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Diagnosis and Treatment of Orbital Malignant Lymphoma: A 14-Year Review at Yamagata University

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Purpose: With the recent increase in the incidence of orbital malignant lymphoma, it is important to make the appropriate decision on effective treatment. The purpose of the current study was to develop a protocol to treat orbital malignant lymphoma based on evidence from histopathological examination.

Methods: In the present study we analyzed the records of 18 cases of orbital lymphoma treated in the Yamagata University Hospital over the past 14 years, including 6 cases of isolated orbital disease and 12 cases of systemic disease. The tentative strategy for selecting the treatment was as follows: the cases at clinical stage I (Ann Arbor criteria) were treated with curative intent, and the cases at stages II–IV were treated with palliative intent. This strategy was evaluated from the viewpoints of efficacy and side effects.

Results: Histopathologically, all 6 cases of isolated orbital disease were classified as low-grade malignancy, 3 of the systemic disease cases were classified as low-grade, and 9 were classified as intermediate-grade malignancy. The isolated orbital disease cases at stage I were treated by radiation or chemotherapy. The systemic disease cases at stages II–IV were treated by chemotherapy and/or radiation. The lymphoma disappeared completely in all 6 isolated orbital disease cases. Although the survival rate was 42% in systemic disease cases after a mean period of 15-month observation, the ocular complications decreased with an improved quality of life.

Conclusions: It is important to determine the histological features and clinical stages in order to choose the appropriate treatment methods. All the isolated orbital disease cases were treated effectively by radiation or chemotherapy. Our strategy for the treatment of the systemic disease cases contributed to the decrease in ocular complications and the improvement in the quality of life for the patients. **Jpn J Ophthalmol 2001;45:305–312** © 2001 Japanese Ophthalmological Society.

Key Words: Clinical stage, histopathological study, orbital malignant lymphoma, quality of life, strategy for treatment.

Introduction

Orbital tumors were a rare condition in the past decade, with an incidence of 0.13–0.34% among all types of ophthalmic diseases.[1–4] Malignant lymphomas have represented approximately 10% of orbital tumors.[5–9] In addition, it has been reported that 5–8% of extranodal lymphomas involve the orbit, and 1.3–2.0% of extranodal lymphomas appear as primary orbital tumors.[7,9–11] Recently, the frequency of malignant lymphoma in the orbital region has increased in Japan.[2–4] This increased frequency is presumed to be attributable to factors such as the environment and lifestyle.[3,4] It is also possible that the development of techniques of histopathological diagnosis, such as immunohistochemistry[7,8,11–14] and genetic molecular biological analysis,[11,15–23] have made a definitive diagnosis possible in certain cases of malignant lymphoma, which in the past may have been diagnosed as reactive lymphoid hyperplasia, pseudolymphoma, or inflammatory pseudotumor.

Although advances in chemotherapy and radiation therapy have led to a better prognosis for pri-

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mary orbital malignant lymphoma,[2,5,8,10,13,19,24–26] some cases have been reported to show recurrences or metastasis.[6,12,27] On the other hand, systemic malignant lymphoma involving the orbital region has a worse prognosis.

It is important to elucidate the clinical and histopathological features of orbital malignant lymphomas in order to choose the appropriate methods to treat them effectively. We have reviewed 18 cases of orbital malignant lymphoma diagnosed and treated in the Yamagata University Hospital during the past 14 years, investigating how decisions on treatment were made.

Materials and Methods

Subjects

Seventy-seven cases were diagnosed histopathologically as having orbital tumors from April 1986 through December 1999 at the Department of Ophthalmology, Yamagata University Hospital. They represented 0.44% of all outpatients (17,632 cases). Of these 77 cases with orbital tumors, 18 cases were orbital lymphomas (23.4%). Clinical information was collected from these 18 cases including age, sex, signs and symptoms at the first visit, laterality, location, clinical stage of disease at presentation (Ann Arbor criteria), evidence of systemic disease, therapeutic method, patient response, and prognosis.

