Primary Orbital Melanoma: Presentation, Treatment, and Long-term Outcomes for 13 Patients

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Background: Periocular melanoma is a rare but often deadly malignancy that arises in the uvea (commonest origin), conjunctiva or orbit (rarest primary site). Melanoma accounts for 5–10% of metastatic/secondary orbital malignancies, but only a tiny proportion of primary orbital neoplasia. Primary orbital melanoma (POM) is exceedingly rare, with approximately 50 cases reported to date.

Methods: All patients seen in the orbital unit at a tertiary referral hospital (1991–2016) with a biopsy-proven diagnosis of POM were identified from a diagnostic database and were studied. The case notes, imaging, surgical approach, and histology were reviewed.

Results: Thirteen patients (five male; 38%) presented with isolated malignant melanoma of the orbit, for which no other primary site was identified at presentation or during an average follow-up of 44 months (median 22; range 0–13 years). The patients presented between the ages of 40 and 84 years (mean 55.5; median 48 years) and typically gave a short history of rapidly increasing proptosis and eyelid swelling. On the basis of history, a malignant lesion was suspected in most patients and all underwent incisional biopsy, with debulking of the mass in 10 (77%) patients, and skin-sparing exenteration in 3/13 (23%). Ten patients underwent orbital radiotherapy and the survival to date ranged from 9 months to 14 years (mean 55 months; median 23 months); two patients received solely palliative care for widespread disease and one patient refused orbital radiotherapy. Five of the 13 (38%) patients died from the disease.

Discussion: POM is a very rare malignancy, but clinical analysis of this cohort gives insight into disease presentation and prognosis. The tumor typically presents with a rapidly progressive, well-defined mass that is, in some cases, amenable to macroscopically intact excision. Unusual for malignant melanoma, some of these patients can show an unusually long period of quiescent disease after surgical debulking and radiotherapy.

Keywords: primary orbital melanoma, orbital malignancy, ocular melanoma, melanoma, orbital surgery

INTRODUCTION

Periocular melanoma is a rare, generally lethal, malignancy that can arise from within the eye (uveal tract), the conjunctiva, or the ocular adnexa (eyelid or orbit) (1). Uveal origin—from the iris, ciliary body or choroid—is the commonest ocular melanoma, with conjunctival melanoma being the second most frequent. The reported incidence of choroidal melanomas has increased in recent decades,
possibly because of greater exposure to UV light (2), or possibly due to greater detection. Eyelid melanomas are very rare, with knowledge limited to small case series (3–5).

Orbital melanoma occurs either as primary disease, as secondary disease (local invasion from a uveal, conjunctival, or eyelid primary tumor), or as metastatic disease from distant origins such as skin. Melanoma accounts for 5–20% of metastatic and secondary orbital malignancies, but only a minute proportion of primary orbital neoplasia (6–11). Primary orbital melanoma (POM) is extremely rare, with only about 50 cases reported to date (Table 1), and is thought to arise from melanocytic cells of the leptomeninges or ciliary nerves, or from ectopic intraorbital nests of melanocytes (12). POM can occur de novo, but it is often reported in association with pigmentary changes within pericocular tissues—such as nevus of Ota, blue cellular nevus, or oculo-dermal melanosis; indeed, over a half of patients with nevus of Ota have pigmentation within the orbit, including oculo-dermal melanosis (13). While POM is reported to have a very poor prognosis, there have been sporadic reports of long-survival, such as one patient who lived for almost 30 years after initial diagnosis (14).

Based on a series of patients with POM, this work aimed to extend the knowledge about clinical presentation, radiological appearance, surgical approach, and prognosis for this extremely rare condition.

