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A case of conjunctival precursor T cell lymphoblastic lymphoma presenting with salmon colored conjunctival mass

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ABSTRACT

Purpose: T-Lymphoblastic lymphoma (T-LBL) is a rare malignant tumor originated from precursor T-lymphocytes that differentiate to T lymphocytes. We report a rare case of T-LBL presenting with conjunctival mass as the first sign.

Observations: A 61-year-old man presented with a right salmon colored conjunctival mass. A biopsy was performed, and histopathologic examination showed dense lymphocyte proliferation in subepithelial substantia propria. Immunohistochemical staining was positive for CD7, CD10, and TdT; and negative for CD20. CD3 was negative in most parts PET-CT revealed abnormal uptake in the left cervix, anterior mediastinum, abdominal aortic lymph nodes, and multiple bones. From the above findings, stage IVA T-LBL was diagnosed. The patient received hyper CVAD therapy (cyclophosphamide + doxorubicin + vincristine + dexamethasone) and HD-MA therapy (high-dose methotrexate + cytarabine). Subsequently, an unrelated bone marrow transplant was performed.

Conclusions and importance: This case demonstrates the importance of considering rare lymphomas such as T-LBL in the differential diagnosis of ocular adnexal lymphoid neoplasms.

1. Background

T-Lymphoblastic lymphoma (T-LBL) is a rare form of high-grade non-Hodgkin lymphomas derived from T lymphocyte progenitor cells, accounting for approximately 2% of all lymphomas.[1] This tumor can arise at any extranodal site, and a mediastinal mass is the most common location, accounting for 50–80% of all T-LBL cases.[2] The tumor commonly affects children to young men in Japan, and adult T-LBL occupies only 3–4% of all cases of T-LBL.[2]

On the other hand, ocular adnexal lymphoma is primarily a disease of older adults. Ocular adnexal lymphoma accounts for 2% of all non-Hodgkin lymphomas, and approximately 6–8% of extranodal lymphomas.[3] Around 80–90% of primary ocular adnexal lymphomas are extranodal marginal zone B-cell lymphomas of mucosa-associated lymphatic tissue (MALT), which have the appearance of salmon pink lesions and are the most common tumor of the ocular adnexa.

We report a case of conjunctival T-LBL that developed in an elderly man, which, to the best of our knowledge, has not been reported before.

2. Case presentation

A 61-year-old man with a 1-month history of right eyelid swelling was referred by a local ophthalmologist to our department for investigation of suspected conjunctival MALT lymphoma. Examination showed a salmon pink elastic swelling extending from the lower palpebral conjunctiva to the bulbar conjunctiva (Fig. 1). There was no pain, no history of trauma, and no systemic complaint. At presentation, his best-corrected visual acuity was 20/20 in both eyes, and intraocular pressure was normal. His left cervical lymph node was swollen. Computed tomography (CT) revealed only conjunctival lesion. Laboratory findings were as follows: white blood cell count 4.1 × 10^9/L (reference range 4–11 × 10^9/L), (neutrophils 63.0%; monocytes 5.8%, lymphocytes 29.1%); C-reactive protein 0.09 mg/dL (reference range <0.30 mg/dL), IgG 1,432 mg/dL(reference range 870–1700 mg/dL), IgA 244mg/dL (reference range 110–410 mg/dL), IgE 24.5 IU/mL (reference range 0–270 mg/dL), IgG4 10.7 mg/dL (reference range 4.5–117 mg/dL), sIL-2 receptor antibody 443 U/mL (reference range 145–519 U/mL). All values were within normal limits. Beta 2-microglobulin (β2-MG) was 1.77 mg/L (reference range 0.64–1.56 mg/L) and slightly elevated.

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Histological examination of a biopsy of the conjunctival mass showed diffuse infiltration in the subepithelial substantia propria of conjunctiva by medium sized atypical lymphoid cells with monomorphous proliferation (Fig. 2A). Occasionally, linear pattern of infiltration was observed. The atypical cells were irregular with scanty cytoplasm and round or convoluted nuclei with finely dispersed chromatin. There were abundant mitoses reflecting the proliferative process.

A panel of immunohistochemical staining was performed on paraffin-embedded sections of the biopsy. Tumor cells were positive for CD7 and CD10, weakly positive for CD8, and negative for CD20. CD3 and CD4 were negative in most parts but positive in some parts. Tumor cells were positive for terminal deoxynucleotidyl transferase (TDT). TdT is known to be a marker specialized DNA polymerase expressed in immature, pre-B, pre-T lymphoid cells, and acute lymphoblastic leukemia/lymphoma cells. Ki labeling index was more than 90%, indicating proliferating lymphocytes that appeared to be undifferentiated T cells (Fig. 2B–D). In addition, flow cytometric analysis showed that the undifferentiated T cell population consisted of large proportions of CD5 (68.5%) and CD34 (52.3%) (SRL Inc.,Tokyo, Japan). The bone marrow aspirate and biopsy revealed normocellular bone marrow with infiltration of TdT-positive cells. A diagnosis of T-LBL of the conjunctiva was made according to these histopathological as well as immunohistochemical study.

