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Laryngeal Angiosarcoma: A Clinicopathologic Study of Five Cases With a Review of the Literature

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Objective: **Primary laryngeal angiosarcoma (LA) is rare without a reported series evaluating these tumors.** ***Study Design/Methods:*** **Five patients with LA were retrospectively retrieved from the Otorhinolaryngic Registry of the Armed Forces Institute of Pathology.** ***Results:*** **Three men and 2 women, aged 29 to 71 years, presented with hoarseness (n = 4) and hemoptysis (n = 1). Two patients had previous neck radiation. The tumors involved the supraglottis (n = 4) with a mean size of 3.1 cm. Histologically, all tumors had anastomosing vascular channels lined by remarkably atypical endothelial cells protruding into the lumen, frequent atypical mitotic figures, and hemorrhage. All cases tested (n = 4) demonstrated immunoreactivity with antibodies to Factor VIII-RA and CD34. All patients had surgery followed by postoperative radiation (n = 3 patients). Three patients died with disease (mean, 17 mo), whereas one patient is alive with no evidence of disease at 18 years.** ***Conclusions:*** **LA is a rare tumor, frequently associated with previous radiation, usually involving the supraglottis with characteristic histomorphologic and immunophenotypic features. LA has a poor prognosis, making appropriate separation from other conditions important.** ***Key Words:*** **Larynx, angiosarcoma, prognosis, treatment, immunohistochemistry.**

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INTRODUCTION

Primary angiosarcomas of the larynx are exceedingly rare, with only eight well-documented, histologically confirmed case reports in the English literature (Table I).[1–9] Angiosarcoma is an uncommon, high-grade neoplasm of vascular endothelial cell origin that can arise in any anatomic site of the body. Despite the fact that nearly 50% of all angiosarcomas occur in the skin and superficial soft tissues of the head and neck, angiosarcoma accounts for less than 0.1% of all head and neck malignancies.[10] There are a number of comprehensive studies of skin and/or soft tissue head and neck angiosarcomas, which generally occur in men in the eighth decade of life, usually limited to the scalp or soft tissues of the face.[10–15] When angiosarcomas are found in the head and neck, nearly 30% of these patients develop metastatic disease to the lung, liver, spleen, and bone.[13,15] Mucosal or organ-based angiosarcomas have been reported to arise in the nasal cavity, paranasal sinuses, orbit, temporal bone, middle ear, thyroid, and larynx.[1–14,16–24] However, no single comprehensive clinicopathologic evaluation of laryngeal angiosarcomas (LA) is, to the authors' knowledge, present within the English literature (MEDLINE 1966–2000). Therefore, it is the intention of this study to provide an analysis of LA encompassing the use of clinical features, histologic findings, immunophenotypic studies, and follow-up information applied to a group of five patients with LA, and then compare these results with those reported in the English literature.

MATERIALS AND METHODS

The records of five patients with tumors diagnosed as "angiosarcoma," "hemangioendothelioma," or "lymphangiosarcoma" were identified in the files of the Otorhinolaryngic–Head & Neck Registry of the Armed Forces Institute of Pathology (AFIP) and represented 3.1% of 163 patients with head and neck angiosarcomas compiled from 1970 to 2000. These five patients represented 0.06% of the 7710 patients with benign and malignant primary laryngeal neoplasms diagnosed during the above-referenced period. The cases were obtained from civilian sources, including one foreign country.

Materials within the files of the AFIP were supplemented by a review of the patient demographics (gender, age, and ethnicity), signs and symptoms at clinical presentation (including duration), and predisposing factors (including prior radiation, tobacco and/or alcohol use). In addition, we reviewed surgical pathology and operative reports and obtained follow-up informa-

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TABLE I.
Review of the English Literature (in order published).

