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Ocular Oncology: Intraocular Metastatic Tumours

By Sohel Somani, MD

The most common form of intraocular malignancy encountered by an ophthalmologist is metastatic disease, with the most common sources being breast and lung cancer. Most metastatic disease involves the posterior choroid, and can be multifocal and/or bilateral. A previous history of primary carcinoma, typical clinical findings, and supportive ancillary tests are essential in differentiating metastatic disease from primary amelanotic melanoma. This is an important distinction to make since the management and prognosis differ between these two entities. Because up to 25% of patients have no history of primary carcinoma, ophthalmologists must still consider the diagnosis in suspected cases and communicate with medical oncologists for a complete systemic work-up. Although intraocular metastatic disease may carry a poor prognosis for survival, radiation treatment of vision-threatening lesions may help ameliorate vision and improve quality of life for patients. This issue of *Ophthalmology Rounds* discusses the diagnosis and treatment of intraocular metastatic disease.

Incidence

Intraocular metastasis is the most common form of intraocular malignancy. It is estimated to occur in 5% to 30% of patients with systemic malignancy.[1] These lesions are not encountered frequently in clinical practice, either because the disease is asymptomatic or the preterminal nature of systemic malignancy precludes ophthalmologic referral. Furthermore, it is approximately 10 times more common than primary uveal melanoma.[1] However, in up to 25% of patients, there may be no history of primary systemic malignancy at the time they present with intraocular metastases.[2] This emphasizes the need for clinicians to be alert to the possibility of systemic malignancy in order to facilitate a prompt diagnostic work-up. Despite an extensive systemic evaluation, in 17% of cases of intraocular metastases, a primary site is never found.[3] Intraocular metastasis occurs primarily in the adult population and is rare in children.

Pathogenesis

Carcinomas account for > 82% of tumours that metastasize to the adult globe.[3] Occasionally, cutaneous melanoma (3%) and carcinoid tumours (1%) can spread to the globe; however, it is rare for sarcomas to metastasize to the globe.[3] While lymphoma or leukemia can have ocular manifestations, they are not included in this discussion.

Embolic tumour cells reach the globe via hematogenous spread from the ophthalmic and ciliary arteries. The strong predilection for posterior choroidal involvement compared to anterior uveal involvement is, possibly, a reflection of the greater presence of short posterior ciliary arteries.

Sources of primary systemic malignancy

Breast cancer is the most common malignancy to metastasize to the uvea, accounting for up to 50% of all intraocular metastatic tumours.[4] Lung cancer (21%) is the second most common source of metastatic disease, followed by gastrointestinal tract

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(4%), kidney, (2%) and skin (2%) tumours.[3] Carcinoid tumour, usually of bronchial origin, has been reported to metastasize in up to 2% of patients.[5] Thyroid, bladder, uterine, prostate, and salivary gland carcinomas do not commonly metastasize to the uvea.[1]

A recent review of 264 patients with uveal metastasis from breast cancer,[4] revealed that the eye was the primary presenting site in up to 14% of these patients, while the literature reports a range of 9% to 37% with eventual ocular involvement.[1,3] The presence of tumour dissemination to more than one organ and/or the presence of lung/brain metastases were identified as risk factors for the development of globe involvement.[4] Furthermore, there is a strong association between the development of brain metastases and uveal involvement, suggesting that all patients should undergo neuro-imaging soon after ocular metastases are detected.

Sites of intraocular metastasis

In 90% of patients, the most common site of ocular involvement is the choroid, followed by the iris (8%) and ciliary body (2%).[1] In a review by Shields et al, the majority of choroidal involvement occurred posterior to the equator (92%), with macular involvement in 12% of cases.[3] One potential reason for the low incidence of anterior uveal involvement may be due to the differential organization of anterior segment circulation compared to the more extensive posterior segment circulation. The retina, optic disc, and vitreous are extremely infrequent sites of intraocular metastasis.[6] Although not included in this discussion, metastatic disease to the orbit occurs second in frequency to choroidal metastasis.

Clinical assessment

History

The symptoms of the presenting patient depend in large part on the site of intraocular metastasis. Symptoms of posterior uveal involvement include decreased vision, decreased visual field, photopsia, and/or floaters. Pain may occur if the tumour invades the ciliary nerves or if secondary glaucoma develops. Symptoms of anterior uveal involvement include decreased vision, visible mass, red eye, and photophobia. Pain can also be a presenting feature due to secondary iritis or secondary glaucoma. Although a complete medical history is important in suspected cases of ocular metastasis, up to 25% of patients may not have a diagnosed primary malignancy at the time of ocular presentation.[2] In some cases, ocular metastases remain asymptomatic and are discovered only on routine examination.

