Anaplastic Lymphoma Kinase-positive Primary Diffuse Large B-cell Lymphoma of the Larynx: A Rare Clinical Entity

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ABSTRACT

Background: Primary lymphomas amount to less than 1% of the primary laryngeal tumors. It is the second most common primary hematologic tumor of the larynx after plasmacytoma. Although squamous cell carcinoma amounts to 90% of the laryngeal tumors, diagnosis of laryngeal lymphoma is very important as nonsurgical management is indicated in all stages of this disease.

Case report: A case of 10-year-old boy with hoarseness of voice with direct laryngoscopic biopsy reported as diffuse B-cell lymphoma. The sections were positive for epithelial membrane antigen (EMA), LCA, CD138, CD4 and Mum1 and ALK. He was managed under MCP 842 protocol. He had complete response after the treatment and was symptom free after 13 months of therapy.

Conclusion: Primary laryngeal lymphoma is a rare entity and should be managed with current chemotherapeutic protocol. Differentiating it between squamous cell carcinoma is important as management protocol in lymphoma is nonsurgical. Aid of immunohistochemistry helps in early diagnosis and management of these cases.

Keywords: Non-Hodgkin lymphoma, Supraglottis, Immunohistochemistry, MCP 842 protocol.

INTRODUCTION

Lymphoma is one of the most common malignancies of the head and neck, second only to squamous cell carcinoma. Primary lymphomas amount to less than 1% of the primary laryngeal tumors. It is the second most common primary hematologic tumor of the larynx after plasmacytoma. Although squamous cell carcinoma amounts to 90% of the laryngeal tumors, diagnosis of laryngeal lymphoma is very important as nonsurgical management is indicated in all stages of this disease.

Lesser than 100 cases of primary laryngeal lymphoma are reported in world literature. They are mainly non-Hodgkin lymphomas (NHL) and are commonly located in the supraglottic region, as this area of the larynx contains follicular lymphoid tissue. Most laryngeal lymphomas present as a submucosal mass or a polypoid tumor as a smooth, nonulcerated and gray-white lesion.

They particularly involve the aryepiglottic folds of the supraglottic larynx and are rarely reported in other laryngeal areas. Diffuse large B-cell type is the commonest among the NHL type primary laryngeal lymphomas while mucosa-associated lymphoid tissue type (MALT) and marginal zone B-cell type are also reported. Early detection of lymphoma allows improved patient care and may result in decreased dissemination of the disease process.

We report a case of diffuse B-cell lymphoma of the larynx presenting with hoarseness of voice in a young boy. Extensive Medline database search revealed only fewer cases of pediatric primary laryngeal lymphomas that are reported.

CASE REPORT

A 10-year-old boy was referred to us with complaints of hoarseness since 6 months. He had undergone micro-laryngeal excision biopsy of the lesion twice and the pathology was inconclusive on the first occasion and was reported as small round cell tumor on the second occasion. No complains of dysphagia, dyspnea or cervical lymphadenopathy was present.

On indirect laryngoscopy small polypoid submucosal supraglottic mass was seen. The lesion was nonulcerative bulge extending to the glottis and to the right pyriform fossa. Rest of the inlet of the larynx were normal with both the vocal cord moved on phonation. Microlaryngoscopic evaluation and biopsy found a smooth mucosal mass in the supraglottis extending to the right pyriform fossa.

Histopathological picture aided by immunohistochemistry came to the conclusion as anaplastic lymphoma kinase (ALK) positive diffuse B-cell lymphoma. The neoplastic cells were positive for epithelial membrane antigen (EMA), LCA, CD138, CD4 and Mum1. ALK shows granular cytoplasmic positivity. They were negative for cytokeratin, desmin, CD30, LMP1, MyoD1, synaptophysin, chromogranin, S100, Melan A, CD3, CD57, CED79a, and CD20 and Ki-67 proliferative index was around 60%. A diagnosis of ALK-positive diffuse large B-cell lymphoma was made (Figs 1 to 3). Other investigations were in normal limits.
Chest X-rays and soft tissue lateral neck X-rays were in normal limits (Fig. 4). Contrast enhanced computed tomography (CT) of neck reported an irregular heterogeneously enhancing lesion in the right pyriform fossa extending to the right true and false vocal cords (Figs 5 and 6). Level V on the right and left paratracheal lymph nodes were enlarged. Sonography of the abdomen was normal, with electrocardiogram showing biventricular hypertrophy and the echocardiography was normal with ejection fraction of 70%.

A final diagnosis of the lesion was done as diffuse large B-cell lymphoma, stage IIE of the right supraglottis and extending to the pyriform fossa. The patient was managed under MCP 842 protocol. The advantages of the protocol include same chemotherapy course for all subsites, excellent tolerability, outpatient treatments, minimal supportive care needed, no total parenteral nutrition, minimal transfusion, growth factor and intravenous antibiotic requirements and
no radiotherapy is included in the protocol. The patient was reviewed after third cycle and then complete response was seen on laryngoscopic examination. The patient was symptom free for 13 months after therapy.

**DISCUSSION**

Malignant lymphomas are neoplastic transformations of lymphoid tissue with the Hodgkins and the non-Hodgkins as the two variants. Most of the lesions occur in the lymph nodes and extranodal involvement occurs only in 25% of the cases.

