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Original Investigation

Retinal Metastasis From Systemic Cancer in 8 Cases

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IMPORTANCE Metastatic tumors of the retina are rare, simulate retinitis, and are associated with poor patient survival.

OBJECTIVE To describe the clinical features and outcomes of patients with retinal metastasis from systemic cancer.

DESIGN, SETTING, AND PARTICIPANTS Retrospective case series of 8 patients with retinal metastasis from cutaneous melanoma (n = 4), breast cancer (n = 2), esophageal cancer (n = 1), and lung cancer (n = 1). At presentation, the mean patient age was 62 years and all were white.

INTERVENTION Treatment included plaque radiotherapy (n = 1) for localized disease or enucleation (n = 3) for extensive tumor hemorrhage (n = 1), total retinal detachment (n = 1), or pain (n = 1). For 4 preterminal patients, observation was preferred.

MAIN OUTCOMES AND MEASURES Clinical features and systemic outcomes.

RESULTS The mean interval from primary cancer diagnosis to retinal metastasis was 63 months. Initial misdiagnosis as retinitis (n = 5), hemangioma (n = 1), choroidal neovascular membrane (n = 1), or nerve fiber layer infarction (n = 1) for a mean interval of 5 months was recorded. Visual acuity in the affected eye was 20/40 to 20/60 (n = 5) or 20/400 to light perception (n = 3). The tumors were unilateral (n = 7), involved the macula (n = 3), and had a mean distance to the foveola of 6 mm. In one case, dense vitreous blood precluded fundus visualization. The mean tumor basal dimension was 7.4 mm, and the mean thickness was 2.3 mm. The tumors appeared white (n = 2), yellow (n = 4), or brown (n = 1); were located in the inner retina (n = 6) or full-thickness retina (n = 1); and had vitreous seeds (n = 3), vitreous hemorrhage (n = 2), retinal hemorrhage (n = 4), subretinal fluid (n = 4), and/or intraretinal exudation (n = 1). Fluorescein angiography disclosed early retinal hypofluorescence and late hyperfluorescence with staining. Fine-needle aspiration biopsy confirmed the diagnoses (n = 4). Metastasis-related death occurred in 5 patients within 1 month in each case. Of the remaining 3 patients, 2 were alive at 4 and 17 months and 1 was too sick to return.

CONCLUSIONS AND RELEVANCE Retinal metastases resemble retinitis, often with delay in diagnosis and poor life prognosis.

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etases to the eye are usually detected in the choroid (88%), iris (9%), or ciliary body (2%), and, rarely, in the retina (<1%). Retinal metastases caused by systemic cancers have been documented in case reports, but, owing to the infrequency of this finding, there has not been extensive experience at any single ocular oncology center. In this article, we examine our 40-year experience treating patients with retinal metastasis. During this time, we have treated several thousand patients with uveal metastasis and hundreds with orbital metastasis but only a few with retinal metastasis. We document the clinical features, treatment, and outcomes of patients with retinal metastasis.

Methods

This retrospective interventional case series included patients with retinal metastasis treated at the Ocular Oncology Service, Wills Eye Hospital, Philadelphia, Pennsylvania, between July 1, 1974, and February 1, 2014. Institutional review board approval was obtained from Wills Eye Hospital.

Patient data were collected from the medical records and included information on previous cancer diagnoses regarding date of detection and management. At presentation to the Ocular Oncology Service, data on demographic features included patient age, sex, and race. Symptoms and visual acuity were recorded. The recorded ocular features included intraocular pressure (millimeters of mercury), tumor laterality (unilateral or bilateral), multiplicity (unifocal or multifocal), and quadrant (superior, inferior, nasal, temporal, macula, or diffuse). Related findings regarding the retina, vitreous, and choroid were recorded.

All findings were documented with large color-coded retinal drawings, fundus photography, and optical coherence tomography, ultrasonography, and/or fluorescein angiography, when available. Fine-needle aspiration biopsy for cytological confirmation was recorded when performed. Management of the retinal tumor and outcomes of management were recorded at each examination. Patient systemic outcome (alive, alive with metastasis, death due to metastasis, and death due to other causes) was noted.

Results

During a 40-year period at an ocular oncology referral center, 8 patients were diagnosed with retinal metastasis. By comparison, there were approximately 2076 patients during this period with uveal metastasis and 382 with orbital metastasis.

