Laryngeal Manifestations of Hematologic Malignancies

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1. Background

- Hematologic malignancies make up less than 1% of all laryngeal malignancies
- This includes a large variety of malignancies including chronic and acute leukemias and lymphomas
- Primary hematologic malignancies of the larynx are most commonly non-Hodgkin's lymphomas and most commonly found in the supraglottis as it contains follicular lymphoid tissue
- Requires high clinical suspicion to diagnose, often requiring multiple deep biopsies to diagnose along with immunohistochemical staining or flow cytometry
- This series aims to describe three different cases of hematologic malignancies presenting in the larynx along with a review of the literature to provide guidelines for when this condition should be considered

2. Methods

- Retrospective case series of three adult patients with hematologic malignancies of the larynx
- Demographic data, medical history, exam including laryngoscopy, histopathology, oncologic treatment, and clinical course were reviewed
- Existing literature was identified via PubMed search and was reviewed and summarized

3. Results

Patient	Age	Gender	Malignancy History	Alcohol Use	Tobacco Use
A	73	Male	CLL/SLL	7 drinks a week	Never
B	72	Male	None	Rarely	Never
C	69	Female	None	Never	Never

Table 1. *Patient Demographics and Head and Neck Cancer Risk Factors.* Patient's age, gender, malignancy history at presentation, alcohol use, and tobacco use history. Patient A was undergoing treatment for CLL/SLL with acalabrutinib (a Bruton's Tyrosine Kinase Inhibitor). CLL – chronic lymphocytic leukemia. SLL – small lymphocytic leukemia

Patient	Presenting Symptom	Location	Diagnosis
A	Dysphagia/Cough	Supraglottis	CLL/SLL
B	Globus Sensation	Epiglottis	DLBCL
C	Dyspnea on Exertion	Subglottis	MALT Lymphoma

Table 2 *Clinical characteristics of patients presenting with hematologic malignancies of the larynx.*. Presenting symptom, location, and final diagnosis. CLL – chronic lymphocytic leukemia. SLL – small lymphocytic lymphoma, DLBCL – diffuse large B-cell lymphoma, MALT – mucosa-associated lymphoid tissue

Patient	Time to Presentation	Surgical Intervention	Time to Diagnosis
A	7 months	DLB	37 days
B	3 months	Awake trach, DLB	6 days
C	2 years	DLB	38 days

Table 3. *Time to presentation, diagnosis, and surgical intervention for patients with hematologic malignancies.* Time to presentation determined by patient reported duration of symptoms before first clinic presentation. Time to diagnosis is calculated as time between first presentation and tissue diagnosis. Surgical intervention; awake trach – awake tracheostomy, DLB – direct laryngoscopy and biopsy.

Patient	Treatment	Outcome
A	Previous BR, Acalabrutinib	PEG, Obinutuzumab, and venetoclax
B	CHOP chemotherapy	PEG, remission, decannulation
C	Radiation	Recurrence-BR, in remission

Table 4. *Treatments and outcomes of patients with hematologic malignancies.* Patient A had known active disease at the time of presentation with laryngeal involvement but required regimen switches due to progression of laryngeal involvement. BR – bendamustine (alkalating agent) and rituximab (anti-CD20 antibody). Obinutuzumab – anti-CD20 antibody. Venetoclax – BCL2 inhibitor. CHOP – Cyclophosphamide, Hydroxydoxorubicin (Doxorubicin), Vincristine, and Prednisone a common multimodal chemotherapy regimen . PEG – percutaneous endoscopic gastrostomy tube.

