D = dead; NED = no evidence of disease; DD = recurrent or distant disease; NR = not reported.

exact tumor location, tumor size and stage, treatment modalities, and current patient and disease status. Hematoxylin and eosin-stained slides from both patients were reviewed for morphologic assessment of chondrosarcoma and for CAMMC. CAMMC was defined by the presence of classic chondrosarcoma in addition to a malignant spindle cell mesenchymal component. This clinical investigation was conducted in accordance and compliance with all statutes, directives, and guidelines of the Code of Federal Regulations, Title 45, Part 46, and Department of Defense Directive 3216.2 relating to human subjects in research.

CASE REPORTS

Case No. 1

A 67-year-old man presented for evaluation with a 12-month history of worsening hoarseness. Initial laryngoscopic evaluation revealed a 4-cm submucosal lesion extending along the right posterior aspect of the subglottis below the true vocal cord. He did not sustain exposure to radiation (environmental or therapeutic) and did not smoke or abuse alcohol. In an effort to preserve the patient's voice, wide enucleation of the lesion was performed and he was discharged to home without any postoperative sequelae. He did not receive any additional therapy (surgery, radiation, or chemotherapy). He never developed recurrence or metastatic disease and died of unrelated causes without evidence of disease 11.3 years after initial presentation.

Microscopically, the native cartilage had undergone endochondral ossification. A neoplastic cartilage matrix-producing neoplasm invaded these areas of normal bone. The chondrosarcoma demonstrated a high cellularity, nuclear pleomorphism, hyperchromasia, tumor necrosis, and increased mitotic figures (6/10 high-power fields). Interspersed between the areas of high-grade chondrosarcoma were sheets of spindled mesenchymal cells arranged in interlacing "herringbone" fascicles. The spindle cells contained hyperchromatic nuclei and scant cytoplasm (Fig. 1). Mitotic figures were easily identified. The aggregate of features was diagnostic for a CAMMC.

Case No. 2

A 41-year-old, otherwise healthy man presented to his primary physician with a 12-month history of hoarseness, dyspha-

gia, and stridor. He was referred to an otolaryngologist where initial examination by flexible nasopharyngolaryngoscopy revealed an approximately 5-cm submucosal lesion along the mid-posterior portion of the subglottic larynx involving the cricoid cartilage. He did not have a history of radiation exposure and did not smoke or drink. At direct laryngoscopy a biopsy was performed. Because of the unusual nature of the neoplasm, outside consultation was sought (from the AFIP). Approximately 1 month after obtaining an expert pathology consultation, a total laryngectomy was carried out. The patient did not have any adjuvant therapy. He did not develop any recurrence or metastatic disease and is alive without evidence of disease at last follow-up 91 months after initial biopsy.

Microscopically, this tumor displayed similar features to the above-referenced case (Fig. 2), except that this case had evidence of a benign chondroma with ischemic change. Bone invasion, mitotic figures, and necrosis were all easily identified. The spin-

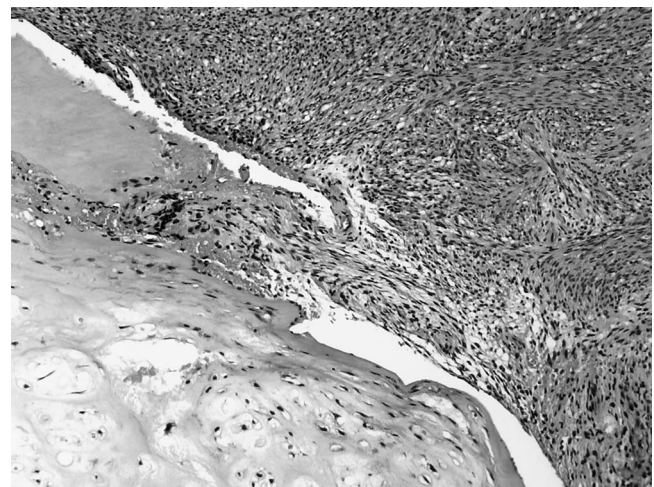


Fig. 1. Invasion by the chondrocytes into areas of endochondral ossification. Remarkable cytologic atypia, increased cellularity, and spindled cells are noted (hematoxylin and eosin, $\times 100$).

