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Case Report

Primary laryngeal lymphoma: a diagnostic challenge

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ABSTRACT

Lymphomas of head and neck constitute 5-15% of malignancies in this region. However, its primary occurrence at the larynx is exceedingly rare due to the paucity of lymphoid tissue. Here, we reported a case of a 41 year old male who presented with a 1 month history of hoarseness and odynophagia. The examination revealed right vocal cord palsy and an ipsilateral subglottic exudate, that was misdiagnosed as infectious disease. The lesion quickly progressed to airway obstruction, requiring a tracheotomy. Multiple biopsies under general anesthesia were needed before reaching the final diagnosis of diffuse large B-cell lymphoma, Epstein-Barr positive. Selected treatment modality included 3 cycles of chemotherapy followed by radiotherapy in moderate dose with complete remission after 2 years of follow up. The tracheotomy was removed, however, the patient did not recover vocal quality. This case highlighted the heterogeneous presentation of extra-nodal head and neck lymphomas and emphasized the need for suspicion of neoplasm when an infection doesn't respond to maximal medical therapy.

Keywords: Larynx, Diffuse B-cell lymphoma, Airway, Epstein-Barr

INTRODUCTION

Lymphomas comprise around 5 to 15% of malignancies of head and neck.[1] Non-Hodgkin lymphomas (NHL) are the most frequent, involving an extra-nodal site in 25% of cases, usually Waldeyer ring or salivary glands.[2]

Larynx is a rare location for primary NHL occurrence due to the paucity of lymphoid tissue and its involvement can be life threatening as it can compromise the airway. The largest series in the literature are based on case reports including multiple histologic subtypes, hampering the establishment of management guidelines.[3] We presented a case report of a patient diagnosed with primary laryngeal NHL, which presented some diagnostic difficulties. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

CASE REPORT

A 41 years old man was admitted to otorhinolaryngology department with a 1 month history of persistent hoarseness, initiated after viral infection. He also mentioned mild odynophagia, mucopurulent productive cough, night sweats and weight loss (4 kilograms in 2 months). He had been treated previously with amoxicillin plus clavulanic acid, ciprofloxacin and prednisolone, with no clinical improvement. He stopped smoking twenty years ago and denied alcohol abuse. Previous medical history was unremarkable.

Flexible fibrolaryngoscopy revealed right vocal fold palsy and a whitish ulcerated lesion on its anterior free border, with a gray-whitish exudate in the ipsilateral subglottic area (Figure 1). There were no palpable cervical lymph nodes or masses.

Computed tomography (CT) scan exposed right vocal fold asymmetry with an underlying paraglottic infiltrative

lesion extending to the subglottic region, with no abnormal cervical lymph nodes (Figure 2). Chest X-ray and blood count were unremarkable. Virologic and immunologic screening was negative. Erythrocyte sedimentation rate and angiotensin conversion enzyme felt within the normal range and protein C reactive was 22mg/dl.

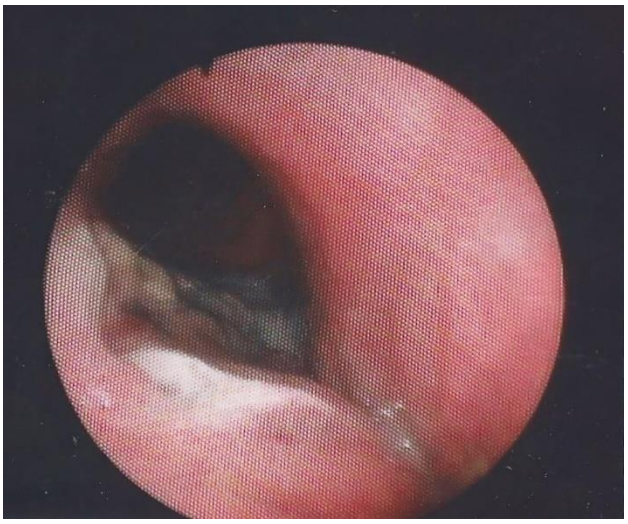

Figure 1: Fibrolaryngoscopy at initial observation showing the subglottic right region containing a grey whitish exudate.