Clinical examination

The ophthalmoscopic examination in patients with choroidal metastasis often yields typical cream-coloured choroidal lesions that are either flat/placoid in appearance or dome shaped (Figure 1). Other important colour characteristics include metastatic cutaneous melanoma that presents as a pigmented tumour and carcinoid tumour. Although the colour is not visible in Figure 2, a carcinoid tumour has a typical orange hue. Large choroidal lesions characteristically produce a secondary exudative retinal detachment, which may be confused with a primary rhegmatogenous retinal detachment. Often, overlying retinal pigment epithelial changes, clumping, or a leopard-skin appearance may be present. In addition, a complete ocular examination should be carried out to rule out multifocal or bilateral findings that may occur in up to 25% of cases.[3] This observation is

Figure 1: Clinical photographs of a choroidal metastasis

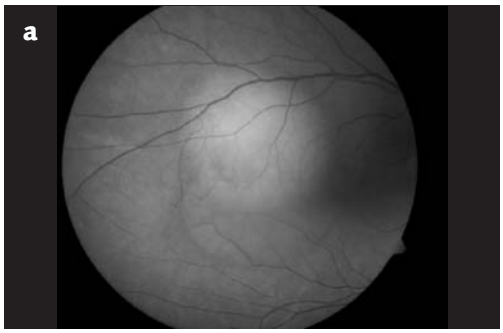


Figure 1a: Clinical photograph of the right eye demonstrating a choroidal metastasis from breast cancer.

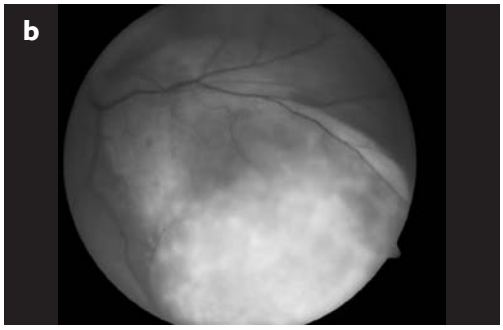


Figure 1b: Clinical photograph of the left eye demonstrating a choroidal metastasis from lung cancer and secondary retinal detachment.

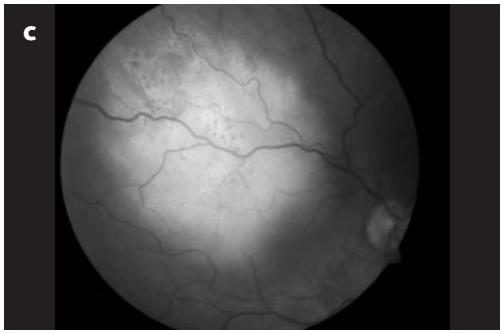
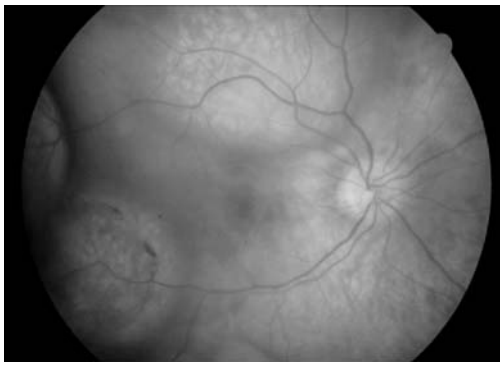


Figure 1c: Clinical photograph of the right eye demonstrating a choroidal metastasis from esophageal carcinoma.

Figure 2: Clinical photograph of the right eye demonstrating a multifocal carcinoid tumour



important since multifocal or bilateral disease does not occur with primary amelanotic melanoma.