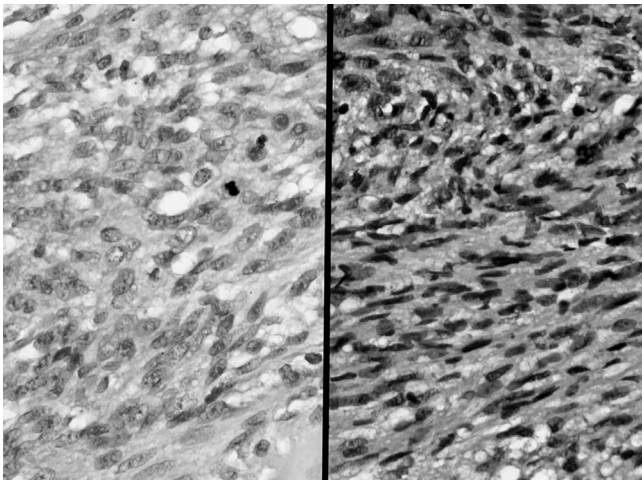


Fig. 2. Areas of malignant spindle cell (mesenchymal) component are seen abruptly arising from the surrounding chondrosarcoma (hematoxylin and eosin, $\times 300$).

dle cell mesenchymal component was not the dominant finding, but was easily identified and qualified the overall tumor as a CAMMC.

DISCUSSION

Chondrosarcomas of the larynx are a rare neoplasm, making up $<2\%$ of all primary laryngeal neoplasms,¹² a finding supported by our referral service data (2.3%). Furthermore, chondrosarcomas of the head and neck in general constitute only 10% of all chondrosarcomas.¹³ Whereas CAMMC of the axial skeleton comprise between 6% to 10% of all chondrosarcomas,^{8,11,14,15} CAMMC seem to make up approximately 1% of laryngeal chondrosarcomas.^{1,10–12,15}

Men are more commonly affected by laryngeal chondrosarcoma than women with a ratio of men to women of up to 4:1.^{2,16} It is with interest we note a ratio of 5:1 for laryngeal CAMMC (Table I), a finding different from the axial skeleton. Laryngeal chondrosarcomas typically occur between 50 and 80 years of age, with a peak in the seventh decade.² The mean age at initial presentation of laryngeal CAMMC in this clinical series combined with those reported in the literature is 63.2 years, no different from laryngeal chondrosarcomas in general.

Nearly all patients with laryngeal chondrosarcomas present clinically with hoarseness, frequently accompanied by dyspnea, dysphagia, and/or a palpable neck mass,² identical to the findings for CAMMC of the larynx. The cricoid location accounts for the esophageal symptoms (dysphagia and odynophagia). Depending on the size of the primary tumor, a palpable neck mass may be identified^{12,17} along with possible vocal cord impairment.

The cricoid cartilage is affected most frequently, accounting for 75% to 80% of all laryngeal chondrosarcomas,^{5,12,18} with the thyroid and epiglottis accounting for most of the remaining neoplasms. Nearly all of the CAMMC of the larynx (reported in the literature and in this clinical series) also involved the cricoid. One of the reported cases does not specifically cite the location of

the primary tumor, but indicates involvement of the thyroid cartilage with recurrent dedifferentiated chondrosarcoma.¹⁰

Histopathologic grading of these neoplasms was first introduced by Lichtenstein and Jaffe⁴ in 1943 and is still followed today using a constellation of microscopic features on a continuum from low grade to high grade. Low-grade tumors have slightly increased cellularity, binucleation in the lacunar spaces, slight nuclear pleomorphism, and hyperchromasia. High-grade tumors have remarkable cellularity, multinucleation of the lacunar spaces, nuclear pleomorphism, nuclear hyperchromasia, necrosis, and mitotic activity, whereas the intermediate grade has medium cellularity and less nuclear pleomorphism (Fig. 3).⁴ This grading system was further evolved by Evans et al.⁷ when combined with patient outcome to yield a declining survival for higher-grade tumors: 5-year survival of 90%, 81%, and 43% for grades I, II, and III, respectively. In the axial skeleton, CAMMC has a median survival of 6 months with an approximate 70% chance of metastases, usually to the lung or soft tissues.^{7,11,15} In sharp contrast to CAMMC of the axial skeleton, patients with laryngeal CAMMC have a better long-term prognosis, although a similar recurrence/metastatic potential is noted (Table I). Whereas 62% of laryngeal CAMMC have local recurrence or metastatic disease, only 2 patients died of disease (mean, 21 mo), whereas 6 of the remaining patients either died of unrelated causes or are still alive without evidence of disease an average of 11.1 years after initial presentation. One patient is still alive with recurrent disease after 36 months. We are unable to suggest a definitive explanation for why laryngeal CAMMC, and laryngeal chondrosarcomas in general, behave in a less biologically aggressive fashion than their axial counterparts.¹⁹ Possible reasons include earlier clinical detection resulting from clinical presentation of hoarseness or difficulty breathing, an overall smaller size of the tumors resulting from the

