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Catch Them if You Can: A Review of Choroidal Metastases

Introduction:
Have you ever encountered a case of choroidal metastasis? Were you able to make the correct diagnosis? As it turns out, while still uncommon, metastasis to the choroid is not as rare as once believed. The estimated incidence of ocular metastases in the United States is 20,000 per year. This is in contrast to ocular melanomas that have an annual incidence of 1,400. While our optometric education focuses mainly on detecting primary malignancies of the eye, in practice it is far more common to encounter secondary ocular tumors. The choroid is the most common intraocular site for development of metastasis due to its abundant vascular supply and favorable microenvironment. On the other hand, iris and ciliary body metastases are far less common. Choroidal metastasis (CM) has been reported to occur in up to 12% of patients with solid tumors, e.g., breast, lung, and others, in autopsy studies. As the life expectancy of patients with cancer increases, the number of patients diagnosed with CM who require ophthalmic screenings will grow accordingly. CM is generally associated with late stage systemic disease and poor prognosis.

In this article we will review:
1) Differential diagnosis for choroidal tumors
2) Clinical features of CM
3) Origin of CM
4) Management options

Case Presentation:
A 54-year-old Caucasian male presented to our clinic for a comprehensive exam with the chief complaint of dry eyes. He was recently diagnosed with stage IV lung adenocarcinoma metastatic to the bones and brain and had initiated chemotherapy 12 days prior. His best-corrected visual acuity was 20/20 in each eye. Pupils were equal, round and reactive to light; no afferent pupillary defect was noted. Extraocular muscles were unrestricted in all gazes without pain or diplopia. Anterior segment evaluation by slit lamp was unremarkable, and intraocular pressures were measured at 16 mmHg OD, OS by Goldmann applanation tonometry at 1:45 pm. His dilated fundus exam revealed an elevated yellow choroidal lesion temporal to the macula in the right eye and a similar but larger lesion nasal to the optic nerve head in the left eye. The lesions had dimensions of ~2x2 disc diameter (DD) and ~5Hx6V DD, respectively. The nerves and maculecte appeared normal in both eyes; there were no holes, breaks or tears in the peripheral retinas. Patient denied symptoms of vision loss, metamorphopsia, or flashes and floaters.

Figure 1: Fundus photograph of the right eye. Note the yellow elevated subretinal mass temporal to the macula.

Figure 2: Fundus photograph of the left eye. Note the large yellow elevated subretinal mass nasal to the nerve.
Patient was referred to an ocular oncologist for suspicious metastatic choroidal lesions in both eyes. A clinical diagnosis of choroidal metastasis from lung cancer was made and the patient was to be re-evaluated in six weeks to assess the response of already on-going systemic chemotherapy. Unfortunately, we were unable to continue in this patient’s care, as he was lost to follow-up.

**Differential Diagnosis:**
The main differential diagnosis for choroidal metastasis includes choroidal melanoma, hemangioma, lymphoma, osteoma, granuloma and sclerochoroidal calcification. Distinct features on funduscopy and use of various imaging modalities help to distinguish these lesions from one another.\textsuperscript{3,5}
**Choroidal melanoma:**
Choroidal melanomas typically present as unilateral dome shaped subretinal tumors with a median basal diameter of 11mm and mean thickness of 4.5mm. A majority of these lesions are pigmented while some can be non-pigmented. The tumors have a hollow appearance on B-scan, and it is common to have some degree of subretinal fluid that is best seen on spectral domain optical coherence tomography (SD OCT). Early detection of these tumors is critical since the patient is at risk for metastatic disease to the liver, lung and skin.\(^2,6\)

<table>
<thead>
<tr>
<th>Pearls to Remember</th>
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<tbody>
<tr>
<td>• Shields et al., found that factors predictive of growth of choroidal melanomas include greater tumor thickness, location touching the optic nerve, presence of orange pigment, subretinal fluid and visual symptoms.(^7) Presence of three of these factors would place the risk of tumor growth at 50%.(^8)</td>
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<tr>
<td>• Ten-year survival rates for choroidal melanomas.(^9,10)</td>
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<tr>
<td>• 81.2% for small melanomas (&lt;10mm in diameter and &lt;3mm in height)</td>
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<tr>
<td>• 60.0% for medium melanomas (10-15 mm in diameter and 3-5mm in height)</td>
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<tr>
<td>• 34.8% for large melanomas (&gt;15mm in diameter and &gt;5mm in height)</td>
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**Choroidal hemangioma:**
Circumscribed choroidal hemangiomas are benign vascular tumors without systemic associations and are considered to be congenital in origin. On the other hand, diffuse hemangiomas are often associated with Sturge-Weber syndrome.\(^12\) Hemangiomas generally appear as an orange-red elevated mass in the paramacular region of the eye. The lesions are more commonly seen in Caucasian individuals and typically present as a unilateral solitary mass.\(^11,12\) The tumor can cause reduced vision if there is associated subretinal fluid, cystoid macular edema, retinoschisis or retinal pigment epithelium changes.\(^13\)