The patient information is shown in the Table. History of systemic cancer was noted in 7 cases, including cutaneous melanoma (n = 3), breast cancer (n = 2), esophageal cancer (n = 1), and lung cancer (n = 1). In 1 case, cutaneous melanoma was diagnosed following ocular diagnosis. The mean interval from primary cancer diagnosis to retinal metastasis diagnosis was 63 months (median, 33 months; range, 0-214 months). Initial misdiagnosis as infectious or inflammatory retinitis (n = 5), hemangioma (n = 1), choroidal neovascular membrane (n = 1), or nerve fiber layer infarction (n = 1) for a mean interval of 5 months (median, 5 months; range, 0.25-11 months) was recorded. On referral to our service, all patients were suspected to have cancer metastatic to the retina. At our examination, the mean patient age was 62 years (median, 58 years; range, 45-85 years) and all were white. Visual acuity in the affected eye was 20/40 to 20/60 (n = 5) or 20/400 to light perception (n = 3).

The anterior segment was unremarkable in all cases except for 1 with posterior synechiae with iris bombe. The retinal metastases were unilateral and unifocal (n = 7) or bilateral and multifocal (n = 1). The tumors appeared white (n = 2), yellow (n = 4), brown (n = 1), or not visible owing to dense vitreous hemorrhage (n = 1). The tumors were located in the macula (n = 3); in temporal (n = 1), superior (n = 1), or diffuse quadrants (n = 2); or were multifocal (n = 1). The mean distance to the foveola was 6 mm (median, 4.3 mm; range, 0-13

Table. Retinal Metastasis Caused by Systemic Cancer in 8 Patients

<table>
<thead>
<tr>
<th>Case No./Sex/Age, y/Race</th>
<th>Primary Cancer Site</th>
<th>Carcinoma or Melanoma</th>
<th>Interval From Cancer to Retinal Metastasis, mo</th>
<th>Basal Diameter, mm</th>
<th>Thickness, mm</th>
<th>Presence of VS/VH/SRF</th>
<th>Treatment</th>
<th>Death (Months of Follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/64/64</td>
<td>Lung CA</td>
<td>103</td>
<td>7</td>
<td>1.7</td>
<td>Y/Y/N radiotherapy</td>
<td>N (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/M/45/W</td>
<td>Skin MM</td>
<td>73</td>
<td>12</td>
<td>3</td>
<td>Y/N/N Enucleation</td>
<td>N (17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/M/59/W</td>
<td>Skin MM</td>
<td>0</td>
<td>11</td>
<td>5.6</td>
<td>N/N/N Enucleation</td>
<td>Y (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/M/85/W</td>
<td>Skin MM</td>
<td>40</td>
<td>9</td>
<td>2</td>
<td>Y/Y/N Enucleation</td>
<td>Y (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/M/56/W</td>
<td>Esophagus CA</td>
<td>26</td>
<td>12</td>
<td>1.2</td>
<td>N/N/Y Observation*</td>
<td>Y (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/F/58/W</td>
<td>Breast CA</td>
<td>214</td>
<td>1.5</td>
<td>2</td>
<td>N/N/Y Observation*</td>
<td>Y (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/F/75/W</td>
<td>Breast CA</td>
<td>20</td>
<td>2</td>
<td>1</td>
<td>N/N/Y Observation*</td>
<td>NA*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/M/55/W</td>
<td>Skin MM</td>
<td>24</td>
<td>5</td>
<td>2</td>
<td>N/N/N Observation*</td>
<td>Y (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CA, carcinoma; MM, malignant melanoma; NA, not available; N, no; SRF, subretinal fluid; VH, vitreous hemorrhage; VS, vitreous seed(s); W, white; Y, yes.

* Patient prognosis was poor and patient ultimately died.
* Patient was too sick to return.
mm). The mean tumor basal dimension was 7.4 mm (median, 8 mm; range, 1.5-12 mm) and mean thickness was 2.3 mm (median, 2 mm; range, 1.5-5.6 mm) (Figures 1, 2, 3, and 4 and eFigure in the Supplement).