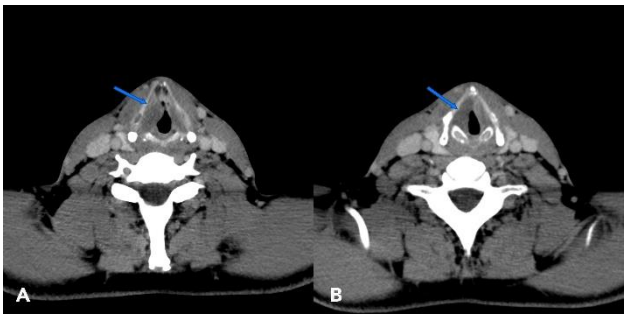

Figure 2: CT scan (axial views) at presentation showing an infiltrative hypodense mass (arrow) in the right paraglottic space (A) with extension to subglottic area (B).

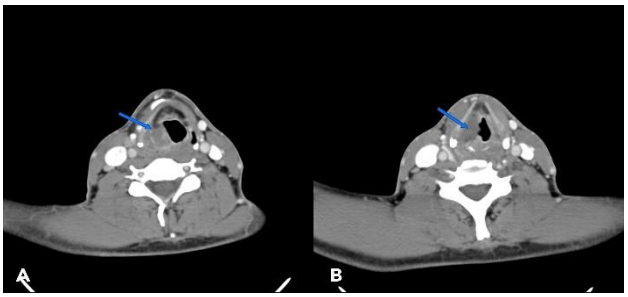

Figure 3: CT scan (axial views) after 1 week of initial observation showing a hypodense mass arrow in the right aryepiglottic fold (A) and the previous lesion in glottis/subglottic area with augmented dimensions (B).

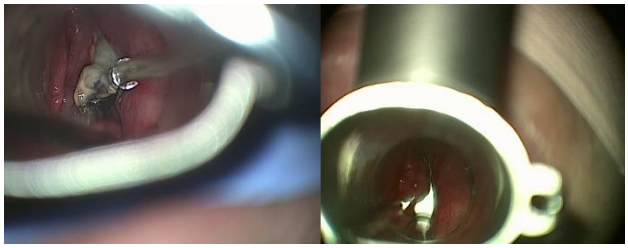

Figure 4: Direct laryngoscopy under general anesthesia. At left, aspiration of a necrotic/fungi thick exudate from subglottic region; right image showing irregular appearance of right vocal cord.

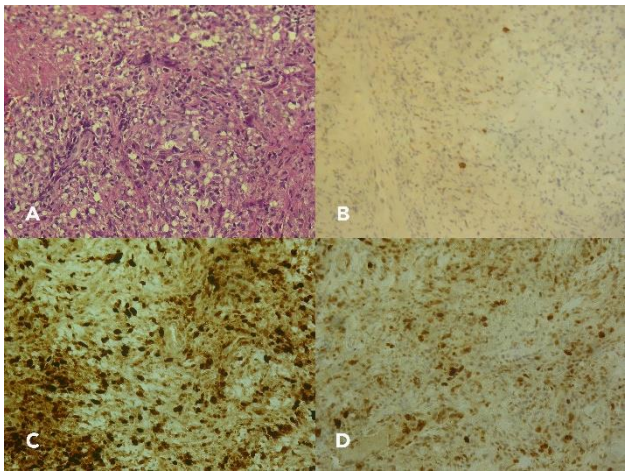

Figure 5: (A) Hematoxylin-eosin staining (100×) showing aggregates of neoplastic cells; (B-D) immunohistochemistry specimen staining showing positivity of CD20 (B), ki67 (C), MUM-1 (D).

