Choroidal Metastasis as the Initial Manifestation of a Pigmented Neuroendocrine Tumor

Ralph C. Eagle, Jr, MD; Hormoz Ehya, MD; Jerry A. Shields, MD; Carol L. Shields, MD

We report the case of a 77-year-old woman in whom choroidal metastasis was the initial manifestation of a primary neoplasm presumed to be a pigmented pulmonary carcinoid tumor. The tumor initially was misdiagnosed cytologically and pathologically as a choroidal melanoma because it contained intrinsic melanin pigment. Positive immunoreactivity for cytokeratin, synaptophysin, chromogranin, and calcitonin and the presence of dense-core neurosecretory vesicles disclosed by electron microscopy established that the metastasis was a neuroendocrine tumor. Findings from systemic evaluation suggested that the primary tumor was located in the lung. The patient subsequently developed an intradural paraspinal metastasis, which also contained melanin pigment. The latter observation confirmed that the melanin in the uveal metastasis was intrinsic and did not represent secondary phagocytosis by tumor cells. Metastases from pigmented tumors of nonmelanocytic derivation are exceedingly rare but present a major diagnostic challenge to ocular pathologists and cytopathologists if the diagnosis is not suspected. Confirmatory immunohistochemical analysis should be obtained when a pigmented choroidal tumor thought to be a melanoma has atypical features.

Nearly all intrinsically pigmented malignant tumors of the uveal tract are primary melanomas derived from uveal melanocytes. Skin melanomas can metastasize to the uvea, usually in patients who are known to have disseminated disease. Nonmelanocytic neoplasms that produce melanin pigment are quite rare. We report a case of uveal metastasis that was the initial manifestation of an occult pigmented neuroendocrine carcinoma. Such tumors present a major diagnostic challenge to ocular pathologists and cytopathologists but are more readily diagnosed by special immunohistochemical analysis if they are suspected. Confirmatory immunohistochemical analysis should be obtained when a pigmented uveal neoplasm thought to be a melanoma has atypical features.

A 77-year-old woman with a 16-month history of gradual loss of visual acuity in the left eye was evaluated at the Oncology Service, Wills Eye Hospital, Philadelphia, Pa, after she was found to have a choroidal mass in her left eye (Figure 1). She did not smoke and had no history of malignancy. Her family history included breast carcinoma on the paternal side. The clinical differential diagnoses included primary amelanotic choroidal melanoma and choroidal metastasis. A metastatic workup was inconclusive. Computed tomography of the brain and abdomen was nonrevealing. Findings from computed tomographic scans of the thorax disclosed a 3-mm-diameter peripheral nodular density in the right mid lung without hilar or mediastinal adenopathy. In addition, there was a questionable breast mass, which was not substantiated by further workup. There was also an...
8-mm-diameter node in the posterior aspect of the right clavicle. Serum carcinoembryonic antigen levels were mildly elevated (4.2 µg/L; reference level, 2.5 µg/L).

A transvitreal fine-needle aspiration biopsy was performed by one of us (J.A.S.) in May 1997 and interpreted by one of us (H.E.) experienced in the evaluation of ocular specimens. The specimen contained numerous medium-sized tumor cells, singly and in small clusters (Figure 2). The cells exhibited hyperchromasia and a high nuclear-cytoplasmic ratio. Although cytoplasmic pigment was present in some cells, the cytologic features were not classic for a uveal melanoma. The cells were pleomorphic, and nucleoli were not visible in most of them. Furthermore, evenly distributed chromatin in tumor cells was reminiscent of neuroendocrine tumors. A panel of immunocytochemical stains also produced inconclusive results. Tumor cells showed focal immunoreactivity for both cytokeratin (AE1/AE3 and CAM 5.2) and melanoma-specific antigen (HMB 45) and negative findings from staining for S100 protein, epithelial membrane antigen, and carcinoembryonic antigen. There was no convincing immunoreactivity for chromogranin and synaptophysin, as only rare tumor cells showed staining for these neuroendocrine markers. Considering the presence of cytoplasmic pigment and the conflicting results of immunohistochemical analysis, a diagnosis of malignant melanoma was favored over that of metastatic carcinoma.