### TABLE 1 | Summary of published cases of primary melanoma within the orbit.

| Number of cases | Gender | Age of onset | Side | Other features | Reference |
|-----------------|--------|--------------|------|---------------|-----------|
| 1               | M      | 34           | L    | Giant divided nevus | (15)      |
| 1               | F      | 8            | R    |                          | (16)      |
| 1               | F      | 34           | L    |                          | (17)      |
| 1               | M      | 45           | L    | Nevus of Ota            | (18)      |
| 1               | M      | 60           | L    | Poliosis                 | (19)      |
| 1               | M      | 50           | R    |                          | (20)      |
| 1               | M      | 22           | R    |                          | (21)      |
| 1               | F      | 64           | R    |                          | (22)      |
| 1               | M      | 59           | L    |                          | (23)      |
| 1               | F      | 43           | R    | Blue nevus              | (24)      |
| 10              | –      | Mean age = 57| –    | Survey of >1,200 orbital neoplasia | (25)      |
| 1               | F      | 36           | R    | Episceral nevus         | (26)      |
| 1               | M      | 40           | L    |                          | (27)      |
| 3               | F      | 45           | Unknown | Orbital nevus        | (28, 29) |
| 3               | F      | 33           | Unknown | Orbital nevus        | (28, 29) |
| 1               | M      | 43           | R    | Orbital nevus           | (30)      |
| 1               | M      | 29           | L    | Ocular melanosis        | (31)      |
| 1               | F      | 49           | L    | Ocular melanosis        | (32)      |
| 1               | F      | 5            | L    |                          | (33)      |
| 21              | –      | Mean age = 42| –    | Review of national pathology registry showed 19/21 had blue nevus | (33)      |
| 1               | M      | 79           | L    |                          | (34)      |
| 1               | M      | 76           | R    |                          | (35)      |
| 2               | M      | 46           | Unknown | Orbital nevus        | (36)      |
| 1               | M      | 59           | Unknown | Orbital nevus        | (37)      |
| 1               | F      | 17           | R    | Ocular melanosis        | (38)      |
| 1               | M      | 27           | R    | Blue nevus              | (39)      |
| 55 cases        | (14 M, 10 F) | Mean age = 44.4 years | –    | –                        | (40)      |
| Case no. | Gender | Age at onset (years) | Side | Primary treatment of orbital disease | Time orbital progression to orbital recurrence (months) | Systemic disease at presentation | Time orbital progression to systemic progression (months) | Systemic therapy | Survival from orbital onset (months) | Age at death (years) | Notes |
|----------|--------|---------------------|------|------------------------------------|-----------------------------------------------------|--------------------------------|------------------------------------------------|-----------------|----------------------------------|-------------------|-------|
| 1        | F      | 81                  | R    | Debulking                          | 3                                                  | N                              | 0                                            |                 |                                   |                   |       |
| 2        | M      | 40                  | L    | Exenteration                       | 0                                                  | Y                              | 0                                            |                 |                                   |                   |       |
| 3        | F      | 40                  | L    | Debulking + RT                     | 4                                                  | Y                              | 40                                           | Alive           | 22                                             | 40                |       |
| 4        | M      | 45                  | L    | Debulking + RT                     | 19                                                 | Y                              | 63                                           | Alive           | 85                                             | 85                |       |
| 5        | M      | 45                  | L    | Debulking + RT                     | 22                                                 | Y                              | 25                                           | Alive           | 24                                             | 25                |       |
| 6        | F      | 84                  | R    | Exenteration                       | 78                                                 | N                              | 12                                           | Y               | 0                                              | 12                |       |
| 7        | F      | 60                  | R    | Debulking + RT                     | 7                                                  | Y                              | 168                                          | Y               | 168                                            | 168               |       |
| 8        | M      | 45                  | L    | Debulking + RT                     | 45                                                 | N                              | 175                                          | Y               | 175                                            | 175               |       |
| 9        | F      | 45                  | L    | Debulking + RT                     | 45                                                 | Y                              | 45                                           | Y               | 168                                            | 168               |       |
| 10       | M      | 55                  | R    | Debulking + RT                     | 5                                                  | Y                              | 2                                            | Y               | 2                                              | 2                 |       |
| 11       | F      | 70                  | L    | Debulking + RT                     | 5                                                  | Y                              | 55                                           | Y               | 5                                              | 5                 |       |
| 12       | M      | 70                  | L    | Debulking + RT                     | 7                                                  | Y                              | 55                                           | Y               | 7                                              | 7                 |       |
| 13       | M      | 55                  | R    | Debulking + RT                     | 7                                                  | Y                              | 12                                           | Y               | 12                                             | 12                |       |

"RT" denotes fractionated external beam radiotherapy. All patients detailed in this table have given written informed consent for the publication of this data.

**Clinical Course and Outcome**

Eight of the thirteen patients are currently alive (at time of manuscript submission), with a mean survival of 44 months (median 22; range 9–175 months) and five have died from the disease—with highly variable survival between 3 and 174 months after diagnosis (mean 44; median 16 months) (Table 2).

Three patients had systemic involvement at presentation: Patients 1 and 2 had hepatic metastases and regional lymph node involvement, and both died within 4 months; patient 7 had temporal lobe metastases at presentation and died 22 months later. Patient 8 developed a liver metastasis at 45 months, underwent partial hepatectomy, and remains in remission at 77 months after the primary orbital presentation. Patient 13 developed liver metastases at 5 months after orbital surgery and is currently being treated with monoclonal antibody therapy, with significant tumor regression.

Three patients had progressive or recurrent orbital disease, this being about 6 months after orbital diagnosis in two patients (Cases 5 and 8; Table 2). The third patient (Case 9) is known to have had diffuse and widespread orbital infiltration at primary
surgery (Figures 2A,B), but remained with clinically and radiologically inactive orbital disease for 161 months (Figure 2C) before developing a rapidly progressive local recurrence that required multiple orbital tumor resections (Figure 2D); after inactive tumor for 13 years, the patient died with disseminated malignancy within 13 months of orbital reactivation.

