Primary laryngeal lymphoma in a child

Hugo Rodríguez¹, Giselle Cuestas¹, Andrea Bosaleh², Desiderio Passali³, Pedro Zubizarreta⁴
Departments of ¹Respiratory Endoscopy, ²Pathological Anatomy and ³Hematology and Oncology, Prof. Dr. Juan P Garrahan Children’s Hospital, Buenos Aires, Argentina, and ⁴Department of Ear, Nose and Throat, University of Siena, Siena, Italy.
E-mail: giselle_cuestas@yahoo.com.ar
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Malignant tumors of the larynx are very rare in children. They are often diagnosed late, since the initial symptoms are attributed to the process of larynx development or to other, more common pediatric diseases. Early visualization of the larynx with the aid of flexible or rigid fiberoptic laryngoscopy is essential in children having symptoms suggestive of laryngeal disease.

Laryngeal lymphoma in children is exceptionally unusual. The certainty of the diagnosis, which is often very difficult to achieve, is generally confirmed by a tissue biopsy. In the present work, we describe the case of a non-Hodgkin lymphoblastic T-cell lymphoma of the larynx in an eight-year-old boy.

Key words: laryngeal lymphoma, lymphoblastic lymphoma, larynx, children.

Laryngeal cancer accounts for less than 0.1% of head and neck malignant tumors in children and adolescents, with squamous cell carcinoma and rhabdomyosarcoma being the two most common laryngeal tumors¹-³.

Non-Hodgkin lymphoma (NHL) of the larynx is extremely rare in children. A review of the world literature on this topic reveals few cases of this type of cancer in childhood ³-⁵. Its etiology is unknown. It is related to primary and secondary immune deficiencies as well as to the Epstein-Barr virus³,⁴. It occurs equally in both sexes, most commonly in the supraglottis⁴. B-cell lymphomas are more frequent than T-cell lymphomas (ratio, 6:1)⁶.

Laryngeal cancer is often ruled out in the differential diagnosis of dysphonia, dysphagia or progressive respiratory failure in children, which can lead to a late diagnosis. When symptoms progress or persist, an endoscopic evaluation and a tissue biopsy of the suspicious lesions are mandatory ⁷.

Although the incidence of laryngeal lymphoma is marginal, the treatments for such lymphomas, which are considered systemic diseases, do not depend on their location but on their biological variety, and do not require local surgery as therapy.

Case Report

An 8-year-old patient presented at the respiratory endoscopy service with a three-year history of dysphonia and progressive respiratory failure. His height and weight were normal, and there was no history of laryngeal papillomas, tobacco smoking, alcohol or radiation.

From the time when the patient was 6 years old, he had undergone five laryngeal microsurgical procedures, including biopsy sampling, to maintain an open airway and avoid tracheotomy. In all cases, the histopathological finding was consistent with benign lymphoid hyperplasia.

Due to symptom persistence, a new direct laryngoscopy under general anesthesia was performed, which revealed epiglottic infiltration, thickened ventricular bands and glottic narrowing (Figs. 1, 2a). The subglottis and trachea maintained an adequate airway caliber (Fig. 2b). Biopsies were performed, and histopathological findings showed the presence of immature and monomorphic lymphocytes of small and medium size, with scant cytoplasm, dispersed chromatin and inconspicuous nucleoli (Figs. 2a, 2b). Immunohistochemistry was positive for TdT and CD3 markers (Figs. 2c, 2d). The analysis of this specimen by multiparametric flow cytometry (MPFC) showed that only 20% of
cells displayed a malignant immunophenotype, with a background of normal B and T cells. Lymphoblasts showed the presence of surface CD45 and CD3 and coexpression of CD4, CD8, CD1a, CD2, CD7, CD5 and, partially, HLA DR. The cytoplasm revealed the presence of TdT, CD3 and, partially, CD79. Pathologists and cytometrists agreed to describe the case as “lymphoblastic T-cell lymphoma”.

Physical examination and computed tomography scan did not show evidence of adenopathies or other affected sites. Lumbar puncture and bone marrow aspiration were normal. It was assessed as extranodal stage I disease. Studies for the detection of Epstein-Barr virus in serum were negative, and serum immunoglobulins were normal.

Combination chemotherapy based on the BFM strategy for the management of non-Hodgkin T-lymphoblastic lymphoma was started, with an early relapse after 10 months of treatment. The child died 16 months after diagnosis due to septic shock during second-line chemotherapy for recurrent tumors.

Discussion

Non-Hodgkin lymphoma (NHL) of the larynx is rare. It accounts for less than 1% of all laryngeal neoplasms. Its incidence in children is extremely low. It is found mainly in the supraglottis, since this area of the larynx contains lymphoid tissue. Most reported cases are B-cell lymphomas. T-cell lymphomas are rarer and have a worse prognosis. Non-Hodgkin lymphoma is the fourth most frequent type of cancer in childhood and adolescence. The current classification of the World Health Organization distinguishes between lymphoblastic lymphoma and lymphoblastic leukemia in terms of bone marrow infiltration. The term lymphoma is conventionally used when the malignant process is restricted to a local mass having minimal or no evidence of peripheral blood or bone marrow involvement. Although the survival rate after 5 years of lymphoblastic disease has significantly improved in childhood during the last decades, currently standing at 80%, the prognosis of patients with relapsed NHL is poor, especially in T-lineage lymphoblastic lymphomas.

