J Clin Exp Hematop
Vol. 53, No. 1, June 2013

Case Study

A Case of Conjunctival Follicular Lymphoma Mimicking Mucosa-Associated Lymphoid Tissue Lymphoma

Lamia Abd Al-Kader,[1,5] Yasuharu Sato,[1] Katsuyoshi Takata,[1] Koh-ichi Ohshima,[2] Yuka Sogabe,[3] Kazuhiro Fujii,[3] Noriko Iwaki,[1,4] and Tadashi Yoshino[1]

Ocular adnexal lymphoma may involve the eyelids, conjunctiva, orbital tissue, or lacrimal structures. The majority are non-Hodgkin's B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) lymphoma type. Follicular lymphomas represent a small percentage of ocular adnexa lymphomas, particularly in Japan. We report a 68-year-old female patient who presented with a salmon pink patch-like lesion of the left conjunctiva, suspected of being (MALT) lymphoma. However, histologic and immunohistologic examinations were consistent with follicular lymphoma. This case demonstrates the importance of considering such rare lymphomas when making a diagnosis of ocular adnexal lymphoid neoplasms. 〔*J Clin Exp Hematop 53(1): 49-52, 2013*〕

Keywords: ocular adnexa, conjunctiva, follicular lymphoma

INTRODUCTION

Ocular adnexal lymphoma is primarily a disease of older adults ; it can involve the eyelids, conjunctiva, orbital connective tissue, or lacrimal structures. The majority are mucosa-associated lymphoid tissue (MALT) lymphoma. MALT lymphoma usually occurs as a primary disease of the ocular adnexa, whereas other types of low-grade B-cell lymphoma often involve the ocular adnexa secondarily. Follicular lymphomas come next in frequency in the Western world, but they represent a small percentage of ocular adnexa lymphomas in Japan.[1,2] In this paper, we report a case of conjunctival follicular lymphoma mimicking MALT lymphoma.

CASE REPORT

A 68-year-old woman presented with nasal conjunctival hyperemia of the left eye. She initially received antibiotic and corticosteroid treatment with no response for two months. The patient then developed a small patch-like lesion on the conjunctiva. She was referred to an ophthalmologist. On examination, a fleshy lesion with a salmon pinkish appearance was seen extending from the nasal fornix to the inferior fornix and involving the bulbar conjunctiva (Fig. 1). There was no pain, no history of trauma, and no systemic complaints. On these findings, the ophthalmologist suspected it to be MALT lymphoma and a biopsy was performed.

A section stained with hematoxylin and eosin on low-

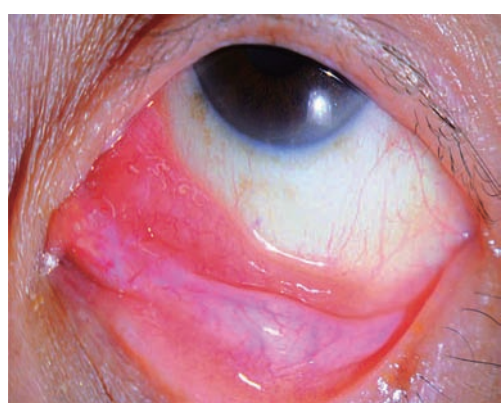

Fig. 1. Conjunctival salmon pink patch-like lesion extending from the fornix.

Received : November 30, 2012
Revised : December 25, 2012
Accepted : January 15, 2013

[1]Department of Pathology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan
[2]Department of Ophthalmology, National Hospital Organization Okayama Medical Center, Okayama, Japan
[3]Department of Ophthalmology, Mitoyo General Hospital, Kanonji, Japan
[4]Cellular Transplantation Biology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan
[5] Department of Pathology, Faculty of Medicine, Mansoura University, Egypt
Corresponding author : Dr. Y. Sato, Department of Pathology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan
E-mail : satou-y@cc.okayama-u.ac.jp