Author/Year	Age/Gender	Symptoms (duration in mo)	Radiation History	Tumor Location	Size (cm)	Treatment	Patient Outcome (mo)
Yankauer/1924[9]	65/M	N/R	None	Vocal cord, pedunculated	2.0	Snare excision	A, NED (12)
*Havens/1941[2]	Various	Hoarseness	None	Various	n/r	Endoscopic removal	D, D (15)
Pratt/1968[5]	66/M	Hoarseness (6); hemoptysis	No (smoker and drinker)	Vocal cord (right)	5	Total laryngectomy; biopsies for recurrences; Rad: 2600 cGy	D, D [lung] (3)
Rathmell/1969[6]	82/F	Hoarseness (2)	None	Vocal cord (right)	0.8	Snare excision	A, NED
Thomas/1979[8]	76/M	Hoarseness	Yes: 7000 cGy (11 yrs)	Supraglottis (epiglottis & false cord)	n/r	Partial pharyngolaryngectomy	D, D (13)
Ferlito/1985[1]	73/M	Pain with swallowing; dysphagia (8)	None	Supraglottis (posterior epiglottis)	2	Wide excision	D, NED (70.1)
McRae/1990[3]	24/F	Discomfort and dyspnea (18)	No	Subglottis (for hemangioma)	0.8	Excision; biopsies; Total laryngectomy, rads and chemotherapy for recurrence	D, D [widespread metastasis] (10)
Pisani/1994[4]	67/M	Dysphagia, dyspnea, dysphonia (1)	No	Supraglottis (pyriform sinus)	4.0	Total pharyngolaryngectomy; Rads: 50 Gy	D, NED (39)
Sciot/1995[7]	60/M	Tightness in throat (3)	No	Supraglottis (pyriform sinus)	n/r	Biopsy; Rads: 6600 cGy; Laryngectomy for recurrence	D, D [local, liver] (45.1)

*Havens et al. reported 7 patients, but does not show histology, except to say they were "fibrous-appearing nodules" and "polypoid-appearing nodule," which does not suggest malignancy. One tumor was described as "grade 3," but there is no illustration; therefore, while we have included his cases for interest, we do not believe they represent angiosarcoma.

Rad = radiation therapy; D, D = dead with disseminated disease; D, NED = dead without evidence of disease; A, NED = alive without evidence of disease; N/R = not recorded.

tion from oncology data services by written questionnaires or direct communication with the treating physician or the patient. Follow-up data included exact tumor location, tumor size, treatment modalities, and current patient and disease status. 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 the Department of Defense Directive 3216.2 relating to human subjects in research.

Hematoxylin and eosin-stained slides from all patients were reviewed for morphologic assessment of LA, with histologic confirmation of the initial diagnosis by a consensus agreement by all the authors for inclusion in this study.

Immunophenotypic analysis was performed in four cases with suitable material by using the standardized avidin–biotin method of Hsu et al.[25] using 4 μm-thick, formalin-fixed, paraffin-embedded sections. Table II documents the pertinent, commercially available immunohistochemical antibody panel used. The analysis was performed on a single representative block in each case with cellular conditioning used as required.

Our review of the English literature was based on a MEDLINE search from 1966 to 2000 with a few specific earlier articles included for balance and background (Table I).

RESULTS

Sociodemographic Characteristics and Clinical Findings

The patients include 3 men and 2 women, aged 29 to 71 years (mean age at presentation, 57.8 y) (Table III).

TABLE II.
Immunohistochemical Panel.

Antigen/Antibody	Primary Antibody	Company	Dilution	Antigen Recovery
Factor VIII RAg	rp	Dako, Carpinteria, CA	1:800	Enzyme digestion
CD34	mm	BioGenex, San Ramon, CA	1:80	Microwave
CD31	mm	Dako	1:40	N/A
Vimentin	mm	BioGenex	1:400	N/A
Smooth muscle actin	mm	Sigma Immuno Chemicals, St. Louis, MO	1:8000	Enzyme digestion
Cytokeratin (AE1/AE3 and CK1)	mm	Boehringer Mannheim	1:50	
Epithelial membrane antigen (EMA)	mm	Biochemicals, Indianapolis, IN, and Dako	1:200	Enzyme digestion
		Dako	1:100	Enzyme digestion

mm = mouse monoclonal; rp = rabbit polyclonal; N/A = not applicable.

TABLE III.
Clinical Parameters, Anatomic Location, and Size, Treatment, and Outcome of Laryngeal Angiosarcoma.

