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Regimen And Response To Chemotherapy On Laryngeal Non-Hodgkin Lymphoma

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ABSTRACT

Background: Non-Hodgkin Lymphoma (NHL) is a malignant neoplasm originating from lymphoid tissue, especially lymph nodes. The incidence of NHL is 3% of all tumors in the head and neck area, 85% of malignant lymphoma are extranodal NHL, and 1% of primary tumors originate from the larynx. Standard management of NHL is chemotherapy or combination with radiotherapy.

Purpose: To report two rare cases of laryngeal NHL, the types of regimens, and their responses to chemotherapy.

Case Reports: Two cases of laryngeal NHL. The first case was a 58-year-old woman who gave a complete chemotherapy response; the second was a 17-year-old boy who gave a complete chemotherapy response.

Treatment: Chemotherapy with six cycles of CHOP regimen (Cyclophosphamide, Oncovin, Doxorubicin, and Prednisone) for the first case and 16 cycles of COMP regimen (Cyclophosphamide, Vincristine, Methotrexate and Prednisone) for the second case.

Conclusion: Six cycles of chemotherapy using the CHOP regimen in adult patients and 16 cycles with the COMP regimen in pediatric patients gave a complete chemotherapy response.

Keywords: *Non-Hodgkin Lymphoma larynx, Chemotherapy, CHOP, COMP, Response to chemotherapy.*

1. INTRODUCTION

Non-Hodgkin Lymphoma (NHL) is a malignant neoplasm originating from lymphoid tissue, especially the lymph nodes. These tumors can occur due to chromosomal translocations, various toxins, infections, and chronic inflammation. The incidence of NHL is around 25%, originating both from tissues other than lymph nodes and organs that do not contain lymphoid tissue, commonly referred to as extranodal lymphoma. Still, most NHL cases involve both lymph nodes and extranodal lymphoids.[1,2]

Non-Hodgkin lymphoma is the sixth most common cause of cancer-related death in the United States.[1] Lymphoma of the larynx usually occurs in the supraglottic area with the most common histological subtype, namely the NHL B cell type. In contrast, Hodgkin Lymphoma (LH) of the larynx is very rare.[3]

The incidence of NHL ranges from 3% of all tumors in the head and neck region, with approximately 85% of malignancies of lymphoma being extranodal NHL and 1% of primary tumors originating from the larynx, NHL being the second most common cause of primary head and neck malignancy. New cases of NHL were 88,200 or 2.1% of new cases of all types of malignancies, and the number of deaths due to NHL was 52,100 or 1.9% of all cancer deaths in 2015 in China, while the incidence of NHL in Indonesia was ranked seventh among all malignancies. in Indonesia with 16,125 new cases and 9,024 people died. [5,6,7] The number of head and neck NHL cases at the Dr. Soetomo General Academic Hospital is still unknown.

The exact cause of NHL malignancy in humans is unknown. Risk factors that cause NHL are oncogenes, Epstein-Barr virus infection, Human T-leukemia Virus-I (HTLV-I), autoimmune diseases, and immune deficiencies. The standard management

of NHL sufferers is the administration of a chemotherapy regimen combined with radiotherapy. Responses to chemotherapy regimens consist of complete response, partial response, no response, or even disease progression. [8]

This case report aims to report two rare cases of laryngeal NHL and the type of regimen and response to chemotherapy.

2. CASE REPORTS

Case 1

A 58-year-old woman with the chief complaint of intermittent hoarseness in the last six months. The hoarse voice worsened until it disappeared completely, accompanied by coughing and shortness of breath with additional complaints of shortness of breath and snoring during sleep. Difficulty swallowing causes the patient to feel a lot of phlegm or saliva, and there are no complaints of lumps in the neck and in other places, such as the armpits or groin area.

