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EDITORIAL

Intraocular lymphoma: A brief review

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A PubMed search for "intraocular lymphoma" turns up over 900 results. A random check of these publications shows that in almost every instance, the authors have used the term "intraocular lymphoma" synonymously with large cell vitreoretinal lymphoma (VRL). Although, this degree of attention to this rare and deadly disease is welcomed, using the term "intraocular lymphoma" as a substitute for VRL can be confusing and misleading. The reason is that there is more than 1 type of intraocular lymphoma. One type is the lymphoma that involves the retina and vitreous (VRL) and the other type is the lymphoma that involves the uvea (uveal lymphoma [UL]). Distinction between these two types of intraocular lymphoma is important as they are different in many aspects.

Extraocular Associations

Both VRL and UL can be associated with extraocular lymphoma and are divided into primary and secondary types, based on absence or presence of a history of past or concurrent systemic lymphoma. VRL is strongly associated with and is considered a subset of central nervous system (CNS) lymphoma. Between 56 and 90% of patients presenting with VRL will eventually develop CNS lymphoma and among patients initially presenting with CNS lymphoma, 15–25% will develop VRL at some point during their disease.[1] A smaller percentage of patients with VRL have a history of past or concurrent systemic large cell lymphoma and this subset is referred to as secondary VRL. In a recent publication, 19% of the patients with VRL were found to have had some type of systemic lymphoma in the past.[2]

UL, in contrast to VRL, has no association with CNS lymphoma but between 23% and 31% of patients with UL have a history of past or concurrent systemic lymphoma (secondary UL).[3,4] In nearly all cases, primary UL has an indolent behavior. Secondary UL, in contrast, usually originates from high-grade forms of systemic lymphoma including diffuse large B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, multiple myeloma, Waldenstrom's macroglobulinemia, and plasmablastic lymphoma and has a more aggressive behavior.[3] Whereas most choroidal lymphomas (69% in one study)[3] are of primary type (and therefore low grade in behavior), majority of lymphomas that involve the iris (54% in one study) are of the secondary type and as such are usually composed of high-grade lymphoma types.[5]

Histologic Subtype

Histologically, both primary and secondary VRLs are high-grade diffuse large B-cell non-Hodgkin lymphomas.[1] Rare cases of VRL of T-cell origin have been reported.[6]

Primary UL, in contrast, is a low-grade, B-cell non-Hodgkin lymphoma of the extranodal marginal zone lymphoma type (also referred to as mucosa-associated lymphoid tissue lymphoma ([MALT lymphoma]).[7] As mentioned above, secondary UL originates from more aggressive and high-grade forms of systemic lymphoma.[3]

Clinical Manifestations

VRL and UL have distinct and different clinical presentations. VRL is bilateral in most cases and in a study on 95 patients, 77% developed bilateral involvement at some point during their disease.[8] VRL usually presents with vitreous cells and yellowish subretinal pigment epithelial (sub-RPE) infiltrates with well-defined margins. It is not associated with subretinal fluid and does not tend to extend through the sclera outside the globe. OCT helps in making the diagnosis of VRL by showing the typical variably sized neoplastic pigment epithelial detachments that were noted on OCT in 64% of eyes in one study.[9] Other less common OCT features of VRL include vitreous opacities, pre-retinal deposits, intraretinal deposits, subretinal deposits, and retinal pigment epithelial abnormalities.[9]

UL presents as diffuse thickening of the uveal tract with no vitreous cells or sub-RPE infiltrates. Early in the course of the disease, the uveal infiltrates are seen as variably sized multifocal creamy-yellow choroidal infiltrates but with disease progression, the infiltrates coalesce and the initial patchy involvement becomes more confluent and homogenous in appearance.[3,4] It should be emphasized that primary UL is very slow growing and it may take several years before noticeable changes are seen on examination. UL is associated with shallow serous retinal

detachment in about half of the cases and tends to extend outside the globe through the sclera.[3,4] Anterior areas of extraocular extension are visible as salmon-colored infiltrates under the conjunctiva. B-scan ultrasound and ultrasound biomicroscopy are both valuable in demonstrating diffuse thickening of the choroid or ciliary body with characteristic low acoustic hollowness in eyes with more advanced UL. B-scan is also useful in showing areas of extraocular extension usually in the macular area or around the optic disc.[3] Enhanced-depth imaging OCT is extremely helpful in diagnosis of early choroidal lymphoma by showing thickening of the choroid.[10] The thickened choroid has a smooth surface early in the course of the disease but develops a rippled or undulating surface with increasing tumor thickness.[10]