**Choroidal lymphoma:**
Uveal lymphoma is divided into primary and secondary categories with the latter developing in patients with preexisting systemic lymphoma. Primary choroidal lymphomas are a rare entity associated with infiltration of choroid by low-grade B-cell lymphoma; these are usually unilateral, with no anterior segment involvement, and do not predispose patients to future development of systemic disease. Secondary choroidal lymphomas can be bilateral and are commonly associated with anterior segment findings and vitreal reaction/infiltration.\(^13,14\)

**Choroidal osteoma:**
Choroidal osteomas are benign tumors that consist of mature bone and have a predilection for young females in the second or third decade of life. The lesions are commonly unilateral and present as yellow-orange calcific plaques with well-defined borders in the peripapillary or perimacular region.\(^15\) They can be associated with choroidal neovascularization, subretinal fluid and photoreceptor atrophy.\(^13\)

**Choroidal granuloma:**
Choroidal granulomas can occur as a result of acute or chronic inflammation secondary to sarcoidosis, tuberculosis or other infectious agents. They can present as unifocal or multifocal lesions of varying size and usually resolve with treatment of the underlying condition.\(^13\)

**Sclerochoroidal calcification:**
Sclerochoroidal calcification most commonly occurs in the elderly white population. It can appear as a small, round, homogenous yellow lesion or as a large geographic area with calcific foci. It is typically located in the superior and inferior arcades and is often bilateral. Most lesions are idiopathic but some reports suggest that they may be associated with systemic conditions such as Gitelman or Bartter syndrome.\(^15,16\)
### Table 1: Clinical Features of Choroidal Lesions

<table>
<thead>
<tr>
<th>Laterality</th>
<th>Location</th>
<th>Surface configuration</th>
<th>Color</th>
<th>Other features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Choroidal melanoma</strong></td>
<td>Unilateral</td>
<td>Non-specific</td>
<td>-Dome (75%)</td>
<td>-Median diameter of 11.0 mm</td>
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<td></td>
<td></td>
<td></td>
<td>-Mushroom (20%)</td>
<td>-Mean thickness of 4.5mm</td>
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<td></td>
<td></td>
<td></td>
<td>-Diffuse (5%)</td>
<td>-Hollowness on b-scan</td>
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<td></td>
<td></td>
<td></td>
<td>-Pigmented (55%)</td>
<td>-Subretinal fluid</td>
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<td></td>
<td></td>
<td></td>
<td>-Non-pigmented (30%)</td>
<td>-Retinal detachment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Mixed pigmented or non-pigmented (30%)</td>
<td></td>
</tr>
<tr>
<td><strong>Choroidal hemangioma</strong></td>
<td>Unilateral</td>
<td>-Dome (67%)</td>
<td>Orange-red</td>
<td>-Median diameter of 6.0 mm</td>
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<tr>
<td></td>
<td></td>
<td>-Mushroom (34%)</td>
<td></td>
<td>-Median thickness of 3.0 mm</td>
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<tr>
<td></td>
<td></td>
<td>-Plateau (98%)</td>
<td></td>
<td>-Serous retinal detachment (81%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>-Cystoid macular edema (17%)</td>
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<tr>
<td><strong>Choroidal lymphoma</strong> (Primary)</td>
<td>Unilateral (80%)</td>
<td>-Macula (84%)</td>
<td>Creamy-yellow</td>
<td>-Mean thickness 3.0 mm</td>
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<tr>
<td></td>
<td></td>
<td>-Macula to equator (98%)</td>
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<td>-Subretinal fluid (48%)</td>
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<td></td>
<td></td>
<td>-Equator to ora serrata (51%)</td>
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</tr>
<tr>
<td><strong>Choroidal osteoma</strong></td>
<td>Unilateral (75%)</td>
<td>-Perimacular</td>
<td>Yellow-white</td>
<td>-Subretinal fluid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Peripapillary</td>
<td>(with varying degrees of brown, orange, or gray pigment)</td>
<td>-Subretinal neovascularization</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>-Hemorrhage</td>
</tr>
<tr>
<td><strong>Choroidal granuloma</strong></td>
<td>Unilateral or bilateral</td>
<td>Non-specific</td>
<td>Dome</td>
<td>Variable</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>-Small detachment of sensory retina (few reported cases)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Choroidal neovascularization (few reported cases)</td>
</tr>
<tr>
<td><strong>Sclerochoroidal calcification</strong></td>
<td>Bilateral (40-80%)</td>
<td>Macula to equator</td>
<td>Flat</td>
<td>Variable</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Yellow</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>-Geographic with white foci</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>-Yellow halo around area of RPE atrophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Small detachment of sensory retina (few reported cases)</td>
</tr>
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**Clinical Features of Choroidal Metastases:**