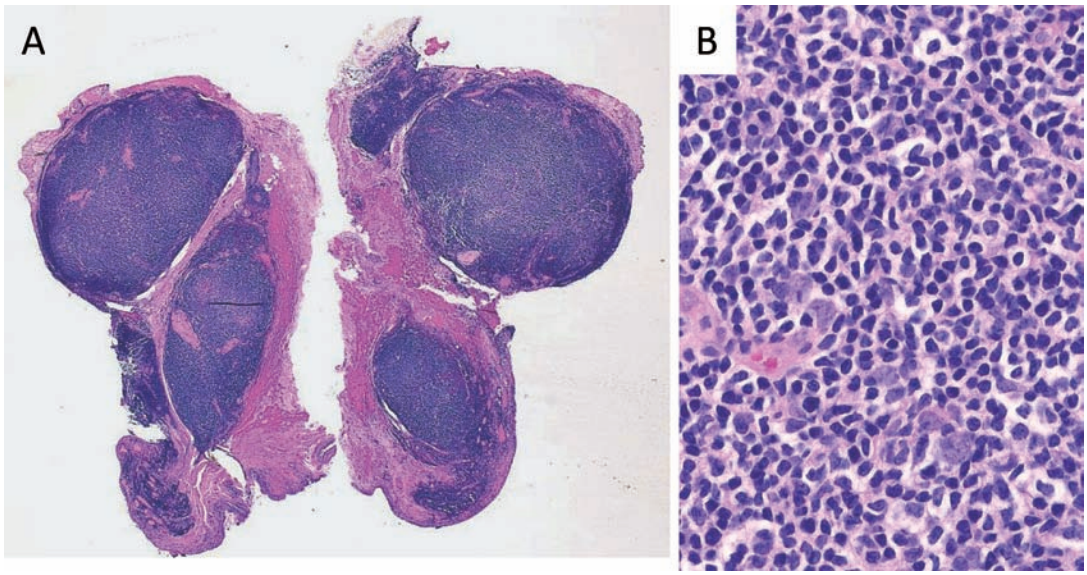

Fig. 2. Histologic findings of the conjunctival mass. (***2A***) Hematoxylin and eosin section showing diffuse lymphoid proliferation within conjunctival connective tissue. (***2B***) Higher magnification shows small centrocyte-like lymphoid cells. (*2A*) ×2, (*2B*) ×400.

power examination revealed a monotonous lymphoid proliferation within conjunctival connective tissue under the epithelium. A follicular pattern was not well appreciated (Fig. 2). Higher magnification showed a proliferation of small to medium-sized centrocyte-like lymphoid cells, with fine chromatin and inconspicuous nucleoli. A panel of immunohistochemical stains was performed. Tumor cells were positive for CD20 and Bcl-2 antigens. Staining for CD21 antigen was also positive, revealing a meshwork of dendritic reticular cells that matched CD10-positive areas. The same areas were also positive for Bcl-2 (Fig. 3). Ki-67 labeling index was low. Both anti-CD3 staining and anti-cyclin D1 staining were negative. A diagnosis of follicular lymphoma (grade 1) of the conjunctiva was made.

Table 1 provides the laboratory data. Bone marrow aspiration biopsy was normocellular with no involvement by lymphoma cells. Fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography revealed no enlarged lymph nodes, with no other sites of involvement. The conjunctival tumor was found to be a solitary primary lesion (stage I). Therefore, the patient received radiotherapy alone. After receiving radiotherapy of 30 Gy/15 fractions, she achieved complete remission.

DISCUSSION

Lymphomas are classified into two major groups, nodal (occurring in lymph nodes) and extranodal (originating outside lymph nodes). Extranodal lymphomas were reported to constitute approximately 24% to 48% of lymphomas. The most common extranodal sites include stomach, tonsils, skin, and small intestine.[3] Ocular adnexal involvement occurs in less than 10% of extranodal lymphomas.[1] They are often of low-grade type, classified as MALT lymphoma with good prognosis.[1,4,5] Follicular lymphoma is one of the most frequent indolent B-cell lymphomas and follows a similar pattern. Most cases arise from the lymph nodes and are at advanced clinical stages at the time of diagnosis.[6] Primary extranodal disease occurs only occasionally and the usual sites are skin and duodenum.[7] Generally, follicular lymphomas are found less frequently in Asian countries than in Western countries, so the prevalence of occurrence in the ocular adnexa in the Japanese is very low.[2]

The clinical picture of conjunctival lymphoma was described in more detail in a series presented by Shields and colleagues. Most patients with conjunctival lymphoma were symptomatic at presentation, generally with minor complaints of a lump, irritation, or ptosis. The most common location was the fornix, followed by the bulbar conjunctiva. The tumors presented over a wide range of age (23-86 years), particularly in the older population, with a median patient age of 63 years.[8]

The anatomic site of tumor in the conjunctiva, orbit, or eyelid has been found to correlate with systemic lymphoma in some reports. Conjunctival tumors had the best prognosis, with systemic lymphoma developing in only 20% of patients, whereas orbit and eyelid involvement correlated with a higher incidence of systemic lymphoma (35% and 70%, respectively). A low Ki-67 proliferation index is another indicator of a good prognosis.[9,10] Shields *et al*. reported that systemic