3. Results

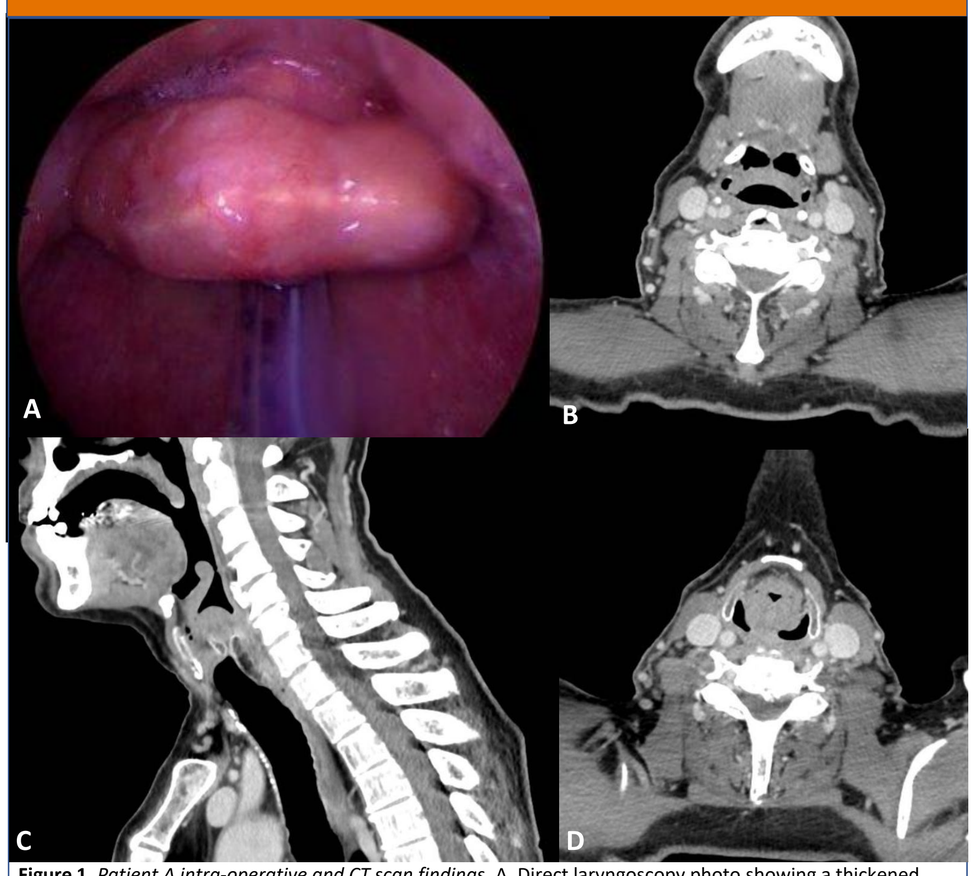

Figure 1. *Patient A intra-operative and CT scan findings.* A. Direct laryngoscopy photo showing a thickened epiglottis which was biopsied. B. Axial cut of initial CT scan demonstrating thickened epiglottis. C. Sagittal cut of initial CT scan demonstrating epiglottic and glottic thickening. D. Axial cut of the initial CT scan demonstrating bilaterally thickened aryepiglottic folds.

