

A rare type of cancer in children: extranodal marginal zone B-cell (MALT) lymphoma of the ocular adnexa

Sonay İncesoy-Özdemir¹, Nazmiye Yüksek², Ceyhun Bozkurt³, Gürses Şahin³, Leyla Memiş⁴, Ayşen Dizman⁵, Ulya Ertem³

Departments of Pediatric Oncology, ¹Konya Training and Research Hospital, Konya, and ²Bülent Ecevit University Faculty of Medicine, Zonguldak, and ³Department of Pediatric Hematology-Oncology, Dr. Sami Ulus Maternity, Children's Health and Diseases Training and Research Hospital, ⁴Department of Pathology, Gazi University Faculty of Medicine, and ⁵Department of Radiation Oncology, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey. E-mail: sinesoy@yahoo.co.uk

SUMMARY: İncesoy-Özdemir S, Yüksek N, Bozkurt C, Şahin G, Memiş L, Dizman A, Ertem U. A rare type of cancer in children: extranodal marginal zone B-cell (MALT) lymphoma of the ocular adnexa. Turk J Pediatr 2014; 56: 295-298.

Primary ocular adnexal mucosa-associated lymphoid tissue (MALT) lymphomas (OAMLs) are mostly seen in the 5th-7th decades of life, with female predominance, and they occur rarely in children. Thus, knowledge about this cancer type is obtained from adult data in the literature, while the data regarding OAMLs in the pediatric population are limited to a few case reports. Herein, we report a 10-year-old boy with OAML who was treated successfully with radiotherapy, and we discuss this uncommon lymphoma in children.

Key words: child, lymphoma, mucosa-associated lymphoid tissue, ocular adnexal lymphoma, orbital neoplasm.

Extranodal marginal zone B-cell (mucosa-associated lymphoid tissue [MALT]) lymphomas are characterized by small B-cell lymphocytes of low-grade malignancy. First described in 1983 by Isaacson and Wright, it was recognized only in 1994 as a distinct type of lymphoma in the revised European-American Lymphoma (REAL) classification, as well as in the more recent classification by the World Health Organization (WHO) ¹⁻³. According to the previous studies, the relative incidence of MALT lymphomas to non-Hodgkin lymphomas (NHLs) varied considerably, from 3% in London to 10% in Hong Kong⁴. The pathogenesis of MALT lymphoma is largely unknown. However, it is generally believed that both chronic antigen stimulation and acquired genetic alterations are involved⁵.

MALT lymphomas occur at various sites, most commonly the gastrointestinal tract, salivary gland, lung, and thyroid gland. Ocular involvement occurs in 2% of extranodal lymphomas, although it is the most common lymphoma subtype in the ocular adnexa. Primary ocular adnexal MALT lymphomas

(OAMLs) are mostly seen in the 5th-7th decades of life, with female predominance, and they occur rarely in children. They are characterized by indolent natural history and good response to radiotherapy^{6,7}.

Herein, we report a 10-year-old boy with OAML who was treated successfully with radiotherapy, and we discuss this uncommon lymphoma in children.

Case Report

A 10-year-old healthy boy presented with a mass (diameter: 1 cm) at the junction of the medial canthus of the right eye and right nasolacrimal sulcus, which had been noted four months earlier and was not associated with pain or other ophthalmic symptoms. The patient's medical history was uneventful, and in particular, no B-symptoms were reported. No regional lymphadenopathy was detected, and the systemic examination was normal. Computed tomography (CT) scans of the orbit showed a mass of 2x1 cm in diameter with a view of soft tissue density adjacent to the right inferomedial orbit extending to the nasolacrimal canal (Fig. 1).

