Uveal metastatic disease: Current and new treatment options (Review)

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Abstract. Choroidal metastasis represents the most common form of intraocular malignancies. It may occur in up to 10% of patients with systemic metastasis with almost half of the patients developing central nervous system disease. The most common primary sites of ocular metastasis are breast cancer in women and lung cancer in men. In most cases, these lesions tend to be asymptomatic and are not evaluated by an ophthalmologist. The diagnosis is generally made by the history of present or prior malignancies and an ophthalmological examination with slit-lamp biomicroscopy and indirect ophthalmoscopy. As with other malignancies, management may vary with each patient. Small tumors, that do not compromise the vision and that have responded previously to systemic treatment, may be closely observed. For larger lesions and for symptomatic ones, external beam radiation offers an excellent alternative to save the eye and stabilize vision. Bevacizumab (Avastin), a potent monoclonal antibody that has also been employed for the treatment of ocular vaso-proliferative diseases, has been used in the treatment of choroidal metastasis and has shown promising results.

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1. Introduction

Technological ophthalmic advances have led to an increase in the reported frequency of uveal metastasis (1). Albert et al found that 2% of 213 patients with systemic cancer had uveal metastasis (2). At present, choroidal metastasis is accepted to be the most common intraocular malignancy (1,3). However, in an ocular oncology practice setting, it is not encountered as frequently as primary uveal melanoma, possibly due to the fact that many of these patients with metastatic systemic disease have asymptomatic ocular lesions and thus are not brought to the attention of the ophthalmologist (2,4,5-7).

Given its very rich blood supply, the uvea is one of the most favored sites in the body for the seeding of tumor cells and the development of metastasis (2,8). In up to 90% of uveal metastasis cases, the posterior aspect of the uvea (choroid) is affected, with the remaining 10% arising from the iris and/or ciliary body (9). Metastasis to other ocular sites such as the retina, optic nerve and vitreous, although described, remains uncommon (10,11).

The most common types of cancer that metastasize to the eye are carcinomas, however, sarcomas and melanomas may also metastasize to the eye (12,13). The prevalence of uveal metastasis from all forms of carcinomas varies from 2.3 to 9.2% in the published series with breast cancer being the most common primary site followed by lung cancer (2,5,9). Other sites of primary malignancies are the kidney, thyroid, prostate, pancreas, testis and other organs (14-19).

2. Patient characteristics

Although the majority of patients have a known history of carcinoma at the time of the diagnosis of uveal disease (9,20,21), Shields et al reported no known history of cancer in 34% of their patients at the time of diagnosis of the uveal metastasis, with up to 10% of the patients remaining with an occult primary cancer (9). Upon diagnosis of uveal metastasis, more than half of the patients had associated systemic metastasis with the lungs being the most frequent site with concomitant involvement, followed by the bone, liver and central nervous system (20,22). Mewis and Young found that 30 out of their 67 patients with choroidal metastasis also developed central nervous system disease (23). Moreover, Wiegel et al described the presence of lung and brain metastasis as the

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only significant risk factors for the development of choroidal
disease in patients with breast carcinomas with an incidence
of 11% in the presence of these factors as compared to 5% in
their absence (5). Kreusel et al found that metastasis in more
than one organ is a significant risk factor for choroidal metas-
tasis in patients with lung cancer (7). The prognosis following
diagnosis of uveal metastasis is poor, with a median survival
of 6-9 months (7,22-24).

3. Symptoms and clinical characteristics

Symptoms of ocular metastasis may vary greatly depending
upon the location and characteristics of the lesion. Although
most of the patients remain asymptomatic (5-7,25), whenever
symptoms appear the most common complaint is blurred
vision (2,5,7,22,26). In cases of choroidal metastasis, the
blurring may be secondary to macular involvement or the
presence of subretinal fluid that may compromise the fovea
(9). Moreover, in cases of iris and/or ciliary body lesions, the
decreased visual acuity is usually secondary to seeding to the
anterior chamber or the development of secondary cataracts
as these lesions tend to produce inflammatory signs more
often than choroidal lesions (27). Other symptoms include
visual field scotomas, floaters, metamorphopsia and photopsia
(22,26). In cases of anterior segment metastasis, a visible mass
can be noted and the patient may notice a red eye (27).