No.	Age/Gender/Race	Symptoms (duration in mo)	Radiation History (time)	Tumor Location	Side	Size (cm)	Treatment	Patient Outcome (mo)
1	71/F/AA	Hemoptysis (1)	Y (7 mo)	Supraglottis	Left	1.5	Excision; radiation to skull for breast metastasis	D, UD* (11)
2	69/M/C	Hoarseness	Y (10 yr)	Supraglottis	Right	9.1	Laryngectomy; radiation; chemotherapy	D, D (7)
3	29/M/C	Hoarseness (3)	None	Supraglottis	Midline	1.5	Wide excision	A, NED (216)
4	61/M/U	N/R	None	Supraglottis	Midline	N/R	Excision; radiation (incomplete course)	D, D (32)
5	59/F/U	Hoarseness	None	True vocal cord	Right	0.4	Excision; radiation	LTF

*Widespread breast carcinoma without angiosarcoma noted, but no autopsy confirmation.
AA = African American; C = Caucasian; U = Unknown; M = midline; D, UD = dead with unknown disease status; D, D = dead with disseminated disease; A, NED = alive with no evidence of disease; N/R = not recorded; LTF = lost to follow-up.

Two patients were white, one was black, and two patients were of unknown race. The patients presented with nonspecific symptoms of hoarseness (n = 3), with one patient reporting hemoptysis for 1 month. A history of tobacco use was elicited in one patient, who was also reported to consume "large" quantities of alcohol.

Two patients had radiation therapy to the neck for other nonvascular malignancies. One patient had presented with lymph node enlargement 10 years previously. Following a right radical neck dissection, a poorly differentiated metastatic carcinoma was diagnosed. After an extensive work-up, no primary tumor was discovered, so the patient was treated with a course of radiation therapy (unknown dose). The second patient had a history of breast carcinoma, which had metastasized to the lower cervical lymph nodes. The patient received 6600 cGy to the left chest and low cervical lymph nodes only 7 months before developing the LA. After the LA was removed, breast metastases to the skull were diagnosed, for which further radiation therapy was instituted.

Pathologic Features

Macroscopic findings. The most frequently involved site was the supraglottis, specifically the epiglottis (n = 4 tumors), with one tumor arising from the true vocal cord. Two tumors were right-sided, one was left-sided, and two tumors were midline. The tumors ranged in size from 0.4 to 9.1 cm (mean, 3.1 cm). The largest tumor was removed as a total laryngectomy specimen from a patient who had previous radiation exposure. The majority of tumors were received as excisional biopsy specimens from direct laryngoscopic examination and were described as purple to red, poorly circumscribed, nodular to polypoid or ulcerative lesions with associated hemorrhage or clot.

Microscopic findings. The surface squamous epithelium was intact in all cases without evidence of carcinoma (Fig. 1). All five tumors demonstrated the typical histomorphologic features of angiosarcoma, with the neoplastic cells infiltrating into the adjacent stroma and extended into the surrounding soft tissues, including the muscle and adipose tissue. These were tortuous and anastomosing vascular channels filled with erythrocytes and lined by atypical, enlarged endothelial cells which occasionally protruded into the vascular spaces (Figs. 2, 3, and 4). The nuclei were remarkably enlarged with coarse and heavy nuclear chromatin deposition, irregular nuclear contours, and prominent nucleoli (Fig. 4). Mitotic figures, including atypical forms, were easily identified. No extracellular eosinophilic hyaline globules could be found. The tumor cells were consistently positive with antibodies to Factor VIII-related antigen (Fig. 3, right), CD 34 and vimentin.

Treatment and Follow-up

All patients were treated with surgical resection, either with an excisional biopsy or a total laryngectomy. The biopsies were considered to be wide local excisions, but did not necessarily imply free surgical margins of resection. Adjuvant radiation therapy was administered to three patients. One patient (patient no. 2) underwent a total laryngectomy with positive surgical margins of resection and received palliative radiation (unknown dose) and chemotherapy (unknown number of cycles), but still died with disease 7 months after presentation. This patient also had previous radiation exposure. The second patient (patient no. 4) received an incomplete course of radiation therapy, which was stopped because of radiation mucositis, and he too died with disease at 32 months. The third patient (patient no. 5) also received radiation therapy, but since she was a foreign patient (from Denmark), long-term follow-up information was not available. The patient with a history of breast cancer (patient no. 1) had been managed with radiation therapy 7 months before the development of the LA. She later developed additional breast cancer metastasis, one of which was to the skull. She received 3000 cGy of palliative radiation to her skull. She died with widely disseminated breast carcinoma, but no autopsy was performed and there was no documentation of recurrent or metastatic angiosarcoma. Therefore, her disease status when she died at 11 months is unknown. Regardless of the adjuvant therapy, the overall prognosis was poor, with 3 of 4 patients dying (mean, 17 mo), and only one patient remaining alive at 18 years after receiving only a wide excisional biopsy (no radiation therapy). Interestingly, this patient was the youngest patient (29 y) in the series.