Histologic examination of an excisional biopsy showed a diffuse atypical lymphoid infiltrate composed of uniform, small-to-medium lymphocytes with irregular, indented, or cleaved nuclei, which extended to the soft tissue and muscle tissue (Fig. 2). Immunohistochemical studies showed atypical lymphocytes strongly and diffusely positive for CD20, while tests were negative for CD10, CD23, cyclin D1, and terminal deoxynucleotidyl transferase (TdT). The Ki-67 proliferation index was 10-20% (Fig. 3). Thus, OAML was diagnosed. The laboratory workup including blood count, erythrocyte sedimentation rate, biochemical profiles, CT scans of the brain, thorax, abdomen, and pelvis, bone marrow aspirations, and biopsies showed no systemic involvement.

The patient was treated successfully with local radiotherapy (36 Gy), and he remained asymptomatic. At nearly four years after the diagnosis, there were no local or systemic recurrences.

Discussion

Primary ocular adnexal lymphoma is defined as a lymphoma originating from the ocular adnexa (eyelid, conjunctiva, orbit, lacrimal gland, or lacrimal sac), provided no evidence of extraorbital disease is detected following a staging evaluation^{8, 9}. The most common type is a MALT lymphoma, although diffuse large B-cell lymphomas, mantle cell lymphomas, follicular lymphomas, and plasmacytomas also occur¹⁰.

Primary OAMLs are rarely seen in children and young adults, and as such, knowledge about this cancer type is obtained from adult data in the literature. OAMLs are a heterogeneous group of malignancies, accounting for approximately 1-2% of NHLs and 8% of extranodal lymphomas. The majority of OAMLs present usually as a primary disease of the orbital soft tissue, conjunctiva, and eyelid; however, 10-32% are secondary tumors in patients with disseminated lymphoma. More than 95% are of B-cell origin, and 80% are low-grade lymphomas⁷.

The pathogenesis of MALT lymphoma is largely unknown. However, it is generally believed that both chronic antigen stimulation and acquired genetic alterations are involved⁵. Microbial pathogens that underlie chronic inflammatory processes play a role in both

malignant transformation and subsequent clonal expansion of the lymphoma in organs including MALT^{5,7}. In gastric MALT lymphoma, *Helicobacter pylori* has been shown to be present in most cases⁵. Among patients with primary OAML, single case reports have reported an association with *H. pylori* and *Chlamydia pneumoniae*⁷. Recently, Ferreri et al.¹¹ detected *C. psittaci* DNA in 80% of the Italian patients with OAML by immunohistochemistry. However, these results have not been substantiated in several subsequent studies from different countries¹²⁻¹⁴.

Primary OAMLs are mostly seen in the elderly population (median age: ~65 years), with female predominance; however, in the Korean population, the patients are younger (median age: ~46 years), with male predominance¹⁵. In the literature, the frequency of site of origin is as follows: orbit (46-74%), conjunctiva (20-33%), and eyelid (5-20%)⁴. Most patients with OAML present with localized disease (stage I), and nodal involvement is stated as 5%. The rate of disseminated disease (stage IV) is 10-15% at initial presentation⁷. The determination of the treatment type is associated with the extent of the disease, impact of the lymphoma on the eye and visual function, and patient- and disease-related prognostic factors. Surgical resection is the main treatment modality in these patients. However, the risk of recurrence is relatively high if no adjuvant chemotherapy or radiotherapy is given. Thus, radiation therapy is the treatment of choice for localized OAML, and chemotherapy is used for disseminated disease. Lastly, immunotherapy with rituximab has been used for some patients with relapsed disease¹⁶⁻¹⁸.

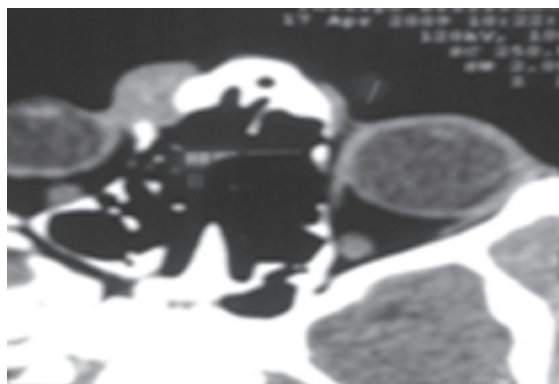


Fig. 1. CT scans of the orbit show a mass adjacent to the right inferomedial orbit extending to the nasolacrimal canal.

