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Congenital uveal malignant melanoma- A rare case report

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ABSTRACT

Purpose: To report a rare case of congenital uveal malignant melanoma from Indian subcontinent in an infant with multiple cutaneous naevi and no distant metastasis.

Observation: An 8 month old male child presented with proptosis and black discoloration in the right eye since birth. Enucleation of the right eye was performed and specimen sent for histopathology and immunohistochemical analysis. Results were strongly suggestive of a malignant melanoma of uvea. No metastasis was found on MRI scan of brain, chest and abdomen. Patient is on close follow up and will be subjected to metastasis workup every 6 months.

Conclusion and importance: This entity of congenital uveal malignant melanoma is rather rare with very few reported cases across the globe and needs further understanding of its correct line of treatment.

1. Introduction

Malignant melanoma is a tumour arising from melanocytes. It originates from various tissues, most common being the skin. Other primary sites include, juxtacutaneous mucous membranes, meninges, and ocular tissues (iris, ciliary body and choroid). Uveal melanoma occurs at an average age of 55 years and is rare in children and young adults.[1]

Various reports have documented the occurrence of uveal melanoma in children, infants, and even new-borns. It has been found that 0.6%–1.6% of all uveal melanomas in a large pathology laboratory were from children and young adults.[2,3] Several overlapping studies on uveal melanoma in adolescents have originated from the Armed Forces Institute of Pathology (AFIP) and have suggested that the tumour in them and children do not differ significantly in clinical appearance or prognosis.[2,4,5] Other studies have indicated that childhood uveal melanoma has a more favourable prognosis.[6–8]

2. Case report

An 8 month old male child, born full term out of a non-consanguineous marriage presented to us, with significant proptosis of the right eye with blackish discolouration temporally which was present since birth and had gradually progressed in its extent (Fig. 1B). There were several raised cutaneous naevi measuring 1 mm–3 mm in diameter found on the back as well as limbs of the child (Fig. 1A). The pigmented lesions revealed characteristics of a typical nevus having smooth surface, distinct borders and round configuration.they were neither vascular nor compressible. The surrounding periocular skin showed no pigmentation ruling out the possibility of oculodermal melanocytosis. Other systems were normal and no lymphadenopathy was noted. There was no family history of pigmentary disorder and examination of mother showed no lesions suggestive of melanoma.

Examination of the right eye revealed proptosis with blackish discolouration of sclera in three quadrants except nasally. There was an island of swelling with central surface ulceration adjoining the cornea (Fig. 1B and C). Examination under anaesthesia confirmed the above findings. Cornea was hazy with an unrecordably high intraocular pressure obscuring further details. The fellow eye was normal.

Magnetic Resonance Imaging of brain and orbit showed no evidence of any mass lesion within the right globe. However, T1 weighted image showed high signal area which corresponded with the anteriorly located nodulo-ulcerative lesion. Scleral thinning with a stretched right optic nerve was documented. The findings were suggestive of right eye staphyloma (Fig. 2B).

Patient underwent an uneventful enucleation with myoconjunctivalization technique and a 16 mm spherical acrylic implant was inserted posterior to the posterior tenons. The child was subsequently fitted with a customised ocular prosthesis (Fig. 1D). Enucleation was performed with gentle dissection and minimal manipulation technique, taking care not to rupture the thinned out sclera in an attempt to prevent extraocular seeding.[9]

Gross examination of the enucleated specimen revealed black

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discolouration of the globe and asymmetric thinning of the sclera. The globe measured 30 mm in length and 25mm in width. Sclera overlying the discolouration was grossly intact posteriorly. However, a breach was noted overlying the thickened nodular lesion anteriorly (Fig. 1C). Optic nerve was 0.5 cm in length and was uninvolved.

Histopathological examination indicated tumour arising from melanocytes. H and E stained slides with serial section of portions of sclera choroid and retina showed densely pigmented melanocytes throughout the choroid. Multiple nodular epitheloid tumour cells with prominent nucleoli with atypia was noted. There was no extraocular extension and multiple sections taken from optic nerve were free from tumour cells (Fig. 2D). The report was suggestive of choroidal malignant melanoma (Fig. 2A). Immunohistochemistry further confirmed the diagnosis with positive titres for S-100 (Fig. 2C) and Human melanoma black 45 (HMB-45) and Melan- A, while negative for Cytokeratin (CK) tumour markers. Molecular prognostic testing to determine melanocytic origin of tumour was offered to the patient but declined by parents.

