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CLINICAL RESEARCH

Primary orbital melanoma: a case series and literature review

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ABSTRACT

Primary orbital melanoma (POM) is a very rare condition. We report further four cases and review all previously reported cases. We present a multicentre retrospective review of patients with POM. Clinical, radiological, surgical, histological, and follow-up data is presented. Four patients with POM were identified between 2000 and 2013. All presented with proptosis and diplopia without reduced vision. Two had known pre-existing blue cell naevi. All were stage T1N0M0. All underwent exenteration with adjuvant radiotherapy. All are disease free at follow-up durations of 24–151 months. The present three cases and review of all cases in the literature suggest a higher likelihood of disease-free survival from primary exenteration (7/8 disease-free survival, 1/8 death from metastatic disease) than wide local excision (7/16 disease-free survival, 9 recurrence or metastasis of whom 4 died). Adjuvant radiotherapy may additionally improve outcomes.

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Adjuvant treatment; blue cellular naevus; congenital ocular melanocytosis; exenteration; Orbit; primary orbital melanoma

Introduction

Primary orbital melanomas (POM) account for around 1% of all orbital tumours.¹ They develop from areas of congenital melanocytic cells in the orbit, which are usually either hypercellular blue naevi (a congenital, thickened, periocular, pigmented naevus of slate grey–blue colour) or congenital ocular melanocytosis (a flat grey–blue area of cutaneous pigmentation associated with episcleral pigmentation).² They typically present with gradual painless proptosis sometimes with distorted or reduced vision. The natural history of POM is poorly described and there is not a consensus on its optimal management. We report four patients with POM followed for a minimum of three years and review the literature on this condition.



Materials and methods

This study was a retrospective case note review of all patients with POM managed at two tertiary referral orbital units in Australia and one in the United Kingdom. Cases were identified in Australia using an Australian and New

Zealand Society of Ophthalmic Plastic Surgeons wide data survey. Only cases with a firm clinical and pathological diagnosis of POM were included. All cases had a complete clinical examination and whole body CT and/or PET/CT scanning to exclude melanoma elsewhere. The following exclusion criteria were used:

- (1) Evidence from clinical history, examination or imaging of primary melanoma elsewhere, including of the uvea or conjunctiva.
- (2) Orbital melanoma with BRAF mutation positivity, as this is suggestive of metastasis of a cutaneous origin.

The case notes of identified cases were reviewed for demographic, clinical, radiological, pathological, treatment and follow-up data. The American Joint Committee for Cancer classifications (TNM Definitions) for solid orbital tumours/carcinomas of the lacrimal gland (e.g. adenoidcystic carcinoma of lacrimal gland) is most applicable to POM and is used in the present study.³

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Precis

Three new cases of primary orbital melanoma are presented and reviewed in conjunction with the 49 previously reported cases.

Colour versions of one or more of the figures in the article can be found online at www.tandfonline.com/iorb.

This article was originally published with errors. This version has been corrected. Please see Corrigendum. (<http://dx.doi.org/10.1080/01676830.2018.1446728>)

Ethical approval was received from the Royal Adelaide Hospital Research Ethics Committee.

Results

Four patients with POM were identified. All were Caucasian, two (50%) were male and the average age was 43. Three presented with proptosis and diplopia but without visual loss and one with reduced vision. Two tumours derived from known pre-existing blue cell naevi, one had a previously unknown orbital blue cell naevus revealed during surgery and the other had no evidence of a lesion of origin. The mean tumour size on imaging was 18.5 mm. In each case, thorough physical and radiological examination (chest x-ray, ultrasonography of the abdomen, and computerised tomography (CT) scan of the neck) did not identify primary or secondary lesions elsewhere. All four tumours were staged as per the AJCC staging system as T1N0M0 and were BRAF mutation negative.

