American Journal of Leukemia Research

Case Report
Published: 21 Feb, 2022

A Rare and Unexpected Pediatric Case of MALT Lymphoma of the Larynx

Santarsiero Sara, De Vincentiis Giovanni, Tucci Filippo Maria, Partipilo Paolo and Sitzia Emanuela*

Department of Otolaryngology, Bambino Gesù Children's Hospital, 00165, Rome, Italy

Abstract

Laryngeal Mucosa-Associated Lymphoid Tissue (MALT) lymphoma is an extremely rare tumor in general population, even more in childhood. Etiopathogenesis remains unknown. Immunological disorders, chronic inflammation and viral infections in genetically predisposed patients are the main suspected causal conditions. Potentially, the tumor may origin in every laryngeal subsite, but supraglottic seems to be primarily involved for the embryological development and the anatomical characteristics of the mucosa and the associated lymphoid system. By consequence, the onset symptoms may be different: Dysphagia, dysphonia, chronic cough, and dyspnea, with progressive worsening in relation to the mass extension in the larynx and hypopharynx. Systemic symptoms as weight loss, night sweats and fever are rare, more often associated with B-cell types or systemic disease. For the first evaluation a fibrolaryngoscopy is required, but the macroscopical aspect of the tumor is not pathognomonic so an incisional or excisional biopsy is needed for histological and immunochemical diagnosis. After diagnosis, the management is mainly oncohematological. ENT specialist may be useful for the first diagnostic approach and for the follow-up of local disease by fibrolaryngoscopy. We reported a rare case of laryngeal, supraglottic MALT in a 9-year-old girl. Surgical removal of the mass had been the only treatment performed in this case, which is still in follow-up, without signs of relapse or persistent disease until now.

We think the fibrolaryngoscopy should be always performed when symptoms are persistent or worsening. In case of doubt, surgical removal and anatomic pathological exams are required even when the lesion's appearance is benign. Early diagnosis may guarantee a better local and systemic control of disease, reducing the risk of wide asportations and adjuvant radiotherapy, chemotherapy, or biological immunotherapy.

Keywords: MALT lymphoma; Laryngeal lymphoma; Laryngeal tumors; Pediatric lymphoma; NHL lymphoma, Marginal zone B-cell non-Hodgkin lymphoma

OPEN ACCESS

Correspondence:
Sara Santarsiero, Department of Otolaryngology, Bambino Gesù Children's Hospital, 00165 Rome, Italy, Tel: +39-3276606045; E-mail: sara.santarsiero19@gmail.com

Received Date: *27 Jan 2022*
Accepted Date: *15 Feb 2022*
Published Date: *21 Feb 2022*

Citation:
Santarsiero S, De Vincentiis G, Tucci FM, Partipilo P, Sitzia E. A Rare and Unexpected Pediatric Case of MALT Lymphoma of the Larynx. Am J Leuk Res. 2022; 5(1): 1023.

Background

Laryngeal tumors account for about 0.1% of all head and neck malignancies in the pediatric population. The most common histological types are squamous cell carcinoma and rhabdomyosarcoma. Other malignant tumors, such as adenocarcinoma, mucoepidermoid carcinoma of the minor salivary glands, primitive neuroectodermal tumor, and laryngeal metastases, have occasionally been described [1,2]. Primary laryngeal lymphomas account for less than 1% of all laryngeal tumors; of the few reported cases, the majorities are in adults and almost all are Non-Hodgkin Lymphomas (NHLs). Although NHL is the fourth most common tumor in pediatric patients, a laryngeal localization is rare [3,4].

NHLs are a heterogeneous group of tumors resulting from the proliferation of malignant cells of lymphoid or histiocytic lineage. The different entities are defined based on their epidemiological, histological, clinical, immunological, molecular, and cytogenetic characteristics. These tumors are unpredictable in terms of their capacity for dissemination, likely due to their origin as immune system cells. Although they generally remain within the lymphoid tissue, non-lymphoid tissue and bone marrow involvement may occur [5]. The World Health Organization (WHO) distinguishes lymphoblastic lymphoma from lymphoblastic leukemia based on bone marrow infiltration. Lymphomas are local masses with minimal or no evidence of peripheral blood or bone marrow involvement, which defines leukemia. Regarding histological subtypes, most cases involve B-cell precursors; T-cell lymphomas are 6-fold less common and have a worse prognosis [6].