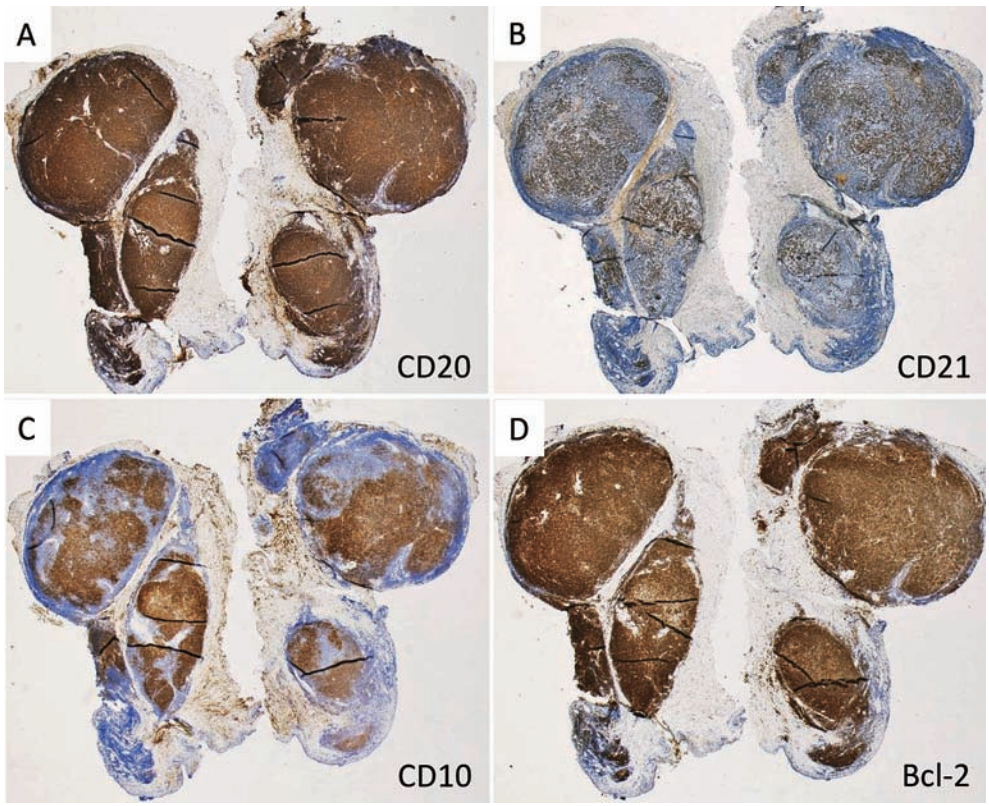

Fig. 3. Immunohistochemical staining result. (***3A***) The tumor cells expressed CD20. (***3B***) A meshwork of dendritic reticular cells revealed by CD21 staining. (***3C***) The same areas were positive for CD10. (***3D***) The same area was also positive for Bcl-2. (3A)-(3D) ×2.

Table 1. Laboratory data

Parameters	Values	Normal range
White blood cells (/μL)	3.2×10^3	$3.5\text{-}8.5 \times 10^3$
Red blood cells (/μL)	3.99×10^6	$3.8\text{-}4.8 \times 10^6$
Hemoglobin (g/dL)	12.1	11.5-14.5
Hematocrit (%)	36.1	35-45
Platelets (/μL)	158×10^3	$150\text{-}350 \times 10^3$
Mean corpuscular volume (fL)	90.5	83-100
Mean corpuscular hemoglobin (pg)	30.3	28-34
Segmented neutrophils (%)	66.4	40-70
Eosinophils (%)	0.6	1-6
Basophils (%)	0	0-2
Monocytes (%)	4.3	2-9
Lymphocytes (%)	28.7	20-50
Lactate dehydrogenase (IU/L)	175	120-240
Total protein (g/dL)	7.6	6.5-8
Albumin (g/dL)	5.1	4-5

lymphoma developed more commonly in patients with bilateral conjunctival involvement than in unilateral cases (47% versus 17%, respectively). Follow up revealed that bilateral disease evolved from initially unilateral disease in 7% of patients over a range of 3 months to 8 years. More importantly, patients who presented with stage I primary conjunctival lymphoma eventually developed systemic disease at 7% at 1 year, 15% at 5 years, and 28% at 10 years. In particular, tumors with an extralimbal site (fornix or midbulbar conjunctiva) were predictive of systemic lymphoma.[8]

