Malignant Lymphoma of The Lacrimal Canaliculi: A Rare Case Report

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Background: Malignant lymphoma in the lacrimal system is a rare case of ocular malignancy. It is often caused by immunosuppressive conditions or associated with older age. We aim to conduct a careful examination of canaliculi mass especially a suspect for malignant to be completed with histopathology and discuss the diagnosis and management of malignant lymphoma in the lacrimal canaliculus.

Results: A woman, 60 years old, presented with a swollen left upper eyelid, red eye, and eye discharge. She had been assessed as blepharoconjunctivitis and received adequate antibiotics for the last four months. However, her complaints persisted. She had ocular pain, itchiness, yellowish thick eye discharge. History of previous tumor was denied. Physical examination revealed a swollen lacrimal punctum on the left upper eyelid, depicted a 'fish mouth appearance' with volume 3.0 x 3.0 x 3.0 mm. Irrigation test showed a negative result with a positive regurgitation discharge. Punctum incision and curettage were performed using local anesthesia. The curettage procedure revealed a dacryolith on the upper side and a purplish-red mass on the lower side. Culture test showed a positive result for *Staphylococcus aureus* infection. The mass was sent to pathology which suggested a lymphoproliferative lesion, suggestive of a malignant lymphoma. The patient was referred to the Hematology-Oncology division to determine the stage and further treatment.

Conclusion: The diagnostic tests needed for malignant lymphoma cases include biopsy, immunohistochemistry, laboratory, and computed tomography scan. Biopsy must be done assuming that the mass is malignant, until proven otherwise. Management of malignant lymphoma itself is based on the type and severity degree of the lymphoma.

Keywords: canalicular lymphoma, lacrimal system, ocular malignancy, TNM staging, ocular adnexal lymphoma

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Introduction

Malignant lymphoma in the lacrimal system is one of the rare cases of ocular malignancy.The majority of these lymohomas are classified into Non-Hodgkin Lymphoma (NHL).[1-2] NHL is a type of malignancy that can originate from 3 types of lymphocyte cells, namely B cells, T cells, and natural killer (NK) cells.[3] The incidence of lymphoma in the lacrimal system is estimated at 0.2 per 100,000 individuals.[2]

Malignant lymphomas are often caused by some conditions such as immunosuppression conditions, HIV-AIDS, the use of immunosuppression drugs, or associated with older age.[4] However, current literature also showed that malignant lymphomas may be associated with bacteria or viruses infection, such as *Chlamydia psitacii, Helicobacter pylori,* Hepatitis-C virus, human herpes virus, human T-cell lymphotrophic virus type-1 (HTLV-1) and Epstein-Barr virus (EBV).[4]

In this case report, we will discuss the examination, diagnosis, and management of a patient with malignant lymphoma in the lacrimal canaliculus.

Case Report

A 60-year-old woman came with a swollen left upper eyelid, red eye, and eye discharge. This patient had been assessed with blepharoconjunctivitis for the last four months. She had received antibiotics yet her complaints were still existed. She also complained about having ocular pain, itchiness, and yellowish thick eye discharge. She had a history of hypertension and diabetes mellitus.

No history of bleeding and decreased visual acuity were found. History of previous tumor or lump in the eye or any part of the body was denied. She had never experienced trauma, previous eye surgery or systemic infection. No history of similar complaints on her family.

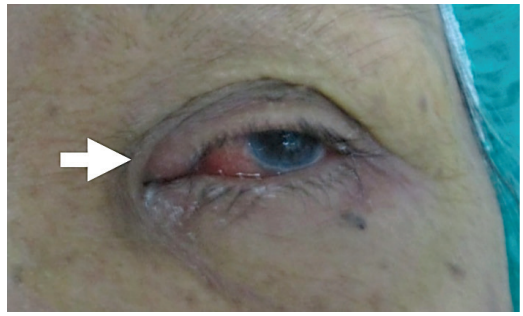

Figure 1. Visible superior canaliculus lumps on the left eyelid was pointed with white arrow.

