Am J Otolaryngol 40 (2019) 102285

Contents lists available at ScienceDirect

Am J Otolaryngol

journal homepage: www.elsevier.com/locate/amjoto

Hematologic malignancies of the larynx: A single institution review

Karuna Dewan*, Ross Campbell, Edward J. Damrose

Division of Laryngology, Department of Otolaryngology-Head and Neck Surgery, Stanford University School of Medicine, United States of America

ARTICLE INFO

Keywords:
Hematologic malignancy
Submucosal mass
Supraglottic mass

ABSTRACT

Background: Primary hematologic malignancies of the larynx are rare diagnoses, accounting for less than 1% of all laryngeal tumors. They most commonly present as submucosal masses of the supraglottis, with symptoms including hoarseness, dysphagia, dyspnea and rarely cervical lymphadenopathy.

Purpose:

1. To present a case series of primary hematologic malignancies of the larynx in patients treated in a tertiary care laryngology practice.
2. To review the literature on primary hematologic malignancy of the larynx.

Methods: Retrospective case series of patients in a tertiary academic laryngeal practice with hematologic malignancy of the larynx presenting over a 10 year period; charts were reviewed for diagnosis, symptoms, treatment, and outcomes.

Results: 12 patients were found to have primary presentation of a hematologic malignancy within the larynx between 2009 and 2019. A submucosal mass was the most common finding, and hoarseness was the most common symptom. Local control of disease was high. Airway obstruction was managed with tracheostomy. Several patients required tube feeding prior to disease control. Most patients underwent radiation therapy and chemotherapy, although surgery alone was effective in patients with isolated disease.

Conclusions: Hematologic malignancies of the larynx are rare but treatable. Biopsy is the mainstay of diagnosis, and imaging may be helpful to exclude diseases with a similar physical presentation (i.e., laryngocele). Prognosis depends on diagnosis but is generally favorable.

1. Introduction

Primary hematologic malignancies of the larynx are exceedingly rare diagnoses, accounting for less than 1% of all laryngeal neoplasms [1]. This group of malignancies includes plasmacytosis, non-Hodgkin lymphoma, Hodgkin lymphoma, acute myelogenous lymphoma (AML) and acute lymphocytic lymphoma (ALL). Malignant lymphomas are further divided into non-Hodgkin lymphomas (NHL) and Hodgkin lymphomas. The subtypes of NHL include diffuse large B-cell lymphoma, mucosa-associated lymphoid tissue (MALT), T-cell lymphoma and natural killer (NK) cell lymphoma. Primary lymphomas of the larynx are most commonly NHL and predominantly involve the supraglottis, as this subsite of the larynx contains follicular lymphoid tissue [1,2]. B-cell lymphoma and MALT are the most common types of NHL found within the larynx.

The presenting symptoms of laryngeal lymphoma include dysphagia, dysphonia, dyspnea and cervical lymphadenopathy. These nonspecific signs and symptoms can make rapid diagnosis of a laryngeal primary presentation of hematologic malignancy difficult. Given their rarity, clinicians may not immediately consider these entities in the differential diagnosis, potentially leading to a diagnostic delay. Flexible laryngoscopy reveals most commonly a polypoid supraglottic submucosal mass that is smooth and nonulcerated. The diagnosis rests on the ability to obtain adequate deep biopsies on which to perform histologic examination.

Hematologic malignancies of the larynx are an important consideration in the differential diagnosis of laryngeal tumors. These entities are treated with a combination of radiation and chemotherapy, rather than surgery. The early detection of this group of malignancies, particularly lymphoma allows for improved patient care and may result in decreased spread of disease [3].