The metastases were located in the inner retina (n = 6) or full-thickness retina (n = 1) and had vitreous seeds (n = 3), vitreous hemorrhage (n = 2), retinal hemorrhage (n = 4), subretinal fluid (n = 4), and/or intraretinal exudation (n = 1). The tumors showed morphologic configurations that were smooth (n = 2), cerebriform (n = 2), or irregular (n = 3) and had intrinsic tumor vessels (n = 2). There were no cases demonstrating dilated tortuous retinal feeder vessels. In 1 case of metastatic cutaneous melanoma, multifocal angiocentric retinal metastases were noted (eFigure in the Supplement). Ultrasonography, performed in 5 cases, showed an echodense mass. Fluorescein angiography, performed in 5 cases, showed early hypofluorescence (n = 3) and hyperfluorescence in the venous (n = 3) and recirculation phases (n = 3). Intrinsic retinal tumor vessels were visible in 4 of 5 cases. Optical coherence tomography, performed in 3 cases, showed an inner (n = 2) or full-thickness retinal mass (n = 1), with optical density and shadowing in 2 cases and subretinal fluid in 1 case.

Fine-needle aspiration biopsy confirmed the diagnoses (n = 4). Treatment included plaque radiotherapy (n = 1) or enucleation (n = 2) for advanced intraocular malignancy vitreous hemorrhage and seeding (n = 1), pain management (n = 1), or total retinal detachment with light perception visual acuity (n = 1). Follow-up information was collected at our examination (n = 2) or examination by the local physician (n = 5). Metastasis-related death occurred in 5 patients within 1 month of examination. Of the remaining 3 patients, 2 were alive at 4 and 17 months and 1 was too sick to return.

A 64-year-old woman with lung carcinoma without metastatic disease developed blurred vision to 20/50 in the affected eye. A, Funduscopy revealed a white retinal mass with intrinsic vascularity and mild overlying vitreous hemorrhage. B, Fluorescein angiography confirmed intrinsic vascularity with staining but without dilated feeding vessels. C, Ultrasonography revealed a dense, domed-shaped retinal mass measuring 1.7 mm in thickness. Optical coherence tomography (horizontal) through the lesion showed full-thickness retinal replacement by tumor (D) and intact macula with minor drusen (E). F, Fine-needle aspiration biopsy showed malignant cells, with positive staining for epithelial markers (G) (AE1/AE3); this is consistent with metastatic lung carcinoma of the retina.
Discussion

Metastatic cancer of the retina is rare. Most intraocular metastases reside in the uveal tract.\(^1\)\(^2\) During the past decades, there have been only a few case reports of retinal metastasis caused by systemic carcinoma.\(^3\)\(^-\)\(^9\) In 1990, Leys and colleagues\(^7\) identified a single case of breast carcinoma and another case of lung carcinoma with yellow retinal metastases; the patients died after 1 and 18 months, respectively. Others have reported single cases of retinal metastasis from gastric, colon, and lung carcinoma as well as cutaneous

Figure 2. Case 7

A 75-year-old woman with breast carcinoma developed blurred vision to 20/40 in the affected eye. A, Funduscropy revealed a yellow retinal mass with intrinsic hemorrhage and surrounding retinal exudation. B, Fluorescein angiography showed a slightly hyperfluorescent mass with intrinsic vascularity and without dilated feeding vessels. C, Optical coherence tomography (vertical) through the lesion showed an inner retinal mass with outer retinal compression and contiguous edema. Note the lack of choroidal tumor. D, Optical coherence tomography (horizontal) through the macula showed outer retinal densities consistent with exudation.

Figure 3. Case 3

A healthy 59-year-old man developed floaters. A, Funduscropy revealed an ill-defined white retinal mass with chorioretinal scarring. B, Fluorescein angiography documented linear intrinsic blood vessels. C, Ultrasonography revealed a moderately echogenic, abruptly elevated intraocular mass. D, Gross pathologic analysis showed the yellow-white multinodular mass arising in the retina and without choroidal invasion. The mass proved to be cutaneous melanoma metastasis to the retina. Subsequently, metastases to other organs were detected.
melanoma and unknown sites. In most cases, the metastases appeared yellow-white, with occasional vitreous seeds or subretinal fluid, and often was misdiagnosed as infectious or inflammatory retinitis. Most patients have been treated with external beam radiotherapy or enucleation. Although local control of the intraocular tumor is usually achieved, systemic outcomes have been overwhelmingly poor in these cases, with death from disseminated metastasis occurring within 2 months to 2 years.

In 1997, Mack and Jakobiec provided a review of 20 articles describing cases of retinal metastasis between 1979 and 1995. The mean age at ophthalmic diagnosis was 51 years. They commented that the retinal metastasis from cutaneous melanoma appeared brown, often with brown vitreous seeds, whereas those from carcinoma appeared white with perivascular infiltration. Management included external radiotherapy (n = 2), chemotherapy (n = 2), or enucleation (n = 9) for ocular pain (n = 6) or for misdiagnosis as choroidal melanoma (n = 2). Survival after diagnosis ranged from 2 weeks to 5 years.

