10.5005/jp-journals-10023-1038
ORIGINAL ARTICLE

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

Sudhir M Naik, A Nanjundappa, Rajshekar Halkud, CS Premlatha, C Ramarao, L Appaji, Sumit Gupta

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.

How to cite this article: Naik SM, Nanjundappa A, Halkud R, Premlatha CS, Ramarao C, Appaji L, Gupta S. Anaplastic Lymphoma Kinase-positive Primary Diffuse Large B-cell Lymphoma of the Larynx: A Rare Clinical Entity. Int J Phonosurg Laryngol 2012;2(2):57-61.

Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

Lymphoma is one of the most common malignancies of the head and neck, second only to squamous cell carcinoma.[1,2] Primary lymphomas amount to less than 1% of the primary laryngeal tumors.[3] It is the second most common primary hematologic tumor of the larynx after plasmacytoma.[4-6] 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.[4-8]

Lesser than 100 cases of primary laryngeal lymphoma are reported in world literature.[9] 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.[9] Most laryngeal lymphomas present as a submucosal mass or a polypoid tumor as a smooth, nonulcerated and gray-white lesion.[3]

They particularly involve the aryepiglottic folds of the supraglottic larynx and are rarely reported in other laryngeal areas.[10] 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.[8] Early detection of lymphoma allows improved patient care and may result in decreased dissemination of the disease process.[11,12]

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 complains 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 immunohisto-chemistry 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.

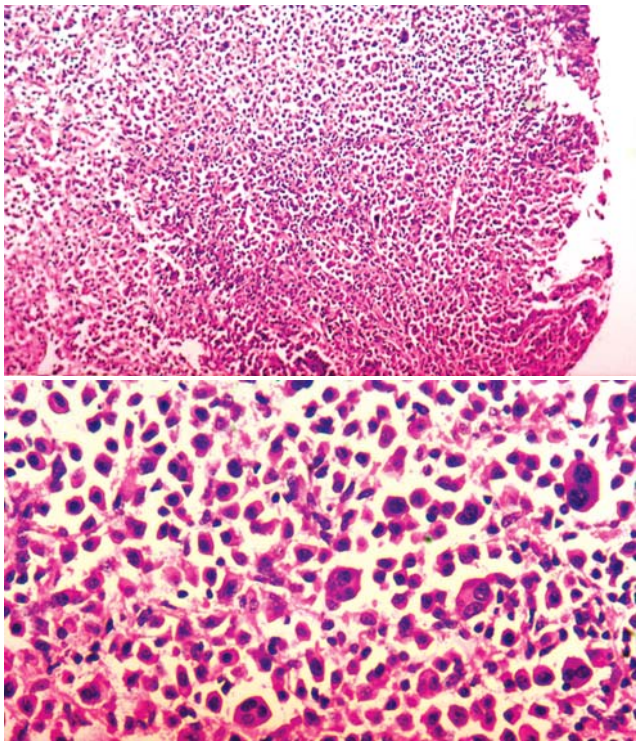

Fig. 1: Low and high magnifications of the diffuse large B-cell lymphoma

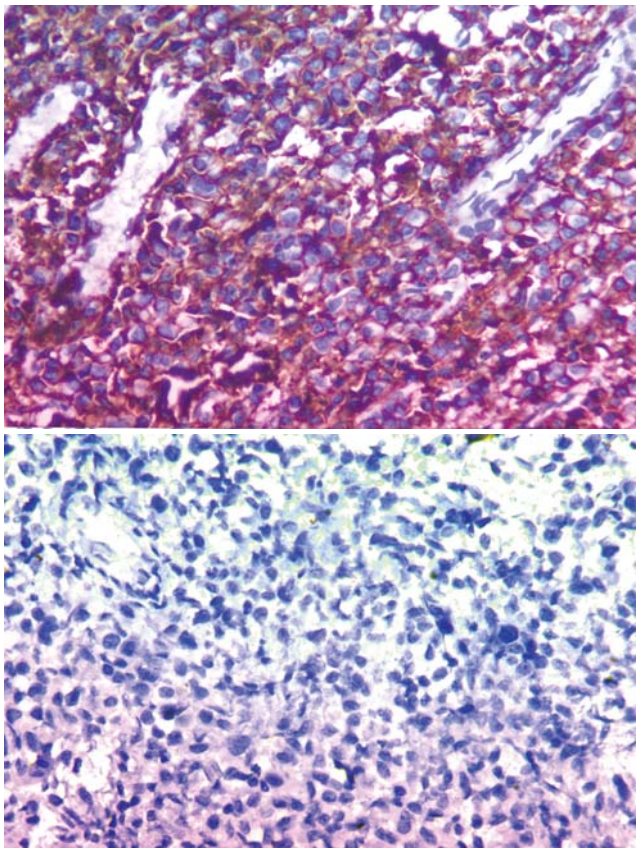

Fig. 2: Sections showing lymphocyte common antigen positive and negative to CD 30