All four patients had excision of the tumour with clear margins with adjuvant orbital radiotherapy (60 grey). Case 1 additionally had temozolamide chemotherapy. They all are disease free at an average of 73 months of post-operative follow-up (case 1: 151 months, case 2: 85 months, case 3: 33 months, case 4: 24 months). Case-specific details are reported below:

Case 1

(Figure 1)

A 27-year-old male had a patch of slate-grey, superior, bulbar scleral pigmentation present from birth. The pigmentation was deep to the conjunctiva and immobile. CT scanning demonstrated a 30 mm maximum diameter, mildly contrast enhancing, well-circumscribed lesion in the superior orbit with excavated, non-lytic bony changes in the adjacent roof of the orbit. An incisional biopsy found a POM, probably arising from a cellular blue cellular naevus. He underwent an extended exenteration, including removal of the orbital roof and frontal dura, which were both heavily pigmented in the area overlying the lesion. The underlying brain was macroscopically normal.

Histopathological examination found densely hypercellular, intensely pigmented tumour with atypical cells, which resembled melanocytes infiltrating into connective tissue. The atypical melanocytes were of mixed type (spindle and epithelioid). The tumour cells showed hyperchromatism, pleomorphism, multinucleation, increased nuclear-cytoplasmic ratio, and atypical mitoses (with a moderate mitotic count of 5–10/40 HPF). The resected margins were free from tumour cells. Immunohistochemistry was BRAF negative with BAP1 lost in both the melanoma and naevus components of the lesion.

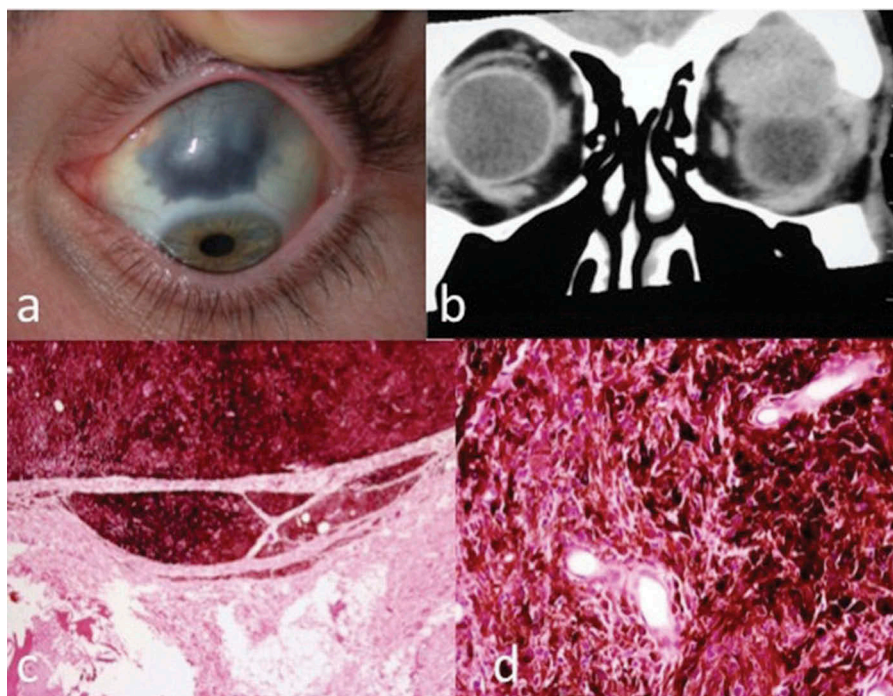


Figure 1. Patient 1. (a) Slate grey scleral pigmentation present since birth. (b) CT scan demonstrated superior orbital mass. (c) H&E $\times 200$ magnification showing tumour arising from internal surface of sclera but also involving episcleral soft tissue. (d) H&E $\times 400$ magnification showing densely hypercellular, intensely pigmented tumour.