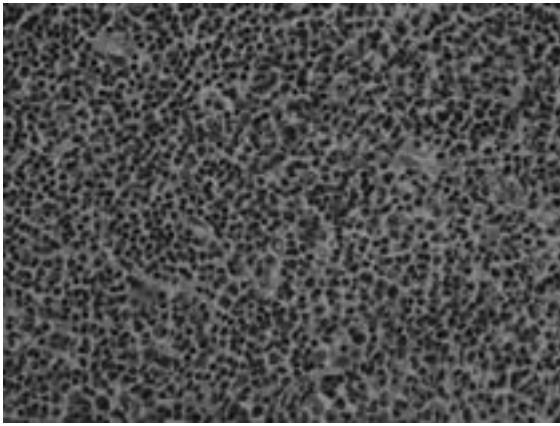


Fig. 2. Histology of ocular adnexal mass biopsy showing diffuse atypical lymphoid infiltrate (hematoxylin X400).

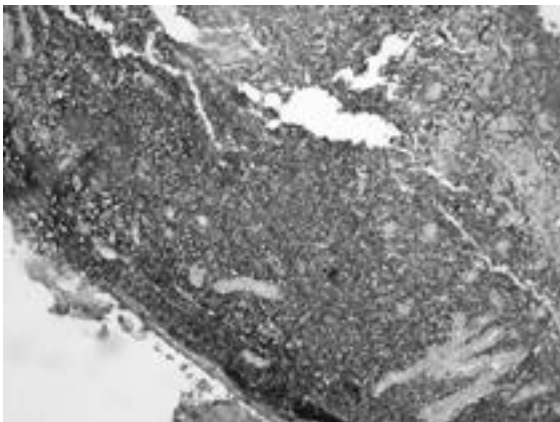


Fig. 3. Immunohistochemical study for CD20 (X100).

Some of the case series about OAML in the literature include children, but they do not present any specific information about the pediatric patients' epidemiological, clinical or laboratory characteristics^{4,5,15}. To the best of our knowledge, four children with OAML have been described in detail in the literature as single case reports. Bakhshi et al.¹⁹ reported that 5 out of 53 cases (9.4%) of *de novo* childhood NHL had ocular or orbital involvement and one of those patients (a 10-year-old girl) was diagnosed as MALT lymphoma involving the conjunctiva. The disease was restricted to the conjunctiva and treated successfully with surgery and additional local cryotherapy²⁰. The second case was a five-year-old girl with hyperimmunoglobulin M and CHARGE (congenital disease characterized by coloboma, genital hypoplasia, choanal atresia, retarded growth, and ear abnormalities) association,

who developed bilateral conjunctival MALT lymphoma and was treated successfully with topical interferon (IFN)- α ⁶. The third patient was a 10-year-old girl who presented with swelling under her right eye (lacrimal sac) that had progressively increased in size over two months and caused intermittent pain. She had no lymphadenopathy or organomegaly. The laboratory evaluation showed no systemic involvement. OAML was diagnosed, and she received local radiotherapy⁹. The last case was a 17-year-old girl with OAML involving the orbit. She was treated with surgery alone²¹.

In conclusion, OAMLs are seen rarely in children, and the knowledge about this lymphoma type is limited. They are primarily low-grade lymphomas that are usually confined to the adnexa at diagnosis (stage I) and respond well to local radiotherapy. Nevertheless, regular follow-up is required, as relapses can be seen during the course of the disease.