The eye was enucleated and fixed in formalin. Macroscopic examination disclosed a lightly pigmented tumor of the posterior choroid measuring 7 mm in largest diameter and 3 mm in thickness (Figure 3). There was a shallow retinal detachment. Findings from microscopic examination disclosed a malignant neoplasm that contained fairly prominent foci of pigmentation, composed of large round melanosomes and pigmented dendriform cells with slender processes (Figure 4 and Figure 5). A preliminary report was issued with the diagnosis of malignant melanoma, mixed-cell type. However, additional microscopic sections from deeper within the paraffin block, special stains for melanin and iron, and a battery of immunohistochemical stains were obtained. The latter were performed because the cytologic appearance of the tumor was unusual and several other unusual features were noted. These included the presence of a separate smaller focus of the tumor in the choroid peripheral to the main mass (seen only in some of the sections that were prepared initially) and many mitoses (42 per 40 high-power fields). Formalin-fixed wet tissue also was submitted for transmission electron microscopy.

The tumor cells did not show immunoreactivity for melanoma-specific antigen HMB 45, S100 pro-
tein, and vimentin, which excluded the diagnosis of uveal melanoma (Figure 6). Instead, the cells were intensely immunoreactive for cytokeratin markers CAM 5.2 and AE1. In addition, there was intense generalized cytoplasmic immunoreactivity for the neuroendocrine markers chromogranin and synaptophysin. There was also unequivocal intense focal immunoreactivity for calcitonin.

Positive reactivity with the Fontana-Masson silver stain and negative reactivity with the iron stain confirmed that the pigment in the tumor cells was melanin (Figure 5, A). Transmission electron microscopy disclosed dense-core neurosecretory granules consistent with a neuroendocrine carcinoma and confirmed the presence of mature and immature melanosomes, which frequently formed compound melanosomes (Figure 5, B and C).

The revised diagnosis was metastatic neuroendocrine carcinoma to the uvea. We questioned whether the primary tumor might be a medullary thyroid carcinoma based on the positive immunoreactivity for calcitonin and suggested that further clinical evaluation should include obtaining serum calcitonin levels. A serum calcitonin level from August 1997 was mildly elevated (165.3 ng/L; reference range, 35-90 ng/L). The patient subsequently developed a cough and was evaluated by a pulmonologist at another institution. Findings from bronchoscopy showed obstruction of the right middle bronchus by an endobronchial tumor, which was obtained for biopsy, disclosing a minute fragment of atypical cells with neuro-
endocrine differentiation (positive for cytokeratin, synaptophysin, chromogranin, and calcitonin). Ultrasonography of the thyroid performed in November 1997 revealed a normal-sized gland with 6 nodules that measured 4 mm to 6 mm in diameter. (A similar thyroid evaluation in July 1997 revealed no abnormalities.) Results of an octreotide scan were negative. (Carcinoid tumors usually have high numbers of somatostatin receptors that allow scintigraphic imaging with the radiolabeled somatostatin analog octreotide.)

Late in March 1998, the patient experienced neurological symptoms, including pain and weakness in her arms caused by an intradural extramedullary paraspinal mass at thoracic vertebra T1. The results of an excisional biopsy performed elsewhere disclosed metastatic neuroendocrine carcinoma that resembled the choroidal and bronchial tumors histologically and immunophenotypically, including focal positive immunoreactivity for calcitonin. The spinal metastasis appeared to be pigmented on macroscopic examination, and the sections contained several unequivocal foci of melanin pigment demonstrated by the Fontana-Masson silver stain. The morphologic appearance of the pigment was similar to that found in the uveal metastasis and included large round melanosomes and dendriform cells with slender processes.

**COMMENT**

The unusual metastasis in the patient described here initially was misdiagnosed as a malignant melanoma on both cytopathologic and histopathologic examination because the tumor cells contained melanin pigment. This article emphasizes that the pathologist must not immediately conclude that a pigmented tumor in the uveal stroma is a primary melanoma of uveal melanocytic derivation. The differential diagnosis also includes metastasis from other pigmented neoplasms, particularly cutaneous melanomas. Diagnosis of metastatic skin melanoma usually is not difficult because patients typically are known to have disseminated disease. Clinically, metastatic cutaneous melanoma to the uvea is more likely to be diffuse, poorly cohesive, multifocal, and bilateral compared with primary uveal melanoma. In addition, metastatic foci of cutaneous melanoma to the uvea have certain histopathologic features that serve to distinguish them from primary uveal melanoma. Metastases from rare lesions, such as the pigmented neuroendocrine tumor described here, present a much greater diagnostic challenge. Such a tumor can readily be misdiagnosed as a melanoma if immunohistochemical analysis is not performed. Immunohistochemical analysis should not be performed routinely in intraocular tumor diagnosis, but they should be obtained if the results of routine light microscopic examination are unusual or atypical.

