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CASE REPORT

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# Experience of ibrutinib in a patient with recurrent mantle cell lymphoma with orbital involvement

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**Abstract**

Mantle cell lymphoma is a subtype of B cell non-Hodgkin's lymphoma with different clinical and molecular features. Extranodal involvement is common in MCL. Bone marrow, liver, spleen, waldeyer ring and gastrointestinal involvement are most common. Lymphomatosis polyposis can be seen in some patients. Central nervous system involvement is rare. Here, we aimed to present a blastoid variant MCL patient who developed orbital recurrence after four lines of systemic therapy and responded to ibrutinib (560 mg/day) monotherapy. The mass disappeared completely in the bilateral orbital MRI taken after the 5th month of the ibrutinib treatment.

**Keywords:** Mantle cell lymphoma, ibrutinib, ocular involvement, atypical presentation

## Introduction

Mantle cell lymphoma (MCL) is a subtype of B cell non-Hodgkin's lymphoma (NHL) with different clinical and molecular features, and it accounts for approximately 3-6% of all NHL cases [1]. Its clinic is mostly aggressive. Most patients are at an advanced stage at the time of diagnosis. Extranodal involvement is detected in 25% of MCL patients at the time of diagnosis [2]. Although the most common extranodal involvement in MCL patients is the gastrointestinal system (GIS), liver and breast, ocular involvement has been reported rarely. MCL constitutes 3-10% of NHLs. It is seen in middle and old age. The median age of incidence is 60. It constitutes 6-9% of all lymphomas in western societies and its annual incidence is 1-2 / 100,000. It is more common in men than women with a ratio of 3: 1 [3]. Extranodal involvement is common. Bone marrow, liver, spleen, waldeyer ring and gastrointestinal involvement is most common. Central nervous system (CNS) involvement is rare.

The diagnosis of MCL is made by excisional lymph node biopsy. Immunohistochemical properties are typically the positive detection of CD20, CD22, CD79 and T lymphocyte markers CD5 [4]. CD10, CD23, and BCL6 are generally negative [5]. Cyclin D1 (BCL1) is expressed in the vast majority (95%) of MCL cases [6]. SOX11 should be investigated in cyclin D1 negative cases. In these cases, SOX11 positivity supports the diagnosis of MCL [7]. In molecular examination, the t [11; 14] mutation strongly supports the diagnosis of MCL [8]. However, the t [11; 14] (q13; q32) mutation is not specific for MCL and can be detected in lower rates in multiple myeloma and other lymphoid malignancies [9]. Most MCL patients (70%) are advanced stage at the time of diagnosis, and approximately one-third have systemic B symptoms such as fever, night sweats and weight loss. While 75% of the patients initially present with lymphadenopathy, the remaining 25% present with extranodal disease. Blastic and pleomorphic morphological variants of MCL with an aggressive course are seen in 10-15% of newly diagnosed MCL cases. Spleen and bone marrow involvement is found in 50-60% of the cases [10-11]. Some cases may present with leukemic stage characterized by pancytopenia or leukocytosis. CNS involvement is rare and usually seen with the leukemic phase. The blastoid variant of MCL usually has a poor prognosis [12]. There are few case reports in the literature reporting orbital and ocular region involvement in MCL

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patients [13-14]. Ocular adnexal involvement of MCL has been reported mostly in elderly male patients [14-15].

Conventional chemotherapies in the treatment of MCL R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone), BR (bendamustine, rituximab), VcR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone), R-DHAP, R-DHAP, doses of cytarabine and cisplatin) and intensive chemotherapy protocols such as R-hyper-CVAD / cytarabine / methotrexate are used. Consolidation with autologous hematopoietic stem cell transplantation (HSCT) is recommended for young (<65 years) MCL patients after induction with conventional chemotherapy. It is supported by data published by European and Scandinavian groups that consolidation with autologous HSCT after first remission benefits significantly to progression-free survival [16]. However, autologous HSCT is not curative in patients with advanced stage MCL, and its superiority in overall survival has not been demonstrated when compared with combination chemotherapy alone [17]. With only conventional chemoimmunotherapy, 78-94% of MCL patients go into remission, and the median remission periods vary between 1.5-3 years. Classical chemoimmunotherapy such as R-ICE (rituximab, ifosfamide, carboplatin, etoposide), R-DHAP can be given in refractory / recurrent MCL patients, and new drugs should be considered in early relapse or refractory cases. Among these, ibrutinib has the highest response rates in patients. In cases where ibrutinib is contraindicated, particularly at high risk of bleeding, lenalidomide may be preferred in combination with rituximab. In addition, it has been shown that bortezomib or temsirolimus is effective along with chemoimmunotherapy [18].