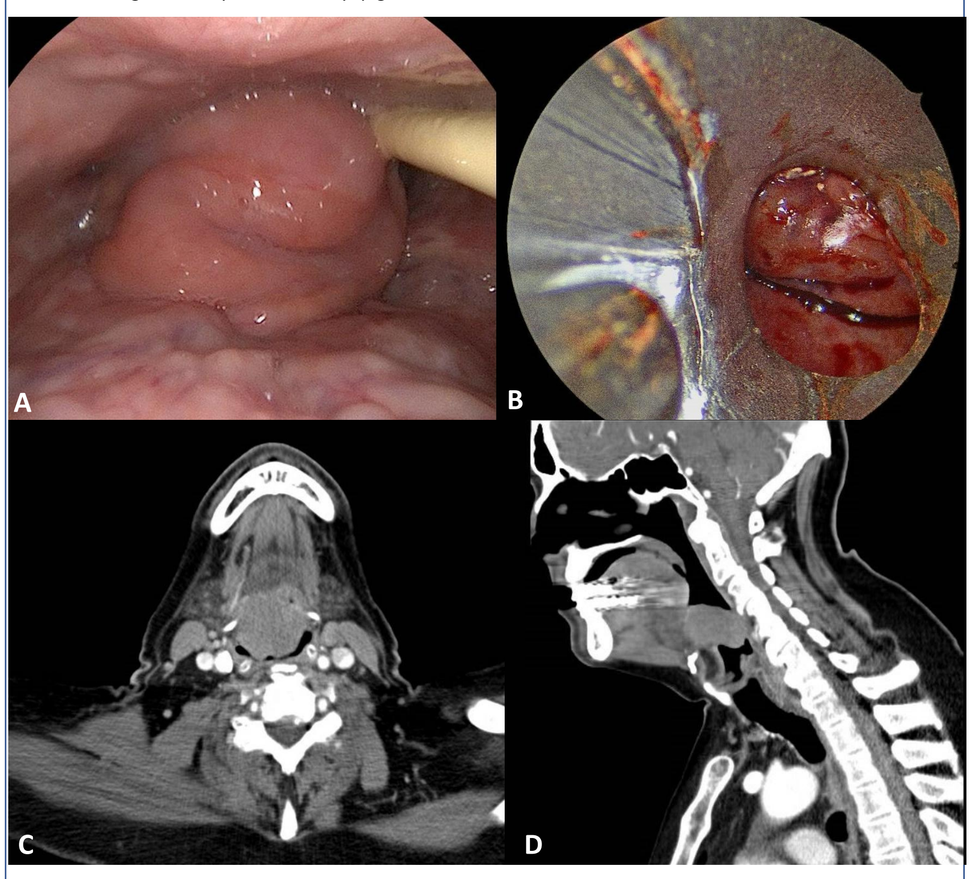

Figure 2. *Patient B flexible and direct laryngoscopy as well as initial imaging.* A. Flexible demonstrating large epiglottic mass blocking airway visualization. B. Direct laryngoscopy intra-operative image showing large epiglottic mass. C. Initial axial cut CT scan demonstrating large epiglottic mass with near complete obstruction of pharynx. D. Initial sagittal cut CT scan demonstrating large epiglottic mass nearly completely obstructing the airway.