Up to 5% of all NHLs are extranodal Mucosa-Associated Lymphoid Tissue (MALT) lymphomas, but they might be more prevalent in the pediatric population [7-10]. In adults, the incidence of MALT is similar between the two sexes. MALT lymphomas are mainly found in the stomach, conjunctiva, spleen, lung, skin, and salivary glands; laryngeal involvement is rare [11,12].

The etiology of laryngeal lymphomas is not well defined, although several studies have shown a correlation with primary and secondary immune deficiencies, as well as with the Epstein-Barr Virus (EBV), particularly for the B-cell subtypes [14,15]. The pathogenesis may be more influenced by immunological factors than other types of tumors. Chronic *Helicobacter pylori* infection appears to increase the risk of gastric MALT lymphoma, but its role in the larynx remains unknown [16,17]. The rarity of laryngeal involvement has prevented the identification of specific risk factors. The chronic inflammation caused by laryngopharyngeal reflux might contribute to its pathogenesis by inducing lymphoid tissue proliferation in the larynx. However, Wöhrer et al. [18] reported a coexisting autoimmune disease in 39% of cases of extra gastric MALT lymphoma. Laryngeal lymphoma does not seem to share any risk factors with carcinoma. The main predisposing factor for laryngeal carcinoma in children is radiotherapy for head and neck neoplasms; typically, this is juvenile laryngeal papillomatosis, although juvenile papillomatosis presents as a precancerous lesion regardless of irradiation [19]. Other risk factors for carcinoma (intrauterine exposure to ionizing radiation, chemical carcinogens, and exposure to tobacco smoke) do not seem to be associated with laryngeal lymphomas.

The clinical manifestations of laryngeal lymphomas are nonspecific; signs and symptoms may differ depending on the site involved, extent of disease, and age of the patient. Dysphagia, ear pain or fullness, odynophagia, dysphonia, chronic cough, stridor, and progressive respiratory distress (due to dyspnea exertional to acute respiratory failure), are all possible. In childhood, these symptoms are usually attributed to more common inflammatory conditions or benign laryngeal diseases; therefore, diagnosis maybe delayed, sometimes in an advanced disease stage. Weight loss, night sweats, and fever are less frequent signs that mainly characterize B lymphomas and systemic disease. Weight loss may also be due to the reduced nutrition associated with dysphagia [20]. In children with suspected symptoms, complete Ear, Nose, and Throat (ENT) evaluations with Fibrolaryngoscopy (FLS), and clinical examination of the lateral cervical lymph nodes, should always be performed. If a laryngeal neoplasm is observed, only a histological examination allows for diagnosis, so suspension microlaryngoscopy for biopsy is required.

Laryngeal lymphoma can be diagnosed in a multidisciplinary setting, but the management is primarily oncohematological. Immunohistochemistry and staging are mandatory for targeted chemotherapy, radiotherapy, or immunotherapy. Staging is based on bone marrow and cerebrospinal fluid studies, ultrasound, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET). Surgery plays a role in diagnostic biopsy, and in unblocking airways in cases of obstructing masses, but total excision of the laryngeal mass can sometimes ensure control of local disease [20], as in the present case.

Here, we present the clinical case of a child with an apparently benign laryngeal "cyst," which unexpectedly turned out to be MALT lymphoma of the larynx.