A patient with iris involvement most commonly presents with a unilateral metastatic nodule, but bilateral involvement is possible (Figure 3). The metastatic iris nodule is typically yellow-white, fleshy, solitary, and inferiorly located.[3] The liberation of friable cells often leads to a secondary iritis, episcleral injection, and occasionally, pseudohypopyon. Secondary glaucoma is a very common presentation in up to 40% of cases.[7] A complete ocular examination is warranted because up to one-third of cases also have an associated ipsilateral choroidal metastases.[7] Only 10% of these metastatic iris deposits demonstrate prominent blood vessels within the tumour. This is contrary to amelanotic iris melanomas in which blood vessels are more visible.[7]

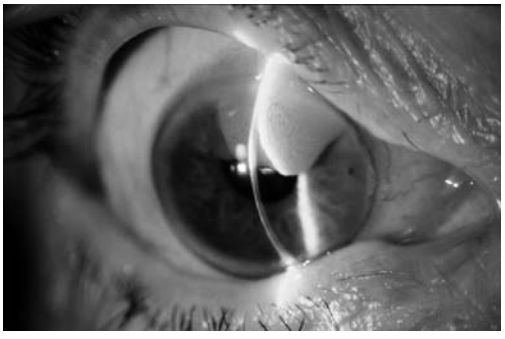
Patients with ciliary body metastasis may present with a large sentinel vessel on the overlying sclera, secondary iridocyclitis, refractive error, or visible mass, typically located inferiorly.

Ancillary tests

Various ancillary tests can aid in the clinical diagnosis of choroidal metastasis. Fluorescein angiography of these lesions typically demonstrates early blocked hypofluorescence, followed by irregular staining of the lesion in mid-arteriovenous phase, followed by late mottled hyperfluorescence as the staining pattern becomes more confluent (Figure 4). Occasionally, the late mottled hyperfluorescence of a metastatic lesion resembles a honeycomb pattern. In contrast, the fluorescein pattern of an amelanotic melanoma often demonstrates mottled hyperfluorescence at an earlier stage. Nevertheless, fluorescein angiography is not always a definitive test in differentiating these two entities.

A-scan ultrasonography typically shows moderate-to-high internal reflectivity with a high initial spike (Figure 5a). B-scan ultrasonography typically demonstrates a flat/placoid or dome-shaped lesion that is acoustically solid with no evidence of choroidal excavation (Figure 5b). Another important distinguishing feature is that these lesions are not usually mushroom-shaped. A mushroom shape typically occurs with primary uveal melanoma after it breaks through Bruch's membrane. Although rare, there have been reported cases of mushroom-shaped choroidal metastasis simulating a choroidal melanoma.[8]

Figure 3: Clinical photograph of an iris metastasis that is located in the superior quadrant of the right iris



(Courtesy of Hugh McGowan)

Figure 4: Choroidal metastasis

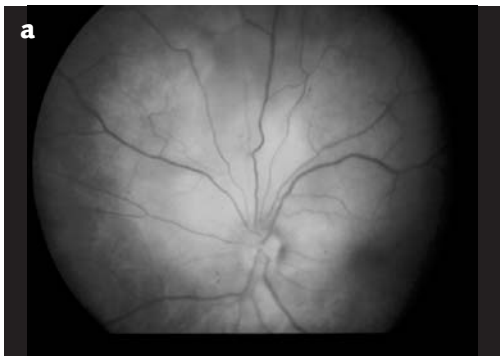


Figure 4a: Clinical photograph of a juxtapapillary choroidal metastasis from breast cancer.

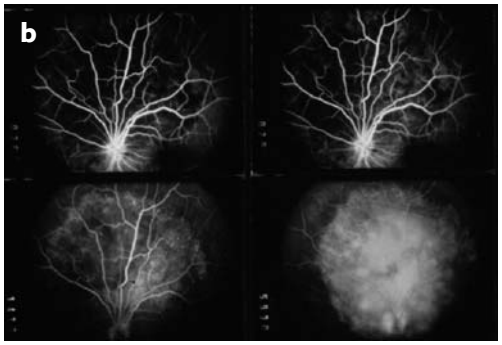


Figure 4b: The 4-panel fluorescein angiogram demonstrates early hypofluorescence with late mottled hyperfluorescence typical of a choroidal metastasis.

(Courtesy of Hugh McGowan)

Figure 5: Metastatic choroidal lesion

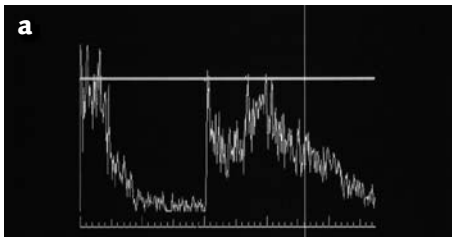


Figure 5a: A-scan of a choroidal lesion demonstrating medium internal reflectivity

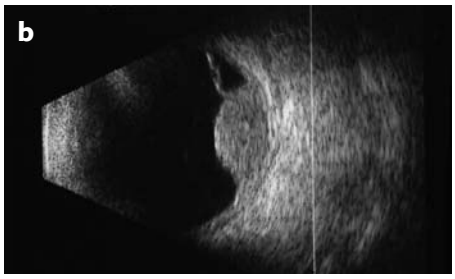


Figure 5b: Corresponding B-scan of a metastatic choroidal lesion demonstrating an acoustically solid dome-shaped lesion with adjacent serous retinal detachment

Although computed tomography (CT) and magnetic resonance imaging (MRI) can demonstrate uveal metastasis, their role in narrowing the differential diagnosis is limited. They play a larger role in the systemic evaluation of primary malignancy and determination of metastatic spread to other locations.

