MANAGEMENT OF NON HODGKIN'S INTRAOCULAR LYMPHOMA WITH INTRAVITREAL METHOTREXATE

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SUMMARY

Intraocular non Hodgkin's lymphoma has traditionally been treated with radiotherapy or systemic chemotherapeutic agents. Unfortunately, radiotherapy rarely leads to a long term remission, and can only be safely administered once. Systemic chemotherapy has limited intraocular penetration. Intravitreal administered methotrexate is highly effective at inducing remission and is well tolerated.
A case report is presented of a recurrent intraocular lymphoma following radiotherapy and systemic chemotherapy which responded to a combination of intravitreal methotrexate and dexamethasone. A response was seen within three weeks of treatment initiation. Toxicity was limited to the progression of a pre-existing cataract. Review of the literature shows that intravitreal methotrexate is well tolerated, with few acute complications. However, with monotherapy, local recurrences have been observed.

RÉSUMÉ

Le lymphome intra-oculaire non Hodgkinien est traditionellement traité par radiothérapie ou par chimiothérapie intraveineuse. Malheureusement, la radiothérapie n'induit que rarement une rémission à long terme. Elle ne peut être administrée qu'une seule fois sans induire de complications sérieuses. La chimiothérapie intraveineuse a une pénétration intraoculaire variable. L'administration intravitréenne du méthotrexate induit rapidement une rémission et est bien tolérée.
Un cas clinique est présenté d'un lymphome intra-oculaire récidivant après radio- et chimiothérapie. Ce lymphome disparut en l' espace de 3 semaines suite à un traitement intravitréen au méthotrexate et à la dexaméthasone. Comme seul effet secondaire, une progression d'une cataracte détectée avant l'initiation du traitement fut notée.
Une revue de la litérature révèle que le méthotrexate intravitréen est bien toléré, avec peu de complications aiguës. Par contre des récidives ont été observées suite à une monothérapie.

KEY WORDS

Intraocular lymphoma, methotrexate, intravitreal injection

MOTS CLÉS

Lymphome intra-oculaire, méthotrexate, injection intravitréenne

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INTRODUCTION

Non Hodgkin's lymphoma of the eye is a rare disorder primarily found in individuals above 40 years of age (24). Although a relatively rare tumor, the frequency of primary CNS non Hodgkin's lymphoma (PCNSL) is increasing (11, 16). Typical clinical findings include vitreous cell clumping, cellular sheets, and subretinal cellular deposits (6), but a variety of clinical manifestations are possible from pseudo-viral retinitis to a vitteliform appearance.

Since the early 1980s the mainstay of therapy for ocular lymphoma has been radiation: commonly 40 to 65 Gray is given in multiple fractions over about one month (18). Response is dramatic, but recurrences either within the eye or the CNS occur in over 80% of individuals within the following 5 years. Radiation is also not without risk, as it can be associated with radiation retinopathy (1, 3), optic neuropathy (2, 5), dry eye syndrome and prolonged corneal epithelial defects (4, 19). For this reason, chemotherapeutic alternatives have been sought, particularly in cases of relapse following radiotherapy (7, 22).

Similarly primary CNS lymphomas were traditionally treated with radiation with 2 year progression free survivals in the order of 27% (15, 20). Combination with chemotherapy improved outcome in patients with PCNSL (median survival of 11 to 33 months), although patients aged older than 60 years may not have benefited as much as younger patients (10, 12, 14). However, the combination was associated with neurocognitive changes similar to Alzheimer, starting roughly 6 months after completing the treatment course (17). More recently, an attempt was made to treat PCNSL patients with chemotherapy alone, with a high complete response rate and a survival rate of 69% at 4.5 years (23). In this context, control of intraocular disease was only achieved in one patient by the addition of intravitreal chemotherapy (7, 9). This approach has subsequently been tried with success in a number of other patients. In this article, we present an instructive case as well as a review of the available literature.

