Clinical pathologic reviews

Bilateral ocular panadnexal mass as initial presentation of systemic blastoid variant of mantle-cell lymphoma

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ABSTRACT

A 66-year-old man developed a slowly enlarging, bilateral, painless, periorbital, and orbital swelling with ptosis, nonaxial proptosis, chemosis, exposure keratopathy, and decreased vision in both eyes. He had fever, night sweats, and weight loss (B-symptoms), along with lymphadenopathy and elevated serum lactate dehydrogenase, with no prior history of lymphoma. A transpalpebral incisional biopsy revealed a rare case of mantle-cell lymphoma of blastoid variant, stage IVB. The main immunophenotype characteristics were cyclin D1\textsuperscript{+}, CD5\textsuperscript{+}, CD10\textsuperscript{−}, CD23\textsuperscript{−}, Bcl-6\textsuperscript{−}/+, and a high (up to 80%) Ki-67 proliferation index. Following an excellent response to the immune-chemotherapy treatment plan, all ocular adnexal lymphoma manifestations disappeared completely; however, 13 months after the initial presentation, there was a recurrence of the disease with rapid worsening and death. The blastoid variant of mantle cell lymphoma, a rare subtype of mantle-cell lymphoma, is a highly aggressive neoplasm, ultimately having a fatal outcome. As the initial manifestation of the disease, ocular adnexal region blastoid variant of mantle-cell lymphoma is an exceptional event, with only one previous case reported.
1. Introduction

Lymphoproliferative lesions of the ocular adnexa represent 1%—2% of all lymphomas and approximately 8% of all extranodal lymphomas.\(^{3,5,10–12,15}\) Lymphomatous involvement of the ocular adnexal region (OAR) may be as follows: (1) primary (extranodal) OAR lymphoma, (2) secondary OAR lymphoma (nodal, extranodal, or systemic; lymphoma in the OAR with known preexisting extraocular disease), and (3) OAR lymphoma as first presentation site of previously unknown or undiagnosed systemic (nodal or extranodal) disease. Lymphoma is the most common orbital malignancy and the second most common conjunctival malignancy.\(^{3,5,10}\) Most OAR lymphomas are localized at presentation—primary extranodal—or involvement of the OAR is a presenting site of systemic lymphoma.\(^{3,5,10–12,15,17}\)

Mantle-cell lymphoma (MCL) rarely affects the OAR, comprising 1%—7% of all OAR lymphomas. The most common location for OAR MCL is the orbit with or without synchronous lacrimal gland or conjunctival or eyelid involvement.\(^{3,5,6,9–17}\) The blastic or blastoid cytological variant of mantle-cell lymphoma (bMCL) is a rare, but distinct, entity that is considered to be a highly aggressive and ultimately fatal subtype of B cell non-Hodgkin lymphoma, with a homogeneous population of cells displaying lymphoblastic morphology.\(^{3,4}\) Here, we describe a case of biopsy and cytogenetically proven, bilateral, synchronous, slightly asymmetrical, massive, ocular pan-adnexal bMCL as an initial presentation of the disease, the second reported case of OAR bMCL in the literature.

2. Case report

2.1. Clinical findings

A 66-year-old man presented in October, 2013, with a 9-month history of slowly enlarging, bilateral (synchronous and relatively symmetrical, but with the right side more prominent), painless, periorbital, and orbital swelling/mass. The patient also presented with mechanical ptosis, proptosis, and downward dystopia (nonaxial proptosis) more severe on his right side, chemosis that was severe on the right side, with exudation and conjunctival keratinization, and lagophthalmos with exposure keratopathy that was also more severe in the right eye (Fig. 1A). There was almost complete loss of vision in his right eye and decreased visual acuity in his left eye. Symptoms also included a feeling of resistance, irritation, and weight loss of 15 kg.

On initial examination, he had light perception without accurate projection in the right eye and 20/60 acuity in his left eye, with no relative afferent pupillary defect. His intraocular pressures were 30 mm Hg right eye and 32 mm Hg left eye. Exposure keratopathy and chemosis, with sticky hard exudate and keratinization, were more pronounced on the right side. Eye movements were restricted. The posterior segments of both eyes were unremarkable.