A review of 520 eyes by Shields et al. 3 revealed that metastasis to the choroid comprises 88% of all uveal metastases. CM often presents as a creamy-yellow subretinal mass, associated with subretinal fluid (73%) and pigment epithelial alterations (57%). There is often a secondary retinal detachment overlying the lesion. The mean base and thickness measurements of CM tumors are 9.0mm and 3.0mm, respectively. CM can occur unilaterally or bilaterally and is multifocal in 20% of the cases. The lesions are most commonly yellow, although some can present as brown-gray or orange. Vast
majority of CM are plateau shaped in configuration, and the lesions are most commonly located between the macula and the equator. \(^3,5,19\) Blurry vision is the most common symptom followed by flashes and floaters, and pain; however, metastasis to the choroid can also be found incidentally on routine dilated exams in an asymptomatic patient. \(^3\) If the metastatic tumor is pigmented, it is likely from a cutaneous melanoma, although it is rare to see cutaneous melanomas metastasize to the eye. If the metastases are bilateral, it’s far more common that they originate from breast rather than lung cancer. Metastasis from lung cancer can be very invasive, infiltrate the sclera, and cause pain more so than breast cancer. \(^3,18\) Fine needle aspiration is performed in about 2% of patients to differentiate metastatic tumors from other choroidal tumors. \(^18\)

<table>
<thead>
<tr>
<th>Pearls to Remember:</th>
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<tbody>
<tr>
<td>• Up to 11% of patients with CM can be asymptomatic(^3)</td>
</tr>
<tr>
<td>• Flashes and floaters could be a symptom of CM and often indicates presence of subretinal fluid(^3)</td>
</tr>
<tr>
<td>• Diagnosis of CM is primarily based on clinical presentation in addition to a number of ancillary ophthalmic procedures</td>
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![Figure 6: Primary sites and clinical features of choroidal metastases](image)
Table 2: Features of Choroidal Metastasis on Ancillary Tests3,5,13

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td><strong>Autofluorescence</strong></td>
<td>• Hypoautofluorescence of tumor&lt;br&gt;• Hyperautofluorescence of lipofuscin and subretinal fluid</td>
</tr>
<tr>
<td><strong>Ultrasonography</strong></td>
<td>• High reflectivity on A-scan&lt;br&gt;• Eco-density on B-scan with significantly lower height to base ratio compared to choroidal melanomas</td>
</tr>
<tr>
<td><strong>Optical Coherence Tomography (Enhanced depth imaging)</strong></td>
<td>• Tumor surface is irregular often with a “lumpy bumpy appearance” in contrast to choroidal nevi or melanomas which often show a smooth dome-shaped topography&lt;br&gt;• Compression of overlying choriocapillaris&lt;br&gt;• Irregularities of the out retinal layers&lt;br&gt;• Subretinal fluid&lt;br&gt;• EDI OCT can detect micro-metastases not apparent on funduscopy</td>
</tr>
<tr>
<td><strong>Fluorescein Angiography</strong></td>
<td>• Hypofluorescent in early arterial phase with hyperfluorescent in late venous phase&lt;br&gt;• Dilated retinal capillaries with a small area of leakage at the border of the tumor seen in 73% of cases</td>
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Etiology of Choroidal Metastases:
Metastatic emboli that travel through the circulatory system to the choroid are carried from their primary origin via the branches of the internal artery. The emboli travel through the internal carotid artery, the ophthalmic artery and the posterior ciliary arteries to make their way to the choroid where they can seek a receptive environment for growth.5,19

Breast cancer is the most common source of CM accounting for up to 53% of the cases and lung cancer is the second - 20-29% of cases.3,5 In general, patients with lung cancer have lower survival rates; this is thought to be the reason for lower percentages of CM in lung cancer patients, despite it being the most common cancer for both sexes.20 According to Shields et al., 34% of patients diagnosed with CM have no known history of cancer. In those with no prior cancer history, the primary cancer site remains unknown in 51% of the patients. In patients where the cancer site is detected, lung cancer is the most common primary source followed by breast cancer.3 These findings suggest that diagnosis of CM can precede that of the primary malignancy, which makes it crucial for eye-care providers to make the appropriate diagnosis and referral.