Although not commonly performed, the technique of intraocular biopsy has been described.[9] This technique may be important when the clinical features and ancillary tests described above fail to conclusively differentiate a lesion as metastatic as opposed to being a primary melanoma, lymphoma. or inflammatory granuloma. Fine needle aspiration can be useful when a systemic work-up fails to diagnose a primary tumour and a tissue diagnosis is required to plan appropriate treatment.

Referral to a medical and radiation oncologist is also prudent to re-stage the patient and plan appropriate treatment.

Differential diagnosis

The differential diagnosis of a cream-coloured choroidal metastasis includes primary amelanotic melanoma, choroidal hemangioma, exudative disciform scar, and choroidal granuloma.[1] In some atypical cases, it may be difficult to differentiate between primary uveal melanoma and uveal metastasis (Figure 6). Understandably, it is important to make this distinction because

Figure 6: Clinical photographs and ancillary imaging of a primary amelanotic melanoma

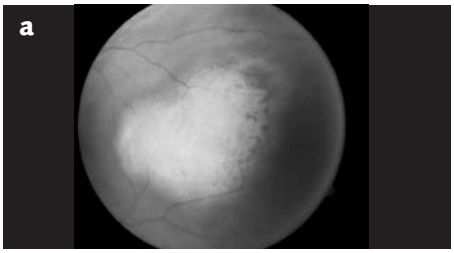


Figure 6a: Clinical photograph of the left eye demonstrating an amelanotic melanoma

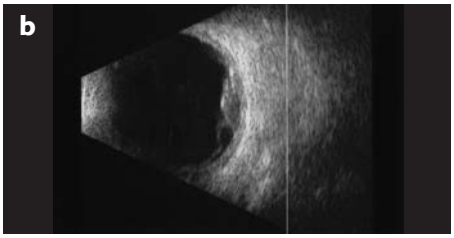


Figure 6b: Corresponding B-scan ultrasound demonstrating a dome-shaped lesion with adjacent serous retinal detachment

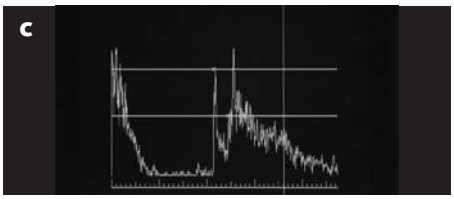


Figure 6c: Corresponding A-scan ultrasound demonstrating low-internal reflectivity

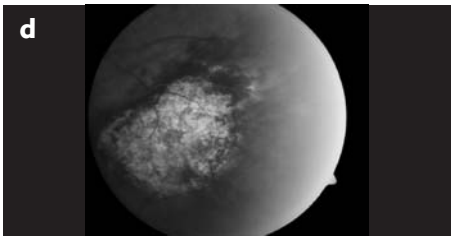


Figure 6d: Corresponding early phase fluorescein angiogram demonstrating early mottled hyperfluorescence.

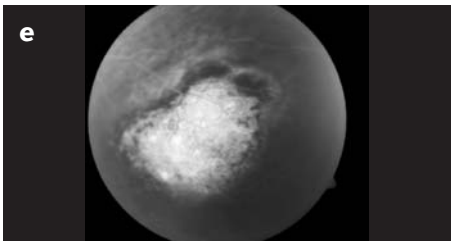


Figure 6e: Late phase fluorescein angiogram demonstrating late staining hyperfluorescence centrally with blocked hypofluorescence at the border.