Physical examination showed that the ear, nose, and throat were within normal limits, but on the right and left neck, a solid, mobile mass was found with clear boundaries of approximately 1x1x0.5 cm. Indirect laryngoscopy (IL) showed a smooth epiglottis, mass in the glottis, firm borders, and redness. Fiber Optic Laryngoscopy (FOL) results revealed a normal epiglottis, a mass with a smooth surface and firm boundaries, making the arytenoids and vocal cords (VC) challenging to evaluate because they were covered by the mass (Figure 1).

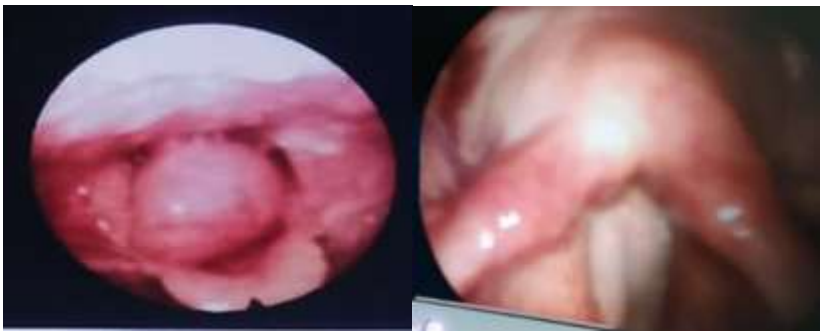

Figure 1. FOL results: **Figure 2. FOL results: Right arytenoid looks swollen (yellow arrow)**

The initial diagnosis was suspected laryngeal carcinoma with upper airway obstruction. Microscopic Laryngeal Surgery (MLS) biopsy and elective tracheotomy were performed. A round mass was found in the glottic area with a smooth surface and springy consistency, measuring 2x2x1 cm. The results of an anatomical pathology examination of the tissue during surgery showed reactive follicular hyperplasia, predominantly small cleaved cells with a differential diagnosis of progressive transformed germinal center and partially involved follicular lymphoma.

Immunohistochemical examination of a cluster of differentiation (CD) 20, BCL2, and Ki67 with positive CD20 results on the tumor membrane, positive BCL2 on the tumor membrane, and positive Ki67 in 10% of tumor cell nuclei. The immunohistochemical examination found a type of NHL defined as follicular lymphoma grade I. The final diagnosis was laryngeal NHL; hence, planned chemotherapy.

Chemotherapy was given two months after surgery, six cycles using the CHOP regimen (Cyclophosphamide, Oncovin, Doxorubicin, and Prednisone). Six months after chemotherapy, there were no signs of recurrence, such as complaints of hoarseness, shortness of breath, coughing up blood, or lumps. In the first evaluation with FOL after chemotherapy, the results showed a wide glottis rim, smooth epiglottis, symmetrical VC movement, dull right arytenoid, with no mass found in the subglottic, glottis or supraglottic and a wide airway (Figure 2). The patient returned to OPD two weeks later for decannulation with no complaints of shortness of breath or hoarseness and could eat and drink well.

Case 2

A 17-year-old boy complained of pain when swallowing since three weeks ago. The pain felt when swallowing solid food persisted and did not get worse. The voice changes (muffled voice), food and drink sometimes come out of the nose, and the lump in the neck appeared one week before going to the hospital and is getting bigger.

Physical examination showed that the throat was hyperemic, other examinations were within normal limits, there was a mass at level IB with a soft consistency, the boundaries were not firm, and there was no pain. Indirect laryngoscopy showed that the epiglottis was smooth, there was standing secretion, the arytenoids had a soft appearance, and the VC was difficult to evaluate. The FOL results of the smooth epiglottis being pushed to the right side show lots of thick yellowish standing secretions, swollen arytenoids, a wide airway, and symmetrical VC movement (Figure 3).