Histopathological Diagnosis

In all the cases, a biopsy was performed to diagnose the orbital lymphoma. The biopsy specimens were fixed in 10% buffered formaldehyde and then embedded in paraffin. The tissue sections were stained with hematoxylin-eosin and examined by light microscopy. Immunohistochemical studies were performed with peroxidase-antiperoxidase (PAP) technique using antibodies to IgG, IgM, κ, λ, CD5, CD10, CD20, CD23, and CD45. All lymphomas were classified on the bases of morphologic features according to the Working Formulation.[28] The cases for which data on the immunophenotype were available were classified according to the Revised European-American Lymphoma (REAL) classification.[29]

Treatment and Evaluation of Outcome

The strategy used to choose the treatment was as follows: the cases at stage I (Ann Arbor criteria) were treated by local radiation or chemotherapy with curative intent, and the cases at stages II–IV were treated by radiation and/or systemic chemotherapy with palliative intent.

The outcomes of the treatment were evaluated with respect to improvement of ocular complications and survival rates.

Results

Clinical Features

Six cases with malignant lymphoma, originating primarily in the orbit and confined to the orbit, were classified as isolated orbital disease. Two cases in whom the orbit was invaded secondarily from the epipharynx and ethmoidal sinus, and 10 cases that showed metastasis to the orbit from various systemic sites, such as lymph nodes or parotid glands, were classified as systemic disease cases (Table 1). Five men and 1 woman (age range, 56–81 years; mean = 70.8 ± 8.7 years) had isolated orbital disease. One man and 1 woman (ages 19 and 68 years, respectively), had secondarily invading lymphoma, and 7 men and 3 women (age range, 10–77 years; mean = 55.0 ± 20.5 years) were metastasizing cases. All 6 isolated orbital disease cases and 8 of the systemic disease cases were unilateral (8 right side, 6 left side). Four metastasizing cases were bilateral.

The common signs at presentation of the isolated orbital disease cases were palpebral swelling (33%) and proptosis (33%). In the systemic disease cases, palpebral swelling (42%) and proptosis (33%) were also common. The clinical stage at presentation of all 6 cases of isolated orbital disease was stage I, as the lymphomas were limited to the orbits and the eyelids. Among the systemic disease cases, 2 secondarily invasive cases were at stage II, 4 metastasizing cases were at stage III, and 6 metastasizing cases were at stage IV.

Histopathological Features

On the basis of the Working Formulation, 5 of the isolated orbital disease cases were classified as having malignant lymphoma of the small lymphocytic type, and 1 was of the diffuse small cleaved cell type (Table 1). The tumor cells in cases 4 and 5 were positive for CD5, CD20, CD45, and negative for CD10 and CD23. These two cases were classified as mantle cell lymphoma type in the REAL classification. Regarding the systemic disease cases, 2 were small lymphocytic type, 5 were diffuse mixed small and large cell type, 4 were diffuse large cell type, and 1 was mycosis fungoid type according to the Working Formulation. Three cases of the diffuse mixed small and large cell type (cases 9, 10, and 11), had tumor cells that were positive for IgM, CD19, CD20 and negative for CD10, CD23, and therefore were classified

Table 1. Summary of Clinical and Histopathological Findings in Orbital Malignant Lymphoma

