SURVEY OF OPHTHALMOLOGY VOLUME 53 • NUMBER 3 • MAY–JUNE 2008

ELSEVIER

MAJOR REVIEW

Cutaneous Malignant Melanoma Metastatic to the Eye, Lids, and Orbit

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Abstract. The incidence of malignant cutaneous melanoma is increasing faster than any other cancer. Thus, it will become an increasingly common source of metastatic disease to the eye, lids, and orbit. Herein, we have performed a systematic review of previously published cases including patient characteristics, clinical presentation, diagnostic techniques, current treatments, and outcomes. At the time of ocular diagnosis, nearly all reported patients had a known history of cutaneous melanoma and synchronous non-ocular metastases. Several aspects help in differentiating the tumors from primary uveal melanomas such as the presence of symptoms, rapidly growing multifocal tumors, vitreous seeding, and histopathological findings. Intraocular metastases (uvea, vitreous, retina, and anterior-segment) are more common and occur in younger patients than extraocular metastases (eyelids, orbit, and extraocular muscles). Palliative radiation therapy is often used for intraocular disease. Orbital metastases from cutaneous melanoma commonly involve the extraocular muscles resulting in diplopia and exophthalmos. The mainstays of extraocular treatment are surgical resection and radiation therapy. Unfortunately, there are few good options for systemic treatment of diffusely metastatic melanoma. Therefore, patients with ocular metastasis should be managed to prevent loss of vision or loss of the eye, and to maximize their quality of life. (**Surv Ophthalmol 53**:187–202, 2008.

Key words. cutaneous • eye • glaucoma • malignant melanoma • metastatic • ocular • orbit • seeding • vitreous

I. Introduction

A. OVERVIEW OF THE LITERATURE

Cutaneous malignant melanoma typically spreads to ocular structures in the setting of advanced metastatic disease.[52] However, it can also be the first sign of metastasis.[3,15,68] As the incidence of metastatic cutaneous melanoma increases, early recognition of ocular metastasis will offer the best chance to preserve the patient's quality of life.[3,15,68]

Several large-scale reviews have described characteristics of various cancers metastasizing to the eye, lids, and orbit. Relatively small reviews on cutaneous malignant melanoma metastasizing to the eye or orbit have been published. They examine a body of literature that is mostly composed of anecdotal case reports, comparisons to primary choroidal melanoma, epidemiology, or small studies focused on genetics or treatment. Autopsy studies have also reported on the incidence of asymptomatic ocular melanoma metastases.[26] To date, we could find no encompassing reviews on metastatic cutaneous melanoma to all ocular structures.

In 2003, Zografos et al reported the largest and most recent study of 12 patients with cutaneous

0039-6257/08/$–see front matter
doi:10.1016/j.survophthal.2008.02.003

melanoma metastatic to the eye and orbit.[80] Similarly, Ramaesh et al summarized literature of intraocular metastases from cutaneous melanoma (reporting a total of 68 eyes).[55] By combining prior reviews and a multitude of case reports together with our clinical experience, we present a comprehensive study of the characteristics of patients with ocular, adnexal, and orbital metastases from cutaneous melanoma. This review summarizes published patient characteristics, ocular presentations, features of metastatic disease, treatments, and patient outcomes.

We realize the potential for selection bias in this type of comprehensive report. Clearly, in such a broad array of studies and reviews, data are gathered differently with various patient populations, analyzed with different measures and objectives, and presented with a variety of purposes. However, in combing this multitude of information we descriptively, albeit not statistically, provide an overall picture of the world's experience with ocular metastatic cutaneous melanoma.

B. SYSTEMIC METASTASES FROM CUTANEOUS MELANOMA

Malignant melanoma is the ninth most common cancer and the leading cause of death from cutaneous malignancy.[72] Although early detection and surgical cures are common, stage IV disease (distant metastases) still accounts for 5% of melanoma cases and is associated with 5-year survival rates of only 22%.[73]

The eye is a rare site of distant metastases from cutaneous melanoma but the lung is common occurring in 18–36% of patients.[27] Although some studies have shown that over half of patients with metastatic cutaneous melanoma have lung metastases, most metastases first spread to the lymph nodes, skin, and subcutaneous tissues (42–57% of patients).[2,27] Liver (14–29%), brain (12–20%), and bone (11–17%) are other common sites of metastasis.[2,27]

C. METASTASES TO THE EYE AND ORBIT

Breast cancer, followed by lung and then unknown primary, are the most common malignancies to metastasize to the eye and orbit (accounting for over 75% of all ocular metastases).[12,29,32] Cutaneous melanoma has been reported to be the 4th or 5th most common although it accounts for less than 5% of all metastases to the eye and orbit.[12,29,32]

Consider the following relatively large studies of intraocular metastatic disease from systemic cancers. Castro reviewed 126 eyes with metastatic tumors finding that 49 eyes had primaries from the breast, 22 from the lung, 22 from unknown primaries, 11 from neuroblastoma, and 4 from cutaneous melanoma.[12] Freedman and Folk reported on 112 patients with metastatic disease to the eye.[29] Of these, breast primaries accounted for 55 patients, lung 16, unknown primaries 9, and cutaneous melanoma accounted for 5.[29] Therefore, cutaneous melanoma accounted for 3.2% and 4.5% of primaries metastatic to the eye.[12,29]

In a review of metastatic tumors to the orbit, Goldberg et al found the breast to be the most common primary source (accounting for 42% of patients), followed by lung and unknown primary at 11% each.[32] Prostate cancer was the primary in 8% and cutaneous melanoma in 5%.[32] Other studies have suggested that cutaneous melanomas can account up to 15% of all orbital metastases.[80]

Autopsy studies typically report larger numbers because they include patients with asymptomatic and end-stage metastatic cutaneous melanoma. The overall incidence of orbital and intraocular involvement has been reported from 1% up to 33% in autopsy series.[26,55] Although up to a third of patients with diffusely metastatic cutaneous melanoma have ocular metastases, it may be related to end-stage dissemination throughout the body prior to death.[80]

D. DIAGNOSIS OF METASTATIC CUTANEOUS MELANOMA

1. History and Clinical Examination

Differentiation between primary and metastatic intraocular melanoma can be difficult. A history of cutaneous melanoma and synchronous nonocular metastases is an important indicator.[15,17,19] Metastatic cutaneous melanomas typically grow more rapidly and are more aggressive than primary uveal melanomas.[3,7] In addition, metastatic melanomas in the uveal tract tend to be relatively flat and multifocal (Fig. 1).[28,33] Like most choroidal metastases, these cutaneous melanoma metastases are not likely to exhibit mature vasculature or fluorescein leakage (Fig. 2). However, exudative retinal detachments can occur. Both primary and metastatic choroidal melanomas will produce a transillumination shadow (Fig. 3). A diagnosis of metastatic cutaneous melanoma must be considered when bilateral, diffuse, and multifocal ocular melanomas are seen (Fig. 1).[17,33]

Clumps of pigmented cells in the vitreous or on the lens surface suggest metastatic cutaneous melanoma but have also been reported with primary uveal melanomas (Fig. 4).[10,35] It has been postulated that metastatic cutaneous melanoma is less likely to produce discrete tumor masses because individual melanoma cells gain access to the vitreous