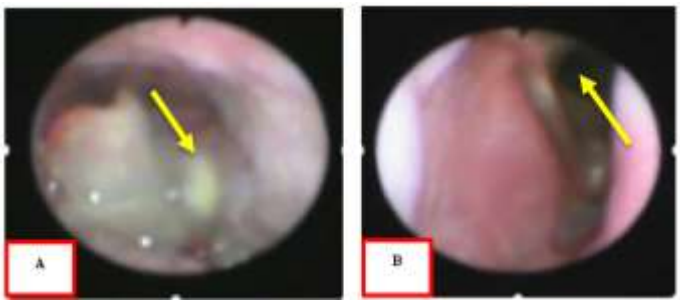

Figure 3. FOL results: A. Standing secretion with a very thick yellowish effect (yellow arrow); B. Clear airway (yellow arrow)

The FOL results supported the suspicion of an infection in the epiglottis area, with the possible cause of the infection being the presence of a foreign body. It was decided to give the patient intravenous antibiotics for three days, followed by an evaluation using the FOL examination. Fiber optic laryngoscopy was performed with the result showing that the epiglottis was smooth and remained pushed to the right side, standing secretion appeared to be reduced from the previous FOL, yellowish in color, the arytenoids were smooth, the airway was wide, the VC movement was symmetrical (Figure 4).

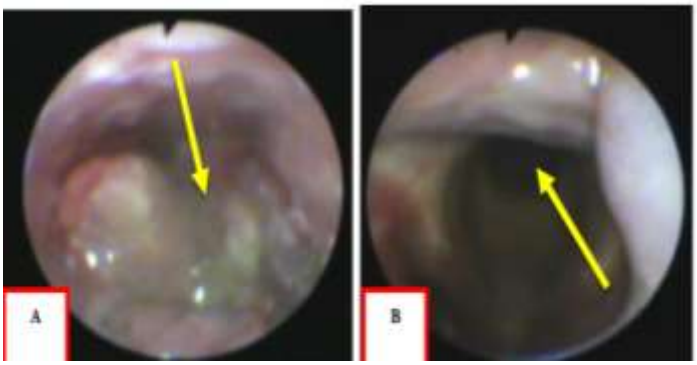

Figure 4. FOL results: A. Standing secretion reduced the effect of the previous FOL in yellowish color (yellow arrow); B. Clear airway (yellow arrow)

The administration of antibiotics was considered to improve the condition. Therefore, an exploratory microscopic laryngeal surgery (MLS) was performed to check for foreign bodies in the larynx area. The exploratory MLS revealed a fragile reddish mass that could bleed easily, pressing on the epiglottis (Figure 5). Subsequently, a biopsy and tracheotomy were performed due to concerns about airway obstruction.

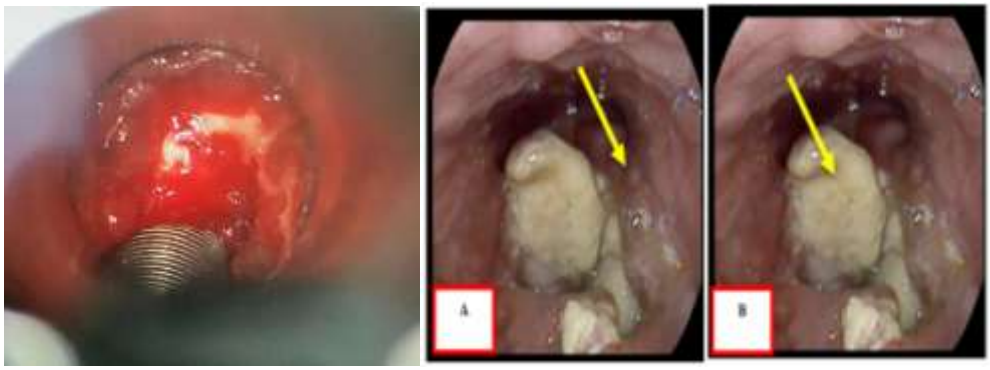

Figure 5. MLS results: A reddish, friable mass that bleeds easily, pressing against the epiglottic; FOL results: A. Smooth mass in left subglottic area (yellow arrow); B. Beslag in the epiglottis area (yellow arrow)