Patient No.	Age (Years)	Sex	Laterality	Presenting Symptom	Location	Clinical Stage (Ann Arbor)	Histopathological Diagnosis	
							Working Formulation*	REAL Classification†
					Isolated Orbital Disease			
1	56	Female	Right	Palpebral swelling	Orbit	I	Small lymphocytic (B)	
2	69	Male	Right	Proptosis	Orbit	I	Small lymphocytic (B)	
3	81	Male	Right	Proptosis	Orbit	I	Small lymphocytic (B)	
4	76	Male	Right	Palpebral Swelling	Orbit	I	Small lymphocytic (B)	Mantle cell lymphoma
5	75	Male	Left	Blepharoptosis	Eyelid, orbit	I	Diffuse small cleaved cell (B)	Mantle cell lymphoma
6	68	Male	Right	Conjunctival congestion	Orbit	I	Small lymphocytic (B)	
					Systemic Disease			
7	19	Female	Right	Visual disturbance	Epipharynx, paranasal sinus, orbit	II	Diffuse large cell (B)	Diffuse large B-cell lymphoma
8	68	Male	Left	Proptosis	Paranasal sinus, orbit	II	Diffuse large cell (B)	Diffuse large B-cell lymphoma
9	67	Male	Right	Palpebral swelling	Lymph nodes, parotid gland, orbit	III	Diffuse mixed small and large cell (B)	Marginal zone B-cell lymphoma (MALT)
10	43	Male	Bilateral	Palpebral swelling	Parotid gland, kidney, orbit	III	Diffuse mixed small and large cell (B)	Marginal zone B-cell lymphoma (MALT)
11	63	Male	Bilateral	Proptosis	Lymph nodes, dermis, orbit	IV	Diffuse mixed small and large cell (B)	Marginal zone B-cell lymphoma
12	39	Male	Left	Visual distrubance	Lymph nodes, orbit	IV	Diffuse large cell (B)	Diffuse large B-cell lymphoma
13	74	Male	Left	Proptosis	Lymph nodes, paranasal sinus, orbit	III	Diffuse large cell (B)	Diffuse large B-cell lymphoma
14	77	Female	Bilateral	Palpebral swelling	Lymph nodes, orbit	IV	Diffuse mixed small and large cell (T)	Peripheral T-cell lymphoma
15	10	Female	Left	Palpebral swelling	Abdominal tumor, orbit	III	Diffuse mixed small and large cell (T)	Peripheral T-cell lymphoma
16	46	Male	Bilateral	Visual disturbance	Lymph nodes, orbit	IV	Small lymphocytic (B)	
17	67	Male	Left	Palpebral swelling	Lymph nodes, orbit	IV	Small lymphocytic, plasmacytoid	Lymphoplasmacytoid lymphoma
18	64	Male	Right	Proptosis	Dermis, orbit	IV	Mycosois fungoides (T)	Mycosis fungoides

*B: B cell type, T: T cell type.
†REAL: Revised European-American Lymphoma, MALT: mucosa-associated lymphoid tissue.

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as marginal zone B-cell lymphoma in the REAL classification. Especially in cases 9 and 10, centrocyte-like cells were seen and lymphoepithelial lesion formation was found in the biopsy specimens from the parotid glands. These cases were diagnosed as so-called mucosa-associated lymphoid tissue (MALT) lymphoma. The remaining 2 cases of diffuse mixed small and large cell type were T-cell type, and were classified as peripheral T-cell lymphoma in the REAL classification.

Four cases of diffuse large cell type (cases 7, 8, 12, and 13) were classified as diffuse large B-cell lymphoma in the REAL classification because of positivity to CD20 and CD45. In addition, case 15 had Chediak-Higashi syndrome systemically.[30] Because case 17, who had small lymphocytic, plasmacytoid type in the Working Formulation, showed lymphoplasmacytoid cells and Dutcher bodies and had primary macroglobulinemia systemically,[31] his disease was diagnosed as lymphoplasmacytoid lymphoma according to the REAL classification.

Treatment and Clinical Outcome

Five of the isolated orbital disease cases were treated only by local radiation (26–46 Gy), and 1 was treated only by systemic chemotherapy: vincristine + cyclophosphamide + 6 mercapto-purine + prednisone (VEMP therapy).

Six cases with systemic disease were treated only by systemic chemotherapy: prednisone + adriamycin + cyclophosphamide + etoposide + cytarabine + bleomycin + vincristine + methotrexate (pro-MACE-cytaBOM therapy) in 2 cases; cyclophosphamide + vincristine + adriamycin + prednisone (CHOP therapy) in 1 case; vindesine + cyclophosphamide + prednisone + doxorubicin (VEPA therapy) in 1 case; cyclophosphamide + vinblastine + prednisone (CVP therapy) in 1 case; and interferon-γ therapy in 1 case.