As mentioned above, most of the uveal lesions involve
the choroid, followed by the iris and the ciliary body (9,20).
Choroidal lesions are more frequently located in the area
between the macula and the equator (9). They usually appear
as creamy or yellow choroidal lesions that may be associated
with subretinal fluid (Fig. 1). Choroidal lesions secondary to
bronchial carcinoid tumors, renal cell carcinoma and thyroid
cancer may often present with an orange color (9). Some lesions
may show the so-called ‘leopard skin’ appearance due to the
brown pigmentation on their surface secondary to lipofuscin-
containing macrophages. In up to 1/3 of the cases, the affected
eye may present with more than one focus of metastasis and up
to 50% of patients may have bilateral involvement (5,20,23,26)
(Fig. 2).

4. Diagnosis

Diagnosis is usually made by the clinical findings noted during
ophthalmic examination with slit-lamp biomicroscopy and
indirect ophthalmoscopy, along with the history of a systemic
malignancy. In cases of doubt, especially in the absence of the
diagnosis of a primary malignant site, the differential diag-
nosis should include other lesions such as granulomas from
tuberculosis or sarcoidosis, amelanotic uveal melanomas and
lymphomas (28-31). Ancillary testing with retinal fluorescein
angiography may show hyperfluorescence of the mass in the
late venous phase. Ocular ultrasound usually reveals a medium
to high internal reflectivity. This test may aid in the diagnosis
and even in management and follow-up of the response of these
lesions to treatment (Fig. 3). A systemic evaluation by a multidisciplinary team is pivotal in the diagnosis and management of these patients, particularly in those cases with an occult primary site and the presence of rapid lesion growth which is characteristic of metastatic disease (9). In defined circumstances, a fine-needle biopsy can be performed in an effort to aid in the diagnosis and to establish the primary malignant site. However, in some cases, the uveal lesion is poorly differentiated making it challenging to determine the primary site and thus requiring immunohistochemical studies (24).

5. Treatment

Treatment of patients with choroidal metastasis is challenging and requires a multidisciplinary team that involves an ophthalmologist, oncologist, a radiation oncologist and other members of the health-care group. More than half of the patients have another metastatic focus at the time the ocular lesion is found (9). Restaging of the disease should be carried out at the moment of a newly diagnosed ocular lesion and early treatment should be initiated in an effort to avoid significant vision loss. Treatment options include radiation, laser, chemotherapy, anti-vascular endothelial growth factor (VEGF) and enucleation of the eye.

Radiation. The treatment of choice remains external beam radiation (22,32). As other forms of radiation, it induces damage of the DNA of the rapidly growing tumor cells. Radiation has also been used for the treatment of other intraocular malignancies such as uveal melanomas, retinoblastomas and lymphomas (31,33,34). Radiation dose varies greatly but it is usually lower than the dose required for uveal melanomas thus decreasing the complications of radiation such as radiation retinopathy (4,20,35). External beam radiotherapy usually requires 3-4 weeks of daily or inter-daily radiation. This technique has proven to be effective in reducing the lesion size and improving or stabilizing visual acuity (21,22,36) (Fig. 4).

Other forms of radiation employed include proton beam therapy that is usually given as fractionated or as a single dose. This technique produces significant tumor regression and thus stabilizes the vision (37). Adversely, this modality is not currently available in several countries and centers as it carries the need for expensive equipment. Plaque brachytherapy that has also been used in the treatment of uveal melanoma, consists of the application of an episcleral plaque that conforms to the curvature of the sclera and contains the radioactive material along its inner surface (38-40). Brachytherapy requires two surgical procedures - one for the insertion of the plaque and a second one for its removal. The advantage of brachytherapy over other forms of radiation includes a more precise and targeted radiation delivery to the tumor site thus decreasing the development of radiation complications (35-41) (Fig. 5).

Laser treatment. Several types of lasers have been shown to provide beneficial results in the treatment of uveal metastasis. One of these techniques is transpupillary thermotherapy (TTT) which consists of delivering heat to the choroid and the retinal pigment epithelium through the pupil using a modified diode laser that produces tumor necrosis (42). Laser photocoagulation with the use of argon or krypton is another modality that was shown to be effective with no ocular complications in 10 patients after a follow-up of 4-30 months (43). Photodynamic therapy (PDT) is a 2-step process in which an intravenous-infusion of verteporfin is followed (typically...
15 min later) by irradiance with a 689-nm laser for approximately 83 sec. Verteporfin binds to low density lipoproteins in the plasma that are then preferentially bound by choroidal neovascular membranes. Application of laser energy results in the formation of toxic oxygen species that induce thrombosis of choroidal neovessels, which have shown efficacy in the treatment of carcinoid tumors (44).