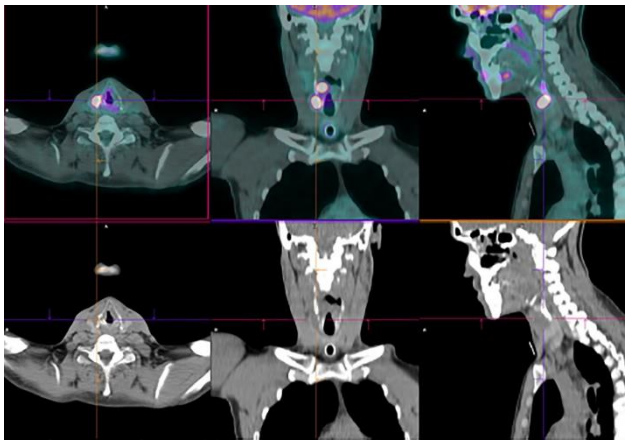

Figure 6: 18-fluorodeoxyglucose PET-CT scan revealing moderate/high metabolic activity in two places in larynx.

The first diagnostic option was infectious acute laryngitis caused by an atypical microorganism. This was supported by the presence of subglottic exudate after a presumptive viral infection, which conventional antibiotics didn't solve. A squamous cell carcinoma needed exclusion given the infiltrative mass in the CT scan and the

patient's previous smoking history. A granulomatous disease such as granulomatosis with polyangiitis was also considered, but the immunologic study was unremarkable. Other diagnostic hypotheses were laryngeal tuberculosis and lymphoma, supported by the presence of nocturnal hyperhidrosis. Therefore, the definitive diagnosis implied histologic characterization, so the patient was referred to biopsy in operating room.

However, the patient returned five days later due to sudden onset of medium effort dyspnea. Fibrolaryngoscopy demonstrated a bilateral supraglottic bulging, with a clear submucosal mass in the right side. Both vocal folds had an irregular contour, reduced mobility and glottis was markedly reduced (Figure 3). After mild improvement with intravenous corticosteroids, the patient was admitted for the biopsy of the affected tissue under general anesthesia. During the biopsy, the grey-whitish exudate was thick and easily removed, with a fungal or necrotic aspect (Figure 4). However, anatomopathological analysis was inconclusive, with necrotic fragments and inflammatory infiltrate.

Further blood studies were conducted. LDH levels and B2-microglobulin were both within normal range. Culture of secretions for mycobacterium tuberculosis was negative. Since the supraglottic bulging kept steadily growing after two weeks, a repeated and deeper biopsy with frozen sections and elective tracheotomy was performed. Nevertheless, histologic results were again inconclusive. In the third biopsy in the operating room, larger fragments from the subglottic region were removed until reaching the underlying cartilage and the supraglottic right mass was partially debulked. The histopathologic analysis finally revealed cells with morphology suggestive of malignancy. Immunophenotyping stained for CD45, CD20 and MUM1 and was negative for CD3, CD5 and bcl-6, so it was lastly classified as diffuse large B-cell lymphoma (DLBCL) (Figure 5). It was also positive for EBER, establishing a possible association with Epstein-Barr virus.

Afterward, thoraco-abominopelvic CT scan and bone marrow biopsy were performed and were unremarkable. Positron emission tomography (PET-CT) revealed the caption of 18-fluorodeoxyglucose (18-FDG) in two distinct sites of the larynx: one adjacent to the right thyroid cartilage at glottis/subglottic level and another in the right aryepiglottic fold (Figure 6). It was classified as stage IIE of Ann Arbor. Therefore, after the oncology team meeting decision, he performed 3 cycles of chemotherapy with RCHOP scheme (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) followed by radiotherapy (40 Gy in 22 fractions of 1,8 Gy for 2 months).

After treatment completion and two years of follow up, the patient remained in complete remission. The tracheostomy was removed after two years, however, he maintained poor vocal quality.