Five systemic cases were treated by both local radiation (27–50 Gy) and systemic chemotherapy: VEPA therapy, CHOP therapy, VEMP therapy, and piraubicin + vincristine + cyclophosphamide + prednisone (THP-COP therapy); and 1 case was treated only by local radiation (36 Gy) (Table 2).

Although total removal of some isolated orbital disease areas was attempted, it failed as the tumors were infiltrative and friable.

The outcome of the treatment for all 6 cases of isolated orbital disease, which were at Stage I, was a complete disappearance of the orbital mass lesions and the ocular symptoms, including the palpebral swelling, proptosis, and blepharoptosis. There were no relapses, metastases to other sites, or lymphoma associated deaths during the follow-up period ranging from 3 to 72 months (mean = 25.8 ± 34.2 months).

In the systemic disease cases, the ocular complications of 2 secondarily invasive cases (stage II) improved after the treatment. In case 7, the visual acuity of her right eye, that was counting fingers at 30 cm before the treatment, improved to 1.2 after the treatment. In case 8, the proptosis diminished after the treatment. Although these 2 patients died after 12 months, their quality of life was improved. Likewise, in 8 of 10 cases with metastasizing lymphomas (III or IV), their ocular complications diminished after the treatment. Case 12 (stage IV), with malignant lymphoma infiltration into the optic nerve of his left eye, was treated not only by systemic chemotherapy with proMACE + cytaBOM, but also by the injection of methotrexate, cytarabine, and prednisone to the bone marrow. The visual acuity in his left eye, that was hand motion before the treatment, improved to 1.0 after the treatment. In contrast, case 13 (stage III), whose general physical condition was so poor that he could not continue chemotherapy, and case 16 (stage IV), who had bilateral malignant lymphoma associated retinopathies, showed no change in their ocular complications. Although 5 metastasizing cases died, the overall improvement of quality of life was achieved during the follow-up period ranging from 1 to 50 months (mean = 15.6 ± 16.3 months) (Table 2).

In the cases who received radiation therapy, redness of the eyelid and congestion of conjunctiva were seen in almost all patients. These complications of irradiation were transient, and topical treatment of steroid gave relief. Although radiation cataract progressed to some degree in all cases, only 1 patient (case 6) required a cataract operation. In addition, he showed radiation retinopathy 20 months after radiation therapy.

Discussion

Clinical Features

Although the frequency of orbital malignant lymphoma was reported to be about 10% of all orbital tumors previously,[5–9] recently an increase in orbital lymphoma has been emphasized.[2–4] The current study revealed that the frequency of malignant lymphoma was 23.4% (18/77) of all orbital tumors, and this is similar to that reported by Uehara et al (14/50, 28.0%),[3] Suzuki et al[4] (12/51, 23.5%), and Nango et

Table 2. Summary of Treatment and Outcome

Patient No.	Age (Years)	Stage	Treatment*	Effect on Ocular Complication	Systemic Course	Follow-up Period (Months)	Status at Last Follow-up
				Isolated Orbital Disease			
1	56	I	R (26Gy)	Right orbital mass disappeared	No recurrence or metastasis	3	No evidence of disease
2	69	I	R (40Gy)	Right orbital mass disappeared	No recurrence or metastasis	5	No evidence of disease
3	81	I	R (40Gy)	Right orbital mass disappeared	No recurrence or metastasis	4	No evidence of disease
4	76	I	R (46Gy)	Right orbital mass disappeared	No recurrence or metastasis	3	No evidence of disease
5	75	I	C (VEMP)	Left orbital mass disappeared	No recurrence or metastasis	68	No evidence of disease
6	68	I	R (40Gy)	Right orbital mass disappeared	No recurrence or metastasis	72	No evidence of disease
				Systemic Disease			
7	19	II	R (50Gy) + C (VEPA)	Right visual acuity improved	Abdominal cavity metastasis	12	Died of disease
8	68	II	R (27Gy) + C (CHOP)	Left proptosis improved	Stomach and liver metastasis	12	Died of disease
9	67	III	R (36Gy) + C (THP-COP)	Right palpebral swelling improved	No progression	10	Alive with disease
10	43	III	R (36Gy)	Bilateral palpebral swelling improved	No progression	7	Alive with disease
11	63	IV	R (32Gy) + C (VEMP)	Bilateral protosis improved	No progression	14	Alive with disease
12	39	IV	C (proMACE+cytaBOM)	Left visual acuity improved	Liver metastasis	9	Died of disease
13	74	III	C (CHOP)	Not improved	Progressive disease	2	Died of disease
14	77	IV	C (VEPA)	Bilateral palpebral swelling improved	No progression	6	Alive with disease
15	10	III	C (proMACE+cytaBOM)	Left palpebral swelling improved	Progressive disease	50	Died of disease
16	46	IV	R (26Gy) + C (CHOP)	Not improved	No progression	18	Alive with disease
17	67	IV	C (CVP)	Left palpebral swelling improved	Progressive disease	39	Died of disease
18	64	IV	C (Interferon-γ)	Right protosis improved	Progressive disease	1	Died of disease