A multislice computerized tomography scan (Fig. 1B) showed a bilateral, homogeneous, expansile, enhancing, well-demarcated, solid, periorbital and orbital mass of soft-tissue density, mainly in the superotemporal quadrant, with involvement of the lacrimal gland, superior and lateral rectus and superior oblique muscles, optic nerve, and lacrimal sac. There was no CNS or sinonasal involvement.

Laboratory investigations showed elevated serum lactate dehydrogenase (612 U/L, normal 220—460), low hemoglobin (115 g/L, normal 138—175), low serum calcium (2.00 mmol/L, normal 2.15—2.65), high white cell count (22.17 \times 10^9/L, normal 3.4—9.7), low neutrophil count (34.9 \times 10^9/L, normal 44—72), high lymphocyte count (55.6 \times 10^9/L, normal 20—46), low platelet count (0.003/L, normal 0.158—0.425), low red blood cell count (4.01 \times 10^12/L, normal 4.34—5.72), and low hematocrit (0.349%, normal 0.415—0.530).

The patient’s past medical history was significant only for low-grade hypothyroidism without substitution therapy. He had worked for 35 years at a paint and varnish factory, and his father died of bone cancer at the age of 70 years. There was no history of Sjögren syndrome, Mikulicz syndrome, IgG4-related disease, Graves disease, systemic lupus erythematosus, bullous pemphigoid, or granulomatosis with polyangiitis. The serologies for human immunodeficiency virus and hepatitis B and C viruses were all negative. There was no prior history of lymphoma. No pathologic skin lesions were present. At presentation, enlarged cervical, axillary, and inguinal lymph glands were found. The spleen was nonpalpable. A chest X-ray and abdominal and pelvic ultrasonography were within normal limits.

The clinical diagnosis was bilateral ocular adnexal lesion suspected of being a lymphoproliferative malignancy, with an International Prognostic Index 5 (high intermediate risk) and a Performance Score (Eastern Cooperative Oncology Group) >1. A transcunaneous, transpalpebral incisional surgical biopsy of the periorbital part of the tumor on both sides was performed under local anesthesia, and the specimens were sent for histopathological evaluation.

2.2. Histopathologic and immunohistochemical findings

After fixation in 10% buffered formalin, the 2 biopsy specimens were whitish-yellowish pieces of tissue, measuring 1.5 cm × 1.1 cm × 0.5 cm and 1.7 cm × 1.1 cm × 0.7 cm, respectively. Microscopy examination (Fig. 2A) revealed a relatively uniform, hypercellular, diffuse, and slightly nodular, malignant lymphoid proliferation of intermediate-sized cells. The cells showed angulated, cleaved, irregular or round nuclear contours, finely dispersed nuclear chromatin, small nucleoli, and a narrow rim of cytoplasm. The cells were limited to the zone surrounding the residual germinal centers that could still be recognized. There was no necrosis. Hypalnized small-sized blood vessels were also present.

Immunohistochemical staining (Fig. 2B-D) demonstrated diffuse and strong positivity for cyclin D1, CD5, CD20, CD44, CD79a, MUM-1, and Bcl-2, with scattered focal moderate positivity for Bcl-6, p53 (<20% of cells), IgM, and lambda light chain > kappa light chain, and a very high percentage of nuclear staining for Ki-67 (60%—80%). The tumor cells were negative for CD3, CD10, CD15, CD23, CD30, CD56, CD68, CD138, IgG, and TdT. Among the tumor cells were a moderate number of small T cells (CD3+) and histiocytes (CD68+). A relatively
disorganized meshwork (alternating loosely structured and tight clusters) of follicular dendritic cells (CD23+) was prominent.

Based on the morphology, histopathological features and the immunohistochemical profile, a diagnosis of bilateral ocular adnexal mantle-cell lymphoma of the blastoid variant was thought most likely. Fluorescence in situ hybridization analysis was performed on formalin-fixed tissue specimens, using LSI IGH/CCND1 dual fusion DNA probe. Fluorescence in situ hybridization revealed 35% of spread single cells with t(11;14) (q13; q32) translocation (Fig. 3).