CASE PRESENTATION

A 68 year old man presented with increasing floaters in his right eye. His pertinent medical history starts six years earlier when he presented with a large centroblastic polymorphous intermediate grade B cell lymphoma in his left epididymis. Spread to the para-aortic nodes was noted on lymphangiogram. On a combination of Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP) he had a complete remission. A year later, CNS recurrence was noted for which whole brain radiation was given (40 Gy) followed by 6x intrathecal Methotrexate. Complete remission was observed. Three years later, a recurrence in the right eye was noted on clinical exam, heralded by a complaint of floaters. No cytologic confirmation was sought. He was treated with 6x systemic Chlorambucil and Prednisone with resolution of the retinal and vitreous infiltrates. Six months later, a third recurrence located in the thalamus was noted and was treated with intravenous Methotrexate, Procarbazine, CCNU and Prednisone. Again resolution was observed. Eight months later, the patient presents to the eye clinic with complaints of decreased vision, again in his right eye.

On examination, his visual acuity was 0.6 (20/30). He was noted to have clumping of cells in the vitreous, and a subretinal infiltrate along the supero-temporal arcade (Figure 1). Fluorescein angiography revealed some RPE mottling in the area of the infiltrate as well as some vascular leakage in the overlying vessels. Cerebrospinal fluid analysis was normal. The patient underwent a diagnostic pars plana vitrectomy which revealed the presence of numerous B cells, some with scanty cytoplasm, but no monoclonality for kappa or lambda light chains. Intravitreal levels of IL-10 were 10 fold higher than IL-6, suggestive of an intraocular lymphoma. However, based on the available evidence, the cytopathologist was unable to confirm a diagnosis of lymphoma. As a definite diagnosis was required by the oncologist prior to the administration of more chemotherapy, a second vitrectomy was performed. In this second procedure, a retinotomy was made at the edge of the subretinal infiltrate, and subretinal material was aspirated. Morphologically, several cells presented a large nucleus with scanty

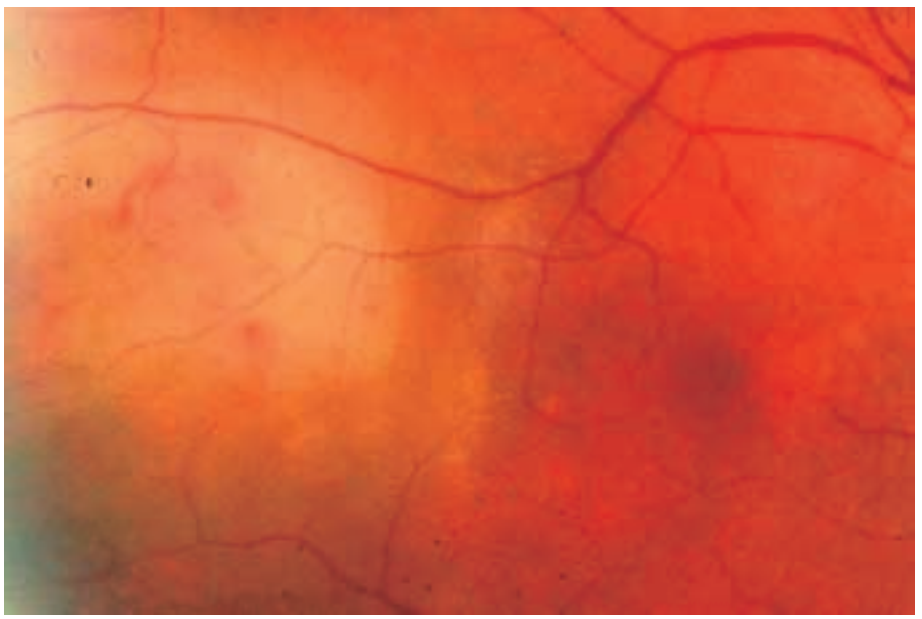
cytoplasm, compatible with a diagnosis of lymphoma. Confirmation was obtained by microdissection and PCR, demonstrating in large lymphoid cells an FR3A band, indicating an IgH gene rearrangement, characteristic of certain non Hodgkin's lymphomas.

