The Use of Ibrutinib in Extranodal Marginal Zone Lymphoma of the Ocular Adnexa with Multifocal Disease that is Refractory to Rituximab

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Received 2023-03-12
Accepted for publication 2023-08-24
Published 2024-06-01

Abstract

Tumors of the ocular adnexa been well documented. The most common ocular adnexal lymphoma is extranodal marginal zone B-cell lymphoma (EMZL), with about a quarter of those occurring in the conjunctiva. We present a case with a patient suspected ocular EMZL, confirmed with biopsy. Positron emission tomography (PET) scan was performed to evaluate for distal lesions and the patient was found to have multiple hypermetabolic lesions throughout the body. Treatment with rituximab was initiated, and after four weekly treatments, subsequent PET scan showed that the original hypermetabolic lesions remained and new lesions appeared. Rituximab was stopped and ibrutinib started. After eight months of ibrutinib treatment, PET scan showed that the original hypermetabolic lesions had disappeared. 19 months from initiation of treatment, a new hilar lesion was found. This progressed into bilateral hilar and mediastinal lymphadenopathy, which was seen on PET scan performed 29 months into treatment. These findings remained stable 35 months post-initiation of treatment. The use of ibrutinib in this patient that initially presented with a lesion in the conjunctiva resulted in an initial resolution of the original systemic hypermetabolic regions on PET scan. While more studies are needed on ibrutinib in the treatment of ocular EMZL, physicians should be aware of the presentation of this disease and the range of treatment modalities.

Keywords: Extranodal Marginal Zone Lymphoma, EMZL, Conjunctival Lymphoma, Rituximab, Ibrutinib

1. Introduction

Most patients with EMZL of the ocular adnexa present with limited stage disease, however up to one-quarter of patients might present with
multifocal involvement (1). We present a case of EMZL that initially presented with a conjunctival lesion. The conjunctival lesion was excised and multiple extranodal areas were found on imaging. The patient was initially treated with four weekly infusions of rituximab, however due to inadequate response, treatment was switched to ibrutinib. An initial resolution of the majority of hypermetabolic regions on PET scan was accomplished with Ibrutinib treatment. There have only been a limited number of cases reported in the literature of ocular EMZL with multifocal disease treated with ibrutinib since the US Food and Drug Administration approved its use in 2017.

2. Case Report

2.1. Patient information


2.1.1. Objective for Case Reporting

Our aim is to present a case of extranodal marginal zone lymphoma that was refractory to traditional treatment. Primary care physicians, optometrists and ophthalmologists should be aware of the potential presentation of an ocular lymphoma and refer the patient to the appropriate care. Early recognition may improve the ultimate outcome for the patient. A 69-year-old-male presented to the ophthalmology clinic with the complaint of discomfort in his eyes, with more discomfort in his left eye than his right. He was referred from his optometrist. He experienced constant irritation, itchiness, and dryness for more than a year and it had gradually been getting worse and more persistent.

He used polyethylene glycol 400/propylene glycol, ketotifen, and prednisolone eye drops in the past. Most recently, he had been on a two-week prescription of fluorometholone eye drops in the left eye four times a day with little relief. The patient also had an InflammaDry eye test with a negative result. He had no history of autoimmune disease. Anterior segment examination was performed by the consulting ophthalmologist which revealed a salmon-colored area of elevation superonasally with engorged blood vessels. Due to the suspicion of conjunctival lymphoma, conjunctivoplasty with biopsy of the lesion was performed. Biopsy confirmed the diagnosis of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue. MRI and PET scan was recommended after the diagnosis was verified. MRI was declined by the patient due to claustrophobia. PET scan showed multiple hypermetabolic regions located in the posterior left orbit, anterior mediastinum, upper right hemithorax, and soft tissue nodules in the right abdomen and pelvis. The patient was asymptomatic and was started on four weekly infusions of rituximab. 10 weeks after the initiation of rituximab, PET scan showed a new lesion in the left lobe of the liver, with little to no response in the previous hypermetabolic regions except in the pelvis area, which showed resolution of the nodule. Rituximab treatment was discontinued and the patient was then started on ibrutinib. Four months into treatment, PET scan showed diminished activity in the left orbit. Eight months after initiation of
treatment, PET scan demonstrated that all previously seen lesions had a decrease in max SUV (standard uptake value) which likely indicated a positive response to therapy. 19 months after initiation treatment, PET scan revealed a new right hilum indistinct lymph node. This progressed to bilateral hilar and mediastinal lymphadenopathy, which was found on PET scan performed 29 months into treatment. These findings were unchanged on PET scan 35 months post-initiation of ibrutinib. The patient has had no new systemic symptoms but three, red, slightly raised skin lesions had appeared on his forehead and temple. It was unclear if this skin involvement was related to the current treatment. He was to be referred to Dermatology and recommended to be followed up.