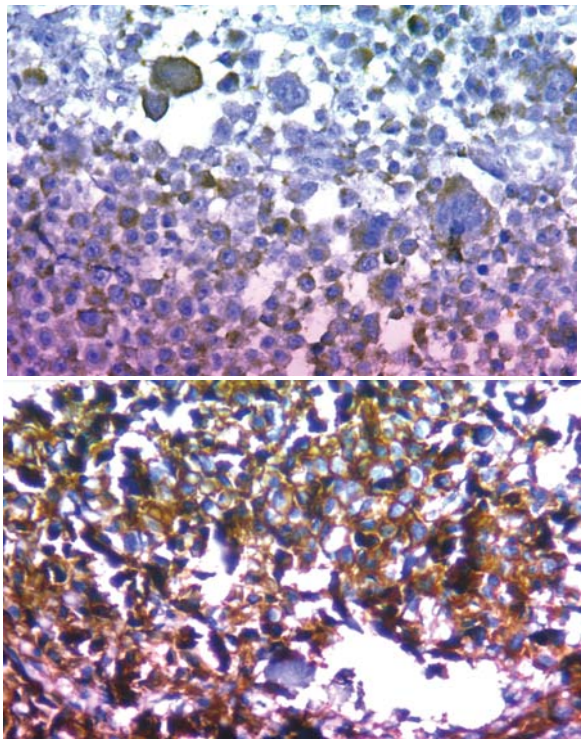

Fig. 3: Sections showing cytoplasmic granules positive for anaplastic lymphoma kinase and membrane positive CD 138