Case Presentation

A 9-year-old female presented at the ENT clinical of Bambino Gesù Children's Hospital (Rome, Italy), with a 6-year history of dysphonia. In 2015, she had been admitted to the Cystic Fibrosis Department of this hospital for poor somatic growth and bilateral clinodactyly of the fifth toe. Her parents had reported a marked lack of appetite in the absence of dysphagia and gastrointestinal symptoms. The only relevant family history was the death of a paternal uncle at 3 years of age from cancer of an unknown nature, and Duchenne syndrome in a maternal uncle. During hospitalization, thyroid, liver and kidney function tests, tumor markers, food intolerances, nutritional indices, and endocrinological and gastroenterological evaluations were performed and showed values within the normal range. Sweat analysis and genetic test results for cystic fibrosis and other major genetic syndromes were negative. The only significant finding was positive serology for EBV, with evidence of viral infection/reactivation in the blood (PCR, 1,311 copies/mL; no viral capsid antigen Immunoglobulin M [VCA-IgM]; VCA-IgG, 2,695 U/mL; and EBV capsid antigen IgG, 22, 91 U/mL), although she did not complain of asthenia or recurrent fever. The patient was discharged and referred for a psychological evaluation and nutritional education.

At 4 years of age, she underwent adenoidectomy at another hospital. Dysphonia was present at that time, but it was so mild and sporadic that her parents did not report it to the clinicians. FLS was not performed in any of the ENT assessments. By July 2021, the dysphonia had worsened, so she presented to our outpatient clinic for evaluation. At that time, FLS was performed and revealed non-obstructive swelling of the left false vocal cord with normal underlying mucosa. The initial diagnostic hypothesis was benign cystic formation of the supraglottic larynx (Figure 1). With the parents' consent, we removed the lesion by suspension microlaryngoscopy and performed a histological examination. No intra- or postoperative complications occurred, and the patient was discharged pending histological diagnosis (Figure 2A-2D).

Unexpectedly, surgical pathology returned a result of "extranodal marginal zone B-cell lymphoma of MALT of a low grade." The patient was referred to the Oncohematology Department for

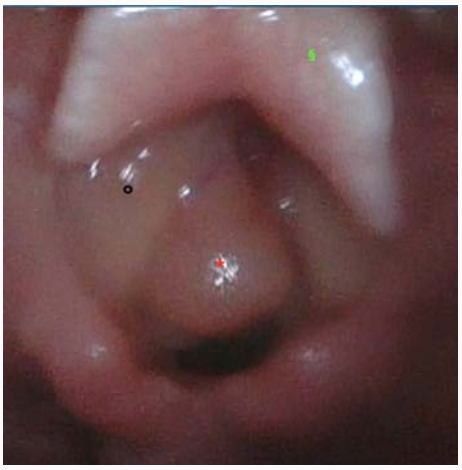

Figure 1: Fibrolaryngoscopy showing a supraglottic, cystic lesion (marked by the red star) with apparent origin from the medial-superior aspect of the false vocal cord (marked by the black hole), which covers the underlying true vocal cords and remains inferiorly the superior margin of the epiglottis (marked by the green section sign).

Figure 2A: Suspension microlaryngoscopy. Laryngoscope positioning to domain the tumor field.

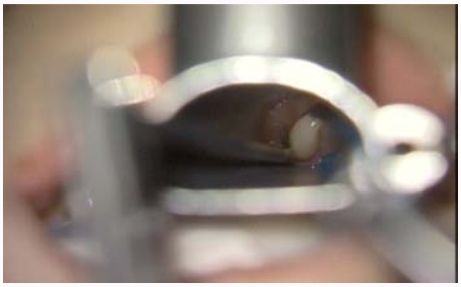

Figure 2B: Suspension microlaryngoscopy. Tumor removal by cold technique.

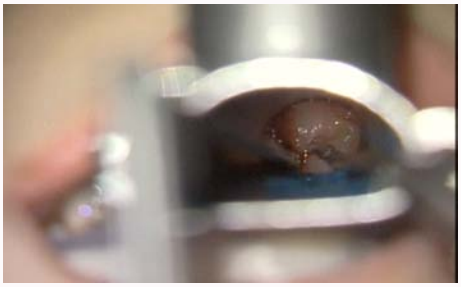

Figure 2C: Suspension microlaryngoscopy. Revealing a cystic aspect.