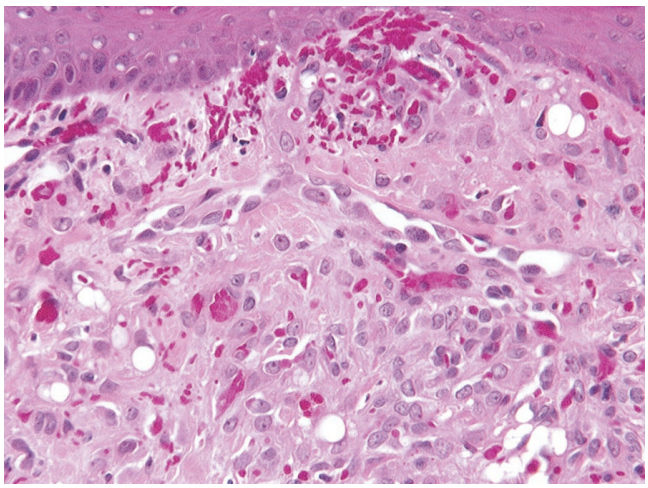

Fig. 1. An uninvolved surface epithelium is seen overlying the vascular proliferation of moderately atypical cells.

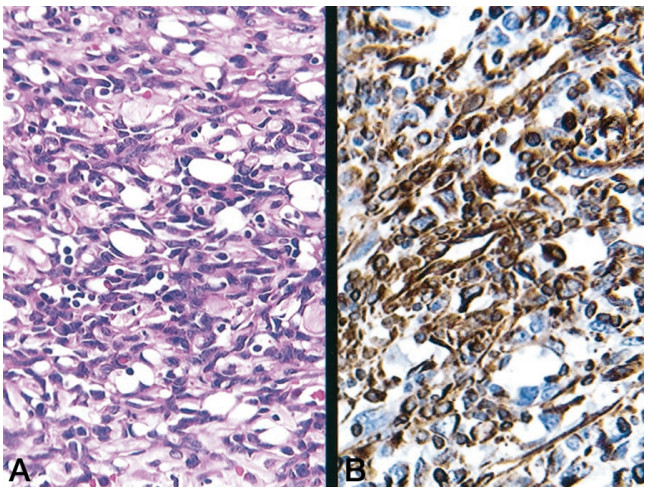

Fig. 3. The atypical cells lining the anastomosing vascular channels (**A**) are strongly and diffusely immunoreactive with Factor VIII-RAg, confirming the vascular origin of the tumor cells (**B**).

DISCUSSION

Primary laryngeal sarcomas, with the exception of chondrosarcomas, are uncommon malignancies, and primary LA is extremely rare with only eight well-documented and histologically confirmed cases reported in the English literature.[1–9] Yankauer reported the first documented case of laryngeal angiosarcoma in *The Laryngoscope* in 1924, although only a single paragraph was devoted to the description.[9] The case reports are summarized in Table I. While the cases reported by Haven et al. have been included in the series review, their descriptions state they were "fibrous-appearing nodules" and "polypoid-appearing nodules," with "low grade tumor" used to describe the unillustrated histology. A clear diagnosis of LA is unconfirmable; therefore, these cases have not been included in a summary of the data.