REFERENCES

1. Isaacson PG, Wright DH. Malignant lymphoma of mucosal-associated lymphoid tissue: a distinctive type of B cell lymphoma. *Cancer* 1983; 52: 1410-1416.
2. 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: 1361-1392.
3. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee Meeting-Airlie House, Virginia, November 1997. *J Clin Oncol* 1999; 17: 3835-3849.
4. Oh DE, Kim YD. Lymphoproliferative diseases of the ocular adnexa in Korea. *Arch Ophthalmol* 2007; 125: 1668-1673.
5. Sjö LD, Heegaard S, Prause JU, et al. Extranodal marginal zone lymphoma in the ocular region: clinical, immunophenotypical, and cytogenetical characteristics. *IOVS* 2009; 50: 516-522.
6. Fuentes-Paez G, Saornil MA, Herreras JM, et al. CHARGE association, hyper-immunoglobulin M syndrome, and conjunctival MALT lymphoma. *Cornea* 2007; 26: 864-867.
7. Stefanovic A, Lossos IS. Extranodal marginal zone lymphoma of the ocular adnexa. *Blood* 2009; 114: 501-510.
8. Köksal Y, Kiratlı H, Varan A, Akçören Z, Büyükpamukçu M. Primary lacrimal sac non-Hodgkin's lymphoma in a child. *Int J Pediatr Otorhinolaryngol* 2005; 69: 1551-1553.

9. Liang X, Stork LC, Albano EA. Primary ocular adnexal lymphoma in pediatric patients: report of two cases and review of the literature. *Pediatr Dev Pathol* 2003; 6: 458-463.
10. Nola M, Lukenda A, Bollmann M, Kalauz M, Petrovecki M, Bollmann R. Outcome and prognostic factors in ocular adnexal lymphoma. *Croat Med J* 2004; 45: 328-332.
11. Ferreri AJ, Guidoboni M, Ponzoni M, et al. Evidence for an association between *Chlamydia psittaci* and ocular adnexal lymphomas. *J Natl Cancer Inst* 2004; 96: 586-594.
12. Daibata M, Nemoto Y, Togitani K, et al. Absence of *Chlamydia psittaci* in ocular adnexal lymphoma from Japanese patients. *Br J Hematol* 2006; 132: 651-652.
13. Mulder MM, Heddema ER, Pannekoek Y, et al. No evidence for an association of ocular adnexal lymphoma with *Chlamydia psittaci* in a cohort of patients from the Netherlands. *Leukoc Res* 2006; 30: 1305-1307.
14. Vargas RL, Fallone E, Felgar RE, et al. Is there an association between ocular adnexal lymphoma and infection with *Chlamydia psittaci*? *Leukoc Res* 2006; 30: 547-551.
15. Cho EY, Han JJ, Ree HJ, et al. Clinicopathologic analysis of ocular adnexal lymphomas: extranodal marginal zone B-cell lymphoma constitutes the vast majority of ocular lymphomas among Koreans and affects younger patients. *Am J Hematol* 2003; 73: 87-96.
16. Song Ek, Kim SY, Kim TM, et al. Efficacy of chemotherapy as a first-line treatment in ocular adnexal extranodal marginal zone B-cell lymphoma. *Ann Oncol* 2008; 19: 242-246.
17. Stafford SL, Kozelsky TF, Garrity JA, et al. Orbital lymphoma: radiotherapy outcome and complications. *Radiother Oncol* 2001; 59: 139-144.
18. Ferreri AJ, Ponzoni M, Martinelli G, et al. Rituximab in patients with mucosal-associated lymphoid tissue-type lymphoma of the ocular adnexa. *Hematologica* 2005; 90: 1578-1579.
19. Bakhshi S, Sidhu T. Pediatric orbital and ocular lymphomas. *Pediatr Blood Cancer* 2008; 50: 940-941.
20. Tiemann M, Haring S, Heidemann M, et al. Mucosa-associated lymphoid tissue lymphoma in the conjunctiva of a child. *Virchows Arch* 2004; 444: 198-201.
21. Chen PM, Chiou TJ, Yu IT. Molecular analysis of mucosa-associated lymphoid tissue (MALT) lymphoma of ocular adnexa. *Leuk Lymphoma* 2001; 42: 207-214.