Figure 2D: Suspension microlaryngoscopy. Supraglottic inspection after the removal.

evaluation and staging, and the tissue was subjected to further immunohistochemical and molecular tests. The EBV genome was not found, and PET and total body CT did not show other disease locations. The patient was subjected to aerodigestive panendoscopy to identify any gastrointestinal involvement in MALT lymphoma. No macroscopically suspicious lesions were identified. Random incisional biopsies were performed of the esophagus, stomach, duodenum, and ileum. They all were negative for lymphoma and *H. pylori* infection; the sample from the terminal ileum revealed a lymphoid hyperplasia and differential diagnosis of MALT lymphoma required clonality analysis by in situ hybridization. Hyperplasia was confirmed; this usually occurs in the terminal ileum.

Bone marrow biopsy and flow cytometry of the cerebrospinal fluid did not reveal the site of disease. EBV-PCR was negative. The patient is still undergoing oncological follow-up, including FLS, imaging, and blood tests. No chemotherapy or radiotherapy has been initiated. No local relapses or distant dissemination of the disease have been reported to date.

Discussion

Although laryngeal MALT lymphoma was first described by Diebold et al. [8] in 1990, the first description of this pathologic entity was actually reported in 1983 in the gastrointestinal tract, which remains the most frequent localization [21]. To date, fewer than 50 cases of laryngeal MALT have been reported. The larynx contains follicular lymphoid tissue, mainly in the supraglottic region, which explains why many primary laryngeal lymphomas originate from this subsite. One study demonstrated the presence of lymphoid tissue in the false vocal cords of 100% of children and 90% of adolescents; this rate decreased to 7.1% among individuals in the sixth decade of life [11,12]. This could explain why MALT prevalence is likely underestimated. Misdiagnosis may occur due to several factors. First, the clinical manifestations are non-specific. The mildness of the initial symptoms may delay FLS in children. Furthermore, even when observed, the lesions are not pathognomonic and often seem benign. The tumor may present as a submucosal swelling, polyp, or circumferential mucosal thickening. The overlying mucosa is generally light pink and non-ulcerated [22,23]. Although variable, in the majority of cases the tumors arise in the supraglottis (epiglottis or aryepiglottic folds), and occasionally in the vocal folds or subglottis [24]. Clinicians should consider several differential diagnoses, such as a benign laryngeal lesion congenital or secondary to phonatory dysfunction or vocal abuse (submucosal cyst, laryngeal polyp), as well as malignant epithelial, myoepithelial, or glandular tumors, and other lymphoproliferative diseases or laryngeal infections (i.e. syphilis, tuberculosis, and mycosis) [25].

The therapeutic management of a laryngeal mass should begin with histological characterization, in patients of all ages. The first step is to perform suspension microlaryngoscopy under general anesthesia, which facilitates understanding of the characteristics of the lesion (i.e. consistency on palpation and extension). Biopsy should be performed according to the characteristics of the individual; excisional biopsy is one possibility, although this requires a slice of apparently healthy tissue. Incisions should be reserved for very large masses, for which staging by imaging is essential before treatment. In the clinical case presented herein, by following these principles, we obtained an unexpected diagnosis and also achieved local control of the disease.

Guidelines for stage I marginal zone non-gastric and non-cutaneous MALT lymphomas recommend surgery for adequate diagnosis. Radiotherapy or surgery is the recommended treatment. After surgery, observation may be considered for patients whose diagnostic excisional biopsy had negative margins, and when adjuvant radiotherapy could result in morbidity. In cases of positive margins, clinicians should consider locoregional radiotherapy [26]. The larynx should be monitored by FLS every 3 to 6 months for 5 years, and annually thereafter, due to the high risk of local recurrence. Multifocal pathology, systemic extension, and recurrence are all indications for chemotherapy and/or immunotherapy.

The histotypes of laryngeal lymphoma most frequently reported in the literature are lymphoblastic T and B cell lymphomas. Some authors have described pediatric cases [27-31]. Immunological status seems to affect the natural history and response to therapy [32]. The recommended treatment is a combination of chemotherapy and radiotherapy, with surgery recommended only for diagnostic purposes or restoration of aerodigestive patency (tracheotomy or debulking).