**Case Report**

A 74-year-old female patient was admitted to the hematology outpatient clinic in 2014 with swelling in the neck. Bilateral cervical and axillary lymphadenopathy (LAP) was detected on physical examination. Conglomerated malignant lymph nodes in the bilateral cervical chain were observed in the neck CT. Diffuse hypermetabolic lymph nodes were observed in PET-CT. MCL blastoid variant was diagnosed as a result of axillary lymph node excision biopsy. Bone marrow involvement was not detected in the bone marrow biopsy. The patient was given 6 cycles of CHOP (cyclophosphamide 750 mg / $m^2$ / day, adriamycin 50 mg $m^2$ / day, vincristine 1.4 mg / $m^2$ / day, prednisone 100 mg / day). Remission was observed in the PET-CT taken after treatment, and the patient was followed up without treatment. Widespread hypermetabolic lymph nodes seen on PET-CT of the patient, who developed neck swelling approximately 10 months after the end of the treatment, were evaluated in favor of recurrence. Excisional LAP biopsy was reported as a recurrent MCL blastoid variant. Two cycles of BORID (bortezomib, rituximab, dexamethasone) were given. Bone marrow involvement was not detected in the patient whose bone marrow biopsy was repeated. Autologous HSCT was performed approximately 4 months later in the patient who was shown to be in remission as a result of the control PET-CT taken at the end of the treatment.

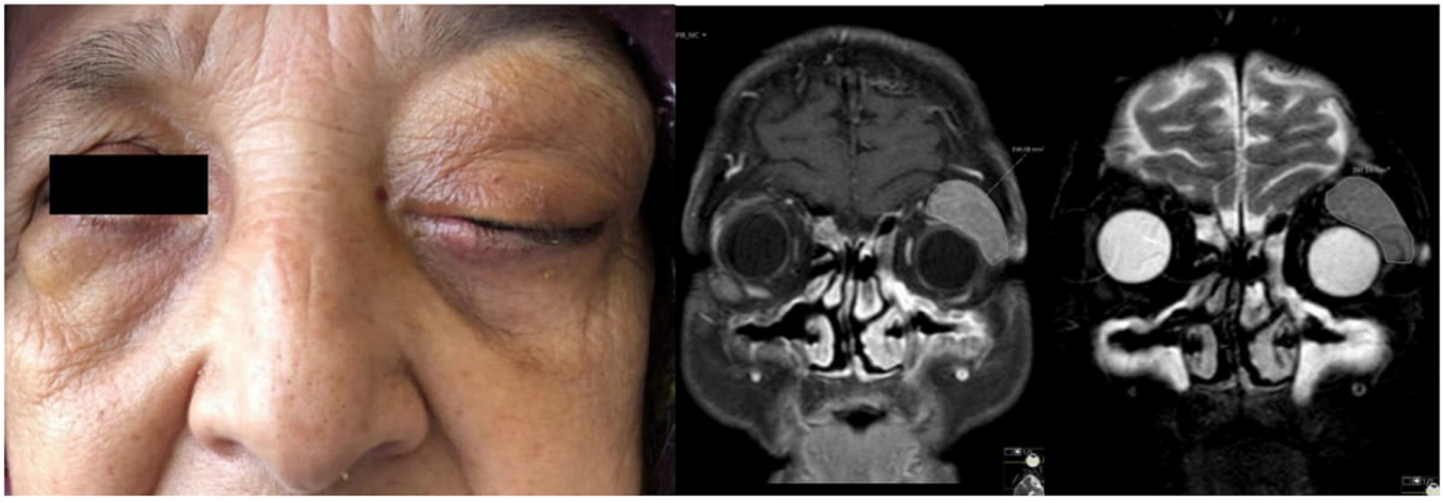

**Figure 1.** Image of the patient and Orbital MRIs before treatment (Asymmetric enlargement and heterogeneous intense contrast enhancement are observed in the left lacrimal gland)

Approximately 30 months after autologous HSCT, the patient applied to eye diseases due to swelling in the left orbit, and an orbital MRI of the patient revealed a homogeneous hyperdense space-occupying lesion of 4x3 cm in the extraconal location in the left orbit. PET-CT of the patient evaluated in favor of MCL involvement was reported as recurrence. LAP biopsy performed for the third time was reported as MCL blastoid variant. The patient was given 4 cycles of R-ICE protocol. In the brain CT taken after the treatment, a homogeneous hyperdense space-occupying lesion of approximately 2.5x1.5 cm in extraconal location in the left orbit was observed. The patient who was evaluated in favor of MCL involvement was started on ibrutinib 560 mg/day treatment. The mass disappeared completely in the bilateral orbital MRI taken after the 5$^{th}$ month of the treatment.

