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Case Report
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# Choroidal and Ocular Adnexal Lymphoma Extension From Systemic Mantle Cell Lymphoma: A Case Report

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Mantle cell lymphoma (MCL) is a rare subtype of B-cell non-Hodgkin lymphoma (NHL) with an annual incidence of 5 per million people. Ophthalmic lymphoma is also rare, accounting for 5%–10% of all extranodal NHL.[1] Primary involvement of ocular adnexa constitutes 8% of all nondisseminated NHL of extranodal origin.[2] According to the largest study published of 353 cases of ocular adnexal lymphomas, mantle cell lymphoma is rare and comprises only 5% of ocular adnexal lymphomas (32% bilateral and 63% with prior lymphoma).[3] Furthermore, intraocular involvement of MCL is extremely rare.[4] We report a case of a 70-year-old man with a history of mantle cell lymphoma in relapse who presented with conjunctival and choroidal involvement.

A 70-year-old man with a history of systemic mantle cell lymphoma in relapse presented with acute redness, blurry vision, and black spot in the right eye. No pain was reported. He was being treated for his mantle cell lymphoma with a new regimen of chemotherapy (Ibrutinib + rituximab) and had undergone a bone marrow transplant 1 year before presentation with a relapse 20 days later.

His history goes back to 7 years before presentation when his MCL was diagnosed and remission achieved with R-Hyper-CVAD/cytarabine/MTX chemoimmunotherapy regimen, which employs rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine. However, the patient relapsed 6 years later and was treated with the chemoimmunotherapy regimen (R-ICE), which combines rituximan, ifosfamide, carboplatin, and etoposide phosphate, followed by autologous hematopoietic cell transplantation (auto-HCT), but he relapsed 20 days post auto-HCT. The patient was subsequently treated with ibrutinib + rituximab.

On examination, his visual acuity was counting fingers at 2 m in the right eye and 20/25 in the left. Ocular motility and intraocular pressures were normal. Hertel exophthalmometry measurements were within normal limits. Ectropion was noted in both eyes.

Slit lamp examination of the right eye showed 2 pink salmon-patch lesions 15 × 10 mm and 25 × 10 mm in size involving the inferotemporal and the superonasal aspect of the conjunctiva, respectively (Fig. 1). There was a white pseudohypopyon and +3 cells in the anterior chamber.

Dilated fundus exam revealed a subretinal mass with serous retinal detachment. B-scan showed a choroidal lesion (Fig. 1). An magnetic resonance imaging of the brain and orbits showed posterior retinal detachment of the right eye with irregular thickening of the choroid anteriorly with homogenous enhancement. There were no orbital lesions.

The patient was scheduled for conjunctival biopsy and an anterior chamber tap. The cytological examination of the conjunctival biopsy touch prints revealed the presence of numerous atypical lymphoid cells showing mostly medium to slightly large size cells with frequently increased nucleocytoplasmic ratios. Nuclei were round or partially clefted and contained relatively open chromatin with occasionally small nucleoli. The cytoplasm was scanty and basophilic with no granules or Auer rods seen. Conjunctival biopsy showed diffuse proliferation of medium sized lymphoid cells occupying extensively the lamina propria. They stained positive for CD5, Cyclin D1, Pax5, CD20, and BCL2; and negative for TDT and CD34. K167 staining was extremely positive (Fig. 2). The immunophenotypic analysis of 100,000 acquired events from conjunctival lesion and anterior chamber cells showed results that were comparable within the 2 analyzed samples. T lymphoid cells represented almost 20% of the total nucleated cells and expressed all the tested pan T-cell markers (CD3, CD5, and CD7). B lymphoid cells were significantly increased representing 70%–80% of the total counted nucleated cells. They were monoclonal and expressed mostly the following immunophenotype: CD5+, CD10–, CD19 (dim), CD20++, CD22+, CD23–, CD34–, CD45+, CD79b+, CD200–, LAMBDA+ (Fig. 2). The findings were consistent with ocular infiltration by mantle cell lymphoma showing immunophenotypic features comparable to those previously described at diagnosis from bone marrow aspirate 7 years before this presentation except for a significantly decreased intensity of CD19 expression. The