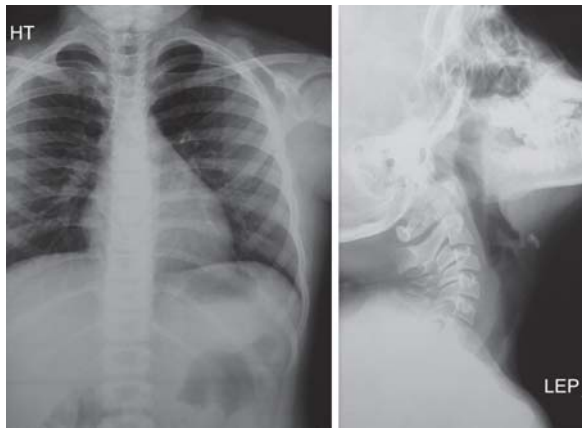

Fig. 4: Normal chest and neck X-rays

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

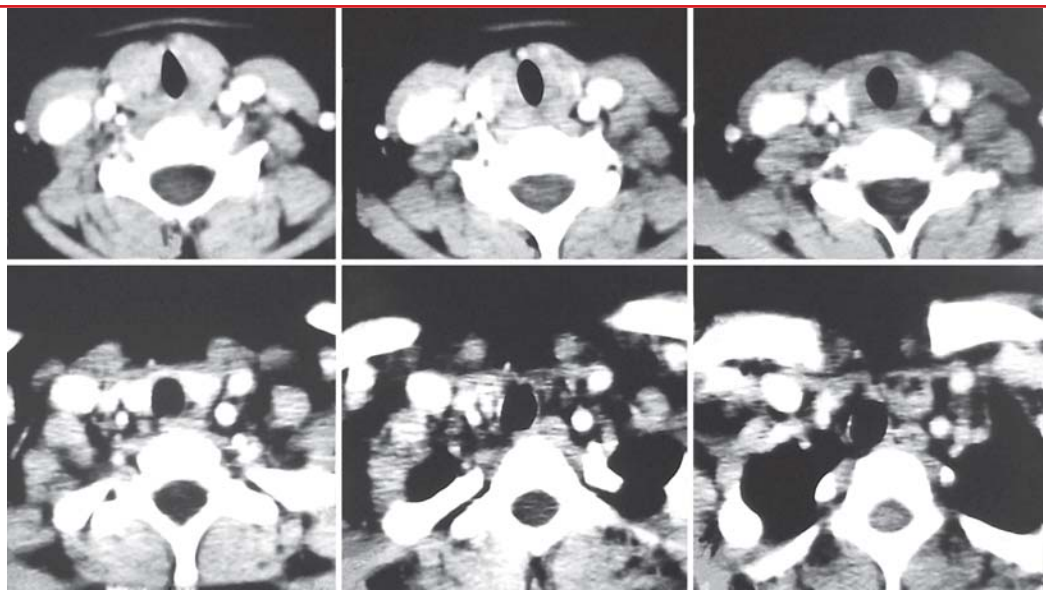

Fig. 5: Lesion seen in the right pyriform fossa and aryepiglottic folds

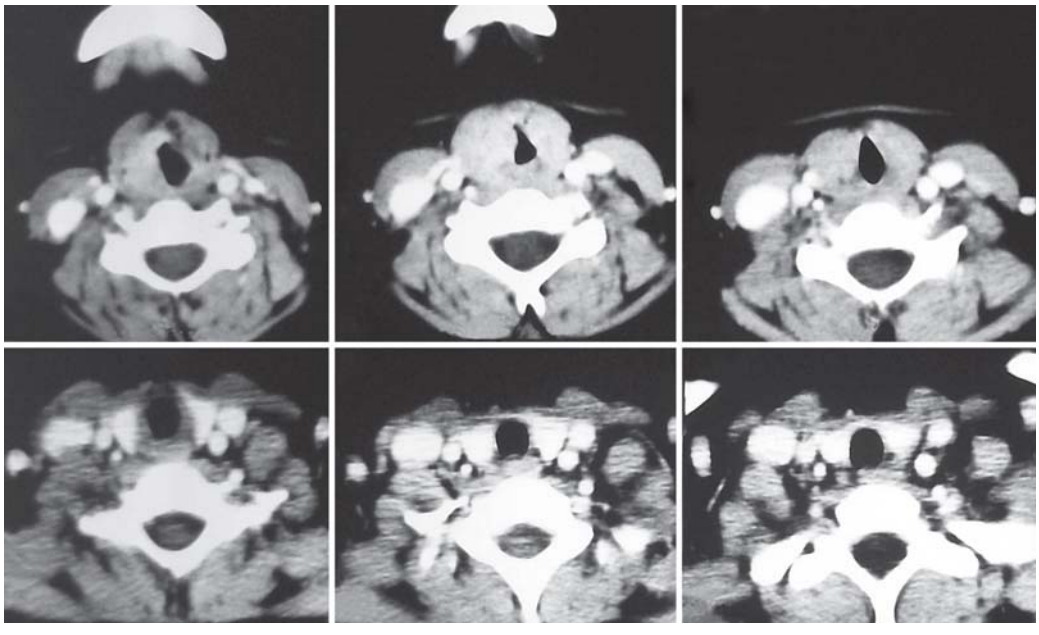

Fig. 6: Right level 5 lymph node and right paratracheal node significant enlargement seen

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.[3] Most of the lesions occur in the lymph nodes and extranodal involvement occurs only in 25% of the cases.[1,3,13,14]

NHLs amounts to the majority of the extranodal lymphomas in the head and neck region.[15-18] Lymphoid aggregations in the Waldeyer's ring is the commonest site in the head neck region for extranodal lymphomas.[15-18] Extranodal primary laryngeal NHLs account to less than 1% of the laryngeal neoplasms.[3] Usually the laryngeal lymphomas are of a high grade and the low grade tumors are usually arising from MALT.[8,9] Age ranges from 4 to 81 years, with mean age of occurrence at 7th decade and the mean age 50 years.[3,19] Varied sex predominance has been reported in different studies.[3,7,19]

Also other types of lymphomas, such as T- or natural killer (NK)-cell lymphomas are rarely reported.[20,21] Most lymphomas involving the larynx involve other sites containing lymphoid tissue extranodally like salivary glands, the thyroid, the nasopharynx and tonsils.[3,8] Usually the patients present with hoarseness, cough, dysphagia, a feeling

of 'a foreign body sensation', stridor or systemic signs, such as weight loss and fever.[3] Duration of the symptoms may vary from 10 days to 1 year.[3] Primary laryngeal lymphomas pose a diagnostic challenge as they have no specific differential characteristics when compared to squamous cell carcinomas.[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.[8,22] Subsite classification include 47% in supraglottis, 25% in glottis and rest present as subglottic or transglottic.[3] Supraglottic region has rich lymphoid aggregations in the lamina propria so the higher incidence.[3,23] The lesions in the glottis and subglottis present early as hoarseness and stridor.[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.[24,25] Markou et al reported a synchronous occurrence of right vocal cord lymphoma and carcinoma *in situ*.[3]

