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Ultra-low-dose (boom-boom) radiotherapy for management of recurrent ocular post-transplant lymphoproliferative disorder

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ABSTRACT

Purpose: To report a case of recurrent iris post-transplant lymphoproliferative disorder (PTLD) treated with ultra-low-dose (boom-boom) radiotherapy (RT).

Observations: A 12-year-old Caucasian male with a history of bilateral, recurrent iris PTLD of the extranodal marginal zone lymphoma (MALT) type presented with persistent bilateral anterior chamber cellular infiltration, which was incompletely controlled on topical corticosteroids, and with elevated intraocular pressure (IOP) in the right eye secondary to steroid response. The patient was diagnosed with PTLD recurrence and was successfully treated with ultra-low-dose RT to both eyes in 2 fractions of 2 Gy. At 15 month follow-up the patient maintained complete disease control with normal IOP off all topical ophthalmic medications.

Conclusions and Importance: Ultra-low-dose RT for ocular PTLD of the MALT subtype represents a novel therapeutic approach that may provide a durable treatment response and could be considered as either primary or adjuvant therapy for this rare condition.

1. Introduction

Post-transplant lymphoproliferative disorders (PTLDs) are common among solid and hematopoietic transplant recipients and may affect both pediatric and adult patients.[1] Ocular PTLD is quite uncommon with a limited number of cases described in the literature. The optimal therapy for this disorder has not been established due to the rarity of this condition, but typically it has been treated with systemic rituximab alone or in combination with low-dose chemotherapy.[2–4] We previously reported the use of systemic rituximab combined with intraocular rituximab and methotrexate.[5] In this report, we provide follow-up of the same case treated with ultra-low dose (boom-boom) radiotherapy (RT) for recurrent PTLD.

1.1. Case presentation

A 12-year-old boy presented for persistent bilateral anterior chamber cellular infiltration in the setting of previously treated iris PTLD. Historical details of the case can be found in the prior report on this patient.[5] In brief, he underwent orthotopic heart transplantation and developed chronic low-grade Epstein-Barr virus (EBV) viremia due to EBV seromismatch. Five years later, he presented with bilateral granulomatous anterior chamber cellular reaction and multiple iris nodules. The patient underwent systemic screening with routine blood work (complete blood cell count, liver enzymes, and electrolytes), brain magnetic resonance imaging, whole-body positron emission tomography, and cerebrospinal fluid analysis, which revealed no systemic lymphoproliferative process. Iris biopsy revealed CD20-positive B-cells intermixed with plasma cells resembling extranodal marginal zone lymphoma (MALT). A diagnosis of iris PTLD with MALT-like features was made, with no associated systemic lymphoproliferative process. Following no improvement with topical 1% prednisolone acetate and cessation of mycophenolate mofetil immunosuppression, he was managed with concomitant systemic rituximab and a total of 5 bilateral intraocular rituximab injections (1 mg/0.1 mL) administered under general anesthesia, with initial disease control. A few months later, recurrence of anterior chamber cellular infiltration and keratic precipitates prompted a single bilateral intravitreal methotrexate (400 mcg in 0.1 mL) injection under general anesthesia. This led to sustained remisson with control of cellular infiltration for 4 months. Subsequent