*R: radiation, C: chemotherapy, VEMP: vincristine + cyclophosphamide + 6mercaptopurine + prednisone; VEPA: vindesine +cyclophosphamide + prednisolone + doxorubicin, CHOP: cyclophosphamide + vincristine + adriamycin + prednisone, THP-COP: piraubicin + vincristine + cyclophosphamide + predinsolone, proMACE+cytaBOM: prednisone + adriamycin + cyclophosphamide + etoposide + cytarabine + bleomycin + vincristine + methotrexate, CVP: cyclophosphamide + vinblastine + prednisone.

al[2] (9/49, 18.4%). The mean age of the isolated orbital disease cases (70.8 ± 8.7 years) was older than that of the secondarily invading cases (43.5 ± 34.6 years) and the metastasizing cases (55.0 ± 20.5 years). Previous reports showed isolated orbital disease was more common in the older age group.[2,3]

The patients in the current study included 13 men and 5 women. In general, non-Hodgkin lymphoma affects men more often than women,[32,33] and a male predominance in ocular lymphoma has been described.[3,4,6,10,12,24,26,27,34] On the other hand, some investigators have reported that the distribution is about the same for men and women,[2,14,18,25] and some have even described a female predominance.[5,11]

In the current study, the symptoms at presentation were palpebral swelling in 7 cases (39%), proptosis in 6 (33%), visual disturbance in 3 (17%), blepharoptosis in 1 (6%), and conjunctival congestion in 1 (6%). Because the common presenting symptoms of orbital tumors, except for malignant lym-

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phoma, were palpebral swelling and proptosis (36/59, 61%) in our hospital, it is suggested that there are no characteristic symptoms for orbital malignant lymphoma. In 3 cases (cases 7, 12, and 16) who complained of visual disturbances at presentation, the malignant lymphoma had affected the optic nerve or retina. Case 7 had visual disturbance and a central scotoma in her right eye due to compression of the optic nerve by the lymphoma.[35] Case 12 had severe visual disturbance, a central scotoma, and optic disk edema with invasion of the lymphoma into the optic nerve of his left eye. In case 16, the lymphoma invaded his orbits and eyeballs bilaterally. The tumor cells had infiltrated the anterior chambers and the vitreous bodies, and the invasive lesions into the retinas were seen bilaterally.

The clinical stage at presentation of all 6 patients with isolated orbital disease was Stage I, while in the systemic disease cases, 2 cases were at Stage II, 4 at Stage III, and 6 were at Stage IV. Three cases (cases 8, 13, and 14) with systemic disease were originally referred to our hospital because of the ophthalmic disorders, and the presence of malignant lymphoma was detected at other systemic sites by further examinations.

Histopathological Diagnosis

After histopathological studies, 5 of the 6 cases of isolated orbital disease were classified as small lymphocytic types, which are low-grade malignancy in the Working Formulation. The remaining case was a diffuse small cleaved cell type, which is considered an intermediate-grade malignancy in the Working Formulation. However, this tumor was classified as a mantle cell lymphoma in the REAL classification, which is classified as low malignancy.