Table 1: Features for differential diagnosis

Characteristics	Primary uveal melanoma	Uveal metastasis
Colour	May be amelanotic	Creamy-yellow
Shape	Mushroom-shaped	Flat or dome-shaped
Associated retinal detachment (RD)	Usually small RD	Usually large RD
Growth pattern	Slow growth	Rapid growth
Number of lesions	Unilateral, one site	Bilateral and multifocal
Ultrasound characteristics	A-scan: medium-high reflectivity B-scan: acoustic hollowness, choroidal excavation, mushroom-shaped	A-scan: low-medium reflectivity B-scan: acoustic solidness

RD = retinal detachment

the management and prognosis vary significantly between these two conditions. Table 1 reviews some distinguishing features of primary uveal melanoma and uveal metastasis.

The differential diagnosis of a non-pigmented iris metastasis includes amelanotic melanoma, amelanotic nevus, granulomatous iritis, lymphoma, leukemia, and leiomyoma.[7] The differential diagnosis of a pigmented iris metastasis from melanoma includes primary iris melanoma, pigmented nevus, adenoma, and iris cysts.[7] A history of primary malignancy in conjunction with a typical clinical examination will help narrow the differential. In the rare event that the diagnosis is still uncertain, a fine needle aspiration biopsy may be indicated.

Prognosis

In general, metastases to the eye and adnexa indicate a poor prognosis for the primary disease. The lag time between diagnosis of the primary carcinoma and globe involvement depends on the type of tumour. Generally, primary tumours that tend to involve the globe early are lung, kidney, and prostate cancers, while breast cancer and cutaneous melanoma metastasize later.[1] In their series, *Metastatic Tumours to the Eye and Orbit*, Freedman and Folk found that the median duration of time between the primary diagnosis and the development of choroidal metastases was approximately 3 years for breast cancer and 1 year for lung cancer.[10]

The median survival time also differs depending on the type of primary disease diagnosed. For instance, the reported median survival time for intraocular metastasis from lung cancer is 6 months and from breast cancer, 22 months.[10] In a more recent review, Shields et al also found the average survival following diagnosis of breast metastasis to the uvea to be 21 months, with an overall survival rate of 24% at 5 years.[4] Breast cancer patients who were older or who had orbital metastases tended to have longer median survival times than younger patients.[10] Similar to the pattern demonstrated with choroidal metastases, median survival times for iris metastases was 13 months for breast cancer and 4 months for lung cancer.[7] Ocular metastases from carcinoid tumours are reported to have longer survival periods, with a mean survival of 34 months in one recent review.[5]

Treatment

Treatment options for metastatic ocular tumours depend on the patient's systemic health, the nature of ocular involvement, and the underlying primary tumour. In addition, any planned treatment requires a discussion with the primary medical and radiation oncologists. Certainly, patients who have either vision-threatening ocular metastases and/or rapidly enlarging tumours may benefit from external beam radiation to improve vision and quality of life. The radiation dose may vary from 20 Gy delivered over 1 week to 40 Gy fractionated over 4 weeks and is typically delivered via a lateral orbital approach.[2] Patient survival time is usually not long enough to experience ocular side effects such as radiation retinopathy or radiation-induced cataracts. Typically, 80%-90% of patients respond successfully to radiation therapy with the tumour flattening by 1-2 months, and with a slightly longer duration for the subretinal fluid to resorb.[1] Other radiation methods include iodine-125 (I-125) plaque brachytherapy and stereotactic radiotherapy.[2]

Chemotherapy is another treatment modality that is effective for those patients with small minimally-active lesions and, in particular, for those who have metastatic disease in other extra-ocular locations.[2] In those patients who progress despite chemotherapy, external beam radiation would then be recommended for treatment of their intraocular metastasis. Observation may be employed for those patients who have clinically inactive, asymptomatic, or small non-vision-threatening lesions.[2] Enucleation may be indicated in patients with a blind and painful eye or in the rare circumstance when a large primary uveal melanoma cannot be definitely ruled out.

Conclusions

For the general ophthalmologist, an understanding of intraocular metastatic disease is

important, since it is the most common form of malignancy found in the eye. Carcinomas, most commonly breast and lung, frequently spread to the eye. However, a history of a primary carcinoma is not always present, requiring the ophthalmologist to maintain a high degree of suspicion. Suspected cases should have a full clinical exam, fluorescein angiography, ultrasonography, and a systemic work-up, to differentiate among similar occurring lesions. The most appropriate management options depend on consultation with medical and radiation oncologists and an understanding of the visual and systemic status of the patient. The majority of patients with vision-threatening lesions respond favourably to external beam radiation. Although intraocular metastatic disease carries a poor prognosis for patient survival, a timely evaluation, an accurate diagnosis, and prompt treatment may aid in improving the quality of life for these patients.

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