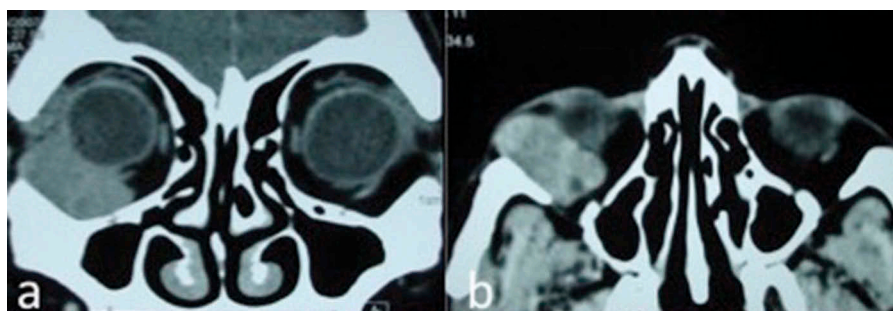


Figure 2. Patient 2. (a) and (b) Coronal CT scan showing extensive infero-lateral orbital mass extending to the orbital apex.

Case 2

(Figure 2)

A 70-year-old female presented with diplopia and right eye proptosis. She had no history of ocular or periocular pigmentation. CT scan demonstrated a 20 mm maximum diameter, slightly irregular and mildly contrast-enhancing lesion in the inferior and lateral quadrants of the orbit. The adjacent bone was normal. An incisional biopsy of the deeply pigmented mass found melanoma. Exenteration of the right orbit was performed. Histopathological examination revealed a mixed cell type melanoma with low mitotic figure count (<5/40 HPF). Ovoid and spindle-shaped tumour cells were seen at the tumour junction as well as infiltrating into underlying connective tissue. Small foci of melanocytic cells were identified in scattered sections of the orbit including the episclera and extraocular muscle. Immunohistochemistry examination found BAP1 staining to be lost and BRAF V600E was negative.

Case 3

(Figure 3)

A 50-year-old man who had had an area of dark pigmentation of the left upper eyelid, since a young age, presented with rapid proptosis that was initially treated as orbital cellulitis. It was followed by gradually progressive proptosis over 3 months. CT scanning revealed a 21 mm maximum diameter, mildly contrast-enhancing lesion in the superior and lateral orbit with secondary excavating, non-lytic bony remodelling changes in the roof and lateral wall of the left orbit. An incisional biopsy diagnosed POM change in a cellular blue naevus. He underwent extended (lateral zygomatic bone) exenteration. The roof of the orbit was noted to be discoloured from the blue cellular naevus changes. Histopathological examination showed densely hypercellular, intensely pigmented tumour with atypical cells that resembled melanocytes infiltrating into connective tissue. The atypical melanocytes were of mixed type