Contrast-enhanced CT show a homogeneous lesion elevating the laryngeal mucosal surface.[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.[10]

These imaging modalities are helpful for assessment of laryngeal lymphoma but histopathological diagnosis aids in the final diagnosis.[7] Deeper biopsies may be needed as superficial ones cannot distinguish safely the neoplastic from inflammatory cells.[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.[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.[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.[3] T/NK lymphomas are more seen in nasal and nasopharyngeal region while MALT lymphomas are seen in the stomach.[3] Diebold et al described 15 cases of MALT lymphoma in larynx.[29]

Management advised to include radiation and chemotherapy with low-grade lymphomas being radiosensitive and responding well to moderate-dose therapy (30-50 cGy).[1,13,14] Combined modality treatment which includes radiotherapy plus chemotherapy or chemotherapy alone is very helpful for recurrent or disseminated cases.[30-32] Surgery has a role in the salvage modality only in laryngeal obstruction and massive hemorrhage.[3] Kania et al reported MALT laryngeal lymphomas to be treated primarily by surgical excision.[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.[3] This helps the oncosurgeons in creating patient-specific treatment protocols.[3]

Nayak et al described laryngeal lymphoma with extensive characterization of its tumor, leading to the application of a specific immunotherapeutic treatment.[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.[35] Debulking of the tumor with CO_2 laser has a role in slow-growing laryngeal lymphomas in postponing the definitive chemotherapy and radiotherapy for sometime.[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.[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

1. Urquhart A, Berg R. Hodgkin's and non-Hodgkin's lymphoma of the head and neck. Laryngoscope 2001;111:1565-69.
2. Urquhart AC. Lymphomas of the head and neck. In: Alper CM, Myers EN, Eibling DE (Eds). Decision-making in ear, nose and throat disorders. New York: WB Saunders 2001:306-07.
3. 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 Apr 32(4): 541-49.
4. Ansell SM, Habermann TM, Hoyer JD, et al. Primary laryngeal lymphoma. Laryngoscope 1997;107:1502-06.
5. Browne JD. Management of non-epidermoid cancer of the larynx. Otolaryngol Clin North Am 1997;30:215-29.
6. Anderson HA, Maisel RH, Cantrell RW. Isolated laryngeal lymphoma. Laryngoscope 1976;86:1251-57.
7. King AD, Yuen EH, Lei KI, et al. Non-Hodgkin lymphoma of the larynx: CT and MR imaging findings. Am J Neuroradiol 2004;25:12-15.