3. Discussion

Marginal zone lymphoma (MZL) comprises about 8% of all B-cell non-Hodgkin lymphomas (NHL) (2) and ocular adnexal lymphomas account for about 2% of NHL. MZL can appear in many organs of the body, and each site usually presents histologically unique features (3). Specifically, conjunctival lymphoma makes up 25% of ocular adnexal lymphomas with nearly all (98%) originating from B-cell lineage. Extranaodal Marginal Zone Lymphoma is the most common subtype with follicular, high-grade mantle cell, and diffuse large B-cell comprising the remaining types. The pathogenesis of EMZL of the ocular adnexa is likely to be derived from either an infectious or autoimmune cause. There is wide debate about the two most popular infectious agents associated with ocular EMZL. A 2004 Italian study found high prevalence of Chlamydia psittaci DNA in both tumor tissue and peripheral blood cells in patients who had ocular adnexal lymphoma (4). This association, however, is not found in other studies. A 2007 meta-analysis found that there is large variability of the presence of Chlamydia psittaci and ocular adnexal lymphomas across geographic regions (5). Helicobacter pylori is another possible causative agent of EMZL of the ocular adnexa as it has a well-established association with gastric EMZL. Once again, there are mixed results. One study found DNA of H. pylori in 15 out of 15 cases of conjunctival EMZL (6) but in another study, no DNA (deleted “was able to be”) was detected (7). Autoimmune disorders such as Sjogren’s may also be have a potential association with EMZL, but the presence of a particular disorder has no significant influence on the course of the lymphoma (8). (fixed the spacing) There are many treatment options for ocular lymphoma. External beam radiation therapy is first-line and has shown success in many cases (9-12). Treatment for systemic disease includes immunotherapy, such as the monoclonal antibody rituximab. The sole symptom presented by our patient in our case report was his eye problems and was unexpectedly found to have multiple hypermetabolic lesions throughout his body. As a result, the oncologist recommended systemic immunotherapy with rituximab instead of radiation therapy. After four weekly infusions, however, there was minimal response to treatment. While there have been several case reports of successful solo usage of rituximab in patients with EMZL (13-16), there also have been instances where regression of the lymphoma was achieved only with adjunct radiotherapy (17). Although the patient was not treated with radiotherapy, a new medication was prescribed following the lack of significant improvement in lesion resolution with Rituximab. Ibrutinib, an oral Bruton tyrosine kinase inhibitor that has been used in chronic lymphocytic leukemia (18) was started after the discontinuation of rituximab. While ibrutinib has clinical benefit in patients with relapsed or refractory marginal zone lymphoma (19), there are not many studies of the usage of ibrutinib in systemic lymphoma patients that initially present with ocular extra nodal marginal zone lymphoma. Eight months into the treatment regimen, most of the hypermetabolic regions that were originally present when the EMZL was diagnosed reduced in intensity on PET scan. Later, there were new mild lesions found in the mediastinal and bilateral hilar regions. However, they stabilized on a PET scan six months later. Further investigation of ibrutinib being used as primary treatment of EMZL of the ocular adnexa with multifocal involvement is needed.

4. Conclusion

While external-beam radiotherapy is the main method of treatment for localized conjunctival lymphoma, there is no universally accepted gold standard for disseminated disease. The usage of rituximab and doxycycline has shown varied responses. Ibrutinib is an additional option in treatment protocols, as its usage in our patient who had EMZL showed initial signs of regression of systemic disease. Further studies are needed to
demonstrate its true efficacy as a primary first-line treatment of ocular EMZL with multifocal disease.

5. Patient Consent

The patient consented to publication of the case in writing.

6. Conflict of Interest

No conflict of interest to report

Acknowledgements

References