Two weeks after the MLS biopsy was performed, the patient underwent FOL evaluation, which found swollen arytenoids, the appearance of normal VC with symmetrical movement, and a smooth mass in the left subglottic area with a visible "beslag" in the epiglottis area. The results of the anatomical pathology examination were malignant round cell tumor, then CD45, CD20, CD3, and Ki67 immunohistochemical examination was carried out with the results of positive CD45 and CD20

on the tumor cell membrane, negative CD3 on the tumor cell membrane, positive Ki67 in 80% of the tumor cell. nuclei. The immunohistochemical examination found a high-grade non-Hodgkin's Lymphoma, B Cell type (CD20 positive). Because the patient was still 17 years old, he was transferred to a pediatric colleague for chemotherapy. Chemotherapy was given for 16 cycles with the COMP regimen (Cyclophosphamide, Vincristine, Methotrexate, and Prednisone). Chemotherapy was given for 16 cycles and divided into two phases: the induction phase of five cycles and the maintenance phase of 11 cycles.

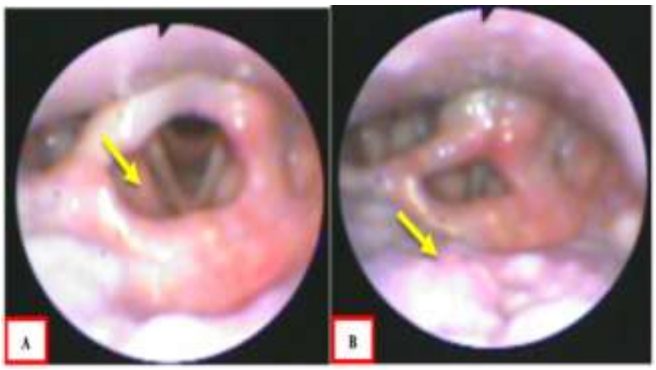

Fig. 6 FOL results: A. Ventricular folds were swollen (yellow arrow); B. Epiglottis was absent (yellow arrow)

Evaluation after receiving chemotherapy for 14 cycles for consideration of decannulation: There were neither complaints of hoarseness, shortness of breath, nor difficulty eating and drinking, yet the patient was scheduled to have another evaluation one month after chemotherapy was finished. FOL evaluation was performed one month after 16 cycles of chemotherapy, which showed that the ventricular folds appeared dull, with absent epiglottis, grade II lingual tonsils, wide airway, and symmetrical movement with complete closure of VC. (Figure 6). Three weeks after decannulation, it was found that the tracheotomy wound was well closed, there was no air from the wound, and there were no complaints of shortness of breath or hoarseness.

3. DISCUSSION

Laryngeal Non-Hodgkin's Lymphoma is a rare case. The two cases above are cases of laryngeal NHL `which were given different chemotherapy regimens and quantity with similar responses. Treatment for NHL in the larynx is the same as NHL therapy elsewhere and is a multidisciplinary treatment by experts in anatomical pathology, radiology, ORL-HNS, radiotherapy, and medical oncology. The main treatment for NHL is radiotherapy, chemotherapy, immunotherapy, or combined therapies.[9]

The treatment of choice for low-grade stage I or II is radiotherapy, and for stage III-IV is chemotherapy using a combination regimen of Chlorambucil, Rituximab, and CVP (Cyclophosphamide, Vincristine, and Prednisone) or six cycles of CHOP. The choice of therapy for intermediate-grade stage I or II is a combination of radiotherapy and chemotherapy with R-CHOP (Rituximab-Cyclophospamide, Doxorubicin, Oncovin, and Prednisone) for three cycles, while for stage III-IV is chemotherapy with an R-CHOP regimen of sixteen cycles.[10]

Administration of Rituximab significantly improved progression-free survival (PFS) in patients who had partial remission after induction treatment and those who had experienced complete remission. Research by Jeong, et al., (2013) used CHOP (53.8%) and R-CHOP (46.2%) with a complete response rate of 72.1% treated with CHOP and 89.1% after R-CHOP therapy .[11] Van Oers, et al., (2014) also stated that the addition of Rituximab to the CHOP regimen (R-CHOP) increased the complete response rate of 85.1%, while for those treated with the CHOP regimen, the result was 72.3%. [12]