General physical examination was normal. Visual acuities were 6/6 for both eyes. There was a swollen lacrimal punctum on the left upper eyelid which depicted a 'fish mouth appearance' with 3.0 x 3.0 x 3.0 mm in volume (see Figure 1). There was reddish discharge from the punctum of lacrimal and tenderness on the left eyelid. Right eyelid was normal as well as the other ophthalmologic examinations.

Irrigation test (Anel test) showed a negative result with a positive regurgitation discharge. Blood test of the patient also showed a normal range (haemoglobin 13.8 g/dL, red blood cell 4.8x1012 cells/L, hematocrit 42.2%, leukocyte 5000/L, platelet 241,000/mm3, random blood glucose 191 mg/dL, HbA1c 6.2%). The patient was assessed with chronic canaliculitis of the left eye. As seen in Figure 2, punctum incision and curettage were performed using local anesthesia. In this patient, curettage revealed a purplish-red mass and the tissue biopsy was sent to

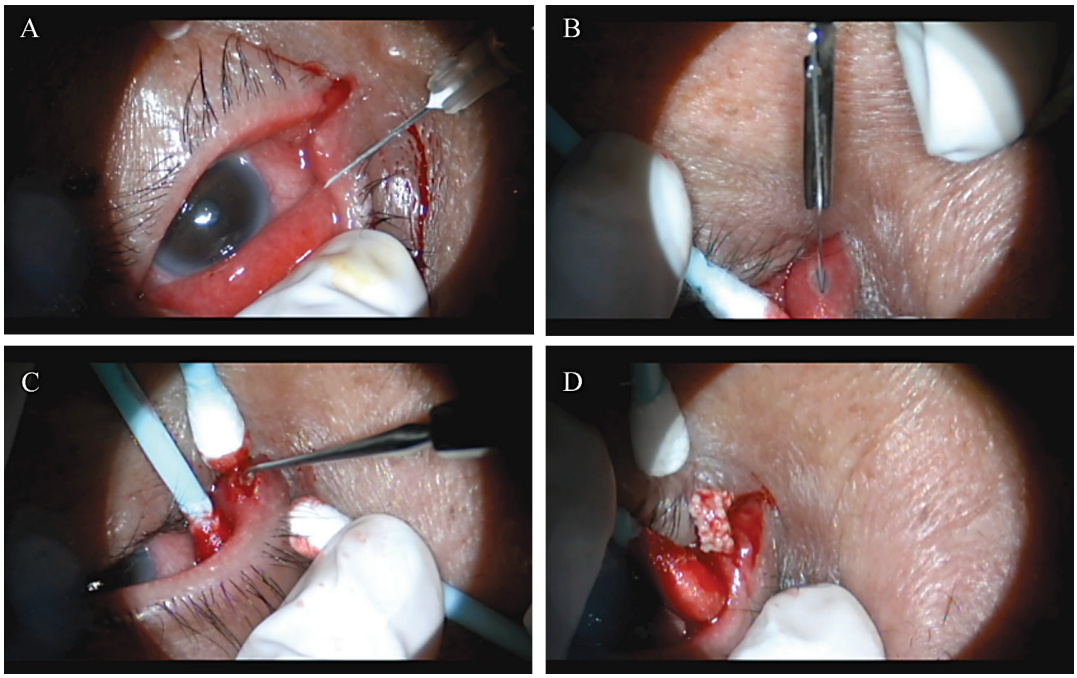

Figure 2. Incision and curettage followed by biopsy. (A) Local anesthesia; (B) Superior lacrimal canalicular incision; (C) Curettage; (D) Mass extraction

pathology anatomy for further examination.

Culture test showed a positive result for *Staphylococcus aureus* infection. Furthermore, the sensitivity test revealed that this patient was sensitive with several antibiotics. On the other hand, the negative sensitivity test showed resistant to piperacillin, benzylpenicillin, and amoxicillin.