On PET-CT performed after biopsy of conjunctiva, abnormal uptake was observed in the left cervix, anterior mediastinum, abdominal aortic lymph nodes, and multiple bones (sacrum, femur, and scapula).

Ann Arbor stage was estimated as IV, and hyper CVAD therapy (cyclophosphamide + doxorubicin + vincristine + dexamethasone) was immediately started as first-line[1] treatment, followed by HD-MA therapy (high-dose methotrexate + cytarabine) in our hematology department. Subsequently, an unrelated bone marrow transplant was performed. At six months after bone marrow transplantation, clinical remission was confirmed by bone marrow aspiration. No recurrence in organs of the whole body has been found for 2 years, and follow-up is ongoing.

3. Discussion and conclusion

T-LBL is a rare malignant tumor. On the other hand, primary ocular adnexal lymphomas including primary conjunctival lymphomas are mostly B-cell lymphomas, and MALT lymphomas are most common. Other types of ocular adnexal lymphomas such as diffuse large-cell lymphoma, follicular lymphoma, mantle cell lymphoma, and aggressive histologic subtypes are less commonly seen.[4] In a report of 353 cases of conjunctival lymphoma, there was no T-LBL and almost all were B-cell lymphomas; the most common type was marginal zone lymphoma (182 cases) followed by follicular lymphoma (80 cases) and mantle cell lymphoma (18 cases).[5] Only three cases of T-LBL involving the ocular adnexa were found in our literature search.[6,7] In addition, these patients were young men. The median age at onset of T-LBL is 16 years (range, 4–84 years). Children and adolescents are the most vulnerable age groups, accounting for 30–40% of all cases of T-LBL, with only 3–4% of the patients being adults.[8] Our patient was an adult male aged 61 years, and the incidence of T-LBL in this population is significantly lower.

All three previously reported cases with T-LBL in ocular adnexa showed infiltration into the orbit and muscles, protruding eyes, restricted eye movement, and decreased visual acuity.[6,7] In our case, CT revealed only conjunctival swelling, indicating that the clinical manifestation was mainly a conjunctival mass. Therefore, this is the first report of T-LBL conjunctival tumor in the elderly. All T-LBL involving the conjunctiva manifested prominent salmon pink lesions, and differentiation from other conjunctival lymphomas is difficult without evaluations by immunostaining and flow cytometry.

The immunophenotypes of T-LBL are heterogeneous but usually reflect T cell lineage with variable expression of T cell antigens including CD2, CD4, CD5, CD7 and CD8.[9,10] During normal T cell development, antigens are expressed. CD7 is the first T cell-associated antigen, followed by CD2 and CD5. Although cytoplasmic CD3 can be detected early in maturation, expression of this antigen on the cell surface occurs much later in maturation. As T cell divergence proceeds, immune phenotypes develop in 3 stages: early cortical stage, later cortical stage, and medullary stage; in which T cells express $CD4^{-}CD8^{-}$, $CD4^{+}CD8^{+}$, $CD4^{+}CD8^{-}$or $CD4^{-}CD8^{+}$, respectively. CD2 and CD7 appear from early cortical stage, and CD1a, CD5, CD3 and T-cell receptor (TCR) emerge from later cortical stage and medullary stage.[11] In our case, tumor cells were weakly positive for CD8, and negative for CD4 in most parts but positive in some parts. These findings suggest that most of the T cells in the current case were in medullary or later cortical stage. CD3 was negative in most parts, which may be because cytoplasmic CD3 tends to appear in later divergence stages.

Even through most malignant lymphomas in the conjunctiva are MALT lymphomas, extreme caution is needed in diagnosis. T-LBL is associated with very poor prognosis, whereas conjunctival MALT lymphoma is not. For T-LBL, the median survival in pediatric patients is usually less than 1 year[12] and the overall 5-year survival rate for adults is 26%.[13–17] However, adequate treatment can extend the life expectancy of T-LBL patients. For instance, the 5-year event-free survival was estimated at 90%[18] for children who were given an acute lymphoblastic leukemia (ALL)-type chemotherapy regimen. Adults have been treated with chemotherapy regimens similar to that used in patients with ALL, such as CHOP, CHOEP, R–CHOP and autologous stem cell transplantation.[19,20] The hyper-CVAD regimen used in the present case normally requires four induction-consolidation courses alternating hyper-CVAD with high-dose methotrexate and cytarabine.[16] For this regimen, complete response rate was 91%, and 3-year progression-free and overall survival was 66% and 70%, respectively.[21] In our case, the patient had relatively favorable outcome. No recurrence has been found in organs in the whole body for 2 years.

