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Case Report

Palpebral non-hodgkin lymphoma with non-specific reactive hepatitis

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ABSTRACT

Extranodal Non-Hodgkin Lymphoma (NHL) remains an odd issue and something to discuss. Clinical evidence and guidelines on the treatment have not yet been broadly published and accessible. Here, we present a case of a thirty-eight years old woman complaining of mass on both lower lids of the eyes. The CT Scan examination showed enhancing solid masses on right-sided and left-sided palpebra inferior that press bulb oculi, suspected as bilateral malignant masses of bilateral palpebra inferior. Laboratory data revealed the surge of liver function marker. The patient was eventually diagnosed with Non-Hodgkin Lymphoma (NHL) of palpebra inferior B cell type high-grade stadium II E. Although there are still ongoing research and development of definitive treatments, R-CHOP a regiment given to this patient has shown complete favorable result with dosage adjustment due to the surge of basal liver function. The regiment was considered safe since no adverse effects reported

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INTRODUCTION

Extranodal Non-Hodgkin Lymphoma (NHL) is a complex and rare case; approximately 30% of NHL are extranodal lymphoma. Extra-nodal NHL can arise from any organ, including palpebra, NHL of palpebra 1-10% of NHL cases. Mean-age diagnosed NHL of palpebra 15 years old and 70 years old (Eckardt, Lemound, Rana, & Gellrich, 2013; Nanthakwang et al., 2019; Vannata & Zucca, 2015)

Extranodal Non-Hodgkin Lymphoma is mainly diagnosed at the advanced stage. The condition of patients was associated with immune-compromised, progressive disease or bulky disease, often relapses, poor prognosis, and rare incomplete response (Vannata & Zucca, 2015). NHL of palpebra was commonly a bulky disease and often partial response, relapses, or recurrent (Svendsen et al., 2017).

According to many case reports, there is no specific treatment for NHL of the palpebra. Triple modalities (surgery, chemotherapy, and radiotherapy) were commonly used for treating NHL of palpebra (Shikino & Ikusaka, 2019; Svendsen et al., 2017). Our case will discuss the diagnostic approach and modalities of therapy from NHL of the palpebra.

CASE

Thirty-eight years old female, married, having two children, lived in Lamongan, East Java. She came with masses on the bilateral palpebra inferior. The first mass was on the right-sided palpebra inferior, which appeared two years ago during her second pregnancy at five months of gestational age. Mass became larger, solid, and grew bilaterally. There was no tenderness, no pus and blood, and discolorization. Right-sided palpebra inferior mass looked like bekel ball, and left-sided mass palpebra inferior looked like a nut. The patient did not have abnormal vision and movement of orbital muscles and destruction structure around orbital. After giving birth, mass was still there, and the patient did not have weight loss and fever without unknown origin.

The patient visited Ngimbang Hospital, Lamongan, in February 2019 since the mass became larger then she was referred to Dr. Soetomo General Hospital in March 2019. CT Scan result showed enhancing solid mass on the right and left sides of inferior palpebra, pressing bulb oculi to be posterior, showed a suspicious bilateral malignant mass of palpebra inferior, showed no extended intra-ocular lesion to the left or right side, and bilateral submandibular lymphadenopathy bilateral as well. (Figure 1).

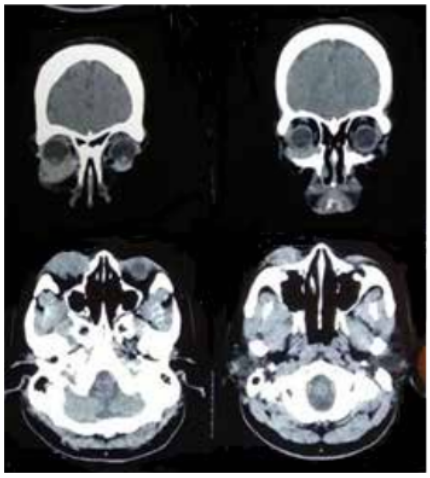

Figure 1. CT-Scan Orbital. Enhancing solid mass size +/- 3,2x1,9x1,75 cm on right-sided inferior palpebra and +/- 2,6 x 0,8 x 1,2 cm on left-sided inferior palpebra, pressing bulb occuli to posterior, suspicious bilateral malignant mass of inferior palpebra, no extended intraocular lesion to left and right sides, submandibular lymphadenopathy.