In systemic disease cases, there were 2 with small lymphocytic type of low-grade malignancy, 5 with diffuse mixed small and large cell type, and 4 with diffuse large cell type (both of which were intermediate-grade malignancy). One case of mycosis fungoides was low-grade malignancy in the REAL classification.

Recently, many investigators have reported that low-grade B-cell lymphoma of the MALT type in the REAL classification is common in primary ocular adnexa lymphoma, particularly in the conjunctiva.[7,8,10,11,13,14,18,19,21,25] In the current study, there were no cases of MALT type lymphoma in the isolated orbital disease group, but 2 cases (cases 9 and 10) of the MALT type were seen in the systemic disease group.

Strategy of Treatment

Our strategy of treatment for the patients at clinical stage I had a curative intent that aimed at complete remission. Generally, patients at stage I are treated chiefly by radiation.[5,6,25–27,34,36,37] On the other hand, some researchers have advocated that chemotherapy should be the first line of treatment in spite of being at stage I because of the side effects of radiation,[10] the advances of the new third-generation chemotherapy,[14] and histopathological malignancies.[8] In the current study, because chemotherapy might pose a risk of myelosuppression and development of secondary carcinoma, and because elderly patients were common at stage I, 5 of 6 stage I cases received radiation. The remaining patient (case 5) had mantle cell lymphoma. Although this type is a histopathologically low-grade malignancy in the REAL classification, its clinical course is reported to be relatively poor.[38] Thus, we selected chemotherapy for this case. Because all 6 cases at Stage I (isolated orbital disease) were shown to be free of lymphoma and revealed good survival rates after treatment, our strategy, with a curative intent, for the treatment of cases at stage I seemed to be effective.

The strategy for treatment of the cases at clinical stages II to IV was palliative intent and was aimed at the resolution of ocular complications caused by the malignant lymphoma, and the improvement of quality of life. For these purposes, systemic chemotherapy was used primarily, and local radiation was added only when necessary.

The 2 cases at stage II, who were shown to have systemic disease and intermediate-grade malignancy histopathologically, received both chemotherapy and radiation. In case 7, a relatively large irradiation dose of 50 Gy was added to reduce the compression of the optic nerve by the lymphoma as soon as possible.[6,35]

For the 4 cases at stage III with systemic disease, 2 cases of intermediate-grade malignancy were treated only with chemotherapy, 1 of MALT type lymphoma with both chemotherapy and radiation, and 1 of MALT type lymphoma with only local radiation. Case 10, although at stage III, received only radiation. As this case had no systemic symptoms (the B-symptoms, Ann Arbor criteria) and showed a sluggish condition, the therapeutic method of "watch and wait"[37] was selected. In this method, the treatment starts when there is progression, systemic symptoms appear, and the bone marrow involvement and pancytopenia are seen. Therefore, this patient received only local radiation for his swollen eyelid.

For the 6 cases at stage IV, 4 cases (2 low-grade malignancy, 2 intermediate-grade malignancy) were treated with only chemotherapy, the other 2 cases (1 low-grade malignancy, 1 intermediate-grade malignancy), with both chemotherapy and radiation.

The ocular complications caused by malignant lymphoma resolved 100% (2/2) in the cases at stage II, 75% (3/4) at stage III, and 83% (5/6) at stage IV. Although the survival rate was 0% in the cases at stage II, 50% at stage III and 50% at stage IV, our strategy of palliative intent for these stages was thought to be effective.

In the histopathologically low-grade malignancy group, 6 of 7 small lymphocytic type patients are alive. One case of small lymphocytic, plasmacytoid type associated with macroglobulinemia and 1 case of mycosis fungoides have died. In the intermediate-grade malignancy group, all 4 cases of diffuse large cell type died, and 1 of 2 of T-cell type diffuse mixed small and large cell type died. As reported previously,[24,36,38] the prognosis for the large cell type and the T-cell type is poor.