To the best of our knowledge, this is the first report of a case of T-LBL involving the conjunctiva presenting with a salmon colored conjunctival mass as the first sign, similar in appearance to conjunctival MALT

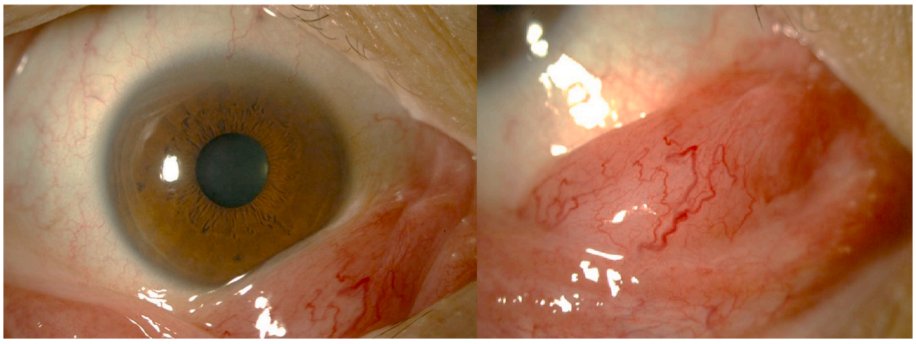

Fig. 1. A conjunctival salmon pink lesion extending from the fornix involving the bulbar conjunctiva. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

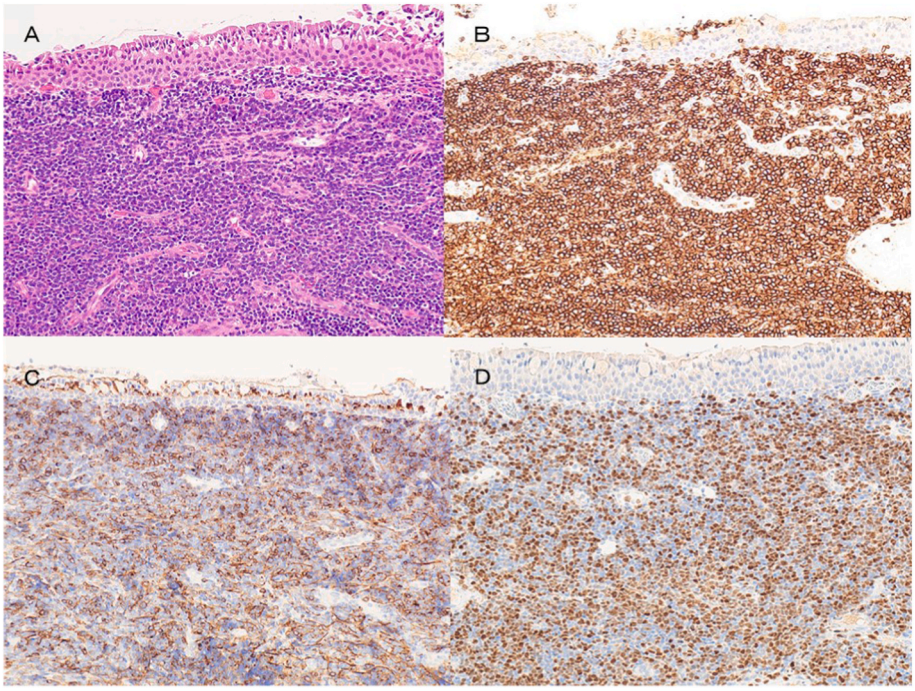

Fig. 2. Immunohistochemical study of the biopsy (A: hematoxylin-eosin staining; original magnifications × 200) revealed positive immunoreactivity for (B) CD7, (C) CD10, and (D) TdT (original magnifications × 200).

lymphoma. Although T-LBL in the conjunctiva is very rare, this case demonstrates that T-LBL should be considered in the differential diagnosis of patients with similar symptoms. Early correct diagnosis and appropriate treatment for T-LBL are imperative and offer patients the optimum chance of long-term survival.

Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Research ethics

Written consent to publish potentially identifying information, such as details or the case and photographs, was obtained from the patient(s) or their legal guardian(s).

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Patient consent

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