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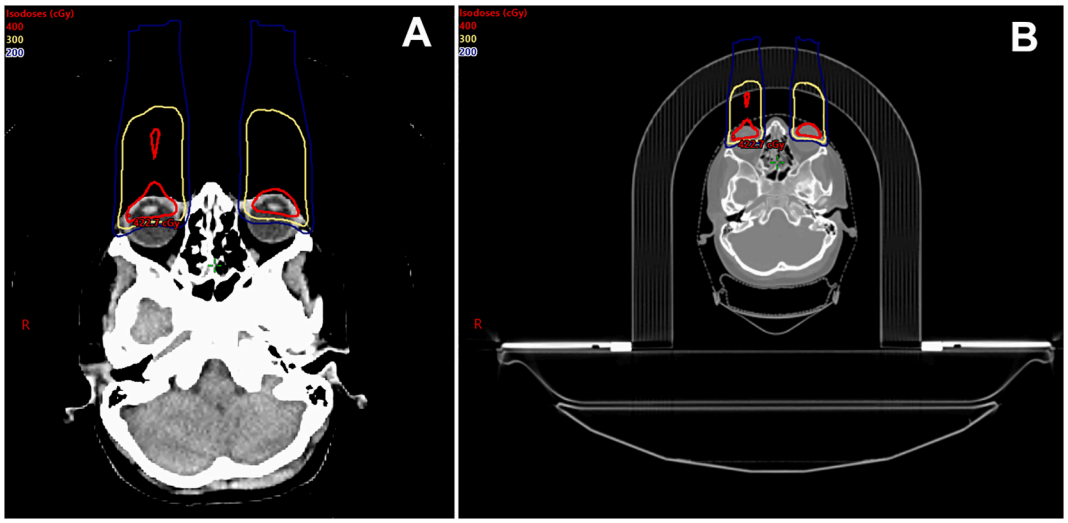

Fig. 1. Ultra–low-dose radiotherapy for bilateral iris PTLD was applied to both anterior chambers and iris with 4 Gy in 2 fractions using a single anterior proton beam accounting for 3 mm setup and treatment uncertainties (A). In order to minimize radiation scatter we delivered the proton beam through a bolus shell of 42 mm water-equivalent thickness placed 3 cm from the patient (B).

follow-up 4 months later showed no evidence of ocular toxicity from methotrexate. However, worsening recurrent cellular infiltration in the interim prompted initiation of topical 1% prednisolone acetate 3–4 times daily and disease progression 11 months after methotrexate injection prompted increase of topical corticosteroids to 6 times daily, with worsening cellular infiltration on several attempts to wean topical therapy. This prompted re-referral of the patient to our ocular oncology service.

The patient was examined 28 months after methotrexate injection with visual acuity of 20/30 and 20/25 and intraocular pressure (IOP) of 32 and 10 mmHg in the right and left eyes, respectively. Anterior chamber examination revealed 1+ and trace cellular infiltration in the right and left eyes, respectively. There were several small keratic precipitates in the right eye and none in the left eye. The 1% prednisolone acetate was tapered and a topical ocular hypotensive agent was initiated in the right eye, while maintaining 1% prednisolone acetate three times daily in the left eye. The patient was examined 1 month later, and IOP had improved to 11 mmHg in the right eye, although there was persistent anterior chamber infiltration and keratic precipitates. The decision was made to proceed with ultra-low-dose "boom boom" RT using a total of 4 Gray (Gy) delivered in 2 fractions of 2 Gy on consecutive days, with the intention to render a curative treatment and enable cessation of topical corticosteroids.

A single anterior proton beam was used to treat each anterior chamber and iris accounting for 3 mm setup and treatment uncertainties (Fig. 1A). To reduce radiation scatter to periocular adnexa, orbital rim bones, and midfacial soft tissues the proton beam was delivered through a bolus shell of 42 mm water-equivalent thickness placed 3 cm from the patient's surface (Fig. 1B). Each of the two treatments was performed under general anesthesia, and ocular alignment was verified by computed tomography-on-rails in the proton treatment room. One month following RT, the patient had neither anterior chamber cellular infiltration nor keratic precipitates. Visual acuity improved to 20/20 in the right eye and was stable at 20/25 in the left eye; IOP was 7 and 10 mmHg in the right and left eyes, respectively. With continued follow-up over several months, topical corticosteroid was gradually tapered and IOP lowering drops were discontinued.