Conclusions

The results of the present study indicate that it is important to diagnose the histological features and clinical stages in order to make appropriate decisions on the treatment of orbital malignant lymphoma. All the isolated orbital disease cases were low-grade malignancy belonging to stage I and were treated effectively. The systemic disease cases were higher-grade malignancy in advanced clinical stages, and our strategy of treatment contributed to the decrease in ocular complications and the improvement in the quality of life of the patients.

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References

1. Tsukahara Y, Morino I, Yamamoto M. Clinicopathological evaluation of orbital tumor in 101 cases over a 10-year period. Rinsho Ganka (Jpn J Clin Ophthalmol) 1988;42:844–5.
2. Nango K, Furumura T, Uyama M. Histopathological analysis of 53 cases of orbital tumors. Nihon Ganka Kiyo (Folia Ophthalmol Jpn) 1992;43:1271–8.
3. Uehara F, Iwakiri N, Ohba N. A twenty-year review of orbital tumor. Atarashii Ganka (J Eye) 1995;12:1177–9.
4. Suzuki K, Ogawa M, Sakurazawa T, Harigai R, Eguchi K, Abe H. A statistical study of clinical and pathological findings in patients with exophthalmos. Nihon Ganka Kiyo (Folia Ophthalmol Jpn) 1998;49:364–70.
5. Dunbar SF, Linggood RM, Doppke KP, Duby A, Wang CC. Conjunctival lymphoma: results and treatment with a single anterior election field. A lens sparing approach. Int J Radiat Oncol Biol Phys 1990;19:249–57.
6. Ohnishi Y. Diagnosis and management of orbital malignant lymphoma. Atarashii Ganka (J Eye) 1991;8:35–40.
7. Witherspoon AC, Diss TC, Pan LX, et al. Primary low-grade B-cell lymphoma of the conjunctiva: a mucosa-associated lymphoid tissue type lymphoma. Histopathology 1993;23: 417–24.
8. Shirai K, Okada Y, Saika S, Ohnishi Y. A case of mucosa-associated lymphoid tissue (MALT) lymphoma of presumed lacrimal gland origin. Ganka Rinsho Iho (Jpn Rev Clin Ophthalmol) 1996;90:604–6.
9. Sakamoto T, Inomata H. Orbital tumor. In: Masuda K, ed. Current encyclopedia of ophthalmology 88 ocular tumor. Tokyo: Nakayama-Shoten, 1999;105–12.
10. Tanaka H, Hirota Y, Iwasaki H, et al. Four cases of primary orbital lymphoma. Jpn J Cancer Clin 1998;44:475–9.
11. Coupland SE, Krause L, Delecluse HJ, et al. Lymphoproliferative lesions of the ocular adnexa: analysis of 112 cases. Ophthalmology 1998;105:1430–41.
12. Sakamoto T, Ishibashi T, Ohnishi Y. Clinicopathological and immuno-histochemical study of malignant lymphoma of the orbit. Nippon Ganka Gakkai Zasshi (Acta Soc Ophthalmol Jpn) 1992;96:1033–9.
13. White WL, Ferry IA, Harris NL, Grove AS Jr, AS. Ocular adnexal lymphoma: a clinicopathologic study with identification of lymphomas of mucosa-associated lymphoid tissue type. Ophthalmology 1995;102:1994–2006.
14. Mimatsu M, Uchio E, Takano M, Fujita H, Nakatani Y, Ohno S. Four cases of periocular MALT lymphoma. Rinsho Ganka (Jpn J Clin Ophthalmol) 1999;53:911–4.
15. Suzuki J, Igarashi Y, Nakagawa T, et al. Gene rearrangement analysis of conjunctival malignant lymphomas. Nippon Ganka Gakkai Zasshi (Acta Soc Ophthalmol Jpn) 1992;96:1142–7.
16. Tanaka Y, Hongou M, Yokota S, Seriu T. Primary subconjunctival B cell malignant lymphoma diagnosed by immunohistochemical and molecular biological analysis. Nihon Ganka Kiyo (Folia Ophthalmol Jpn) 1993;44:305–9.
17. Hagihara M, Hara T, Kinoshita Y. Cases of orbital lymphoma diagnosed by gene rearrangement. Atarashii Ganka (J Eye) 1993;10:473–7.
18. Hyakumachi N, Suzuki J, Igarashi Y, et al. Review of twenty-eight cases of ocular lympho-productive diseases. Rinsho Ganka (Jpn J Clin Ophthalmol) 1993;47:693–6.
19. Suzuki J, Oguri-Hyakumachi N, Rho Y, et al. Genotypic identity of B lymphocyte clone in bilateral conjunctival malignant lymphomas. Rinsho Ganka (Jpn J Clin Ophthalmol) 1995;49:259–63.
20. Nakazawa M, Kawamoto K, Miyanaga Y. Diagnosis of a case of orbital malignant lymphoma by genetic molecular analysis. Rinsho Ganka (Jpn J Clin Ophthalmol) 1996;50:149–52.
21. Kawamoto K, Miyanaga Y, Toriyama S. A case of bilateral MALT (mucosa-associated lymphoid tissue) type conjunctival malignant lymphoma. Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc) 1996;100:246–52.
22. Nanjoh Y, Takamaki K, Sotozono C, Nishida K, Kinoshita S. A case of conjunctival malignant lymphoma diagnosed by genetic molecular analysis. Rinsho Ganka (Jpn J Clin Ophthalmol) 1997;51:1017–20.