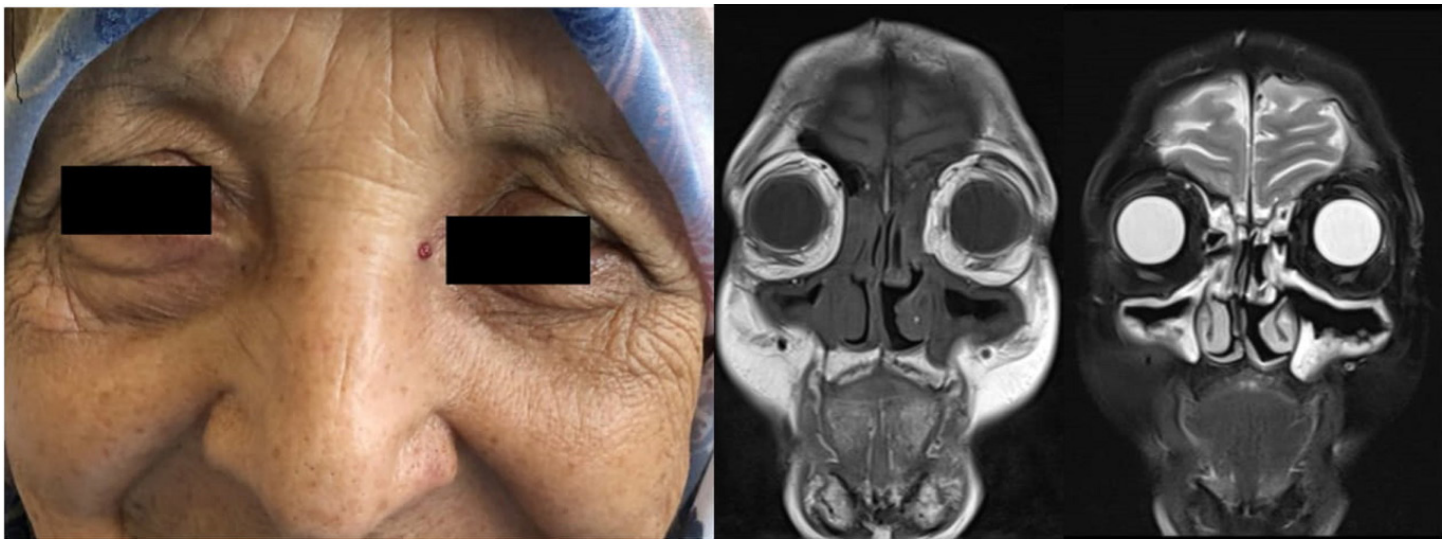

**Figure 2.** Image of the patient and Orbital MRIs after treatment

## Discussion

MCL patients are usually a subtype of NHL that remission with 1st line therapy but relapse is common. Patients are mostly diagnosed with advanced stage disease. Only 6-8% of the patients are diagnosed at an early stage (stage 1-2) [2]. Therefore, our knowledge about treatment options and results in early stage disease is limited. Extranodal involvement is common. Involvement is most common in the GIS. Waldeyer ring, liver, skin, soft tissue and CNS involvements can be seen in addition to the GIS. In addition, although it is less common, orbital and eye involvement has been reported [13-14]. Depending on the age, performance and risk score of the patient, either untreated follow-up or radiotherapy and chemotherapy options should be preferred. Selection of chemotherapy regimen in patients with advanced stage of MCL treatment; It varies depending on age, comorbidities, side effect profiles and the experience of the physician. Combination therapies such as R-CHOP, R-DHAP, R-hyper-CVAD / cytarabine / methotrexate are frequently used as chemotherapy regimens. Currently, the standard treatment is the combination of rituximab and chemotherapy, but it is the application of autologous HSCT for consolidation after the first complete response in young and advanced stage patients with good performance scores [2]. In the recurrent or refractory patient group, Bruton tyrosine kinase inhibitor ibrutinib, second generation Bruton tyrosine kinase inhibitor akalabrutinib, immunomodulatory agent lenalidomide, BR, aggressive combination chemotherapy (such as R-ICE, R-DHAP), bortezomib, temsirolimus inhibitor Agents such as can be used. In the Ray study conducted by Rule, it was found that two-thirds of 77 patients given ibrutinib monotherapy gave at least a partial response and the median progression-free survival was longer than 15 months [19]. Bernard et al. reported that two of three patients with CNS involvement who were given ibrutinib monotherapy had a complete response and one had a partial response [20]. In addition, Nishiyama - Fujita et al. reported that they got a complete response with ibrutinib monotherapy in an MCL patient with ocular adnexal involvement [21]. The standard initial dose of ibrutinib recommended in relapse / refractory MCL is 560 mg per day. Allogeneic HSCT as a second-line treatment in patients with recurrent MCL is a high-risk treatment approach with potential cure potential [22]. Due to the advanced age of the patient group, allogeneic HSCT with reduced-density regimens has also been reported [23].

## Conclusion

MCL is a disease with an aggressive course and a short first remission period. Extranodal involvement is common, but orbital involvement has been reported in limited numbers in the literature. In our case, the orbital mass disappeared completely with ibrutinib monotherapy in a patient with recurrent MCL with extraconal localization involvement. We aimed to present a case of orbital recurrence MCL with complete response with ibrutinib monotherapy.

**Conflict of interests**
*The authors declare that they have no competing interests.*

**Financial Disclosure**
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**Patient Informed Consent**
*Consent form was obtained from the patients before the article.*

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