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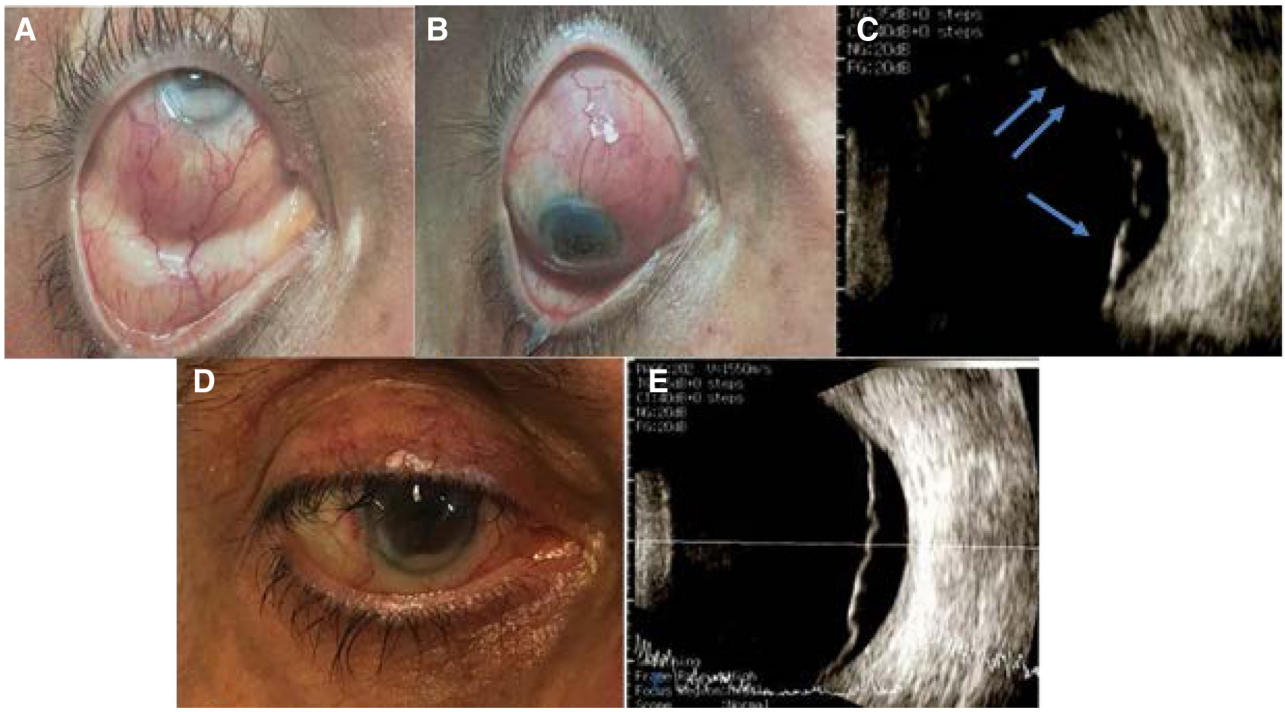


**Figure 1. Clinical photographs and B-scan ultrasound images of the right eye at diagnosis (A–C) and posttreatment (D and E).** (A), 15 × 10 mm lesion of the inferotemporal conjunctiva. (B), 25 × 10 mm lesion of the superonasal conjunctiva. (C), B-scan Ultrasound shows a choroidal mass (double arrows) with serous retinal detachment (arrow). (D), Clinical image shows resolution of the conjunctival lesions 2 weeks posttreatment. (E), B-scan Ultrasound 2 weeks posttreatment shows resolution of choroidal mass with residual retinal detachment.

patient was also referred back to oncology for management of systemic condition.

The chemotherapy regimen was changed to ibrutinib, rituximab, gemzar, oxaliplatin, and dexamethasone. On follow-up, 2 weeks later, visual acuity was improved markedly to 20/25 in the right eye. On slit lamp examination, the conjunctival lesions resolved completely, the pseudohypopyon was reduced, and the anterior chamber cells decreased to +1. Dilated examination showed only mild subretinal fluid inferiorly with no mass. B-scan done confirmed mild subretinal fluid inferiorly and resolved choroidal mass.