Fifteen months after RT, the patient remained free of all topical ophthalmic medications. Visual acuity was 20/30 and 20/40 and IOP was 7 and 8 in the right and left eyes, respectively. There was no evidence of an anterior chamber cellular reaction, flare, keratic precipitates, or iris nodules in either eye. The remainder of the examination was unremarkable without evidence of lenticular or fundus changes, and updated brain and spine MRI showed no concerning features for lymphoma. Given stable clinical examination, the reduction in the measured visual acuity was thought to be due to fluctuation in patient effort due to changes in systemic antiepileptic medications.

2. Discussion

PTLD is the most common malignancy associated with both solid-organ and hematopoietic stem-cell transplantation.[1] For solid organ transplantation, the incidence density (adjusted for time under immunosuppression) of PTLD is highest for lung (5.7 per 1000 person-years) followed by liver (2.4), heart (2.2), and kidney (1.6) transplantation. EBV seromismatch (donor positive/recipient negative) is a major risk factor for pediatric PTLD as most transplant recipients are EBV seronegative.[1] For children receiving solid-organ transplant, the standardized incidence ratio (the rate of observed cases in the transplanted group with respect to age-specific rates from a reference population) of non-Hodgkin PTLD may exceed 200-fold.[6] Other risk factors for PTLD development include male gender and Caucasian race, all of which were present in our patient.[1]

Among all organs affected by PTLD, the eyes are very rarely affected with only a few dozen cases reported. Prior reports have described treatment of ocular PTLD with systemic therapy combining rituximab with low-dose chemotherapy.[2–4] Our patient was previously treated with systemic and intraocular rituximab followed by intraocular methotrexate for recurrence, with disease control for 5 months.[5] Unfortunately, recurrence of ocular PTLD occurred, prompting initiation of topical corticosteroids, which resulted in secondary ocular hypertension.

The goal of using fractionated ultra-low-dose RT (termed "boom boom" RT) was to induce remission and enable discontinuation of topical corticosteroids to prevent glaucoma and cataract development. We chose not to administer intravitreal rituximab or methotrexate again because of only temporary disease control with those agents previously, and to eliminate repeated general anesthesia to administer such therapy (6 prior visits under general anesthesia versus 2 with RT).

Ultra-low-dose RT has been successfully used for ocular adnexal lymphoma with excellent disease control (ranging from 96 to 100%) and minimal side effects.[7,8] These lymphomas are typically low-grade indolent non-Hodgkin lymphomas, similar to the type found in our patient, and are exquisitely radiosensitive. RT has also been effective for

treating choroidal lymphoma.[9] We are unaware of other reported cases of ocular PTLD that were successfully treated with ultra-low-dose RT. We did not detect any adverse effects at 15 month follow-up, and the RT was efficacious in inducing disease remission and allowing rapid taper of topical ophthalmic medications. This therapeutic approach may be especially useful in pediatric PTLD cases as it could provide durable disease control without the need for repeated general anesthesia. It is possible that local RT treatment could replace systemic therapy with rituximab and chemotherapies that have considerable risks in the setting of an immunosuppressed patient. In addition, given the very low total radiation dose delivered in this protocol, retreatment with RT for potential future recurrences is likely to be well-tolerated, as suggested by data from studies in extra-ocular lymphoma.[10] Our patient was not treatment naïve and thus we cannot be certain that RT would have been as efficacious if he hadn't received prior systemic and local treatment. However, given a quick and robust initial response to this treatment with sustained remission for many months, it is likely that this approach could be utilized as a primary treatment modality. Additional investigation of ultra-low-dose RT for ocular PTLD is warranted.

3. Conclusions and importance

Ocular PTLD is a rare disorder with a paucity of evidence to determine standard of care treatment. We presented a case of recurrent iris PTLD in a pediatric patient treated with ultra-low-dose (boom-boom) fractionated RT. Excellent disease control was maintained for at least 15 months, suggesting this may be a viable alternative treatment option and possibly a cure. Ultra-low-dose RT for ocular PTLD could be considered as an initial therapeutic approach or when other forms of therapy have shown suboptimal response.

Patient consent

The patient's parent consented to publication of the case in writing.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

All of the authors report no financial disclosures.

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