Liver function marker showed AST/ALT 65/110, negative HbsAg negative, negative anti HCV, negative IgM anti HAV, and normal AFP (3.3 mg/ml). Abdominal ultrasound showed parenchymal liver disease. In the meantime, the result of Fibroscan F2 from the right-sided palpebra inferior showed a suspicious

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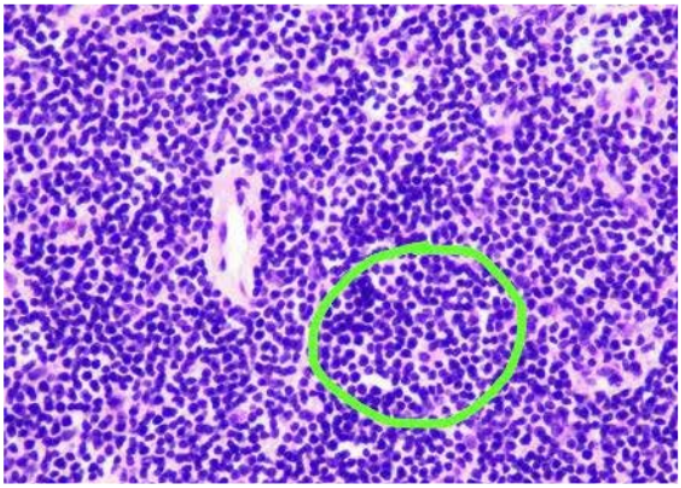

Figure 2. Histopathology of NHL biopsy specimen taken from right palpebra.

lymphoid tumor with Non-Hodgkin Lymphoma (NHL) and inflammatory pseudotumor as differential diagnosis. (Figure 2). IHC result showed positive CD 20 positive, negative CD 3, Ki 67 proliferation index 40%, Non-Hodgkin Lymphoma, B cell type high grade.

The patient was diagnosed with NHL of palpebra inferior B cell type high-grade Stadium II EA. Chemotherapy using regiment R-CHOP was performed every three weeks and six cycles. After the first chemotherapy, we started adjusting the dose due to the surge of AST/ALT level to 109/152. Dosage was not modified until six cycles finished.

The fourth cycle and sixth cycle chemotherapy evaluation showed complete response with ADE grade 0 without significant increase of AST/ ALT level (82/93). No abnormality of vision, orbital muscle movement, and destruction structure around orbital during and after sixth cycle chemotherapy. The patient didn't undergo radiotherapy. CT-Scan evaluation after six months of chemotherapy showed no relapse or recurrence of the palpebral mass.

DISCUSSION

Palpebral NHL is one of extranodal NHL; it is a rare and aggressive form of lymphoma. Palpebral NHL is lymphoma that infiltrates the pre-septal tissue, which includes the skin, subcutaneous, and/or orbicularis oculi muscle. Palpebral NHL is also part of ocular adnexal lymphoma (OAL). Since the palpebra is made up of skin, there is also a palpebral lymphoma in the form of cutaneous lymphoma. Palpebral NHL affects mainly 52% of men and 48% of women with 56% of B-cell origin and 44% of T-cell origin. Patients diagnosed with palpebral LNH were mainly at the age between 15 and 70 years. The most common type of B-cell lymphoma was extranodal marginal zone lymphoma (MALT) (14%) and diffused large B-cell lymphoma (9%). Palpebral LNH is part of the ocular adnexal lymphoma (OAL) in only about 8% of cases. Most cases occur in Asia and Europe (Eckardt et al., 2013; Nanthakwang et al., 2019; Priego, Majos, Climent, & Muntane, 2012; Svendsen et al., 2017).

History taking from the patients revealed a record of a lump that enlarged slowly with or without visual disturbances. Visual

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disturbances are caused by a pressing mass in the orbital area. History of visual disturbances, worsening quality of visual fields, and restricted orbital muscle motion suggest that primary lymphoma may not come from the palpebra but the orbit or systemic disease. Past medical history of patients with autoimmune diseases such as Sjörgen Syndrome, Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), autoimmune thyroid disease enhances the risk of palpebral NHL development. Besides, a history of HIV / AIDS which bring patients to an immunosuppressive state also increases the risk of developing palpebral NHL (Borghi et al., 2013; Eckardt et al., 2013; Hahn et al., 2001; Mbulaiteye, Parkin, & Rabkin, 2003; Nutting, Shah-Desai, Rose, Norton, & Plowman, 2006; Priego et al., 2012; Svendsen et al., 2017).