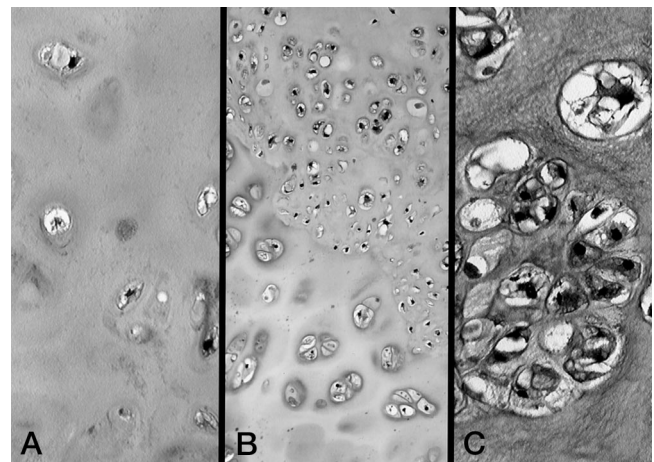


Fig. 3. Normal cartilage (A, $\times 150$); grade 1 chondrosarcoma (B, $\times 150$); grade II chondrosarcoma (C, $\times 300$). The spectrum of changes in cellularity, pleomorphism and multinucleation can be appreciated in these images of normal cartilage to grade II chondrosarcoma as a point of comparison with high-grade chondrosarcoma (hematoxylin and eosin).

confines of the larynx, and the relative ease of complete tumor resection.

Preservation of laryngeal function while achieving complete surgical eradication of the neoplasm is the preferred management of laryngeal chondrosarcoma.^{12,19–21} Controversy exists as to whether voice-sparing wide excision is better than total laryngectomy because there does not seem to be a significant difference in patient outcome (77% vs. 86%).^{5,21} However, initial conservation surgery followed by more aggressive surgical management for recurrent disease or higher-grade tumors does seem to yield the longest preservation of laryngeal function and result in a good long-term clinical outcome.^{2,11,15,22} In fact, such an approach was used for the majority of the patients with laryngeal CAMMC, yielding a good long-term clinical outcome, as reported above. In general, for laryngeal chondrosarcoma and for laryngeal CAMMC, there is little evidence to support the use of radiation therapy or chemotherapy,^{11,12} except perhaps in patients who pose a high intraoperative risk.⁵

It has been suggested that dedifferentiation occurs as a result of previous radiation exposure. However, in the cases reported in the literature, as well as the 2 patients in this clinical series, there is no documented radiation exposure either of a therapeutic or environmental nature. Therefore, no specific etiologic factor is known or suggested by the results of this study.

CONCLUSION

In summary, laryngeal CAMMC tend to occur more frequently in adult men in their 60s who present clinically with hoarseness and/or dysphagia, usually present for <12 months. The tumors involve the cricoid cartilage and are all larger than 2 cm in greatest dimension. By microscopic examination, the tumors demonstrate high-grade chondrosarcoma with bone invasion, high cellularity, nuclear pleomorphism, nuclear hyperchromasia, bi- and multinucleation of the lacunar spaces, tumor necrosis, and increased mitotic activity along with areas of dedifferentiation (usually spindle cell mesenchymal component or a primitive mesenchymal component). Wide surgical excision without adjuvant therapy (radiation and/or chemotherapy) at initial presentation can be followed by more aggressive surgical management for recurrent or metastatic disease, if it develops. CAMMC of the larynx seems to portend a better long-term clinical prognosis than their axial skeleton counterparts.

Acknowledgments

The opinions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of Defense.

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