Based on a compilation of the English literature and this clinical series, LA occurs in men twice as frequently as women (male:female ratio, 2.3:1), with a mean age at presentation of 61.7 years.[1–9] Most patients present with symptoms related to the tumor location, with hoarseness being the most common (n = 6), along with dysphagia, dysphonia, dyspnea, hemoptysis, and pain. The symptoms are usually present for a mean of 5 months, with a range of 1–18 months reported.[1–9]

Three of 13 (23.1%) patients (2 from this clinical series and 1 from the literature[8]) had received previous adjuvant radiation therapy for other malignancies but subsequently developed a LA. It is well known that radiation exposure is a likely predisposing risk factor for cutaneous and mucosal angiosarcoma.[10,21] However, while radiation-associated LAs may occur in a number of patients (23%), the development of LA in more than 75% of patients who have not been exposed to radiation suggests that radiotherapy is an etiologic factor, but perhaps not a major pathogenic factor. The determination of radiation risk is further complicated by the exposed patients receiv-

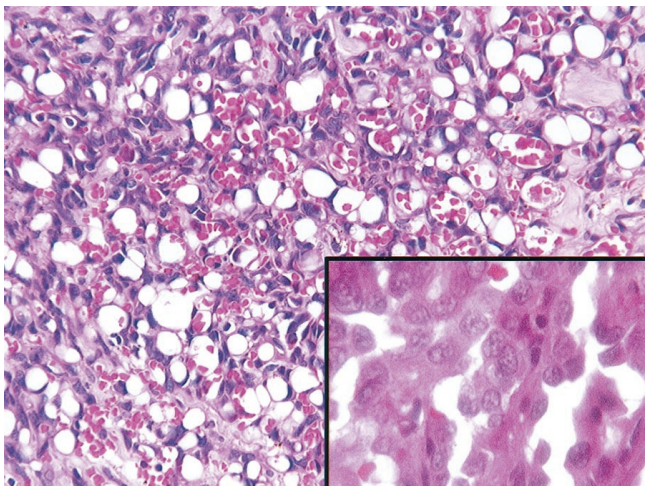

Fig. 2. Intermediate power demonstrating the anastomosing vascular channels lined by atypical endothelial cells. The inset demonstrates "hobnailing" of the atypical endothelial cells into the vascular lumen.

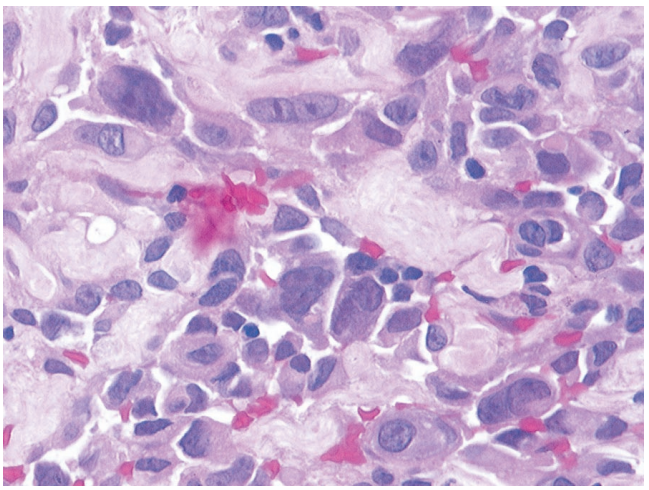

Fig. 4. High power demonstrating remarkable cytologic atypia of the endothelial cells in a laryngeal angiosarcoma.

ing variable doses and differing latent periods (in this clinical series between 7 mo and 10 y) from the radiation exposure to development of the LA. In fact, the development of an angiosarcoma only 7 months after radiation therapy (patient no. 1) is etiologically suspect, because, in general, the latent period is usually longer.[10]

Even though there are only a few patients to report, the majority of LAs develop in the supraglottis (61.5%), with the epiglottis involved most often. The remaining tumors develop in the glottis (30.8%) or the subglottis (7.7%). Patient no. 2's tumor was described as 9.1 cm in size and originating from the supraglottis. However, given its dimensions as well as positive surgical margins, the tumor likely involved the glottis. With so few cases, it is impossible to determine whether the site (supraglottis, glottis, or subglottis) makes a significant difference in the clinical outcome, even though in this clinical series supraglottic tumors had a better overall outcome (mean follow-up, 54.2 mo) than patients with glottic (mean follow-up, 7.5 mo) or subglottic (died at 10 mo) tumors. The analysis of a greater number of tumors would be needed before a meaningful statement about site of involvement could be made.