The intrinsic melanin pigment in the uveal metastasis, which was a major factor in the preliminary cytologic and histopathologic misdiagnoses of melanoma, ini-
Melanin production has been reported in both medullary thyroid carcinomas and pulmonary carcinoid tumors. One of 3 cases comprising a small series of pigmented pulmonary carcinoid tumors reported by Gal et al contained melanin pigment within dendritic sustentacular cells that had slender processes. The pattern of pigmentation shown in Figure 2 in that report bears striking similarity to the pigment in our case. Furthermore, transmission electron microscopy of the same case showing similarity to the pigment in our Figure 2 in that report bears striking similarity to the pigment in our case. Furthermore, transmission electron microscopy of the same case showed that the melanin pigment confirmed by the Fontana-Masson silver stain, which were identical morphologically to that found in the choroid.

Melanin production has been reported in both medullary thyroid carcinomas and pulmonary carcinoid tumors. One of 3 cases comprising a small series of pigmented pulmonary carcinoid tumors reported by Gal et al contained melanin pigment within dendritic sustentacular cells that had slender processes. The pattern of pigmentation shown in Figure 2 in that report bears striking similarity to the pigment in our case. Furthermore, transmission electron microscopy of the same case showed that the melanin pigment confirmed by the Fontana-Masson silver stain, which were identical morphologically to that found in the choroid.

The spinal specimen contained several unequivocal foci of melanin pigment confirmed by the Fontana-Masson silver stain, which were identical morphologically to that found in the choroid.

Melanin production has been reported in both medullary thyroid carcinomas and pulmonary carcinoid tumors. One of 3 cases comprising a small series of pigmented pulmonary carcinoid tumors reported by Gal et al contained melanin pigment within dendritic sustentacular cells that had slender processes. The pattern of pigmentation shown in Figure 2 in that report bears striking similarity to the pigment in our case. Furthermore, transmission electron microscopy of the same case showed that the melanin pigment confirmed by the Fontana-Masson silver stain, which were identical morphologically to that found in the choroid.

The primary source of the pigmented neuroendocrine tumor in our patient is not known with certainty, but it is thought to be a pulmonary carcinoid tumor. The differential diagnosis includes a pigmented pulmonary carcinoid tumor that metastasized to the choroid, thyroid, and spine, or a pigmented medullary thyroid carcinoma that metastasized to the choroid, lung, and spine. Initially, the primary tumor was thought to be a medullary thyroid carcinoma based on the positive immunoreactivity for calcitonin. Medullary thyroid carcinoma, which is a neoplasm derived from the calcitonin-secreting C cells of the thyroid, characteristically shows intense immunoreactivity for calcitonin. Patients with medullary thyroid carcinoma typically have markedly elevated levels of serum calcitonin. However, some carcinoid tumors are also immunoreactive for calcitonin and may cause moderately elevated (<300 ng/L) serum calcitonin levels in rare instances. The serum calcitonin level in our patient has remained at about 160 ng/L, consistent with ectopic calcitonin production. Furthermore, the thyroid nodules detected ultrasonographically in October 1997 were not present 4 months previously. The latter observation makes metastasis to the thyroid more likely and provides additional evidence that the occult primary tumor is a pulmonary carcinoid that is producing ectopic calcitonin. Bronchial carcinoid tumors are known to metastasize to the uvea, whereas carcinoid tumors of the lower gut typically metastasize to the orbit.

Accepted for publication January 27, 2000.

Supported by the Noel T. and Sara L. Simmons Endowment for Ophthalmic Pathology, Wills Eye Hospital, Philadelphia, Pa (Dr Eagle); the Eye Tumor Research Foundation, Philadelphia; the Paul Kayser Award in Retinal Research, Houston, Tex (Dr J. A. Shields); and the Macula Foundation, New York, NY (Dr C. L. Shields).


Reprints not available.

Corresponding author: Ralph C. Eagle, Jr, MD, Department of Pathology, Wills Eye Hospital, 900 Walnut St, Philadelphia, PA 19107-5597.