The eight currently alive patients have a wide variation in follow-up times (9–72 months), but the side-effect profile of debulking surgery with adjuvant radiotherapy appears to be good. There have been no complaints of serious post-operative pain or diplopia. Visual acuity has been affected in all individuals, but to varying extents, but some useful vision was retained in all patients after debulking surgery and radiotherapy.

**DISCUSSION**

We present the clinical characteristics, treatment approaches, and long-term outcomes for 13 patients with POM, this representing the largest clinical series for this disease. Previous solitary case reports are consistent with our demographic findings—namely that most individuals are of white Northern European descent and present from the 5th decade (median age 48 years; range 40–84). One patient was West African and this would appear to be unique. Review of previously published cases suggests onset at a mean age of 44 (median 42 years), with the youngest case occurring in an 8-year-old girl and the oldest patient being 79 years (Table 1) (16, 38). Interestingly, two of our patients presented in their ninth decade, this being exceptionally late for POM. There does not appear to be any gender bias—with 19 affected men (14 previously reported + 5 in this study) and 18 affected women (10 previously reported + 8 in this study).

Imaging of patients consistently showed a well-circumscribed lesion that looked typically like a benign tumor or arteriovenous malformation; this characteristic has been previously described and might lead to delay in diagnosis and treatment of disease (39). MRI signal characteristics will generally help differentiate melanoma from benign lesions, such as cavernous hemangioma and could be considered in cases where there is diagnostic uncertainty (39). Our patients all had incisional biopsy and, where possible, resection of the mass, and all were considered for high-dose fractionated orbital radiotherapy to attempt control of residual local disease. Six patients underwent exenteration—three (Cases 2, 4, and 6) to control disfiguring orbital disease, two (Cases 5 and 8) for rapid disease progression after initial debulking, and one patient (Case 9) for very late recurrence of the orbital disease.

Despite reasonably uniform management, the outcome for this cohort of POM patients was highly variable: for example, two patients died very shortly after diagnosis, while three have survived 6 years or more. It would seem that this variable course does not depend solely on the presence of metastasis or systemic progression, as one of the longest surviving patients (Case 8) had partial hepatectomy for a liver metastasis. The surviving group (eight individuals, with three of these progressing to exenteration) was insufficiently large to draw conclusions about long-term visual outcomes in this patient group. There have, however, been other larger studies of more common orbital malignancies treated
with a combination of surgery and radiotherapy that have shown good visual outcomes. For example, in a study of orbital rhabdomyosarcoma, one third of patients maintained vision better than 6/9 in their treated eye, and approximately half maintaining vision of 6/9–6/60 (40).

Choroidal melanomas have been broadly classified as “type I” or “type II,” these following “aggressive” or “relatively indolent” courses, respectively. Several genetic signatures have been found for “type I” tumors—with monosomy 3, present in a half of uveal melanomas, being the most significant chromosomal aberration and strongly associated with metastasis and death (41, 42). Monosomy 3 affects prognosis due to tumor haploinsufficiency of BAP1—an important tumor suppressor gene (43, 44). Other chromosomal abnormalities, such as loss of 6q and gain of 8q, have been associated with poor prognosis in uveal melanoma (41). Point mutations in GNAQ and GNA11 have been identified in 80–90% of uveal melanomas and lead to activation of the MAPK/MEK/ERK pathway (43). It would be valuable to establish whether these genetic aberrations are present in POMs, and whether these relate to prognosis.

One patient (Case 9) is particularly interesting: despite receiving only orbital radiotherapy for widely infiltrating melanoma at the time of diagnosis (Figures 2A,B), she remained with no evidence of tumor proliferation until more than 13 years later. After tumor reactivation, however, it followed a very aggressive course (Figure 2C), requiring several palliative procedures, and the patient died 13 months later. Late metastatic or secondary melanoma to the orbit has been reported (45), and similar genetic factors might possibly control the late recurrence of both primary and secondary orbital melanomas; alternatively, the orbital milieu might pre-dispose to a prolonged tumor latency before late recurrence.

In summary, POM is an extremely rare malignancy of rather variable prognosis after treatment, for which local resection with adjuvant radiotherapy remains the mainstay of therapy. Disease can remain quiescent for extended periods of time before following an aggressive course. Immunotherapy might play a role in the future, but in this cohort, genetic testing did not suggest response to currently available agents in the majority of individuals. Further genetic investigation of these rare tumors might elucidate underlying molecular mechanisms of oncogenesis, thereby improving prognostication and treatment for this patient group.

ETHICS STATEMENT

This study received ethics approval from Moorfields Eye Hospital Biobank ethics board (15/SW/0104).

AUTHOR CONTRIBUTIONS

Concept and design of study—AR, CJ, DV, and GR. Clinical/histological examination of patients—PL, DV, and GR. Data collection—AR. Data analysis—AR and GR. Manuscript preparation and review—AR, PL, CJ, DV, and GR.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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