There are several therapeutic options. Bhatia *et al*. reported radiotherapy as a curative treatment for conjunctival lymphoma.[11] Takahira *et al*. reported successful treatment with anti-CD20 antibody Rituximab and low-dose involved-field radiotherapy.[12] Other studies recommended complete excision plus cryotherapy of the underlying sclera if the mass is small. For larger tumors that are not amenable to full resection, incisional biopsy and low-dose radiotherapy can be used,[8,13] and some used cryotherapy by liquid nitrogen spray for conjunctival lymphomas and reported a 98% eradication rate within 3 treatments.[14] Our patient had unilateral primary conjunctival disease with no evidence of systemic involvement (stage I). Ki-67 proliferation index was low. These findings suggest a favorable course.[8,9] She received radiotherapy of 30 Gy/15 fractions and is now in complete remission. However, extralimbal location of the tumor (fornix and midbulbar conjunctiva) warrants caution. Long-term regular follow up for the development of bilateral or systemic disease is strongly recommended.[8]

To the best of our knowledge, there are only a few reports of primary conjunctival follicular lymphoma in the literature on both children and adults.[1,12,15] The differentiation of follicular lymphoma from other variants is important because these lymphomas exhibit different clinical behaviors and outcomes.[2] The early clinical picture and age of presentation may overlap with a simple case of dry eye irritation.[8] In conclusion, the rarity of conjunctival follicular lymphoma together with the nonspecific clinical presentation makes first-hand diagnosis rather difficult. Considering such a rare variant when faced with a case of a conjunctival lump facilitates early diagnosis and improves therapeutic and curative options for the patient.

DISCLOSURE/CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1 Ferry JA, Fung CY, Zukerberg L, Lucarelli MJ, Hasserjian RP, *et al*.: Lymphoma of the ocular adnexa : A study of 353 cases. Am J Surg Pathol 31:170-184, 2007

2 Otomo T, Fuse N, Ishizawa K, Seimiya M, Shimura M, *et al*.: Japanese case of follicular lymphoma of ocular adnexa diagnosed by clinicopathologic, immunohistochemical, and molecular genetic techniques. Clin Ophthalmol 4:1397-1402, 2010

3 Freeman C, Berg JW, Cutler SJ: Occurrence and prognosis of extranodal lymphomas. Cancer 29:252-260, 1972

4 White WL, Ferry JA, Harris NL, Grove AS Jr: Ocular adnexal lymphoma. A clinicopathologic study with identification of lymphomas of mucosa-associated lymphoid tissue type. Ophthalmology 102:1994-2006, 1995

5 Cahill M, Barnes C, Moriarty P, Kennedy S: Ocular adnexal lymphoma - comparison of MALT lymphoma with other histological types. Br J Ophthalmol 83:742-747, 1999

6 Sato Y, Ichimura K, Tanaka T, Takata K, Morito T, *et al*.: Duodenal follicular lymphomas share common characteristics with mucosa-associated lymphoid tissue lymphomas. J Clin Pathol 61:377-381, 2008

7 Chan JKC, Quintanilla-Martinez L, Ferry JA, Peh SC: Extranodal NK/T-cell lymphoma, nasal type. In : Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, *et al*. (eds) : World Health Organization Classification of Tumours, WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed, Lyon, International Agency for Research on Cancer (IARC), pp.285-288, 2008

8 Shields CL, Shields JA, Carvalho C, Rundle P, Smith AF: Conjunctival lymphoid tumors : Clinical analysis of 117 cases and relationship to systemic lymphoma. Ophthalmology 108:979-984, 2001

9 Knowles DM, Jakobiec FA, McNally L, Burke JS: Lymphoid hyperplasia and malignant lymphoma occurring in the ocular adnexa (orbit, conjunctiva, and eyelids) : a prospective multiparametric analysis of 108 cases during 1977 to 1987. Hum Pathol 21:959-973, 1990

10 Coupland SE, Krause L, Delecluse HJ, Anagnostopoulos I, Foss HD, *et al*.: Lymphoproliferative lesions of the ocular adnexa. Analysis of 112 cases. Ophthalmology 105:1430-1441, 1998

11 Bhatia S, Paulino AC, Buatti JM, Mayr NA, Wen BC: Curative radiotherapy for primary orbital lymphoma. Int J Radiat Oncol Biol Phys 54:818-823, 2002

12 Takahira M, Okumura H, Minato H, Urushisaki N, Sakurai M, *et al*.: Primary conjunctival follicular lymphoma treated with the anti-CD20 antibody rituximab and low-dose involved-field radiotherapy. Jpn J Ophthalmol 51:149-151, 2007

13 Shields JA, Shields CL, De Potter P: Surgical management of conjunctival tumors. The 1994 Lynn B. McMahan Lecture. Arch Ophthalmol 115:808-815, 1997

14 Eichler MD, Fraunfelder FT: Cryotherapy for conjunctival lymphoid tumors. Am J Ophthalmol 118:463-467, 1994

15 Gaffar M, Thebpatiphat N, Przygodzki R, Jacobs S, Miller MM: Primary follicular lymphoma of the conjunctiva in a 6-year-old child. J AAPOS 14:538-540, 2010