Laryngeal MALT lymphomas are particularly responsive to radiotherapy [34], which is considered the definitive treatment for localized disease [33]. We believe that radiation therapy in pediatric cases should be the second choice for supraglottic or glottis MALT lymphomas with limited local extension, which can be fully removed *via* microlaryngoscopy and/or an endoscopic approach, because of the functional impact and actinic damage to head and neck structures. In cases with subglottic involvement or extension into the hypopharynx, demolitive surgical treatment might promote patient morbidity more so than radiation. The final treatment choice should consider general health status, the oncological prognosis, quality of life, socio-economical status, and the patient's and parents' preferences.

Early microlaryngoscopy and excision ensure early diagnosis, and may thus prevent wide spread excision and partial removal (which require subsequent radiotherapy or extensive revision surgery). It is essential to apply a multidisciplinary approach; oncological management allows monitoring of the possible involvement of other sites, especially gastrointestinal and splenic ones, in which MALT may arise.

Conclusion

Primary MALT lymphoma of the larynx is a very rare entity. Compared to laryngeal lymph sarcoma, the treatment choices and responses thereto, and thus also the prognosis, are better. Local healing and a conservative approach require early diagnosis. FLS should always be performed, and the removed lesion should be sent for histopathological analysis because there are no established morphological markers.

The overall management is mainly oncological, but the ENT specialist can make a diagnosis by performing laryngeal biopsy; if excisional, this may be sufficient to control the disease. To restore the patency of the upper aerodigestive tract, tracheostomy or debulking is needed. For the follow-up of local recurrence, periodic FLS for evaluation of functional outcomes, in conjunction with speech therapy and specialist dysphagia treatment, are needed.

References

1. Cavalot AL, Preti G, Vione N, Nazionale G, Palonta F, Fadda GL. Isolated primary non-Hodgkin's malignant lymphoma of the larynx. J Laryngol Otol. 2001;115(4):324-6.
2. McGuirt WF, Little JP. Laryngeal cancer in children and adolescents. Otolaryngol Clin North Am. 1997;30(2):207-14.
3. Manish J, Pankaj C, Prathamesh P, Devendra C, D'Cruz Anil PG. Carcinoma larynx in children. Int J Head Neck Surg. 2010;1(1):49-51.
4. Ferlito A, Rinaldo A, Marioni G. Laryngeal malignant neoplasms in children and adolescents. Int J Pediatr Otorhinolaryngol. 1999;49(1):1-14.
5. Shad A, Magrath I. Malignant non-Hodgkin's lymphomas in children. In: Pizzo P, Poplack D. Principles and practice pediatric oncology. 3rd Ed. Lippincott-Raven. 1997:545-87.
6. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th Ed. Lyon, France: IARC. 2008.
7. Chung EM, Pavio M. Pediatric extranodal lymphoma. Radiol Clin North Am. 2016;54(4):727-46.
8. Diebold J, Audouin J, Viry B, Ghandour C, Betti P, D'Ornano G. Primary lympho- plasmacytic lymphoma of the larynx: A rare localization of MALT-type lymphoma. Ann Otol Rhinol Laryngol. 1990;99(7 Pt 1):577-80.
9. Liu M, Liu B, Liu B, Cui X, Yang S, Wang Q, et al. Mucosa-associated lymphoid tissue lymphoma of the larynx: A case report and literature review. Medicine (Baltimore). 2015;94(17):e788.
10. 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(3):258-62.
11. Kuo JR, Hou YY, Chu ST, Chien CC. Subglottic stenosis induced by extranodal mucosa-associated lymphoid tissue lymphoma. J Chin Med Assoc. 2011;74(3):144-7.
12. Kutta H, Steven P, Tillmann BN, Tsokos M, Paulsen FP. Region-specific immunological response of the different laryngeal compartments: Significance of larynx-associated lymphoid tissue. Cell Tissue Res. 2003;311(3):365-71.
13. Kroft SH, Finn WG, Singleton TP, Ross CW, Sheldon S, Schnitzer B. Follicular large cell lymphoma with immunoblastic features in a child with Wiskott-Aldrich syndrome: An unusual immunodeficiency-related neoplasm not associated with Epstein-Barr virus. Am J Clin Pathol. 1998;110(1):95-9.
14. Yoshida K, Minegishi Y, Okawa H, Yata J, Tokoi S, Kitagawa T. Epstein-barr virus-associated malignant lymphoma with macroamylasemia and monoclonal gammopathy in a patient with Wiskott-Aldrich syndrome. Pediatr Hematol Oncol. 1997;14(1):85-9.
15. Ashamalla M, Teng MS, Brody J, Demicco E, Parikh R, Dharmarajan K, et al. A case of a laryngeal MALT lymphoma in a patient with a history of gastric MALT. Case Rep Hematol. 2015;2015:109561.
16. Beswick EJ, Suarez G, Reyes VE. H pylori and host interactions that influence pathogenesis. World J Gastroenterol. 2006;12(35):5599-605.
17. Wöhrer S, Troch M, Streubel B, Zwerina J, Skrabs C, Formanek M, et al. MALT lymphoma in patients with autoimmune diseases: A comparative analysis of characteristics and clinical course. Leukemia. 2007;21(8):1812-8.
18. Olgun Y, Erdag TK, Aydin B, Mutafoglu K, Ozer E, Ikiz AO, et al. Pediatric laryngeal cancer with 5-year follow up: Case report. Int J Pediatr Otorhinolaryngol. 2013;77(7):1215-8.
19. Majoros M, Devine KD, Parhill EM. Malignant transformation of benign laryngeal papillomatosis in children after radiation therapy. Surg Clin North Am. 1963;43(1963):1049-61.
20. Tan E, Mody MD, Saba NF. Systemic therapy in non-conventional cancers of the larynx. Oral Oncol. 2018;82:61-68.
21. Isaacson P, Wright DH. Malignant lymphoma of mucosa-associated lymphoid tissue. A distinctive type of B-cell lymphoma. Cancer. 1983;52(8):1410-6.
22. 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.
23. Andratschke M, Stelter K, Ihrler S, Hagedorn H. Subglottic tracheal stenosis as primary manifestation of a marginal zone B-cell lymphoma of the larynx. *In Vivo*. 2005;19(3):547-50.
24. Zanetta A, Cuestas G, Méndez Venditto N, Rodríguez H, Tiscornia C, Magaró M, et al. Laryngealcancer in children: Case report. Arch Argent Pediatr. 2012;110(3):e39-42.

25. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in oncology (NCCN Guidelines), B-Cell Lymphomas. 2021.

26. Cohen SR, Thompson JW, Siegel SE. Non-Hodgkin's lymphoma of the larynx in children. Ann Otol Rhinol Laryngol. 1987;96(4):357-61.

27. Wang CC. Malignant lymphoma of the larynx. Laryngoscope. 1972;82(1):97-100.

28. De Santo LW, Weiland LH. Malignant lymphoma of the larynx. Laryngoscope. 1970;80(6):966-78.

29. Rodríguez H, Cuestas G, Bosaleh A, Passali D, Zubizarreta P. Primary laryngeal lymphoma in a child. Turk J Pediatr. 2015;57(1):78-81.

30. Quero-Hernández A, Garnica Castillo A, Socorro López Z, CarrascoDaza D, Reyes-Gómez U. Linfoma no Hodgkin de células T. Revisión: A propósito de un niño con un tumorlaríngeo. Rev Mex Pediatr. 2006;73:287-91.

31. Palenzuela G, Bernard F, Gardiner Q, Mondain M. Malignant B cell non-Hodgkin's lymphoma of the larynx in children with Wiskott Aldrich syndrome. Int J Pediatr Otorhinolaryngol. 2003;67(9):989-93.

32. Yilmaz M, Ibrahimov M, Mamanov M, Rasidov R, Oktem F. Primary marginal zone B-cell lymphoma of the larynx. J CraniofacSurg. 2012;23(1):e1-2.

33. Johnson AO, Stevens BP, Lam JT, Schweinfurth JM. Two cases of rare subglottic MALT lymphoma of the larynx. Am J Otolaryngol. 2020;41(6):102736.