DISCUSSION

Primary hematopoietic laryngeal malignancies account for less than 1% of all laryngeal tumors, being DLBCL, one of the most frequent.[2] However, while DLBCL generally occurs around the seventh decade, in this case, the patient was slightly younger.

The clinical presentation includes non-specific symptoms like dysphagia, dysphonia, cough, dyspnea, globus sensation and systemic symptoms, which may delay diagnosis.[2-6] The duration of symptoms ranges from days to months.[3,5] In this case the lesion was relatively stable at presentation, suffering a rapid growth after one month that prompted urgent intervention.

The site most commonly involved in larynx is the supraglottis (47%), probably because of the presence of higher amount of lymphoid tissue in comparison with glottis and subglottis.[2,3,5,7] In our case there were two lesions, the first involving the glottis and subglottis and then progressing to another lesion in supraglottis.

Macroscopically, these tumors presented as smooth submucosal masses in supraglottic region, however, in this case, the initial presentation of a subglottic exudate and vocal cord palsy initiated after viral infection confused the case and delayed the diagnosis due to suspicion of an infectious disease. As far as we were concerned, this presentation had been barely described for laryngeal lymphoma.

The definitive diagnosis is given by histology, however, the present case highlighted the histologic difficulties in diagnosing lymphomas because of the need for large samples or excisional biopsies, which are sometimes difficult to obtain due to involved vital structures and the morbidity caused such as larynx. On the other side, the handling of samples for anatomopathological processing must be meticulously careful and expeditious, to improve diagnostic precision. Moreover, the cataloging of lymphoma according to WHO classification required integration of morphological, molecular and immunophenotyping features, which took some time to achieve, further delaying diagnosis.[8]

The presence of EBV had been implied in etiology of these tumors, especially in the setting of immunosuppression or older age and have been linked to poorer prognosis.[9] This case, in contrast, was positive for EBV in an immunocompetent younger patient, which had barely been described in literature. Furthermore, this finding supported recent evidence of increasing nodal EBV+DLBCL in younger patients, with better prognosis than originally thought.[10]

Primary laryngeal lymphomas are rare, so there aren't currently available guidelines for staging and treatment, being extrapolated from lymphomas of other sites. Some centers stage DLBCL based on the classic Ann Arbor system, while others adopted the more recent Lugano classification, which enhanced the role of PET-CT for staging these tumors over CT scan alone in avid 18-FDG DLBCL.[11] In the present case, the PET-CT showed two separate lesions at larynx level, so it was classified as stage IIE of Ann Arbor and IIE of Lugano.

The standard of care for DLBCL had been combined modality therapy with chemotherapy followed by radiotherapy. The addition in recent years of rituximab, an anti-CD20 antibody for B lymphocytes, to the chemotherapy scheme had markedly improved survival.[12] Rarely, when the mass compromises airway such in the present case, a tracheostomy is needed.[5,7] Usually the overall survival in initial disease (stages I and II of Ann Arbor) is favorable, especially for younger patients as laryngeal DLBCL seems to be quite radiosensitive.[3] Due to the apparent good prognosis, there are currently some reports evaluating the possibility of applying chemotherapy or radiotherapy alone in laryngeal lymphoma.[3,13] The revised international prognostic index (R-IPI) is the main model used for prognosis assessment in DLBCL and it included patient's age, performance status, the quantity of extra-nodal sites involved and the elevation of LDH. This case only had one risk factor (involvement of more than one extra-nodal site), so he had an R-IPI score of one, giving around 80% of overall survival at 5 years.[14]

CONCLUSION

This study highlighted the need of suspicion and prompt diagnosis of primary laryngeal lymphomas since there was no need for laryngectomy, as with other laryngeal malignancies and it was an unusual place for their occurrence. Besides, it enhanced the variable clinical presentation of these neoplasms. The early diagnosis can avoid tracheotomy in younger patients, since these tumors have the ability of sudden growth.

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