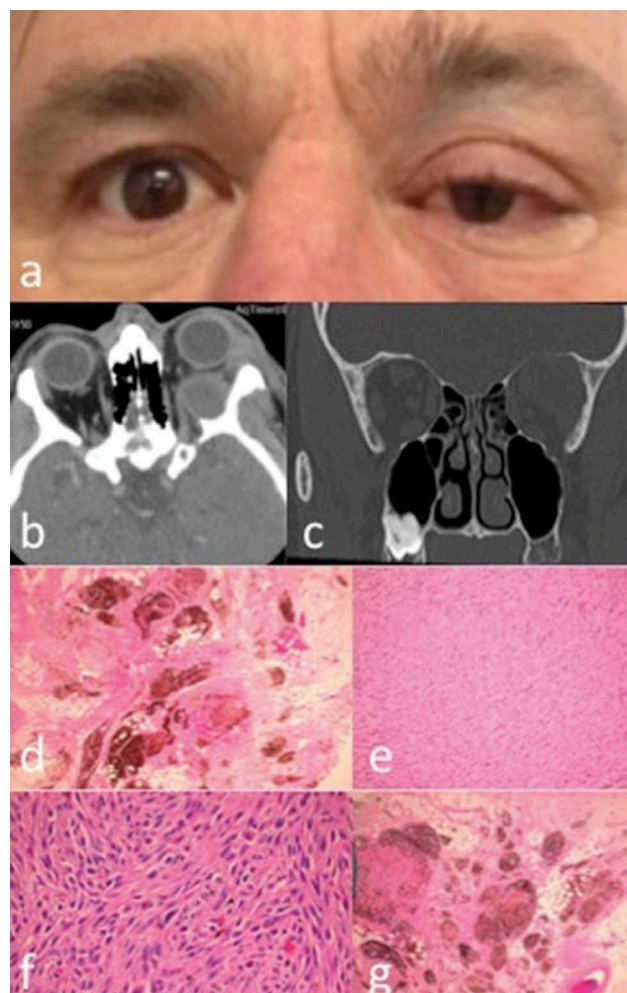


Figure 3. Patient 3. (a) Clinical photo at presentation showing ptosis, proptosis, and mild periocular erythema on affected side. (b) and (c) CT scans showing a large well circumscribed left retrobulbar mass with associated osteolytic changes. (d) H&E $\times 4$ magnification showing cellular blue naevus. (e) H&E $\times 20$ magnification showing spindle cells. (f) H&E $\times 40$ magnification showing cellular atypia. (g) H&E $\times 20$ magnification showing infiltrative focus.

(spindle and epitheloid). The tumour cells showed hyperchromatism, pleomorphism, multinucleation, increased nuclear-cytoplasmic ratio, and atypical mitoses (low mitotic count <5/40 HPF). The resection

margins were uninvolved. Immunohistochemistry found BAP1 to be retained and BRAF to be negative in both the melanoma and naevus components of the lesion.

CASE 4

A 26-year-old lady presented with a 2-week history of diplopia, reduced left eye vision, morning headaches, subconjunctival haemorrhage, and periocular swelling. On examination, there was marked restriction of left lateral gaze and upgaze and two millimetres of proptosis. MRI and CT scanning demonstrated a well-defined, irregularly contoured, contrast enhancing, intraconal soft tissue mass of homogenous signal intensity in the postero-lateral that was distorting the globe and displacing the optic nerve. The vision worsened rapidly despite treatment with intravenous methylprednisolone and was no perception light two weeks later. The lesion was firm and yellow on biopsy. Histopathological examination showed a partly necrotic mass of spindle and epithelioid cells which focally contained brown pigment material and were positive for HMB45, S100, AE1/3, CAM 5.2, MNF, and CK7. It was negative for CD3, CD10, CD34, CK14, CK5/6, CK19, CK20, Desmin, ER, PR, SMA, and HMC. Cytogenetic analysis found no evidence of NRA or BRAF mutation. The patient underwent exenteration with an irradiated socket allograft and adjuvant radiotherapy. The resection margins were uninvolved and she has been followed-up for two years without evidence of recurrence or systemic disease.

Discussion

POM is a rare condition. Including the present four cases, only 50 confirmed cases have been reported (Table 1). POM develops from rests of orbital melanocytes. In half of cases (25/49 cases), pre-existing skin pigmentation is present. In the other half, the tumour presumably derives from clinically unapparent foci of melanocytes, or subcutaneous orbital naevi, which may be seen as blue discolouration of bone or surrounding tissue that is sometimes noted intraoperatively. Pre-existing skin pigmentation is invariably either a blue cell naevus or oculodermal melanocytosis (naevus of Ota), with one reported case of giant divided naevus.⁴ However, these lesions have overlapping clinical appearances and similar histopathological features and the terms appear to have been used interchangeably in some reports. Blue cell naevi are collections of dermal

Table 1. Demographic, clinical, treatment and outcome data from 54 cases of primary orbital melanoma, comprised of 51 reported cases and the 4 present cases.