Therapy was instituted with intravitreal Methotrexate (400μg) and Dexamethasone (400μg) given once a week until tumor regression was observed. By the third injection, the subretinal infiltrate had disappeared. The patient was placed on bi-weekly injections. Following the fourth injection, an ERG was performed, showing no changes from baseline measurements. The injections were well tolerated, the only complication being a further progression of a posterior subcapsular cataract noted at the time of surgery. Shortly after the fifth injection, his mental status deteriorated. Vision was 0,5 (20/40). He died of leptomeningeal recurrence of his lymphoma shortly thereafter, $6^1/_2$ years after the initial diagnosis of lymphoma, $2^1/_2$ years after the first presumed ocular involvement, and 5 months after the onset of the latest ocular symptoms.

DISCUSSION

As patients with lymphoma achieve longer survivals, the traditional approaches used to manage intraocular extensions have to be re-evaluated from the standpoint of efficacy and potential drawbacks. While effective in inducing regression, radiation does not prevent recurrences, and can only be safely administered once. Radiation also limits the effectiveness of subsequent chemotherapy. Systemically administered agents can penetrate the eye, but therapeutic levels are only maintained for a short period of time. To achieve sustained intraocular levels, disruption of the blood ocular barrier must be present or induced (9). Sustained intraocular levels can also be achieved by direct intraocular delivery. In a previous patient, we demonstrated that tumoricidal levels of Methotrexate could be maintained intraocularly for 5 days with an initial intravitreal concentration of 100μg/mL (7). This lead us to modify our protocol from bi-weekly to weekly intraocular injections of Methotrexate (8). As in the previous case, we decided to combine Meth-

Figure 1: Fundus photograph showing the subretinal infiltrate present along the supero-temporal arcade, smaller satellite foci are located closer to the fovea. Fluorescein angiography did not show any signs of leakage located outside of this particular area.



otrexate with a second tumoricidal agent as monotherapy, particularly in the setting of recurrent disease, is unlikely to lead to a prolonged remission. In this particular case, we decided to use Dexamethasone. This present combination lead to a rapid resolution of lymphoma infiltrates at a rate comparable with published series, and was not associated with any significant toxicity.

Including the present case report, treatment with intraocular Methotrexate has been reported in 18 patients (7, 13, 21, 25). All patients responded well to the intravitreal injections, with tumor regression occurring within 1 month of treatment initiation. In 16 of these patients, ocular treatment was limited to Methotrexate alone, usually given at a fixed dose of 400 μg, irrespective of the volume of the vitreous cavity. Treatment was initially given twice weekly, followed by weekly treatments for 1 month, then monthly for 9 months to one year. On twice weekly injections, filamentary keratitis was noted in a few patients. This resolved with addition of topical folinic acid (0.003% solution), or following a reduction in the frequency of intravitreal injections to once weekly. Other observed complications included transient conjunctivitis, mild vitreous hemorrhage, and cataract formation. No retinal detachment has so far been induced.

Ocular recurrences have been observed in three of 18 patients. These responded well to reinstitution of the intravitreal injections of Methotrexate. Despite ocular treatment, a number of patients have died from CNS disease. The longest reported remission has been achieved when intravitreal treatment was combined with aggressive systemic and intrathecal therapy (7). Limiting therapy to only the site of recurrence in the CNS or in the eye, is likely to miss microfoci of dissemination. The patient is then exposed to multiple courses of chemotherapy each addressing the site which was not previously included in the treatment protocol. With each new course, treatment options diminish, or the patient increases his risk of developing side effects of the treatment. At the time of his last ocular recurrence, the oncologist was urged to also give systemic chemotherapy. However, the patient was felt to be a poor candidate for further courses of systemic treatment. As noted, he died a few months later of a CNS recurrence.

While we do not yet have a curative protocol for intraocular lymphoma, intravitreal Methotrexate either alone or in combination with other chemotherapeutic agents appears to be well tolerated by the eye. It can be used to treat patients with newly diagnosed or recurrent disease previously treated with radiotherapy or intravitreal agents. On a limited series of patients, its short term safety profile is equal or better than radiotherapy. Further studies will demonstrate its long term safety and efficacy in ocular lymphoma.

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