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Vol 45: 305–312, 2001

23. Azumi A, Nakayama I, Inoue M. A case of lymphoproliferative lesion in ocular adnexa: limitation of pathologic diagnosis using immunohistochemistry. Ganka Rinsho Iho (Jpn Rev Clin Ophthalmol) 1999;93:225–8.
24. Takamura H. A clinicopathological study of malignant lymphoma in the orbital region and other sites. Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc) 1994;98:695–703.
25. Galieni P, Polito E, Leccisotti A, et al. Localized orbital lymphoma. Haematologica 1997;82:436–9.
26. Lau HY, Chua ET, Yang IL, Chua EI. Orbital lymphoma: results of radiation therapy. Ann Acad Med Singapore 1998;27:474–7
27. Erkal HS, Serin M, Sak SD, Cakmak A. Radiation therapy for stage I primary orbital non-Hodgkin's lymphomas. Tumori 1997;83:822–5.
28. The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classification of non-Hodgkin's lymphomas: summary and description of a Working Formulation for clinical usage. Cancer 1982;49:2112–35.
29. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the international lymphoma study group. Blood 1994;84:1361–92.
30. Takamura H, Takahashi S. A case of Chediak-Higashi syndrome associated with malignant lymphoma. Rinsho Ganka (Jpn J Clin Ophthalmol) 1993;47:1513–17.
31. Takamura H, Yamaguchi K, Takahashi S. A case of primary macrogloburinemia associated with orbital tumor. Nihon Ganka Kiyo (Folia Ophthalmol Jpn) 1998;49:726–31.
32. Medeiros LJ, Harris NL. Lymphoid infiltrates of the orbit and conjunctiva: a morphologic and immunophenotypic study of 99 cases. Am J Surg Pathol 1989;13:459–71.
33. Knowles DM, Jakobiec FA, McNally L, Bruke 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 1990;21:959–73.
34. Esik O, Ikeda H, Mukai K, Kaneko A. A retrospective analysis of different modalities for treatment of primary orbital non-Hodgkin's lymphomas. Radiother Oncol 1996;38:13–8.
35. Suzuki I, Igarashi S, Sato T, Takahashi S. Orbital infiltration and optic nerve involvement in a case of primary malignant lymphoma of the epipharynx. Nihon Ganka Kiyo (Folia Ophthalmol Jpn) 1990;41:908–18.
36. Sakamoto T. Ocular malignant lymphoma. Atarashii Ganka (J Eye) 1996;13:1495–501.
37. Niikura H. Management of low-grade lymphoma. Hematol Oncol 1997;35:39–45.
38. Tobinai K. Treatment of non-Hodgkin's lymphoma based on REAL classification. Pathol Clin Med 1998;16:407–13.