2.3. Therapy and follow-up

The patient was referred to a hematologist for further evaluation and treatment. A bone marrow biopsy was also positive for a lymphoproliferative malignancy, with paratrabecular and centromedular neoplastic growth. He was staged according to TNM seventh edition and Ann Arbor staging system as follows: T3N3M1c, pT3M1b, IVB. After 8 cycles of immunochemotherapy (R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) at the regional oncology center, all ocular adnexal tumor manifestations had disappeared or regressed significantly. The patient did not experience an OAR bMCL recurrence after 11 months of ophthalmic follow-up. In September 2014, generalized lymphadenopathy and bilateral proptosis recurred, with worsening of the patient’s general condition. In October, 2014, R-DHAP regimen (rituximab, dexamethasone, cytarabine, and cisplatin) was introduced for 1 cycle of immunochemotherapy. In November, 2014, 13 months after presentation, the patient died from massive pleural effusion, chemotherapy-induced diarrhea, neutropenic fever, and heart failure.

3. Discussion

3.1. General information about bMCL

The blastic or blastoid variant form of MCL is considered to be a highly aggressive subtype of non-Hodgkin lymphoma comprising up to 17% of all MCL types, and the clinical and biological characteristics do not differ from those of the common form of MCL.1,2,20 The distribution according to the modified International Prognostic Index is similar to that of the classic forms of MCL. About half of the patients are low risk, and the other half are high risk.1,7 The term blastic or blastoid variant of MCL has been generally used to describe cases with a homogeneous population of cells displaying lymphoblastic morphology, associated with high proliferative activity and a poor prognosis.1

The blastic or blastoid variant of MCL is usually diagnosed on initial presentation.1 Most patients have primarily stage IV disease, lymphadenopathy, and extranodal involvement.1,2,20 In addition to the patients who initially present with blasts, others may eventually develop blastic transformation, usually within a few years.1,2,4,7,18–20 Increased lactate dehydrogenase levels are observed with the same frequency, up to 63%, in bMCL as in the common forms of MCL.1,2,20

3.2. Histopathological features in bMCL—morphology, immunophenotyping, and cytogenetics

Blastic variant of MCL encompasses the following: intermediate-sized blasts, with a morphology intermediate between that of a centrocyte and a centroblast, with finely dispersed chromatin, barely distinct nucleoli and scant indistinct cytoplasm. Some cases display centroblastic morphology with large cells having round nuclei, fine
chromatin, prominent nucleoli, and a moderate amount of basophilic cytoplasm.1,2,4,18

The diagnosis of bMCL is validated by the CD5+/CD10+/CD23+/Bcl-6+/Bcl-2+/Bcl-6-/- immunophenotype and/or cyclin D1 over-expression.1,2,4,18

A disorganized meshwork of follicular dendritic cells, detectable by staining for CD21, CD23, or CD35, is prominent.1 In bMCL, a high proliferative activity is present (Ki-67 positive cells >40%).1,8

Blastoid variant of MCL, as well as MCL, is associated with the t(11; 14) (q13; q32) translocation, which results in the positioning of the CCND1 (BCL-1) gene (11q13) near the immunoglobulin heavy-chain gene (14q32) and leads to upregulation of CCND1. This translocation results in the overproduction or aberrant expression of cyclin D1 protein, an important regulator of the G1/S phase of the cell cycle.1,2,4,18–20

The chromosomal translocation t(11;14) is the molecular hallmark of bMCL.2,20

3.3. Clinical features of OAR bMCL patients

In the OAR, the blastoid variant of MCL is an exceptional event. The only previously reported case8 of bMCL of the

Fig. 2 – Morphology and immunophenotype of bMCL. A: The transpalpebral incisional biopsy specimen displays diffuse and slightly nodular proliferation of intermediate-sized cells. The cells showed angulated, cleaved, irregular, or round nuclear contours; finely dispersed nuclear chromatin; small nucleoli; and a narrow rim of cytoplasm (arrows indicating blasts). B: Diffuse and strong CD20 membrane staining. C: Cyclin D1 stains the nuclei of the entirety of the incisional biopsy specimen. D: The overall Ki-67 proliferation index was estimated to be 60%—80%. (A, hematoxylin and eosin, 400×; B–D, immunoperoxidase reaction, diaminobenzidine chromogen, hematoxylin counterstain, 400×). bMCL, blastoid cytological variant of mantle-cell lymphoma.