Hong, et al., (2003) stated that the treatment options for laryngeal NHL are radiotherapy, chemotherapy, or a combination of both (radiochemotherapy). Surgical options are rarely made unless there are obstructive symptoms. The choice of radiotherapy alone or chemotherapy alone compared with chemoradiation did not provide a significant difference. Therefore, the option of chemotherapy alone for the three patients in this case report was appropriate.[3] The response to chemotherapy regimens consisted of various types, such as complete response, partial response, no response, and even progress toward the disease.[8]

The first patient was given six cycles of chemotherapy using the CHOP regimen and showed a complete response to chemotherapy, as evidenced by the FOL results; there was no visible mass in the larynx six months after chemotherapy. The second patient was given a 16-cycle COMP chemotherapy regimen divided into two phases: an induction phase of five cycles and a maintenance phase of 11 cycles, which showed a complete chemotherapy response.

Chaker, et al., (2021) reported the use of the CHOP regimen for one cycle in patients with laryngeal NHL showing a complete chemotherapy response and 18 months after chemotherapy evaluation found no signs of recurrence on the FOL

examination.[13] Another study by Cavalot, et al., (2001) also reported a case of laryngeal NHL given chemotherapy with the CHOP regimen showing a complete response after two cycles. No signs of recurrence appeared during the 16-month evaluation period.[14]

Ayyaswamy, et al., (2022) reported that a 9-year-old child with laryngeal NHL who also received COMP regimen according to the protocol showed improvement in symptoms.[15] Research by Fridrik, et al., (2017) comparing the response to chemotherapy when using R-CHOP and R-COMP showed that the overall response rate of the R-COMP group was 97.5% with a complete response of 75%. The overall response rate with R-CHOP is 82%, with a complete response of 69.7%.[16]

The decision to give the CHOP regimen to the first patient is in accordance with Reksodiputro, et al., (2003), which states that the standard protocol for aggressive initial NHL therapy is a chemotherapy protocol using the CHOP regimen.[8] The COMP regimen administration to the second patient shows a complete therapeutic response in accordance with Aguayo, et al., (2000), who stated that the COMP regimen is suitable for NHL patients because this regimen is well tolerated and does not cause allergic reactions and is very good for recurrence cases. Methotrexate is a therapeutic option because there are no complications, such as allergic reactions, pancreatitis, or bleeding. Encephalopathy is the only serious complication of methotrexate use.[17]

Chemotherapy response is categorized as a complete response when all target lesions disappear, where all pathological lymph nodes, both target and non-target nodes, must be less than 10 mm in size. Partial response is a decrease in the diameter of the target lesion by at least 30% of the diameter of the initial target lesion. Progressive disease is an increase in the diameter of the target lesion by at least 20%. The target lesion used as a reference is the lesion with the smallest diameter. Progressive disease can also be characterized by an absolute increase in lesion diameter of at least 5 mm or the appearance of one or more new lesions. Stable disease is no shrinkage of the target lesion that is sufficient to meet the partial response criteria or an increase in the diameter of the lesion that does not meet the response criteria for progressive disease.[18] Lymphoma can recur both in the lymph system and in other parts of the body (extranodal).[19]

4. CONCLUSION

Two cases of Non-Hodgkin's Lymphoma (NHL) of the larynx were reported to have received chemotherapy with different regimens but showed complete chemotherapy responses. The first case was given six cycles of chemotherapy using the CHOP regimen (Cyclophosphamide, Oncovin, Doxorubicin & Prednisone), and the second case was given 16 cycles of chemotherapy with the COMP regimen (Cyclophosphamide, Vincristine, Methotrexate, and Prednisone). This case report can be used as a reference point to select a chemotherapy regimen in laryngeal NHL patients.

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