The larynx is a rare site of localization of a primary lymphoma because of the relatively low lymphoid content of this area [4]. Imaging techniques including computed tomography (CT) and magnetic resonance imaging (MRI) are helpful, as is visualization with laryngoscopy. A smooth submucosal swelling or polypoid mass without

* Corresponding author at: 801 Welch Road, Palo Alto, CA 94305, United States of America.
E-mail address: kdewan@stanford.edu (K. Dewan).

https://doi.org/10.1016/j.amjoto.2019.102285
Received 3 June 2019
0196-0709/ © 2019 Elsevier Inc. All rights reserved.

ulceration are the usual physical examination findings of primary laryngeal lymphomas [5]. Primary laryngeal lymphomas usually arise from the supraglottic region, specifically from the epiglottis and aryepiglottic folds [3]. Histopathologic examination is essential for definite diagnosis. Phenotypic analyses are often necessary including flow cytology or immunohistochemistry. Treatment is nonsurgical with chemotherapy and radiation being the most common modalities. The purpose of this investigation is first to present a case series of primary hematologic malignancies of the larynx in patients treated in a tertiary care laryngology practice, and secondly to review the literature on primary hematologic malignancies of the larynx. The underlying goal of this work is to expand the recognition and understanding of this distinct entity eventually leading to improved recognition and diagnosis.

2. Materials and methods

This study protocol was approved by the institutional review board. From a single-institution Otolaryngology patient database, a patient list was gathered by identifying specific International Classification of Diseases (ICD-9) diagnosis codes (C81– C96) for malignant neoplasm of lymphoid, hematopoietic or related tissue over the 10-year period between January 2009 and January 2019. A retrospective chart review was performed of all identified patients who subsequently underwent direct laryngoscopy with biopsies identified using Current Procedural Terminology (CPT) codes 31535, 31540, and 31541. Demographics, clinic notes, operative reports, pathology reports, hospital records and follow-up data were recorded. Patients were included in the study if they were at least 17 years old at the time of diagnosis of primary laryngeal hematologic malignancy. Post-treatment complications and ultimate treatment outcomes were reviewed. Exclusion criteria included: age under 17 years at time of diagnosis, laryngeal involvement in hematologic malignancy with primary lesion located elsewhere in the body, other head and neck malignancy.

Demographic and clinical data recorded included age at the time of presentation, gender, pathologic diagnosis, presenting symptoms, site of malignancy within the larynx, method of diagnosis, treatment, outcome, tracheostomy status and gastrostomy tube status.

3. Results

Between January 2009 through January 2019, 12 patients were diagnosed with a primary hematologic malignancy of the larynx (Table 1). The average age at the time of diagnosis was 69.3 ± 15.4 years. The cohort was 42% male. The most common presenting symptom was hoarseness (75%). Other presenting symptoms included dyspnea (16.7%), globus pharyngeus (8.3%), odynophagia (8.3%), Otalgia (8.3%). B symptoms were noted at the time of presentation in 8.3% of the cohort. Similarly, 8.3% of the cohort presented with palpable cervical lymphadenopathy. An overwhelming majority of tumors, 83.3% were located in the supraglottis. Laryngeal neoplasm comprised 8.3% of the cohort as did subglottic neoplasm. The was considerable heterogeneity in the various pathologies and treatment. 58.3% of the cohort was treated with chemotherapy alone. Radiation therapy alone was utilized in 16.7% of the cohort. A combination of chemotherapy and radiation therapy was used for 8.3%. Surgical excision was the sole intervention for 8.3% and lastly, one patient (8.3%) elected not to undergo any treatment and was managed with palliative care. The majority of the cohort (75%) achieved remission. One patient is currently undergoing treatment and two patients (16.7%) have died. Of the 75% who attained remission, two patients subsequently recurred and ultimately succumbed to their disease. Therefore, within the 10 year study period, 33% of the cohort died from hematologic malignancy.