In our 8 cases of retinal metastasis, there was an initial suspicion of infectious or inflammatory retinitis in 5 cases. Only later, when the condition did not resolve with standard antiinflammatory measures, was a neoplastic condition considered. All but 1 patient had known primary cancer. In that case, cutaneous melanoma was diagnosed within 1 month following ocular diagnosis. Systemic metastasis had been identified in 6 cases before ocular diagnosis. In the remaining 2 cases, disseminated metastases were discovered within 1 month following ocular diagnosis.

The metastases commonly infiltrated the inner retina (n = 7), produced vitreous seeding (n = 4), and occasionally had retinal hemorrhage (n = 4) and/or exudation (n = 1). These features were suggestive of retinitis. None of our patients demonstrated dilated feeder vessels or choroidal invasion. The vitreous hemorrhage was mild in 1 case and dense in another, precluding a fundus view. Findings of fine-needle aspiration biopsy directly into the retinal mass were sufficient to establish the diagnosis in 4 cases. The eye was treated with enucleation in 3 patients who demonstrated retinal metastasis caused by previously treated cutaneous melanoma (n = 2) and undiagnosed cutaneous melanoma (n = 1). In the latter case, the cutaneous melanoma was discovered following histopathologic evaluation of the globe. Enucleation was performed to treat ocular pain from iris bombe with secondary glaucoma (n = 1), dense vitreous hemorrhage and tumor seeding with light perception visual acuity (n = 1), and total retinal detachment with large tumor and light perception visual acuity (n = 1). Observation was advised in 4 patients whose prognosis was poor. One patient who was in fairly good health at presentation was treated with plaque radiotherapy but was diagnosed with brain metastasis 1 month later that necessitated chemo-

A 45-year-old man with a 6-year history of cutaneous melanoma with multisystem metastasis developed decreased visual acuity to 20/400 OS. A, Funduscopy revealed chorioretinal scars with overlying serous retinal detachment. B, Fluorescein angiography documented ill-defined staining indicative of metastasis; based on general poor prognosis, observation was advised. C, Eight months later, ultrasonography revealed dense vitreous debris. D, Gross pathologic analysis of the enucleated eye showed diffuse vitreous hemorrhage with yellow material that proved to be melanoma metastasis. The retina was infiltrated with metastatic melanoma and the choroid showed no tumor.
therapy. In eyes with retinal metastasis, we prefer to be conservative, treating patients with observation or globe conservation with radiotherapy methods, especially when poor ultimate prognosis is known. However, enucleation was necessary in some cases with unusual circumstances. Other treatments for retinal metastasis include local excision and photodynamic therapy.

Most cases of infectious retinitis manifest as a yellow-white, ill-defined, occasionally hemorrhagic process, similar to the appearance in several of our cases. However, our cases of retinal metastases differ from infectious and/or inflammatory retinitis in that fluorescein angiography showed focal tumor staining but no remote leakage elsewhere in the fundus; there was no photophobia, vitreous fibrosis, or related cataract, and there was no response to antiinflammatory medications or antibiotics. In our cases, the diagnosis was suspected clinically and confirmed, in some cases, with fine-needle aspiration biopsy or enucleation.

In our 8 cases of retinal metastasis, the tumors originated from cutaneous melanoma in 4 cases and appeared yellow (n = 2), brown (n = 1), or not visible owing to vitreous hemorrhage (n = 1). Others have identified retinal or vitreous metastases from cutaneous melanoma as either brown or golden yellow. The 2 tumors caused by breast carcinoma appeared yellow, and the tumors caused by lung or esophageal carcinoma appeared white. In 1 patient with multifocal metastatic cutaneous melanoma, 1 site was yellow and nodular, whereas most of the retinal metastases were flat, feathery, angiocentric, and brown in color, similar to the case reported by Letson and Davidorf (eFigure in the Supplement).

The most striking finding in this small case series was the uniformly poor systemic prognosis. Retinal metastasis appears to be a finding encountered near the end stage, with malignancy entering the eye by a hematogenous route and presumably with diffuse dissemination to all organs. Overwhelming systemic metastasis typically led to death within a median of 1 month in this series.

Conclusions

In summary, less than 1% of intraocular metastases are found within the retina. Retinal metastases are often confused with infectious or inflammatory retinitis. Cutaneous melanoma represents the most common malignancy to demonstrate retinal metastasis. Systemic prognosis is poor.