Pathology anatomy result showed that the tumor was a lymphoproliferative lesion, raising a suspect of a malignant lymphoma. Furthermore, it is crucial to classify the staging of malignant lymphoma by immune-histochemical and genetic testing. The examinations would lead to proof the type of lymphoma before further treatment. However, the immune-histochemical and genetic testing had not been performed since the patient was reluctant due to financial matter. The patient was consulted to the Hematology-Oncology division Internal Medicine for determining the definitive therapy, although the patient was lost to follow up at our hospital.

Discussion

Malignant lymphoma cases in the lacrimal system are one of the rare conditions in the ocular malignancy. Based on reports in the United Kingdom, a third of lacrimal system lymphoma cases are MALT lymphoma type and a third of them are DLBCL type. Other data from Japan states that DLBCL has an incidence rate of 46.2%, while MALT lymphoma has an incidence rate of 15.4%.1 Several other studies have also shown that MALT lymphoma and DLBCL are the two types of lymphoma that most commonly occur in the lacrimal system.[2]

Early development of malignant lymphoma in the lacrimal system begins with a sudden growth of the mass, which

is followed by a slow progression.[3] In this patient, swollen eyelids appeared for the previous 4 months. There were no other non-specific symptoms of malignant lymphoma found in this patient, namely, enlargement of lymph nodes, malaise, weight loss, fever, and night sweats.

Both irrigation and curettage procedures were planned based on the 'fish mouth appearance' that was found in the physical examination. Despite the negative irrigation test, canaliculectomy was still managed to be performed. If there is no improvement in the patient's symptoms despite the adequate medication, incision and curettage followed by a mass biopsy should better be performed. After an adequate duration of treatment with antibiotics for four months, the culture test was also done to have a further look at the possible etiology. In this case, if we referred to the outcome of the culture-sensitivity test, there was a secondary infection from *Staphylococcus aureus*. These gram-positive bacteria are found in the respiratory system which is very close to the lacrimal system.

Blockage in the lacrimal system due to malignant lymphoma can trigger an infection around the lacrimal system. At the end of the procedure, a mass was found in situ but it was not a dacryolith. Therefore, we sent the mass to the pathology anatomy.

Age ranges from 50 to 70 years old is considered as carrying the highest risk of malignant lymphoma, hence, our sixty-year-old patient is classified as having the peak age.[4] The diagnosis process of malignant lymphoma begins

TNM Clinical Staging for Ocular Adnexal Lymphomas (OALs)[a]

Primary tumor (T)	
TX	Lymphoma extent not specified
T0	No evidence of lymphoma
T1	Lymphoma involving the conjunctiva alone without orbital involvement
T1a	Bulbar conjunctiva only
T1b	Palpebral conjunctiva ± fornix ± caruncle
T1c	Bulbar and nonbulbar conjunctival involvement
T2	Lymphoma with orbital involvement ± any conjunctival involvement
T2a	Anterior orbital involvement,[b] but no lacrimal gland involvement (± conjunctival disease)
T2b	Anterior orbital involvement with lacrimal gland involvement (± conjunctival disease)
T2c	Posterior orbital involvement (± conjunctival involvement ± any extraocular muscle involvement)
T2d	Nasolacrimal drainage system involvement (± conjunctival involvement but not including nasopharynx)
T3	Lymphoma with preseptal eyelid involvement[2,3,c] ± orbital involvement ± any conjunctival involvement
T4	Orbital adnexal lymphoma extending beyond orbit to adjacent structures, such as bone and brain
T4a	Involvement of nasopharynx
T4b	Osseous involvement (including periosteum)
T4c	Involvement of maxillofacial, ethmoidal ± frontal sinuses
T4d	Intracranial spread
Lymph node involvement (N)[d]	
NX	Involvement of lymph nodes not assessed
N0	No evidence of lymph node involvement
N1	Involvement of ipsilateral regional lymph nodes[d]
N2	Involvement of contralateral or bilateral regional lymph nodes
N3	Involvement of peripheral lymph nodes not draining ocular adnexal region
N4	Involvement of central lymph nodes
Distant metastasis (M)	
MX	Dissemination of lymphoma not assessed
M0	No evidence of involvement of other extranodal sites
M1	Lymphomatous involvement in other organs recorded either at first diagnosis or subsequently
M1a	Noncontiguous involvement of tissues or organs external to the ocular adnexa (eg, parotid glands, submandibular gland, lung, liver, spleen, kidney, breast)
M1b	Lymphomatous involvement of the bone marrow
M1c	Both M1a and M1b involvement