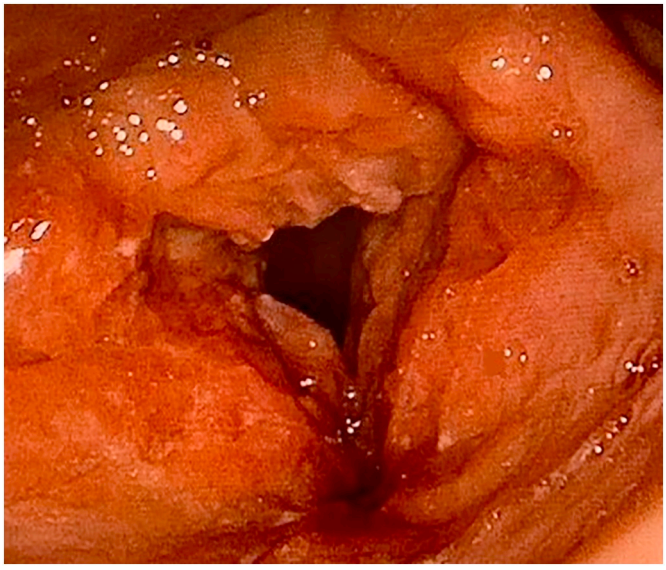

Fig. 1. Flexible fiberoptic laryngoscopy of a patient with NK-T cell lymphoma at the time of initial presentation.

Within this cohort, B-cell malignancy was the most common (41.7%), closely followed by plasmacytosis (33.3%). Surprisingly 16.7% of the cohort was diagnosed with NK/T cell lymphoma. One case (16.7%) of T-cell lymphoma was identified. Within the cohort 41.7% presented with stage I disease, 41.7% with stage 2 disease and 16.7 presented with advanced, or stage 4 disease.

4. Discussion

Hematologic malignancies of the larynx are an uncommon but treatable cause of hoarseness, airway obstruction, globus and chronic cough, if diagnosed early in their course. They present as supraglottic submucosal masses and require multiple deep biopsies for accurate

Table 1
Cohort characteristics.

Patient	Age	Gender	Symptom	Diagnosis	Location	Lymphadenopathy	Treatment	Outcome
1	67	F	Hoarseness	Plasmacytosis	Supraglottis	No	Chemotherapy	Local control
2	74	F	Hoarseness	MALT	Supraglottis	No	Surgical excision	Cure
3	66	F	Hoarseness	NKT cell lymphoma	Supraglottis	No	Chemotherapy & Radiation	Recurrence
4	41	M	Hoarseness	NKT cell lymphoma	Supraglottis, larynx, nasopharynx	Yes	Chemotherapy	Ongoing treatment
5	92	F	Hoarseness	Diffuse B cell lymphoma	Supraglottis	No	Chemotherapy	Recurrence
6	83	M	Hoarseness	Diffuse B cell lymphoma	Supraglottis	No	Chemotherapy	Cure
7	56	F	Dyspnea	T-cell lymphoma	Subglottis	No	Chemotherapy	Cure
8	67	M	Hoarseness	AML	Supraglottis (left)	No	Chemotherapy	Death
9	77	F	Hoarseness	Follicular lymphoma	Supraglottis (left)	No	Radiation	Local control
10	54	F	Globus	Plasmacytoma	Supraglottis (left)	No	Radiation	Cure
11	62	M	Hoarseness	Follicular lymphoma	Supraglottis (left)	No	Chemotherapy	Cure
12	93	M	Dyspnea	Hodgkin lymphoma	larynx	No	Palliative care	Death