**Pearls to Remember:**
- When a primary cancer is present elsewhere in the body, CM should be high on the differential list for a newly detected choroidal lesion
- Up to one-third of patients with CM are unaware of any systemic cancer; in these instances, the optometrist may be the first physician to speculate presence of a primary tumor
- Be mindful of CM in patients with a previous or current history of breast and lung cancer, as these have the highest potential for metastasis to the choroid
Management of Choroidal Metastases:
Survival time from diagnosis of uveal metastasis is between 7-21 months. A number of treatment options are available, including radiotherapy, e.g., external beam, plaque brachytherapy, Gamma Knife, and proton beam, laser therapy, cryotherapy, resection, intravitreal injections, and observing for effectiveness of systemic therapy. The choice of treatment depends on the patient’s specific clinical condition.

Systemic therapy has been shown to be effective for controlling metastatic tumors of the choroid and is considered to be the preferred treatment option. This treatment is thought to be effective due to the absence of a blood ocular barrier and easy diffusion of systemic medication to the choroid via the fenestrated endothelium of the choriocapillaris. Regression of CM with use of systemic chemotherapy alone has been noted.

To date, radiotherapy is the most frequently used method of treatment for CM, but has several complications including cataract, exposure keratopathy, iris neovascularization, radiation retinopathy and radiation papillopathy. External beam radiotherapy (EBRT) has been shown to result in tumor regression in 85-93% of patients; however, the extensive treatment period of 3-4 weeks can be impractical in patients with a limited life expectancy. In comparison, plaque radiotherapy provides more targeted therapy and can be completed in only a few days. Proton beam radiotherapy has also proven to be effective and allows for more focused irradiation compared to Gamma Knife radiosurgery.

Intravitreal anti-VEGF agents have recently gained attention in treatment of small, circumscribed choroidal metastases in the absence of a retinal detachment. The injections may be repeated every 4-6 weeks similar to the treatment for choroidal neovascular membranes in age-related macular degeneration.

The decision to treat locally has to take into account important considerations such as patient preference, overall health, location and extent of the lesions, and visual symptoms. In general, treatment goals revolve around improving vision and avoiding enucleation to preserve quality of life.
Summary:
Choroidal metastases are the most common intraocular malignancy in the adult population, yet they are not frequently encountered in practice.\textsuperscript{1,3-5} This is likely due to the fact that a majority of patients with CM have advanced systemic disease drawing the attention away from ophthalmic examination.\textsuperscript{20} Nevertheless, it is essential that eye care providers are familiar with the clinical features of this condition for two main reasons: 1) as cancer survival rates increase, more patients with CM are likely to be seen by their eye-care professionals; and 2) correct identification of such metastatic tumors could facilitate localization of the primary, if still undiagnosed at the time of ocular metastasis. In patients where CM is detected, the goal of treatment is to improve visual acuity as well as the patient’s overall quality of life during the remaining life span.

References:

19. Ferry AP, Font RL. Carcinoma metastatic to the eye and orbit: A clinicopathologic study of 227


1) What is the estimated incidence of ocular metastases in the United States?
   a) 1,400
   b) 5,000
   c) 10,000
   d) 20,000

2) Which of the following conditions often presents bilaterally?
   a) Choroidal melanoma
   b) Choroidal hemangioma
   c) Primary choroidal lymphoma
   d) Sclerochoroidal calcification

3) Which of the following is the most common shape of a choroidal metastasis?
   a) Dome
   b) Plateau
   c) Mushroom
   d) Excavated

4) What is the most characteristic color of choroidal metastasis? Choose one.
   a) Yellow
   b) Gray
   c) White
   d) Dark brown

5) Which of the following clinical feature is consistent with choroidal metastasis? Choose one.
   a) Low reflectivity with A-scan ultrasonography
   b) Hyper-autofluorescence of tumor
   c) Subretinal fluid in optical coherent tomography
   d) “Dark choroid” with fluorescein angiography

6) Which presenting symptom is most common in patients with choroidal metastasis?
   a) Pain
   b) Red eye
   c) Flashes and floaters
   d) Blurry vision

7) In patients with a known history of primary cancer, which of the following sites is most associated with choroidal metastasis?
   a) Lung cancer
   b) Skin cancer
   c) Kidney cancer
   d) Liver cancer
   e) Breast cancer

8) In patients with an initially unknown history of cancer, which of the following sites is most associated with choroidal metastasis?
   a) Lung cancer
   b) Skin cancer
   c) Kidney cancer
   d) Liver cancer
   e) Breast cancer

9) Which of the following has been done in an attempt to treat choroidal metastasis?
   a) Proton beam radiotherapy
   b) Anti-VEGF intravitreal injection
   c) Resection
   d) Plaque brachytherapy
   e) All above

10) What are the two most important goals of treatment?
    a) Complete regression of tumor
    b) Prevention of metastasis to other sites from choroidal tumor
    c) Frequent office visit
    d) Maintaining quality of life
    e) Improving vision