Parameter	Summated data from 54 cases
Age	46 (5–84)
Gender	66.7% male
Racial distribution	Caucasian: 38 Asian: 2 SE Asian: 4 African Black: 2 Unreported: 9
Origin of tumour	Ocular melanocytosis: 30 Blue cell naevus: 10 Unreported: 15
Duration of symptoms	3–156 months
Presenting symptoms	Proptosis: 42/54 patients Dystopia: 13/54 Decreased VA: 13/54
Mortality	15/50 cases with follow-up data
Primary treatment (Data for 45)	Exenteration only: 4, 10 Wide excision only: 6 Exenteration + RTX: 2, 6, 4 Exenteration + CTX: 1 Exenteration + RTX & CTX: 1, 4, 1 Wide excision + RTX: 3 Wide excision + CTX: Wide excision + RTX & CTX: 2 RTX only: 2 CTX only: 1

dendritic melanocytes that do not involve the epidermis (the deeper location causes the blue appearance) with an associated change in the dermal collagen structure.⁴ They are most commonly located on the dorsal surface of the hands and feet, the scalp, and the buttocks. Oculodermal melanocytosis (naevus of Ota) is a very similar collection of melanocytes, but with less concentrated aggregates of pigmented dendritic melanocytes than blue naevi. The malignant transformation of both these lesions is very rare and the pathophysiology is poorly understood.

There was a male preponderance in previously reported series. The reason for this is not known and contrasts with ocular/oculodermal melanocytosis having equal sex distribution and anecdotal reports of blue naevi being more common in females.⁵

A thorough clinical and radiological examination and histopathological assessment of the specimen are required to confirm the diagnosis of POM (as compared to a secondary lesion from melanoma elsewhere). POM consists of spindle cells, epithelioid cells, or a mixture of these. Around half of cases (21/45 reported cases in which histopathological descriptions provided) are spindle cell tumours, 6/45 epithelioid, and the remainder mixed. The epithelioid granular melanosomes are round and uniform. Immunohistochemistry of primary lesions is positive for S100, antimelanoma-specific antibody, HMB 45 and are negative for BRAF

mutations. These features are almost identical to those of uveal melanoma, although orbital melanoma usually does not have satellite specks of flat brown melanosis that are seen in uveal melanoma. Metastatic orbital melanomas are comprised predominantly of one cell type (usually epithelioid cells), which are larger and display greater atypical and higher mitotic counts than POM cells, and S-100 staining is equivocal or absent.

Orbital exenteration with clear margins and adjuvant radiotherapy has had excellent outcomes in the present T1N0M0 cases. The favourable outcome in our patients may be related to a combination of the tumours having a mixed cell population with low mitotic rates (in three of four cases) and clear excision margins in all cases. Outcomes reported in the literature favour exenteration as the primary treatment. Adequate surgical and follow-up data is present in 25 reports of POM.^{6–24} A total of 9 of these underwent exenteration as the primary treatment of whom 1 died and 8 had disease-free survival at 1–4 years post-operatively. The other 16 underwent wide local excision, of whom 7 were disease free at similar follow-up timescales, but 9 had recurrence or metastasis of whom 4 died and the others underwent further wide local excision or secondary exenteration. However, this is a heterogeneous group of tumours, with varied cellular composition, mitotic count, and staining patterns. The cell type does not appear to influence outcomes, but the mitotic count is unsurprisingly critical; Tellada et al. report poor outcomes when the mean mitotic count was greater than 10 per high power field.² Three of the four present cases have low mitotic counts and it is therefore possible that wide local excision may have been equally successful.

There is inadequate data in the literature to infer the benefit of adjunctive radiotherapy or chemotherapy. However, if high-dose radiotherapy is planned, the vision or even globe may not be preserved which may further support exenteration as the primary therapy to both maximise the chance of clearance and minimise the likelihood of further surgical procedures to manage recurrence or a painful blind eye.

The present four cases with long-term follow-up add further evidence to the literature that POM can be effectively treated with orbital exenteration and radiotherapy.