On follow-up, 2 weeks later, the findings were rather stable except for complete absence of anterior chamber cells and almost totally resolved pseudohypopyon. Dilated fundus examination and B-scan showed no tumor recurrence and decreased subretinal fluid inferiorly.

The patient passed away few months after the last follow-up. As the patient was lost to follow up, the reason of death remained unknown.

Our patient presented with unilateral ocular adnexal lymphoma with involvement of the conjunctiva by 2 separate lesions and was known to have mantle cell lymphoma in relapse. In addition, he had intraocular lesions involving the choroid and anterior segment. Lymphoma can present in the eye and orbit as 2 forms: primary lymphoma or secondary extension of a known primary lymphoma.[5] Therefore, our patient represents a rare case of secondary ocular and ocular adnexal lymphoma of the mantle cell type.

Intraocular involvement with MCL is extremely rare with only 7 case reports in the literature (Table 1).[6] Although involvement of the ocular adnexal region (OAR) with MCL is more common in secondary (63%) compared to primary (37%) disease,[3] involvement of the intraocular region appears to be almost always associated with a prior history of systemic disease. Rowley et al[7] reported the only case of primary intraocular MCL presenting as a choroidal mass. The remaining 6 reports described secondary ocular involvement; however, none of the cases consisted of unilateral ocular and adnexal involvement like our case. To the best of our knowledge, our case is unique as it is the first to involve unilaterally the choroidal and adnexal regions simultaneously.

MCL is classified into 4 subgroups or variants based on the cytology: small cell, marginal zone-like, pleomorphic, and blastoid. The blastoid and pleomorphic variants behave more aggressively than other MCL variants.[8] Median overall survival time is 14.5 months for the rare blastoid variant as compared to 53 months for patients with more common forms of MCL such as those composed of homogeneous population of small- to medium-sized cells, confirming the very poor prognosis of the blastoid variant.[9] Our patient cytological examination showed atypical lymphoid cells consistent with blastoid variant with medium to slightly large sized cells and frequently increased nucleocytoplasmic ratios. Our patient relative prolonged survival (7 y) can be partly explained by the addition of rituximab to his chemotherapy regimen. The leukemic cells from the anterior chamber tap and ocular lesions had decreased CD19 antigen expression as compared to those from the bone marrow aspirate. This finding can be due to the effect of the ocular medium on these cells.