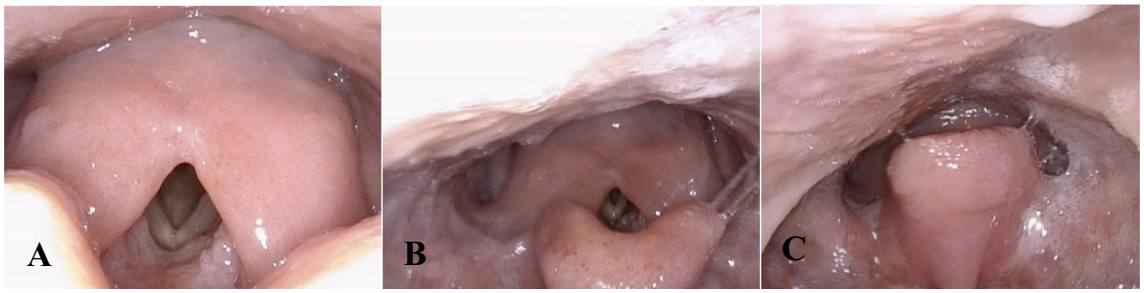

Fig. 2. Flexible fiberoptic laryngoscopy showing A: enlarged false vocal folds, B: enlarged epiglottis, C: enlarged lingual surface of the epiglottis secondary to plasmacytosis.

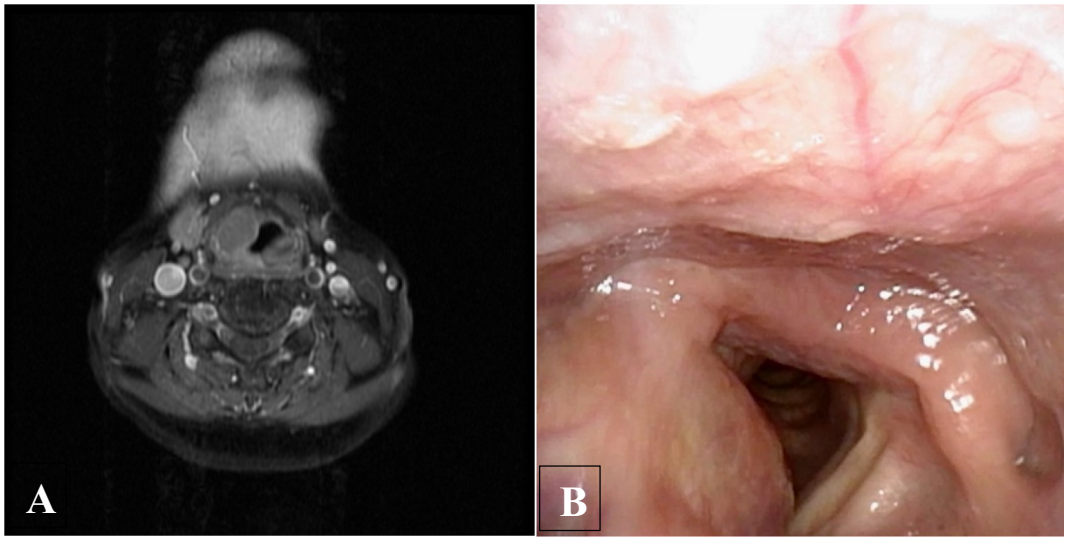

Fig. 3. A: MRI demonstrating uniformly enhancing supraglottic mass. B: Flexible fiberoptic laryngoscopy demonstrating supraglottic mass later diagnosed as marginal zone lymphoma.

diagnosis. A high index of suspicion on the part of the Otolaryngologist is crucial to make the diagnosis, which is often delayed due to non-specific signs and symptoms at presentation. As noted here and throughout the literature, this group encompasses two main types of malignancy, most commonly Non-Hodgkin lymphoma and rarely Hodgkin lymphoma.

4.1. Non-Hodgkin lymphoma

The head and neck is the second most common extranodal site of involvement of non-Hodgkin lymphoma, however the larynx is rarely involved, with structures typically affected being Waldeyer's ring, ocular adnexal structures, the nasal cavity, nasopharynx, paranasal sinuses, thyroid gland and salivary glands. Primary non-Hodgkin lymphoma of the larynx was initially reported by MacKenty in 1934 [6]. The average age within the literature of NHL of the larynx is the seventh decade with male predominance [7]. While the average age of this cohort was 69.3 ± 15.4 years, consistent with the accepted average age, the cohort presented here was only 41.7% male. This cohort was small, containing only 12 patients, and therefore it is within reason that less than half were male even though this is a male-dominated pathology. The most common types of Non-Hodgkin lymphoma in the larynx include mucosa-associated lymphoid tissue (MALT) lymphoma, plasmacytoma and diffuse large B-cell lymphoma. T-cell laryngeal lymphoma is much less common than B-cell lymphoma. The cohort presented here reflects these differences 83.3% of the cohort was diagnosed with non-Hodgkin lymphoma. This group was comprised of plasmacytoma (20%), NK-T cell lymphoma (20%), diffuse large B cell lymphoma (20%), Follicular lymphoma (20%), T cell lymphoma (10%) and MALT (10%).