A patient with NHL palpebra came complaining of a solid and painless mass. The superior palpebrae were more frequently affected; most cases were unilateral mass with a similar ratio of the right and left palpebrae (51% vs. 49%) rather than bilateral. The constitutional symptoms at the time of diagnosis of palpebral NHL are uncommon, but they indicate a poor prognosis if they emerged. Physical examination may reveal palpebral swelling and prolapse with single or multiple lymphadenopathies. Palpebral masses may be accompanied by ulcers that cause a secondary infection. Eye examination of palpebral NHL may be accompanied by disturbance of orbital muscle movement and intraocular pressure increase due to mass pressure. Visual field disturbance indicates a systemic lymphoma. The role of an ophthalmologist when performing intraocular and extraocular evaluations is vital before beginning the following diagnostic steps (Eckardt et al., 2013; Marcus, Sweetenham, & Williams, 2014; Svendsen et al., 2017).

We used CT-Scan, MRI, or PET scan to evaluate the extension of the mass to the orbital, lacrimal gland, and intracranial. CT-scan shows a well-defined mass adhering to the surrounding orbital structure with a homogeneous and heterogeneous density. Homogeneous densities describe no bone destruction, while heterogeneous densities describe one and indicate high-grade lymphoma. CT scan could assist in the biopsy process with a CT-guided biopsy if there were an extension to the orbit or structures around the orbit. MRI evaluation helps determine intraconal or extraconal involvement of the LNH palpebra. If intraconal was involved, the radiological differential diagnosis could be meningioma, glioma, or cavernoma; while the differential diagnosis of extraconal involvement could be pseudotumor inflammation, tumor of the lacrimal gland, thyroid orbitopathy, or metastases. A PET-Scan examination is used to figure out the extent of involvement of the affected lymph nodes. This radiological examination helps the ophthalmologist to determine the location of the biopsy and evaluate the complete resection if needed. It also aids the interventional radiologist in planning radiotherapy (Amit, Purwar, Agarwal, & Kanchan, 2012; Pfeffer et al., 2004; Priego et al., 2012).

A palpebral biopsy was performed to obtain pathological specimens as a diagnostic tool. The anatomical pathology of palpebral NHL shows large lymphoid cells with a nucleus doubled in size of normal lymphocyte nuclei and no Reed Stenberg cells. These pathologic features can be differentially diagnosed with pseudotumor inflammation, which is the most common feature on a biopsy of a palpebral mass. The IHC examination will be beneficial in determining the mass of B-cell or T-cell lymphoma. IHC that were determined are CD3, CD5, CD 10, CD20, CD23 CD43, CD 79a, bcl-6 and Ki67. The Ann-Arbor system is used in LNH staging (Marcus et al., 2014;

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Vallinayagan, Krishnamoorthy, Vijayakumar, & Suryawanashi, 2017; Wali & Al-Mujaini, 2010).

The standard of therapy for palpebral NHL is currently still unclear. Palpebral NHL is a rare case, and there is no yet prospective randomized clinical trial available. Complete excision is performed on solitary low-grade lymphoma and combined with chemotherapy or radiotherapy. Two cases of palpebral NHL in the form of ocular adnexal lymphoma showed satisfying results with surgery alone. Unfortunately, surgery alone showed a high relapse rate in other types of palpebral LNH, and long-term post-operative monitoring without adjuvant chemotherapy is unknown. The role of a craniomaxillofacial surgeon is undoubtedly needed in a multidisciplinary team if the palpebral NHL is to dissect the orbits and the structures around the orbit (Marcus et al., 2014; Nola et al., 2004; Svendsen et al., 2017).

Chemotherapy on palpebral NHL is used for high-grade tumors with or without radiotherapy. Since the rituximab era began after 2006, there had been an improvement in the prognosis of patients with palpebral LNH (Chihara et al., 2019; Olsen et al., 2019; Svendsen et al., 2017). The first-line chemotherapy regimen used to treat palpebral LNH is primarily CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone); if CD20 is positive, we use R-CHOP (Rituximab, cyclophosphamide, doxorubicin/ epirubicin, vincristine, prednisone) every 21 days for 6-8 cycle. The dosage of Rituximab is 375 mg / m2, cyclophosphamide 750 mg / m2, Doxorubicin 50 mg / m2, and Vincristine 1.4 mg / m2, Prednisone oral 50 mg / m2 per day for 5 days (Skeel & Khleif, 2011).