Systemic workup including MRI brain, chest and abdomen showed no evidence of metastasis. Since extraocular and optic nerve involvement was ruled out, and no distant spread was detected, we, in concurrence with the oncologists, decided to keep the child on close follow up and advised a thorough metastatic workup at regular intervals. We intend to perform MRI of brain and orbit quarterly till the age of 1 year and then half yearly up to the age of 5 years. Liver MRI and liver function tests will be sought half yearly for lifetime (Dr. Carol Shields, written communication, August 17, 2020).

3. Discussion

Congenital uveal malignant melanoma is exceedingly rare, only 5 confirmed cases have been documented since 1966.[10–14] After detailed review of literature we believe our patient is the first case reported from the Indian subcontinent.

Singh et al.[15] concluded that Congenital uveal melanoma can pose a diagnostic dilemma. It has an Asian predominance and presents with hyperpigmented buphthalmos. It can be associated with cutaneous nevi and shows characteristic histopathologic features including diffuse uveal involvement and a tendency for extraocular extension.

In our patient, the morphological features of tumour cells, histopathological findings and positive immunohistochemical values strongly suggests malignant melanoma arising from choroid. On microscopic evaluation, densely pigmented melanocytes were seen with multiple epithelioid tumour cells showing a large nucleus, prominent nucleoli and atypia confirming epithelioid type of congenital choroidal malignant melanoma. These findings help differentiate it from a melanocytoma which shows highly pigmented polyhedral cells with abundant cytoplasm and relatively small nuclei, fewer nucleoli and a low N/C ratio.[16]

Melanocytic lesions, including malignant melanoma, are typically immunoreactive for S-100 protein, Neuron Specific Enolase (NSE), and vimentin but negative for CK, Glial Fibrillar Acidic Protein (GFAP), and neurofilament.[17–21] HMB45, a marker of the cytoplasmic premelanosomal glycoprotein gp100, was one of the first melanoma 'specific' markers discovered.[22] It is not as sensitive as S100 but has greater specificity.[23] K.J. Busam et al. proved that Melan A antibodies (A103 and M2-7C10) seem most suitable for the detection of metastatic melanoma and both antibodies appear slightly more sensitive than HMB-45.[24] In our patient, S100, HMB45 and Melan -A were positive, further establishing the diagnosis.

It could be presumed our patient had tumour that was secondary to primary lesion elsewhere in the body but clinical evaluation and imaging done, excluded this possibility.

All the five previously reported cases show varied presentation of congenital malignant melanoma with no established protocol of management, owing to its rarity. Details of the case reports have been tabulated (Table 1).

Although clinical and histological characteristics of this tumour in our patient favours the diagnosis of primary malignant melanoma of choroid, possibility of familial atypical multiple mole melanoma syndrome (FAMMM) can be considered as a differential diagnosis. FAMMM