Rahman et al. indicated that the most commonly reported symptoms, like those experienced by members of this cohort are progressive hoarseness, dyspnea, dysphagia, globus and dysphonia [8]. Some patients also suffer from chronic cough unresponsive to any treatment. Early symptoms are nonspecific; therefore it is difficult to confirm the diagnosis. Patients with primary laryngeal non-Hodgkin lymphoma most often present without systemic “B-type” symptoms of fever, night sweats and weight loss [9]. In this cohort only one patient presented with B symptoms. Additionally, Kim et al. found that the presence of B-symptoms is a significant prognostic indicator when assessing the efficacy of treatment [10]. Those patients with primary laryngeal NHL are unlikely to have very advanced disease as they tend to present early with voice changes and unrelenting hoarseness. Endoscopic examination usually shows a localized polypoid submucosal and non-ulcerated swelling with a smooth surface on endoscopy [11] (Fig. 1). Non-Hodgkin lymphoma is commonly localized in the supraglottic area and subglottic areas as there is more lymphoid tissue in these areas (Fig. 2.) This lymphoid tissue exists primarily in the lamina propria and the ventricles. In certain cases, lymphoma may affect the glottis, however, the majority of cases occur in the supraglottic or transglottic regions [12]. Lymphomas can also involve surrounding structures including the salivary glands, thyroid, nasopharynx and tonsils. Dissemination may eventually occur to other sites in the respiratory tract, stomach, lung, orbit or skin.

Typical imaging characteristics include large uniformly enhancing lesion without central necrosis and cervical lymphadenopathy [3]. This

is consistent with the presentation of all 12 patients in this cohort (Fig. 3). A number of deep biopsies and flow cytometry analysis are required to distinguish the tumor from inflammatory cells. A meta-analysis by Kim et al. report an average of 1.4 biopsies are required to establish diagnosis of primary laryngeal lymphoma [10]. It may become necessary to perform a bone marrow biopsy if primary hematologic malignancy of the larynx is suspected. A misdiagnosis of undifferentiated tumor or chronic inflammation due to ambiguous morphology is not uncommon [9].

Wang et al. indicated that most patients with NHL already exhibit bone marrow or peripheral blood involvement at the time of diagnosis, as well as mediastinal masses, lymphadenopathy and organomegaly [13]. This was not true of the patients in the cohort presented here. None of the 12 patients in this group demonstrated bone marrow or peripheral blood involvement at the time of diagnosis. While only one patient in our cohort demonstrated cervical lymphadenopathy, other cohorts have reported the presence of cervical lymphadenopathy upon initial presentation.

Radiotherapy and chemotherapy are the most common therapeutic strategies used for the treatment of primary laryngeal lymphomas. T-cell lymphoma represents a group of aggressive diseases requiring chemotherapy with or without radiation. Within this cohort 50% of those who died had a T-cell malignancy.

Surgery may be essential as the first line of treatment if laryngeal obstruction or massive hemorrhage is identified [1]. Within this cohort 33% required tracheostomy for control of airway. Half of those patients were able to be decannulated after completion of treatment for their hematologic malignancy. 25% of the cohort required a feeding tube at some time during their treatment. One of these patients was able to have the feeding tube removed at the conclusion of treatment. For those patients who continued to require either tracheotomy or feeding tube after treatment completed, the radiation treatment was a key component in reducing laryngeal function leading to aspiration.