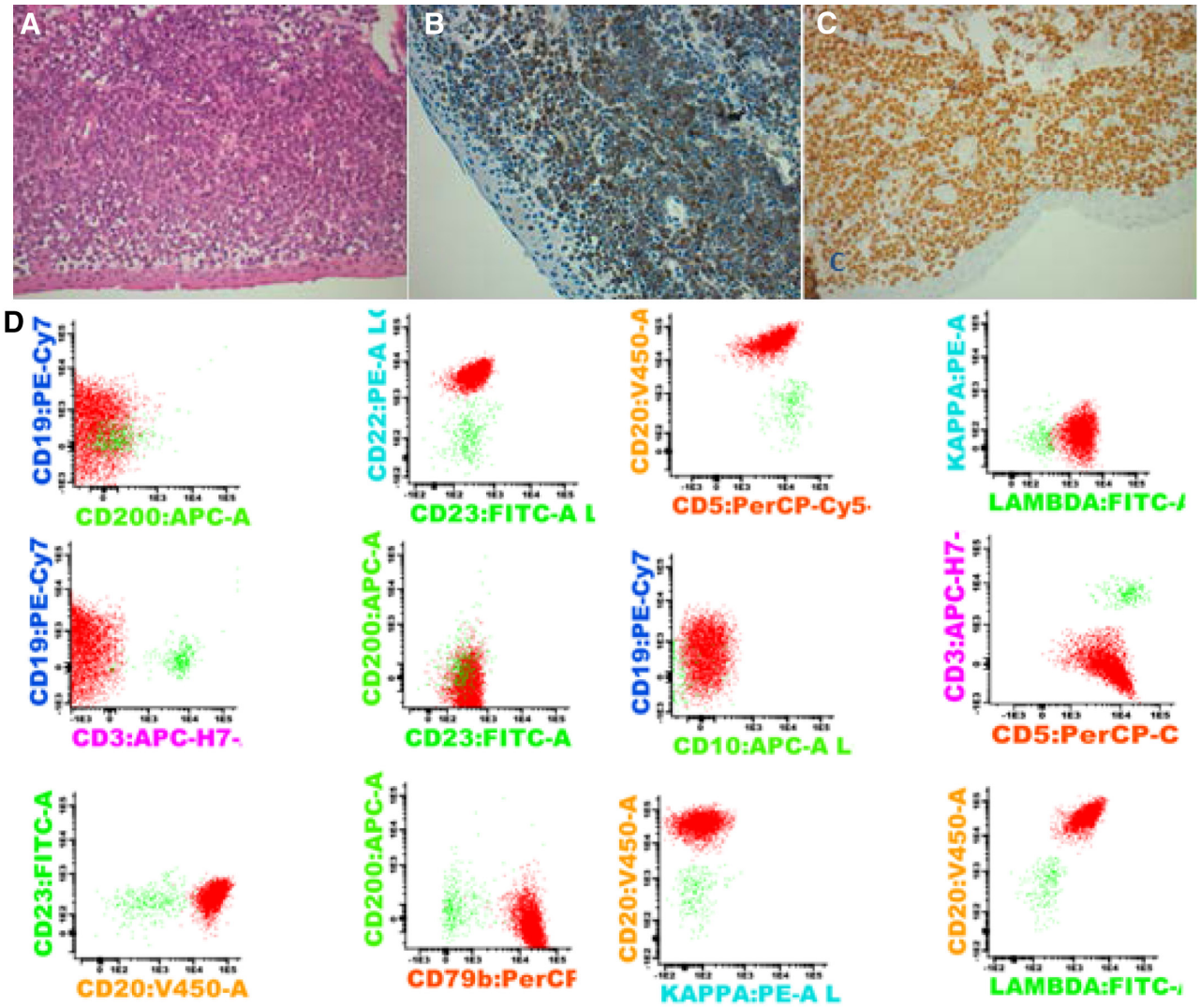


**Figure 2. Conjunctival biopsy (A–C) and Immunophenotyping (D) of lymphoma cells.** (A), hematoxylin and eosin (H&E) staining (20×). (B), Cyclin D1 by immunostaining (20×). (C), Pax5 by immunostaining (20×). (D), Immunophenotyping of lymphoma cells (population in red) by flow cytometry as performed on ocular fluid showing CD5+, CD10–, CD19 (dim), CD20++, CD22+, CD23–, CD34–, CD45+, CD79b+, CD200–, LAMBDA+.

Many treatment regimens have been evaluated for recurrent MCL with various success rates. There is no clear consensus on the optimal treatment regimen for MCL. Also, several studies reported different responses to treatment of recurrent MCL with ocular and OAR involvement (Table 1). In general, treatment of localized OAL is with external beam radiotherapy (EBRT), while systemic disease is treated with chemoimmunotherapy with or without EBRT. EBRT is the gold standard treatment in isolated conjunctival lymphoma with 5-year local control rates ranging from 89% to 100%. The optimal dosing of EBRT is unclear but doses higher than 35 Gy exacerbated post-treatment toxicity and morbidity while low, fractionated doses alleviated it.[10] Combining chemotherapy with rituximab for stage IVE MCL is superior to chemotherapy alone with better 10-year disease-specific survival.[11] Our patient with systemic involvement of MCL was treated with a chemoimmunotherapy-based regimen including iburtinib, rituximab, gemzar, oxaliplatin and dexamethasone. Our patient's median survival in relation to initial diagnosis of his systemic disease was favorable when compared with studies that employed regimens without rituximab,[9] which might be due to the efficacy of this molecule in treating MCL.