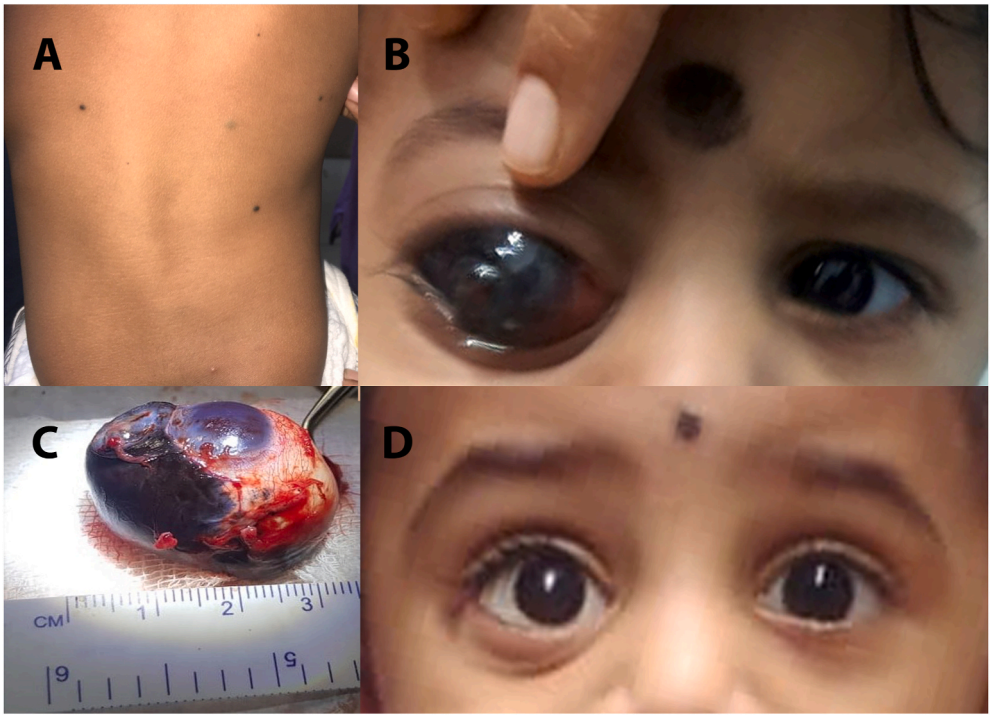

Fig. 1. Clinical photo-congenital malignant melanoma.
A- Multiple cutaneous naevi on the back of the patient.; B- Right eye with proptosis and blackish discolouration present since birth; C- Enucleated right eye showing temporal discolouration of sclera with anterior ulcerated swelling adjoining the cornea; D- Right eye post enucleation with prosthesis in place.

syndrome (B–K mole or dysplastic nevus syndrome) presents with multiple atypical nevi or primary melanomas that affect multiple organ systems, including the skin and eye. Patients may have hundreds of moles and a significant family history of melanoma. There is also an increased risk for other primary malignancies like, pancreatic cancer.[25] Our patient had no family history of melanoma or dysplastic naevus in first or second degree relatives and the naevi found on the body were all smaller than 5mm with no atypical features (Fig. 1A). The cutaneous nevi could also be confused with the ones found in blue rubber bleb syndrome. They are characterised by lesions in the form of angiomas which are rubbery and soft in consistency, being haemorrhagic and compressible.[26] However, no such features were seen in our patient. According to Nakul Singh et al.,[27] uveal melanoma can have several phenotypic associations like oculodermal melanocytosis, which involves congenital hyperpigmentation of episcleral, uveal tissue, orbit, skin and meninges with occurrence of uveal melanoma on the ipsilateral side of the ocular and dermal hyperpigmentation. Our patient showed no features of dermal or periocular hyperpigmentation. They found BAP1 mutations in families with uveal and cutaneous melanoma and in patients diagnosed with familial uveal melanoma, suggesting a strong association between cutaneous and uveal melanoma. Although, this mutation also predisposed to other cancers like, malignant mesothelioma, and meningioma.

Most commonly found gene mutations in uveal melanoma are the GNAQ (G protein subunit alpha Q) and GNA11 mutations.[28] Naevi frequently show initial activating mutations for example BRAF (B- Raf proto-oncogene) or GNAQ/11, and additional mutations are usually needed for progression to malignant melanoma. The specific mutations commonly found in uveal melanoma are in splicing factor 3b subunit 1 (SF3B1), eukaryotic translation initiation factor 1A X linked (EIF1AX) or BRCA1 (breast cancer gene 1) -associated protein (BAP)1. BAP1 mutations are associated with poor prognosis compared to SF3B1 and EIF1AX.[29]

Broadway et al. showed that response to chemotherapy of malignant melanoma in children was more favourable than in adults but the number of patients studied were few and all had distant metastasis.[11] Vincristine Actinomycin and Cyclophosphamide or VAC regime is considered ideal for children with malignant melanoma.[11,14,30]

The prognosis of malignant melanoma is reported to be better in children compared to adults. Shields and colleagues reported lower tumour-related metastasis and death in young patients (≤20 years) compared to older adults and better prognosis in children was independent of tumour size.[31]

Absence of extraocular spread and distant metastasis in our case prompted us to withhold chemotherapy and adopt a strategy of half yearly follow up to rule out recurrence, development of new lesions in the other eye, change in the appearance or size of cutaneous lesions and metastatic spread. At six-month follow-up, the child was free of recurrence or metastasis.

4. Conclusion

Congenital uveal malignant melanoma is extremely rare with few reports emerging across the globe occasionally. Follow-up time for majority of cases is less than 5 years. Further studies are indicated to define a protocol in managing them.

Patient consent

The patient's legal guardian consented to publication of the case in writing.