8. 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;191:130-38.
9. Horny HP, Ferlito A, Carbone A. Laryngeal lymphoma derived from mucosa-associated lymphoid tissue. Ann Otol Rhinol Laryngol 1996;105:577-83.
10. Word R, Urquhart AC, Ejercito VS. Primary laryngeal lymphoma: Case report. Ear Nose Throat J 2006;85:109-11.
11. Zinzani PL, Magagnoli M, Galieni P, et al. Nongastrointestinal low grade mucosa-associated lymphoid tissue lymphoma: Analysis of 75 patients. J Clin Oncol 1999;17:1254.
12. Marioni G, Marchese-Ragona R, Cartei G, et al. Current opinion in diagnosis and treatment of laryngeal carcinoma. Cancer Treat Rev 2006;32:504-15.
13. Morgan K, MacLennan KA, Narula A, Bradley PJ, Morgan DA. Non-Hodgkin's lymphoma of the larynx (stage IE). Cancer 1989;64:1123-27.
14. Swerdlow JB, Merl SA, Davey FR, Gacek RR, Gottlieb AJ. Non-Hodgkin's lymphoma limited to the larynx. Cancer 1984;53:2546-49.
15. Gleeson MJ, Bennett MH, Cawson RA. Lymphomas of salivary glands. Cancer 1986;58:699-704.
16. Carbone A, Gloghini A, Ferlito A. Pathological features of lymphoid proliferations of the salivary glands: Lymphoepithelial sialadenitis versus low-grade B-cell lymphoma of the MALT type. Ann Otol Rhinol Laryngol 2000;109(12 Pt 1):1170-75.
17. Sasai K, Yamabe H, Kokubo M, et al. Head-and-neck stages I and II extranodal non-Hodgkin's lymphomas: Real classification and selection for treatment modality. Int J Radiat Oncol Biol Phys 2000;48:153-60.
18. Guermazi A, Brice P, de Kerviler EE, et al. Extranodal Hodgkin disease: Spectrum of disease. Radiographics 2001;21:161-79.
19. Kato S, Sakura M, Takooda S, Sakurai M, Izumo T. Primary non-Hodgkin's lymphoma of the larynx. J Laryngol Otol 1997;111:571-74.
20. Marianowski R, Wassef M, Amanou L, Herman P, Tran-Ba-Huy P. Primary T-cell non-Hodgkin lymphoma of the larynx with subsequent cutaneous involvement. Arch Otolaryngol Head Neck Surg 1998;124:1037-40.
21. Hadjileontis CG, Kostopoulos IS, Kaloutsi VD, Nikolaou AC, Kotoula VA, Papadimitriou CS. An extremely rare case of synchronous occurrence in the larynx of intravascular lymphoma and in situ squamous cell carcinoma. Leuk Lymphoma 2003;44:1053-57.
22. Ho FC, Choy D, Loke SL, et al. Polymorphic reticulosis and conventional lymphomas of the nose and upper aerodigestive tract: A clinic-pathologic study of 70 cases, and immuno-phenotypic studies of 16 cases. Hum Pathol 1990; 21:1041-50.
23. MacKenty JE. Malignant disease of the larynx. Arch Otolaryngol 1934;20:297-328.
24. Podoshin L, Fradis M, Schalit M. Lymphosarcoma of the larynx. J Laryngol Otol 1971;85:1063-68.
25. Dogra TS. Lymphosarcoma of larynx. J Laryngol Otol 1972;86:535-41.
26. Mok JS, Pak MW, Chan KF, Chow J, Hasselt CA. Unusual T- and T/NK-cell non-Hodgkin's lymphoma of the larynx: A diagnostic challenge for clinicians and pathologists. Head Neck 2001;23:625-28.
27. Monobe H, Nakashima M, Tominaga K. Primary laryngeal natural killer/T-cell lymphoma—report of a rare case. Head Neck 2008;30:1527-30.
28. MacLennan KA, Schofield JB. Haemopoietic neoplasms. In: Ferlito A (Ed). Neoplasms of the larynx. New York: Churchill Livingstone 1993:327-36.
29. Diebold J, Audouin J, Viry B, Ghandour C, Betti P, D'Ornano G. Primary lymphoplasmacytic lymphoma of the larynx: A rare localization of MALT-type lymphoma. Ann Otol Rhinol Laryngol 1990;99(7 Pt 1):577-80.
30. Wang CC. Malignant lymphoma of the larynx. Laryngoscope 1972;82:97-100.
31. Ghosh KC, Chatterjee DN, Mukherjee D, Mondal A, Mukherjee AL. Primary non-Hodgkin's lymphoma of larynx (a case report). J Postgrad Med 1986;32:103-04.
32. Cohen SR, Thompson JW, Siegel SE. Non-Hodgkin's lymphoma of the larynx in children. Ann Otol Rhinol Laryngol 1987;96:357-61.
33. Kania RE, Hartl DM, Badoual C, Le Maignan C, Brasnu DF. Primary mucosa-associated lymphoid tissue (MALT) lymphoma of the larynx. Head Neck 2005;27:258-62.
34. Nayak JV, Cook JR, Molina JT, et al. Primary lymphoma of the larynx: New diagnostic and therapeutic approaches. ORL J Otorhinolaryngol Relat Spec 2003;65:321-26.
35. Brusamolino E. First line therapy of CD20+ diffuse large B-cell lymphoma: Facts and open questions. Hematologica 2009;94(9):1194-98.
36. Bradley PJ. Treatment of the patient with upper airway obstruction caused by cancer of the larynx. Otolaryngol Head Neck Surg 1999;120:737-41.
37. Paleri V, Stafford FW, Sammut MS. Laser debulking in malignant upper airway obstruction. Head Neck 2005;27: 296-301.

ABOUT THE AUTHORS

Sudhir M Naik (Corresponding Author)

Fellow, Department of Head and Neck Oncosurgery, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India
e-mail: sud223@gmail.com

A Nanjundappa

Professor, Department of Head and Neck Oncosurgery, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India

Rajshekar Halkud

Associate Professor, Department of Head and Neck Oncosurgery Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India

CS Premlatha

Associate Professor, Department of Pathology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India

C Ramarao

Professor, Department of Pathology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India

L Appaji

Professor, Department of Pediatric Oncology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India

Sumit Gupta

Fellow, Department of Head and Neck Oncosurgery, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India