NHLs amounts to the majority of the extranodal lymphomas in the head and neck region. Lymphoid aggregations in the Waldeyer’s ring is the commonest site in the head neck region for extranodal lymphomas. Extranodal primary laryngeal NHLs account to less than 1% of the laryngeal neoplasms. Usually the laryngeal lymphomas are of a high grade and the low grade tumors are usually arising from MALT. Age ranges from 4 to 81 years, with mean age of occurrence at 7th decade and the mean age 50 years. Varied sex predominance has been reported in different studies.

Also other types of lymphomas, such as T- or natural killer (NK)-cell lymphomas are rarely reported. Most lymphomas involving the larynx involve other sites containing lymphoid tissue extranodally like salivary glands, the thyroid, the nasopharynx and tonsils. Usually the patients present with hoarseness, cough, dysphagia, a feeling

**Fig. 5:** Lesion seen in the right pyriform fossa and aryepiglottic folds

**Fig. 6:** Right level 5 lymph node and right paratracheal node significant enlargement seen
of ‘a foreign body sensation’, stridor or systemic signs, such as weight loss and fever.\textsuperscript{3} Duration of the symptoms may vary from 10 days to 1 year.\textsuperscript{3} Primary laryngeal lymphomas pose a diagnostic challenge as they have no specific differential characteristics when compared to squamous cell carcinomas.\textsuperscript{3}

Horny et al analyzed the published data and stated that most of these lesions are initially seen as nonulcerated smooth or polypoid masses in the epiglottis and the arytenoepiglottic folds.\textsuperscript{8,22} Subsite classification include 47\% in supraglottis, 25\% in glottis and rest present as subglottic or transglottic.\textsuperscript{3} Supraglottic region has rich lymphoid aggregations in the lamina propria so the higher incidence.\textsuperscript{3,23} The lesions in the glottis and subglottis present early as hoarseness and stridor.\textsuperscript{3} They remain localized for longer periods and may disseminate to distant mucosal sites rather than to peripheral lymphoid tissue with isolated recurrences in gastric mucosa, lung and orbit.\textsuperscript{24,25} Markou et al reported a synchronous occurrence of right vocal cord lymphoma and carcinoma in situ.\textsuperscript{3}

Contrast-enhanced CT show a homogeneous lesion elevating the laryngeal mucosal surface.\textsuperscript{10} Magnetic resonance imaging usually show varying densities lesion with high and intermediate signal intensity on T2-weighted images and homogeneous of intermediate signal intensity on T1-weighted images.\textsuperscript{10}

These imaging modalities are helpful for assessment of laryngeal lymphoma but histopathological diagnosis aids in the final diagnosis.\textsuperscript{7} Deeper biopsies may be needed as superficial ones cannot distinguish safely the neoplastic from inflammatory cells.\textsuperscript{26,27} Primary laryngeal lymphomas usually show a intact overlying mucosa, benign appearing mass which can be differentiated from squamous cell carcinoma but has irregularity and ulceration involving the free margins of the laryngeal structures.\textsuperscript{28} Immunohistochemical analysis is required for accurate diagnosis as numerous antibodies are used to delineate the lymphoid nature of the cells and provide more specific information about the classification of B-cell or T-cell lineage subsets.\textsuperscript{3} B-cell lymphomas amount to 70\% of the cases among laryngeal lymphomas and T/NK-cell and MALT lymphomas, are distinct clinicopathologic entities of laryngeal NHLs.\textsuperscript{3} T/NK lymphomas are more seen in nasal and nasopharyngeal region while MALT lymphomas are seen in the stomach.\textsuperscript{3} Diebold et al described 15 cases of MALT lymphoma in larynx.\textsuperscript{29}

Management advised to include radiation and chemotherapy with low-grade lymphomas being radiosensitive and responding well to moderate-dose therapy (30-50 cGy).\textsuperscript{1,13,14} Combined modality treatment which includes radiotherapy plus chemotherapy or chemotherapy alone is very helpful for recurrent or disseminated cases.\textsuperscript{30-32} Surgery has a role in the salvage modality only in laryngeal obstruction and massive hemorrhage.\textsuperscript{3} Kania et al reported MALT laryngeal lymphomas to be treated primarily by surgical excision.\textsuperscript{33} Flow cytometry and karyotypic analysis accurately helps in diagnosis and subclassification of lymphomas as well as in the determination of prognostic indicators by extensive cellular phenotypic characterization of the tumor specimen.\textsuperscript{3} This helps the oncosurgeons in creating patient-specific treatment protocols.\textsuperscript{3}

Nayak et al described laryngeal lymphoma with extensive characterization of its tumor, leading to the application of a specific immunotherapeutic treatment.\textsuperscript{34} Five-year relapse free survival rate with current multimodality treatment is around 40 to 70\% with no major meta-analysis done on the condition.\textsuperscript{35} Debulting of the tumor with CO\textsubscript{2} laser has a role in slow-growing laryngeal lymphomas in postponing the definitive chemotherapy and radiotherapy for sometime.\textsuperscript{36,37} Dissemination to other extranodal sites, such as the upper respiratory tract, stomach, orbit, or skin, with a long disease-free interval are seen with radiotherapy and/or chemotherapy being effective for both primary and disseminated tumors.\textsuperscript{13}

CONCLUSION

Primary laryngeal lymphoma is a rare entity and should be managed with current chemotherapeutic protocol. Differentiating it between squamous cell carcinoma is important as management protocol in lymphoma is nonsurgical. Aid of immunohistochemistry helps in early diagnosis and management of these cases.

REFERENCES


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