Fig. 3 – Interphase fluorescence in situ hybridization analysis showing single nuclei (arrows) with t(11; 14) (q13; q32) with 2 fusion signals and single red (native CCND1) and single green (native IGH) signals (×600).
OAR also as an initial presentation of the disease, was in a 53-year-old man in China. This patient had a 15-day history of skin nodules and plaques on the head, trunk, and lower extremities, with hypercalcemia and swelling of the left periorbital region for 4 days. Immunophenotyping from a skin nodule biopsy revealed positivity for Cyclin D1 and Ki-67+ (>80%) and negativity for CD5. The patient died of pneumonia 1 month after presentation having received only 1 cycle of R-Hyper-CVAD chemotherapy. Of note, there are 8–5,10–12,15–17 large, well-controlled studies (>40 OAR MCL cases described and analyzed per study) in the literature. Among 1020 reported and analyzed OAR lymphoma cases in those articles, there were only 51 MCL (5%), and only 1 bMCL in a study of 353 OAR lymphoma cases by Ferry and colleagues,5 but without any clinical and anatomical data or any other relevant histological and immunohistochemical findings provided.

3.4. Therapy and survival status of bMCL patients

The optimal therapy for bMCL patients is still debated and has been limited to palliative therapy.1,2,19,20 Surgery alone is never enough, even for localized small tumors. The major differences between therapy for MCL and bMCL patients lie in the response to therapy, especially the duration of response.1 Thus far, there is no proven therapeutic paradigm that can be considered as standard of care for OAR MCL, and the overall prognosis is poor despite the success of stem cell transplantation.2,4,7,20 Patients have received diverse treatments, although most received anthracycline-based chemotherapy, that is, cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP), combined with anti-CD20 antibody (rituximab) before or without autologous stem cell transplantation.1,2,4,7,19,20 In most cases, the front-line therapy includes (R)CHOP or (R)VAD+C regimen (rituximab, vincristine, adriablastin, dexamethasone, chlorambucil), and the second-line therapy for relapsing or refractory patients includes (R)DHAP (rituximab, dexamethasone, cytarabine, cisplatin) or (R)ESAP (rituximab, etoposide, cytarabine, cisplatin, methylprednisolone).1,2,4,7,19,20 Patients receiving immunochemotherapeutic treatment had a significantly better 5-year survival rate than those receiving chemotherapy treatment without rituximab.14

Many studies have found that MCL has one of the poorest prognoses among all lymphomas and that bMCL is one of the worst forms of NHL, with a median survival of 14.5 months (vs 53 months for the common forms of MCL) and a disease-free survival of 13 months.1,4,7,20 The Mantle-Cell Lymphoma International Prognostic Index, the prognostic model most often used,7 incorporates the Eastern Cooperative Oncology Group performance status, age, leukocyte count, and lactic dehydrogenase level. A modification of the Mantle-Cell Lymphoma International Prognostic Index also adds the Ki-67 proliferative index, if available. High-dose therapy, Ann Arbor staging, and involvement of the bone marrow or blood have no influence on the survival or clinical outcome of patients with bMCL. Only a high Mantle-Cell Lymphoma International Prognostic Index has a significant influence on survival.2,4,7,20

4. Conclusion

Mantle-cell lymphoma with blastic transformation of the ocular adnexal region as the initial manifestation of systemic disease is an exceptional event that is aggressive in nature and incurable with currently available therapeutic options, ultimately having a fatal outcome. Our case is unique because of the bilateral massive panadnexal involvement. There was no prior history of lymphoma, with extranodal manifestation as the first sign of systemic disease, the presence of B-symptoms, a high intermediate International Prognostic Index and performance score >1, a mixed histopathological subtype with blastoid cytology and a high index of proliferation.

5. Disclosures

The authors report no proprietary or commercial interest in any product or concept discussed in this article.

REFERENCES