Previous treatment for Hodgkin lymphoma, especially radiation therapy, is a primary risk factor in the development of subsequent lymphoma [14]. In the cohort presented here only two of the 12 (16.7%) patients had a history of malignancy. They both had Hodgkin lymphoma that was treated with radiation. One patient developed recurrent Hodgkin lymphoma, presenting within the larynx. The incidence of Hodgkin lymphoma within the larynx is exceedingly rare.

5. Conclusion

Primary laryngeal hematologic malignancies may present a diagnostic challenge given that they are rare and can present with nonspecific phonatory or respiratory symptoms. It is imperative that otolaryngologists be vigilant when evaluating patients with prolonged hoarseness and supraglottic submucosal masses. Primary laryngeal hematologic malignancy should be considered when formulating differential diagnosis of mases in the neck region, especially the supraglottis. Given low suspicion for disease and heterogeneity in morphology and non-specific phenotypic findings, these conditions may be underdiagnosed as reactive inflammation or misdiagnosed as non-hematologic tumors. It is important to consider not only the laryngeal examination but also the presence of B-symptoms during initial examination.

References

[1] Markou K, Goudakos J, Constantinidis J, Kostopoulos I, Vital V, Nikolaou A. Primary laryngeal lymphoma: report of 3 cases and review of the literature. Head Neck 2010;32(4):541–9.
[2] Horny HP, Kaiserling E. Involvement of the larynx by hemopoietic neoplasms. An investigation of autopsy cases and review of the literature. Pathol Res Pract 1995;191(2):130–8.
[3] Siddiqui NA, BFt B, Hamilton BE, et al. Imaging characteristics of primary laryngeal lymphoma. AJNR Am J Neuroradiol 2010;31(7):1261–5.
[4] Laurini JA, Perry AM, Boilesen E, et al. Classification of non-Hodgkin lymphoma in Central and South America: a review of 1028 cases. Blood 2012;120(24):4795–801.
[5] Gokdogan O, Koybasioglu A, Ismail E, et al. Hoarseness: an unusual presentation of primary thyroid lymphoma with laryngeal infiltration. Braz J Otorhinolaryngol 2016;82(6):737–40.
[6] Franzen A, Kurrer MO. Malignant lymphoma of the larynx: a case report and review of the literature. Laryngorhinootologie 2000;79(10):579–83.
[7] Ansell SM, Habermann TM, Hoyer JD, Strickler JG, Chen MG, McDonald TJ. Primary laryngeal lymphoma. Laryngoscope 1997;107(11 Pt 1):1502–6.
[8] Rahman B, Bilal J, Sipra QU, Riaz IB. All that wheezes is not asthma: a case of diffuse large B-cell lymphoma of the larynx. Case Rep Oncol Med 2017;2017:7072615.
[9] Broadwater DR, Peker D. Systemic non-Hodgkin T cell lymphomas presenting in the head and neck region: an institutional experience of a rare entity. Head Neck Pathol 2018;12(4):481–7.
[10] Kim KH, Kim RB, Woo SH. Individual participant data meta-analysis of primary laryngeal lymphoma: focusing on the clinical characteristics and prognosis. Laryngoscope 2015;125(12):2741–8.
[11] Liu M, Liu B, Liu B, et al. Mucosa-associated lymphoid tissue lymphoma of the larynx: a case report and literature review. Medicine (Baltimore) 2015;94(17):e788.
[12] King AD, Yuen EH, Lei KI, Ahuja AT, Van Hasselt A. Non-Hodgkin lymphoma of the larynx: CT and MR imaging findings. AJNR Am J Neuroradiol 2004;25(1):12–5.
[13] Wang L, Ma Y, Chen B, Tang F, Xu X, Lin G. Primary laryngeal manifestation in precursor T-cell acute lymphoblastic leukemia. Oncol Lett 2015;9(2):691–4.
[14] Henry-Amar M. Second cancer after the treatment for Hodgkin's disease: a report from the International Database on Hodgkin's Disease. Ann Oncol 1992;3(Suppl. 4):117–28.