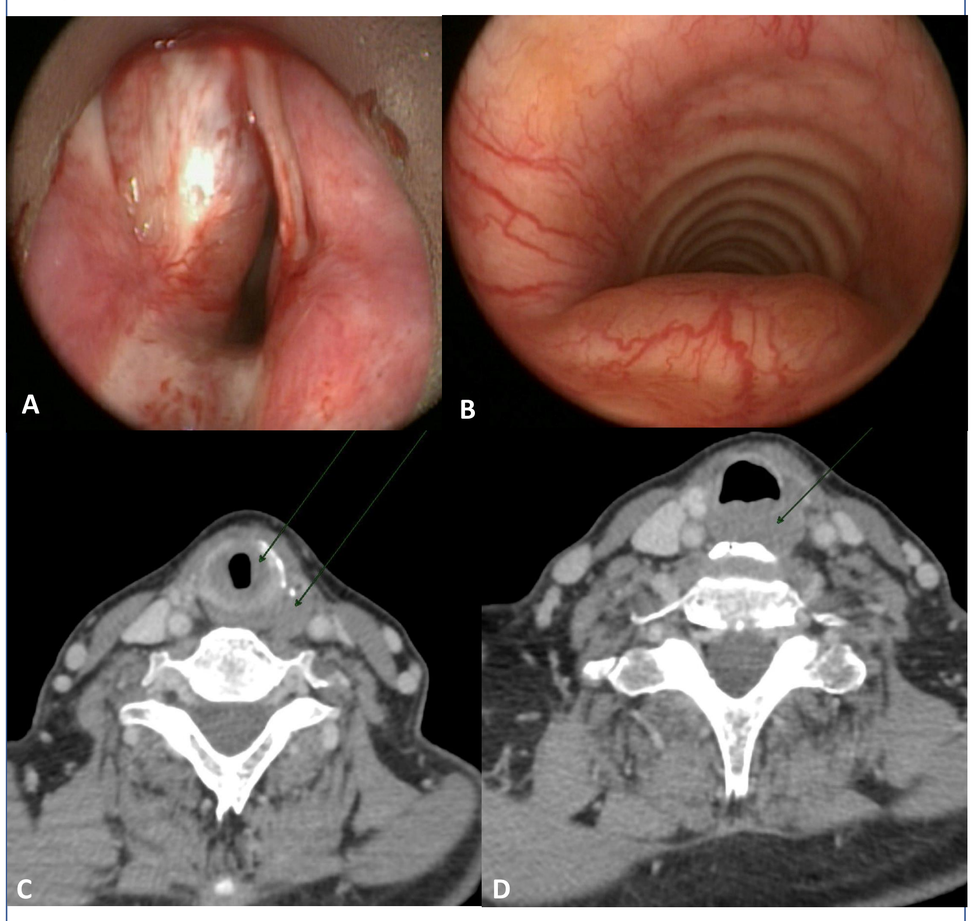

Figure 3. *Patient C direct laryngoscopy and initial imaging.* A. Direct laryngoscopy following initial evaluation and treatment with steroids demonstrating glottic mucosal irregularity. B. Direct laryngoscopy post-steroids demonstrating subglottic posterior wall submucosal mass/thickening C. Initial axial CT scan pre-steroids following initial in clinic evaluation demonstrating mucosal thickening/mass at the level of the glottis (arrows indicate thickening). D Initial axial CT scan demonstrating posterior tracheal wall thickening in the subglottis (arrow indicates thickening).

4. Discussion

In all three cases, patients presented with painless submucosal masses after several months of symptoms.

- The most common manifestations of primary laryngeal lymphoma include hoarseness, cough, dysphagia, globus sensation, stridor, and systemic symptoms

Two out of three of our patients had supraglottic cancers, both involving the epiglottis, although patient A had diffuse supraglottic disease and known CLL.

- The supraglottis is the most common site of primary hematologic malignancies of the larynx because there is more naturally occurring lymphoid tissue

All patients were taken to the operating room within a month for direct laryngoscopy and biopsy for prompt diagnosis and commencement of treatment. Flow cytometry was sent for all at initial biopsy.

- A meta-analysis by Kim et al. (2015) found that accurate biopsy was one of the few prognostic factors for patients diagnosed with a hematologic malignancy of the larynx

Two patients in our cohort required feeding tube placement and one required tracheostomy

- Similar to other head and neck malignancies, dysphagia and airway obstruction are not uncommon particularly if radiation is used as a treatment. This should be discussed with the patient once a diagnosis is established.

All patients were treated with some type of systemic therapy, although patient C was initially treated with radiation alone.

- Primary laryngeal lymphomas were traditionally treated with high dose radiation alone. The creation of targeted systemic therapies may be changing this approach. Population analysis by Hong *et al*. (2018) found no significant positive prognostic value of treatment with either chemotherapy or radiation, attributing this to often indolent course. Female sex and staging were only positive predictors

5. Conclusion

- Hematologic malignancies of the larynx are exceedingly rare cancers, but acute life-threatening laryngeal manifestations can be the first sign of disease
- In our cohort, these cancers were found in older patients without traditional risk factors for laryngeal cancer and without any pain symptoms
- Patients all underwent direct laryngoscopy and biopsy for tissue diagnosis, expedited biopsy (processed as fresh tissue for flow cytometry) leads to expedited diagnosis and treatment
- Otolaryngologists are critical to involve early in management due to the need for urgent airway intervention—specifically possible need for tracheostomy during treatment, as well as frequent monitoring for recurrence or progression in the larynx

6. References

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