Compared to primary choroidal lymphoma, secondary choroidal lymphoma grows at a faster rate, presents with worse visual acuity, is more likely to involve both eyes, has higher rate of iris or ciliary body involvement, and is more likely to be associated with vitreous cellular reaction.[3]

As mentioned above, most iris lymphoma are of the secondary type with aggressive behavior.[5] The most common signs of iris lymphoma include iris thickening or mass, anterior chamber cells, keratic precipitates, congested conjunctival or episcleral blood vessels, hyphema, pseudohypopyon, elevated intraocular pressure, and anterior extraocular extension of the lymphoma under the conjunctiva.[5] Although rare, iris lymphoma should be considered in the differential diagnosis of steroid-resistant anterior uveitis in middle aged of elderly patients.

Treatment

Most cases of VRL, whether unilateral or bilateral, are treated with intravitreal injections. The most commonly used drug is methotrexate but other medications including melphalan and rituximab have also been used.[11-13] At present, intravitreal injections have no role in treatment of UL.

Both VRL and UL are sensitive to systemic chemotherapy but this treatment modality is generally reserved for cases with an evidence of active systemic or CNS involvement. To reduce the risk of future CNS lymphoma, some ocular oncologists have recommended systemic chemotherapy in patients with bilateral,[14] or even unilateral, primary VR lymphoma although the effectiveness of this approach has not been proven.[15] Systemic rituximab has been used successfully for the treatment of secondary UL.[4] Aronow *et al*. also recommend systemic rituximab for the treatment of bilateral, multifocal ocular only UL.[4]

Radiotherapy is a well-recognized and effective treatment modality for both VRL and UL. The recommended dose for VRL is 3000–4500 cGy in 18–25 fractions.[16] The standard radiation dose for UL has been somewhat lower in the range of 1200–3600 cGy.[17] Recently, some ocular oncologists have reported good results using ultra-low-dose radiation (4 Gy delivered in two fractions) for the treatment of ocular adnexal and choroidal lymphoma but ultra-low-dose radiation is not recommended for the treatment of VR lymphoma.[18]

Treatment Outcome

Because of its association with CNS lymphoma, VR lymphoma – even when aggressively treated with systemic chemotherapy or whole brain radiation – has a poor life prognosis. In a recent study, the median survival of patients with CNS lymphoma was 31 months.[19] Visual outcome of VRL mainly depends on extent and location of retinal lymphoma. In a recent study, final VA was 20/40 or better in 49% and worse than 20/200 in 19%. Visual acuity outcome was found to be significantly worse in eyes with sub-RPE infiltrates compared to those the presented with isolated vitreous cellular infiltration.[20]

Primary UL, in contrast to VRL, is low grade and has an excellent life prognosis. Due to its association with higher grade lymphoma subtypes, secondary UL has a less favorable life prognosis. In one study, none of the 33 patients with primary choroidal lymphoma had died during a follow-up period of 50 months, whereas of the 18 patients with secondary lymphoma, 6 (33%) had died from systemic lymphoma during a mean follow-up period of 14 months.[3] In the same study, final visual acuity was more than 20/50 in 47% and less than or equal to 20/200 in 25% of the eyes.[3]

Recurrence of VRL has been reported after systemic chemotherapy or localized forms of treatment such as radiation or intravitreal injections.[21-24] In one study, of the 10 eyes treated with intravitreal methotrexate, four eyes relapsed after a mean interval of about 6 months.[24] In contrast, recurrence of UL after initially successful treatment is extremely rare. In a study on 25 eyes with choroidal lymphoma treated with external beam radiation (mean dose of 2867 cGy), recurrent lymphoma developed in only 1 eye (4%).[17]

Final Word

Intraocular lymphoma encompasses two different types of lymphoma: Vitreoretinal and uveal. These two types of lymphoma are distinct entities with different histology, extraocular associations, clinical presentation, treatment, and prognosis. To avoid confusion, it is, therefore, important for authors to specify the anatomic site of involvement by lymphoma in the eye (vitreoretinal or uveal) and avoid using the term intraocular lymphoma as equivalent to VRL.

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