Figure 3. TNM Lymphoma Ocular Adnexa Staging

with the staging process of the disease. Several references can be used for staging lymphoma, including REAL, Ann Arbor, and TNM.[5] For lymphoma cases in the orbital/ocular adnexa, the staging system using TNM provides a more specific result (see Figure 3).

Based on the staging system, staging T explains the expansion of the primary lymphoma tumor. In the case of adnexal ocular lymphoma, lymphoma expansion ranges from the conjunctiva to the entire structure in the periorbital structure. Staging N explains the involvement of lymph nodes. Lymph nodes involvement ranges from ipsilateral regional lymph nodes to central lymph nodes. Staging M explains the metastasis away from the lymphoma. The degree of metastasis is ranged from external organs from ocular adnexa to bone marrow involvement. In this case, the only staging that can be done is T2d-NX-MX which involved the nasolacrimal system with or without conjunctival involvement and no involvement of nasopharynx with no examination of lymph node (N) and distant metastasis (M) involvement.

The diagnostic tests needed for malignant lymphoma cases include biopsy, immunohistochemistry, laboratory, and computed tomography or positron emission tomography (PET) scan. Biopsy examination is done by taking a tissue sample and a biopsy of the nearest lymph node (sentinel lymph node biopsy). In the case of the lacrimal system lymphoma, the favorable closest lymph node taken is from pre-auricular, cervical, and supraclavicular lymphoma. The biopsy process is followed by routine histopathological examination to determine the cell type and continued with an immunohistochemical examination.[5,6]

The biopsy result of this case showed a lympho-proliferative lesion with a possibility of malignant lymphoma. Ideally, to find

Neoplasm	sIg; cIg	CD5	CD10	CD23	CD43	CD103	BCL6	IRF4/ MUM1	Cyclin D1	ANXA1
CLL/SLL	+;-/+	+	-	+	+	-	-	(+PC)	-	-
LPL	+/-;+	-	-	-	-/+	-	-	+*	-	-
Splenic MZL	+;-/+	-	-	-	-	-	-	-	-	-
HCL	+;-	-	-	-	-	+	-	-	+/-	+
Plasma cell myeloma	-;+	-	-/+	-	-/+	-	-	+	-/+	-
MALT lymphoma	+;+/-	-	-	-/+	-/+	-	-	+*	-	-
Follicular lymphoma	+;-	-	+/-	-/+	-	-	+	-/+#	-	-
MCL	+;-	+	-	-	+	-	-	-	+	-
Diffuse large B-cell lymphoma	+/-;-/+	-***	-/+##	NA	-/+	NA	+/-##	+/-**	-	-
Burkitt lymphoma	+;-	-	+	-	+/-	NA	+	-/+	-	-

+, >90% of cases +; +/-, >50% of cases +; -/+, <50% of cases +; -, <10% of cases +. IRF4/MUM1, interferon regulating factor 4; ANXA1, Annexin A1; PC, proliferation centres; *, plasma cell component positive; #, some grades 3a and 3b; ##, DLBCL of germinal centre B-cell type (GCB) express CD10 and BCL6; **, DLBCL of activated B-cell type (ABC) are typically positive for IRF4/MUM1; ***, some DLBCL are CD5+; NA, not applicable; LPL, lympho-plasmacytic lymphoma; MZL, marginal zone lymphoma; MCL, mantle cell lymphoma.

Figure 4. Immunohistochemical characteristics of malignant lymphomas originating from B-cells

out more about the type of lymphoma, an additional examination is needed, such as immunohistochemical examination and genetic testing.