The size of cutaneous and soft tissue angiosarcomas is found to be a significant prognostic indicator,[10] and there is a trend for LAs of a larger size to be associated with a worse outcome. Nonetheless, because of the small number of cases, no statistical inferences can be made until additional cases are analyzed.

Surgical excision is the treatment of choice for angiosarcomas.[1–10,15] While adjuvant radiation therapy has a role in advanced local and regional disease and for recurrences,[3,5,7,13] in general, based on this series and the cases reported in the literature, complete surgical excision achieves a slightly longer patient survival (mean follow-up, 64.4 mo) than patients treated with a combination of surgery and radiation therapy (mean follow-up, 22.9 mo).[13] When a patient develops recurrence, wide surgical excision followed by adjuvant therapy (radiation or chemotherapy) may be of value in prolonging the survival, but not in changing overall mortality. Therefore, it can be inferred from review of this series and the English literature that radiation therapy may not yield a distinct survival advantage. Given the limited number of cases, however, no specific recommendations can be made about therapy at this point, especially because a number of different protocols were used over a wide period of time and from multiple different centers.

Overall, 55% of patients in whom follow-up was available died of their disease with a mean survival of 18.4 months. The patient outcome does not appear to be influenced by gender, age, anatomic site, or treatment. The size of the tumor may be of significance. The average survival of patients who had been previously exposed to radiation was much shorter (mean survival, 10.3 mo) than the average survival for patients who had not been exposed to radiation (mean survival, 53.4 mo). Therefore, these findings suggest that a patient with a LA and prior radiation exposure appears to have a lower survival rate versus a patient without radiation exposure.[8] This may be secondary to a more aggressive tumor type. Once again, with only a limited number of patients, it is difficult to make a definitive statement.

While angiosarcoma has characteristic histomorphologic and immunophenotypic features, it has often been confused histologically with other vascular entities, including angiolymphoid hyperplasia with eosinophilia (ALHE), intravascular papillary endothelial hyperplasia (Masson's disease), contact ulcer, lobular capillary hemangioma, hemangiopericytoma, Kaposi's sarcoma, malignant melanoma, and fibrosarcoma.[1,26–29] ALHE and lobular capillary hemangioma are not lesions that occur in the larynx. Masson's disease involves a large vessel or an area of clot organization and is usually without cytologic atypia.[27] A contact ulcer usually involves the posterior glottis, usually has a known antecedent event, and has a rich granulation tissue with surface ulceration and fibrinoid necrosis. Cellular atypia is characteristically absent.[26] Hemangiopericytoma has a distinctive architectural arrangement with monotonous small- to medium-sized cells with ovoid nuclei and usually without cytologic atypia.[28] Malignant melanoma has a protean histology and is immunoreactive with S-100 protein and HMB-45. Fibrosarcoma is not immunoreactive with the vascular markers (FVIII, CD34, CD31).[30] Kaposi's sarcoma is composed of compact, coalescing, and sheet-like interlacing fascicles of tumor cells but without anastomosing vascular channels. Even though the endothelial spindle cells are atypical, they tend to be monotonous and uniform. Extravasated erythrocytes and hemosiderin pigment are easily identifiable, along with characteristic eosinophilic, glassy-hyaline globules found both intra- and extracellularly. Furthermore, human herpesvirus-8 is known to occur in Kaposi's sarcoma and not in angiosarcoma.[29,31]

CONCLUSION

In summary, patients with LA typically present clinically with hoarseness, dysphagia, or hemoptysis with many of the lesions located in the supraglottis. Prior radiation exposure is likely a contributing factor in its evolution. Adjuvant radiation therapy may not be of therapeutic benefit, although given the limited number of cases in this series, no definitive conclusions can be drawn about therapy. Despite surgical excision with or without adjuvant radiation therapy, patients have a poor prognosis regardless of anatomic location, gender, or race. Large tumor size and previous radiation exposure seem to be associated with a worse patient outcome. Early detection of these uncommon, aggressive sarcomas requires a high degree of clinical as well as pathologic suspicion and is paramount in maximizing patient survival. Further study involving a larger cohort of patients is necessary to determine if other factors may be of significance in predicting patient outcome.

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