According to the 2015 European Society for Medical Oncology (ESMO) guidelines, patients with large extranodal NHL <10 cm in size and a score of zero according to the International Prognostic Index (IPI) will receive R-CHOP chemotherapy every 21 days for six cycles with radiotherapy (Tilly et al., 2015). Meanwhile, based on the guidelines of The National Comprehensive Cancer Network (NCCN) in 2019 for stage II with bulky disease, the recommended regimen is R-CHOP 6 cycles with or without radiotherapy (Zelenetz et al., 2019).

Chemotherapy side effects are evaluated through the onset, target organs, and severity. Based on the onset of drug side effects, they are divided into acute (less than 1 hour after drug administration), early (1-48 hours after drug administration), delayed (2 days - 2 months after drug administration), and slow (2 months after drug administration). For monitoring of target organs and severity, it is divided into grades 0 to 5. Grade 0-2 means that it is quite safe, does not need therapy, grade 3 means that you need to be aware that sometimes you need therapy, grade 4 means that danger signs can occur that death needs early and adequate treatment, and grade 5 means the patient is dead. Side effects that often occur less than 1 hour or 1-24 hours cause symptoms such as nausea and vomit, febrile, hypotension, and symptoms of such as severe pain, erythema, and hematoma at the injection site of chemotherapy drugs. Symptoms that arise from the slow type of chemotherapy were fatigue, weakness, tingling, difficulty concentrating, heart problems, reduced lung capacity, kidney and urinary disorders, and liver problems (Ashariati, 2015).

Adjustment of chemotherapy doses can be considered after liver function or creatinine clearance measurement (Skeel & Khleif, 2011). A surge in AST/ALT by 2.5-10 times of expected value indicates a liver disorder that requires chemotherapy dosage adjustment. The chemotherapy dose in this situation is reduced by about 50% of the initial dose. If it increases> 10 times the normal value or Total bilirubin > 3 mg/dl, then the chemotherapy drug must be stopped (Hendrayana, Wilmer,

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Kurth, Schmidt-Wolf, & Jaehde, 2017). Chemotherapy drugs from the R-CHOP regimen that are metabolized in the liver include Cyclophosphamide, Doxorubicin / Epirubicin, and Vincristine, three chemotherapy drugs that need to be adjusted in patients with liver disorders. Adjustment of chemotherapy dose with the liver disorder can be reduced by increasing AST/ALT level and minimizing the risk of adverse reaction of chemotherapy (Chu & DeVita, 2018).

Eye evaluation after chemotherapy by an ophthalmologist is needed to see whether the reduced palpebral mass causes visual disturbances, visual field disorders, impairment of orbital movement, and disturbs the anterior and posterior eye segments, intraocular and extraocular part (Eckardt et al., 2013; Priego et al., 2012; Svendsen et al., 2017).

In palpebral NHL, the median months of disease-free survival are 15-24 months with a median recurrence rate of 2-26 months, depending on the type of histopathology. Treatment response at the early stage (stage I-II) showed a complete response. At stage III, 80% of cases showed partial response, 5% were progressive, and 31% of cases relapsed. A complete response to the histopathological type diffuse large B-cell lymphoma (DLBCL) in 70% of cases was found at stage IE, and one in nine patients experienced recurrence after being given Rituximab. Palpebral NHL B-cell type recurrence occurred in 27% of cases. The lowest recurrence rate came from histopathologic type extranodal marginal zone lymphoma (EMZL) and extramedullary plasmacytoma (EMP). The recurrence rate of DLBCL type reached 33% of cases, and one-third of cases experienced a relapse. (Svendsen et al., 2017).

CONCLUSION

We reported a case of a thirty-eight years old woman with bilateral inferior palpebral NHL B cell type high grade, stage IIEA CD 20 +, non-specific reactive hepatitis. Examination of vision, orbital muscle movement, intraocular pressure, anterior and posterior eye segments showed no abnormalities. For patients treated using R-CHOP with post-chemotherapy evaluation on the seventh day, the AST/ALT level surge was found insignificant. The dosage adjustment was made on the second chemotherapy due to the increase of AST/ALT to 1.43 times by the normal limit. Evaluation of IV chemotherapy gave a complete response with grade 1 ESO. Evaluation of 6th chemotherapy was full in response also with grade 1 ESO. Post chemotherapy eye examination showed no disturbances in vision, visual field, orbital muscle movement, and anterior and posterior eye segments were fine.

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