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Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

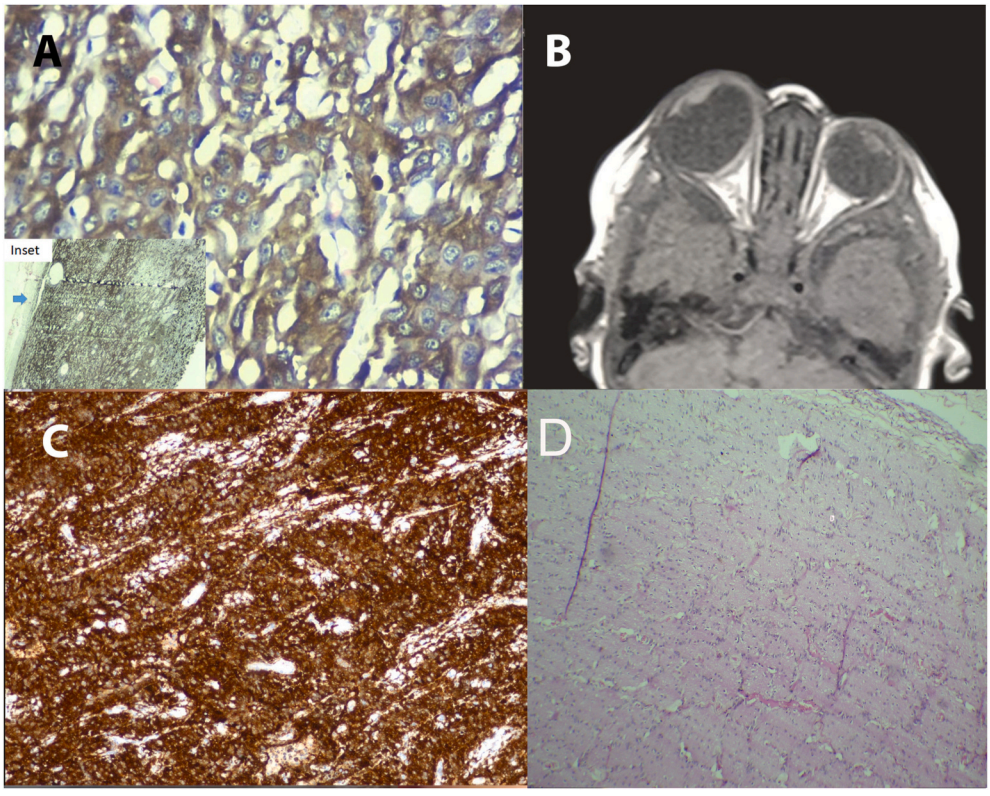

Fig. 2. Investigation findings-congenital malignant melanoma.
A- Microphotograph showing pigmented melanoma cells in the choroid with the use of Haematoxylin and Eosin stain. The tumour cells are large with residual chromatin in the nucleus and prominent nucleoli. Inset showing 4× magnification of the choroidal pigmented tumor. Blue arrow shows the sclera; B- MRI brain and orbit showing staphyloma with increase in anteroposterior diameter of the right globe; C- Immunohistochemistry showing positive for S100. D-haematoxylin and Eosin stained section of optic nerve showing no invasion of tumor cells. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Clinical presentation, treatment and outcome of reported cases of malignant melanoma across the globe.

AUTHOR, YEAR OF PUBLICATION	SEX AND AGE AT PRESENTATION,	SITE	ASSOCIATED FEATURES	PATHOLOGY	TREATMENT	FOLLOW UP	OUTCOME
Greer[11] 1966	5 day old male, left eye	Iridociliary	Cutaneous nevi	Predominently mixed cells	Enucleation	2 years	Alive, well
Broadway[12] 1991	At birth, female, left eye	Diffuse uveal with extraocular extension	Cutaneous nevi and hepatic metastasis	Epitheloid cells	Enucleation, chemotherapy	2 years 10 months	Alive, well
Posnick[13] 1993	At birth, female, left eye	Diffuse uveal with extraocular extension		Epitheloid cells	Radiation, chemotherapy, exenteration	2 years	Alive, well
Palazzi[14] 2005	At birth, male, right eye	Ciliochoroidal with extraocular extension	Cutaneous nevi and melanoma	Mixed cell cells	Enucleation, chemotherapy	10 years	Alive, well
Pukurushpan[15] 2014	7 week, female, left eye	Iridociliochoroidal with extraocular extension	None	Epitheloid cells	Subtotal exenteration, chemotherapy	4 years 3 months	Alive, well

Declaration of competing interest

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