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

References

1. Shields JA, Bakewell B, Augsburger JJ, Flanagan JC. Classification and incidence of space-occupying lesions of the orbit. A survey of 645 biopsies. *Arch Ophthalmol.* 1984;102(11):1606–1611.
2. Tellada M, Specht CS, McLean IW, Grossniklaus HE, Zimmerman LE. Primary orbital melanomas. *Ophthalmology.* 1996;103(6):929–932.
3. Edge S, Byrd DR, Compton CC, Fritz AG, Green FL, Trotti A. *AJCC Cancer Staging Manual.* 7th ed. New York: Springer-Verlag; 2010.
4. Patterson JW. *Weedon's Skin Pathology.* London, UK: Churchill Livingstone. 2016.
5. Gonder JR, Ezell PC, Shields JA, Augsburger JJ. Ocular melanocytosis. A study to determine the prevalence rate of ocular melanocytosis. *Ophthalmology.* 1982;89(8):950–952.
6. Alsuhaibani AH, Alhumayed M. Primary orbital melanoma with poliosis and a palpable mass. *Arch Ophthalmol.* 2011;129(10):1382–1383.
7. Coppeto JR, Jaffe R, Gillies CG. Primary orbital melanoma. *Arch Ophthalmol.* 1978;96(12):2255–2258.
8. De Potter P, Levecq L, Godfraind C, Renard L. Primary orbital melanoma treated with iodine-125 plaque radiotherapy. *Am J Ophthalmol.* 2006;142(5):864–866.
9. Delaney YM, Hague S, McDonald B. Aggressive primary orbital melanoma in a young white man with no predisposing ocular features. *Arch Ophthalmol.* 2004;122(1):118–121.
10. Drews RC. Primary malignant melanoma of the orbit in a Negro. *Arch Ophthalmol.* 1975;93(5):335–336.
11. Elibol O, Yuksel N, Egilmez HR, Arici S, Mizrak B. A case of primary orbital melanoma treated by local excision. *Br J Ophthalmol.* 1995;79(12):1146–1148.
12. Friedrich RE, Grzyska U, Schafer H, Li L. Navigation-assisted resection of a primary extraocular melanoma of the orbit. *Anticancer Res.* 2007;27(4A):1799–1803.
13. Ijiri R, Tanaka Y, Kato K, Sekido K, Sato H, Ito D. Primary orbital melanoma in a child. *Med Pediatr Oncol.* 2000;35(2):142–143.
14. Ke Y, Ren X, Zhu L, et al. Primary orbital melanoma combined with giant divided nevus of the eyelid. *J Craniofac Surg.* 2014;25(1):e4–7.
15. Koranyi K, Slowik F, Hajda M, Banfalvi T. Primary orbital melanoma associated with oculodermal melanocytosis. *Orbit.* 2000;19(1):21–30.
16. Krishnakumar S, Lakshmi S, Abhyankar D, Biswas J. Loss of antigen-processing molecules in primary orbital melanoma. *Orbit.* 2003;22(4):265–270.
17. Lee V, Sandy C, Rose GE, Moseley IM, Cree I, Hungerford JL. Primary orbital melanoma masquerading as vascular anomalies. *Eye (Lond).* 2002;16(1):16–20.
18. Mandeville JT, Grove AS Jr., Dadras SS, Zembowicz AM. Primary orbital melanoma associated with an occult episcleral nevus. *Arch Ophthalmol.* 2004;122(2):287–290.

19. Patrocinio LG, Lourenco C, do Prado Silva C, Db B, Patrocinio JA. Primary malignant orbit melanoma. *Braz J Otorhinolaryngol.* 2006;72(5):716.
20. Polito E, Leccisotti A. Primary and secondary orbital melanomas: a clinical and prognostic study. *Ophthal Plast Reconstr Surg.* 1995;11(3):169–181.
21. Radhadevi CV, Charles KS, Lathika VK. Orbital malignant melanoma associated with nevus of Ota. *Indian J Ophthalmol.* 2013;61(6):306–309.
22. Rice CD, Brown HH. Primary orbital melanoma associated with orbital melanocytosis. *Arch Ophthalmol.* 1990;108(8):1130–1134.
23. Rottino A, Kelly AS. Primary Orbital Melanoma. Case report with review of the literature. *Arch Ophthalmol.* 1942;27(5):934–949.
24. Shields JA, Shields CL, Eagle RC Jr., De Potter P, Oliver GL. Necrotic orbital melanoma arising de novo. *Br J Ophthalmol.* 1993;77(3):187–189.