**Chemotherapy.** Chemotherapy depends upon the type of primary cancer. Several classes of cytotoxic agents have been employed with promising results. The mechanism of action and associated toxicities depend on the type of agent used. Most of the available data on the use of chemotherapeutic agents for the treatment of uveal metastases are limited to case reports (20,21,23,45). The use of newer therapeutic agents, in particular, has caused tumor size reduction and even complete regression in some cases (46,47).

**Anti-vascular endothelial growth factor-targeted treatment.** Bevacizumab (Avastin, Genentech) is a potent monoclonal antibody that blocks all VEGF-A isoforms. It was the first anti-VEGF therapy approved by the FDA for the treatment of colorectal, breast and lung cancer (48). Based on the fact that bevacizumab has been shown to benefit patients with different type of cancers, several trials were initiated to test its efficacy in treating metastatic disease including choroidal metastasis. Kim et al showed resolution of a choroidal metastatic lesion from a non-small cell cancer and improvement of visual acuity after intravitreal bevacizumab (2.5 mg) injections in combination with oral erlotinib (49). Amelem et al reported the case of a 57-year-old woman with stage IV non-estrogen-sensitive breast carcinoma with bone and lung metastasis that received treatment with oxaliplatin and vinorelbine who presented with a solitary and elevated choroidal metastatic lesion in the right eye. She was offered treatment with an intravitreal injection of 4 mg of bevacizumab. Her visual acuity improved and the choroidal lesion decreased in size 3 weeks after the injection (50). Kuo et al reported the case of a 65-year-old woman with colorectal adenocarcinoma that underwent 6 months of chemotherapy with fluorouracil, leucovorin calcium and oxaliplatin. After treatment, the carcinoembryonic antigen levels dropped to within normal range and the treatment was suspended. Two years later, the patient developed decreased visual acuity in the left eye. Upon examination, a large and elevated, orange choroidal lesion was noted that encouraged giving treatment with oxaliplatin and vinorelbine who presented with a solitary and elevated choroidal metastatic lesion in the right eye. She was offered treatment with an intravitreal injection of 4 mg of bevacizumab. Her visual acuity improved and the choroidal lesion decreased in size 3 weeks after the injection (50). Kuo et al reported the case of a 65-year-old woman with colorectal adenocarcinoma that underwent 6 months of chemotherapy with fluorouracil, leucovorin calcium and oxaliplatin. After treatment, the carcinoembryonic antigen levels dropped to within normal range and the treatment was suspended. Two years later, the patient developed decreased visual acuity in the left eye. Upon examination, a large and elevated, orange choroidal metastatic lesion was noted that encouraged giving an intravitreal injection of bevacizumab (1.25 mg). Visual acuity improvement was noted 5 days after the injection (51). Lin et al found similar results after offering an intravitreal injection of 4 mg of bevacizumab to a 43-year-old man with a colon adenocarcinoma who developed bone and choroidal metastasis and was on treatment with oxaliplatin and fluorouracil (52). Yao et al recently presented analogous results in a 50-year-old woman with metastasis to the lungs, mediastinal lymph nodes and choroid, treated with paclitaxel, gemcitabine and adjuvant 2.5 mg of intravitreal bevacizumab (53).

Although the use of systemic and intravitreal bevacizumab have shown promising results in case reports, one should take into account that those patients were also treated with systemic chemotherapeutic agents, that have been shown to produce reduction in choroidal metastatic lesions without the combination with anti-VEGF agents (54). This raises the need to carry out more extensive trials that would better assess the benefit of this intervention.

**6. Conclusions**

Uveal metastasis is the most common malignancy of the eye (5,9,23). Early detection and treatment may help avoid significant visual loss and in some cases may even aid in making the primary diagnosis. Patients with a known history of a malignancy, particularly breast or lung, who develop visual symptoms, should have a complete ophthalmic examination in search of any ocular involvement. Moreover, a multidisciplinary approach is required in those cases with a newly diagnosed uveal metastasis, as there is a significant association with the presence of central nervous system metastasis and elsewhere in the body (9).

To date, the treatment of choice for these lesions remains external beam radiotherapy that consistently produces tumor reduction and preserves vision (22,32). Chemotherapeutic agents may play an important role in the future as they have been shown to be effective in the control of uveal metastasis (20,21,23,45). The use of anti-VEGF therapy has become almost routine in the ophthalmology practice for many types of ocular diseases such as age-related macular degeneration, proliferative diabetic retinopathy and other ischemic diseases (55-58). Its role in the treatment of uveal metastasis remains to be determined as further reports become available in the literature. However, it may eventually help avoid the need for other more damaging and expensive treatments.

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