In summary, this case presents an extremely rare example of secondary ophthalmic MCL unilaterally involving the conjunctiva and the choroid. Although more studies are needed to establish best management options, early diagnosis with tissue biopsy and a combination of chemoimmunotherapy appears to be effective for secondary ocular and ocular adnexal MCL. The immunophenotypic study of both ocular and peripheral leukemic cells is important, especially when immunotherapy is planned. More studies of ocular and adnexal MCL are needed to better characterize its clinical behavior and to enable meaningful conclusions regarding treatment response.

**Table 1**

**Mantle Cell Lymphoma With Intraocular Involvement.**

| Authors, (Year) | Sex/ Age | Primary/ Secondary | Ocular and Adnexal Involvement | Cytologic Features | Treatment after Ocular Involvement | Time to Respond + Status |
|---|---|---|---|---|---|---|
| Reid et al. (2014)[5] | M/71 y | Secondary | Left eye iris | Not reported | Chemo/XRT | Improved 90 days later. Worsened 120 d post chemo/XRT. Died 2 wks after last examination |
| Agarwal et al. (2015)[6] | M/58 y | Secondary | Right iris and anterior chamber | Blastic variant | Systemic Ibrutinib and intravitreal injections of MTX, ranibizumab, and Rituximab. Ibrutinib therapy tapered after 3 mo due to concern of side effects | Partial Remission at 1 wk and 3 mo |
| Rowley et al. (2000)[7] | M/57 y | Primary | Left choroidal mass | Small lymphocytes, convoluted nuclei, single nucleolus | EBRT 34 Gy | No disease recurrence 34 mo after EBRT |
| Ahn et al. (2010)[12] | M/57 y | Secondary | Bilateral choroidal involvement | Not reported | Dexamethasone + EBRT 2000 cGy (200 cGy × 10 fractions) + Bortezomib for systemic involvement | Almost complete regression of ocular disease 2 wks after treatment but progression of systemic adenopathy |
| Chappelow et al. (2008)[13] | F/51 y | Secondary | Bilateral pan ocular involvement[a] | Not reported | Prednisone. EBRT 14 Gy (2 Gy × 7 fractions) + Tositumomab started 1 wk later for widespread cutaneous involvement | Bilateral resolution of ocular disease 1 wk after EBRT initiation. Ocular examination unremarkable 7 wks after presentation |
| Economou et al. (2007)[14] | M/71 y | Secondary | Bilateral iris | Polygonal lymphoid cells | Fludarabine + cytosine arabinoside achieved partial regression in 2.5 mo. One month later, right iris recurrence was treated with Rituximab + EBRT 100 Gy (20 Gy × 5 fractions) | Complete resolution of ocular involvement 7.5 mo after initial ocular presentation. Paratracheal involvement 12 mo after initial ocular presentation led to death from bilateral pneumonia 4 mo later |
| Pei et al. (2019)[15] | M/59 y | Secondary | Bilateral ciliary body masses | Small malignant cells | EBRT 40 Gy (2 Gy × 20 fractions) bilaterally + intravitreal MTX in left eye | Complete remission of symptoms in 1 mo. Disappearance of ciliary body masses in 12 mo. Relapsed 29 mo after EBRT with peripheral LN involvement and rapid deterioration. Death 1 mo later from chemo side effects |
| Our case | M/70 y | Secondary | Right uvea and conjunctiva | Blastic variant | Ibrutinib + Gemcitabine + Oxaliplatin + Dexamethasone + Rituximab | Complete resolution of ocular lesions 2 wks after treatment. Patient passed away few months later (unknown cause of death) |

[a]Cutaneous eyelid nodules bilaterally; salmon patch of right bulbar conjunctiva; Pseudohypopyon, iris thickening, vitreous infiltration bilaterally.
Chemo/XRT = chemotherapy/radiotherapy; EBRT = external beam radiation therapy; LN = lymph node; MTX = methotrexate.

## Disclosures

The authors have no conflicts of interest to disclose

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