Immunohistochemical examination in malignant lymphoma cases is used to differentiate the histopathological character of the lymphoma cells. This examination aims not only to diagnose the lymphoma cell, but also to determine the management for patient. Figure 4 shows various characteristics of the types of lymphomas that are associated with differences in immunohistochemical examination.

There are various regimens available for immunohistochemical examination of malignant lymphoma cases, including CD10, CD20, CD3, CD5, CD19, CD45, bcl-2, bcl-6, Ki-67, MUM1.[5,8] Laboratory tests that can support the diagnosis of malignant lymphoma

Table 1. Low-Grade and High-Grade Malignant Lymphoma[12]

Low Grade	High Grade
· MALT Lymphoma	· Mantle Cell Lymphoma
· SLL (Small Lymphocytic Lymphoma)	· DLBCL (Diffuse Large B-Cell Lymphoma)
· MZL (Marginal Zone Lymphoma)	· Burkitt Lymphoma
· Lymphoplasmacytic Lymphoma	· T-Cell Lymphoma
· Follicular Lymphoma	

are routine haematological examinations (haemoglobin, haematocrit, leukocytes, platelets, type counts), peripheral blood morphology, SGOT, SGPT, bilirubin, LDH, albumin, ureum-creatinine, and electrolytes. Other examinations that can help are detection of Hepatitis C, tuberculosis, and HIV.[5,9] In this case, a relatively normal laboratory result was obtained from this patient.

Management of malignant lymphoma is based on the severity of the lymphoma. There are 2 groups of severity, low grade (Ki-67 <30%) and high grade (Ki-67>30%) lymphoma.[5, 9, 10] The table below shows the types of lymphomas based on the degree of severity.

The first-line therapies of low-grade lymphoma and small size lymphoma (<7.5 cm) are chemotherapy with R-CHOP regimen (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) for 3 cycles, followed by radiotherapy. For high-grade lymphoma, the first-line therapies are chemotherapy with the R-CHOP regimen (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) for six cycles and continued with radiotherapy. In patients with cardiac disorders, the chemotherapy regimen can be replaced with alternative regimens such as RCEPP (Rituximab, Cyclophosphamide, Etoposide, Procarbazine, Prednisone), RCDOP (Rituximab, Cyclophosphamide, Liposomal, Doxorubicin, Vincristine, Prednisone, Procarbazine), DA-EPOositu (DA-EPO), RCEOP (Rituximab, Cyclophosphamide, Etoposide, Vincristine, Prednisone), and RGCVP (Rituximab, Gemcitabine, Cyclophosphamide, Vincristine, Prednisone).[5,9]

Radiotherapy in lymphoma cases show good efficacy. Radiotherapy has a local tumor control level of 86-100% and a local recurrence rate ranged from 0% to 15%. Radiotherapy or External Beam Radiation Therapy (EBRT) is given externally. The targets of this radiotherapy include the localized area of the lymphoma tumor and nearby lymph nodes involved. CT Simulator is used to plan the radiotherapy. PET Scan can help determine the target volume of radiotherapy. The dose given is approximately 30 – 36 Gy for cases that respond to chemotherapy, or 40 – 50 Gy in cases that do not respond to chemotherapy. The dose is given in 15 – 20 divided doses.[5,9,12]

In general, malignant lymphoma in the lacrimal system has a good prognosis for low-grade type. The five year survival rate for this condition varies from 50-94%.[5] Excision therapy or surgery alone is not enough to prevent tumor recurrence. For small-sized tumors, therapy with multiple modalities is recommended such as chemotherapy followed by radiotherapy. This therapy is useful to prevent recurrence and the development or metastasis of the lymphoma to other organs.

Conclusion

Malignant lymphoma in the canalicular system is a rare case in ocular malignancy. This condition may be related to immunosuppressive condition, such as HIV-AIDS and the use of immunosuppressive drugs, or associated with older age. The most common type of malignant lymphoma is Non-Hodgkin Lymphoma. It is imperative that biopsy must be done assuming that the mass is malignant, until proven otherwise.

Acknowledgement

None.

Conflict of interest

None.

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