The main predisposing factors for the development of this type of lymphoid neoplasm, especially the B-cell type, are primary immunodeficiencies and the Epstein-Barr virus. In our patient, the immunological study was normal and the serum sample tested for Epstein-Barr virus serology gave negative results. These findings would be expected, since the tumor was a T-lymphoblastic lymphoma. The conventional risk factors, such as radiotherapy, laryngeal papillomatosis, intrauterine exposure to ionizing radiation, chemical carcinogens or exposure to tobacco smoke are absent in many children suffering from laryngeal cancer, and are generally present in malignant epithelial tumors. It is likely that laryngeal cancer at this unusual age is the result of the interaction of immunological and genetic factors. A T-lymphoblastic lymphoma at this age would be expected in the mediastinum or as an expression of T-lymphoblastic leukemia. This case did not show the usual biology of T-lymphoblastic lymphoma onset and evolution.

The clinical manifestations of a laryngeal lymphoma may include dysphony, dysphagia, cough and progressive dyspnea and, less frequently, weight loss and fever. Malignant laryngeal disease in children is often diagnosed late due to the fact that the rate of clinical suspicion is low. The symptoms are often attributed to more common benign childhood conditions, such as respiratory infections or prepuberal voice changes. In the present case, diagnosis was based on the findings of resected material as a result of several resections performed over the course of three years due to laryngeal obstructions.

The lesion is generally a submucosal, polypoid, non-ulcerated light pink mass, located in the epiglottis or the aryepiglottic folds. It is occasionally found in other locations, such as the vocal cords or the subglottis. In the case presented here, the neoplastic infiltration affected the epiglottis, the ventricular bands and the glottis. Laryngeal thickening was assumed to be a lymphoma finding.

Direct laryngoscopy under general anesthesia as well as bronchoscopy makes it possible to determine the extent of the lesion and to rule out multiple lesions. The diagnosis is confirmed by the lesion biopsy. Immunohistochemical testing is important to establish the cell type.
In the early stage of the disease it is very difficult to differentiate atypical lymphoid cells from reactive inflammatory cells, due to the diversity of cell infiltration and the presence of dispersed atypical cells. Therefore, multiple biopsies are often required over time until an accurate diagnosis of lymphoma is made, especially in the case of post-thymic T-cell and T/NK-cell lymphoma\textsuperscript{6,9}. Paraffin sections with the appropriate immunohistochemistry are the mainstay of lymphoma diagnosis, together with molecular and genetic studies. But common pediatric lymphomas (mature B-cell and lymphoblastic B- and T-cell lymphomas) may be clearly and rapidly diagnosed by MPFC in any kind of sample (bone marrow, peripheral blood, pleural or peritoneal effusions, cerebrospinal fluid or solid tissue biopsies, as in this case). Other NHLs were considered and subsequently ruled out by pathologists (i.e., anaplastic large-cell lymphoma, NK/T-cell nasal type, peripheral T-cell lymphoma, etc.).

In order to correctly stage the disease, bone marrow and cerebrospinal fluid studies are performed, as well as ultrasound, computed tomography or magnetic resonance imaging studies.

Differential diagnosis includes benign tumors, squamous cell carcinoma and other lymphoproliferative diseases, as well as syphilis, tuberculosis and laryngeal mycosis, among other disorders\textsuperscript{7}.

Treatment of pediatric laryngeal cancer derived...
from cells of epithelial lineage is difficult due to the aggressive nature of this type of tumor as well as to the vulnerable anatomical structure and specific psychological factors of pediatric patients. Due to its rare occurrence, there is no medical consensus as to its treatment; therefore, this is based on the experience gained in treating adults.

Regarding primary lymphoma of the larynx, it is considered that this type of tumor is an unusual presentation of the lymphoma and not a different disease; therefore, it should be treated in agreement with current trends regarding the management of this disease. Chemotherapy is the most commonly accepted therapeutic strategy for the treatment of primary lymphoma of the larynx. Surgery may be an essential option to maintain a safe airway in the case of a lymphoma presenting with respiratory obstruction or massive bleeding.

The treatment for a lymphoblastic lymphoma consists in a first stage of intensive polychemotherapy courses for induction and consolidation, followed by prolonged continuation chemotherapy until the completion of 24 months of treatment. In the case of our patient, the treatment used was similar to that described above, based on the guidelines of the BFM study group from Germany. Induction of a remission phase was followed by consolidation therapy including high-dose metotrexate.

The best outcomes have been achieved with combination chemotherapy regimens in mature B-cell lymphomas, in precursor B- or T-cell lymphoblastic lymphomas and in anaplastic large-cell lymphoma, but not in peripheral T-cell lymphomas, which are generally associated with a poor prognosis.

In conclusion, a high level of clinical suspicion is required for an early diagnosis of lymphoma of the larynx, which is of significant therapeutic importance due to the aggressive nature of the disorder. A tissue biopsy and subsequent histological and immunohistochemical evaluations and the sampling of fresh tissue to be processed by flow cytometry, as well as cytogenetic and molecular studies, are crucial for an accurate diagnosis. Prognosis will depend on, among other factors, the histological subtype and the initial response to treatment.

REFERENCES


