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REVIEW ARTICLE

Intraocular malignant melanoma- A Study of twelve years

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Manuscript Info *Abstract*

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Objectives: To study the incidence of uveal melanoma in M and J institute Civil, Ahmadabad with reference to age, gender, site and microscopic variants.
Method: A retrospective study of ocular tumors were done over a period of 12 years from 2001 to 2012.Detailed history, clinical examination, radiological investigation and histopathological examination were done along with IHC as and when required.
RESULTS: Total 215 cases of ocular tumors were diagnosed out of which 42 cases were of ocular malignant melanoma. Mean age of presentation was 55years with predisposition in males. Most common microscopic type was mixed cell type(86%).sclera invasion was in 7.14% extra ocular spread in 4.76% and optic nerve invasion was not found in any case.

Introduction

In adults melanoma is most common primary intraocular cancer followed by primary intraocular lymphoma.It is the second most common type of melanoma after cutaneous. It arises from melanocytes situated in conjunctival membrane and uveal tract of the eye. Although rarely, it can also arise from melanocytes located in the orbit. Great majority of ocular melanomas are primary however, metastatic melanoma from primary cutaneous site can also occur in the ocular region, and it accounts for less than 5% of all metastases to the eye and orbit[1].

Uvea is the most frequent site of origin of ocular melanomas and comprises 82.5% of all of them, while conjunctival melanoma is far less common. It can affect any part of the uveal tract, but choroidal melanoma is predominant (86.3%), while iris and ciliary body melanomas are far less frequent. Choroidal and ciliary body melanoma are together named posterior uveal melanoma and have some different features compared to iris or anterior uveal melanoma. Intraocular melanoma can simultaneously involve more than one uvealstructure.Iris melanoma is the least common uveal melanoma, but has more benign clinical course compared with posterior uveal melanoma.

Ocular melanoma rates are 8-10 times higher among whites compared with blacks, but although obvious this difference is less pronounced compared to cutaneous melanoma which shows 16 times higher rates among whites [2].It is generally estimated that the occurrence of uveal melanoma in asian patients is somewhere between that found in black and white populations.Zimmerman estimated that the incidence of uveal melanoma in white patients is three fold greater than in certain asian groups.

There is a higher incidence of uveal melanoma in men than women. Sun exposure is believed to be an independent risk factor for choroidal and ciliary body melanoma in Australia.[3]Congenital melanosisoculi, nevus of ota as well as nevi predispose to development of uveal malignant melanoma. However the calculated rate of malignant transformation is estimated to be less than 1 in 15000 nevi per year . Most case are sporadic[4].

The average age of patients at the time of diagnosis is 55 years. it is rare in children and adolescents. However melanoma of iris occur at an earlier age and exhibit more benign cell types[5,6]

Malignant melanoma is almost always unilateral[4].Its presentation mainly depends on size and location of the tumor and can vary from asymptomatic, detected incidentally on eye examination, over various visual disturbances to visual loss in the affected eye. At the time of diagnosis majority of patients with uveal melanoma are symptomatic, but still up to 30% could be asymptomatic [7]. The most common symptoms are blurred vision, visual field defect, photopsia, irritation and pain, but symptoms as metamorphopsia, floaters, redness and pressure can also occur[7]. Diagnosis of uveal melanoma is mostly established by ophthalmic examination including slit lamp biomicroscopy, indirect ophthalmoscopy, and ancillary diagnostic testing such as ultrasonography, fluorescein angiography and optical coherence tomography. Accuracy of diagnosis established by clinical examination is nowadays very high, over 99% [7].

Choroidal melanoma usually presents as dome or mushroom shaped subretinal mass, or less common it shows diffuse growth configuration [7].They classically divided into three groups small (<10x10x3mm)medium (between 10x10x3 mm and 15x15x5mm)and large(>15x15x5mm)[4].

The combined cytologic and histopathologic classification proposed originally by Callender in 1931 demonstrated prognostic significance and was the basis for subsequent modification. The original Callender classification included six cell types; Spindle A, Spindle B, Fascicular, mixed, epitheloid and necrotic. The collaborative Ocular Melanoma Study group defined an intermediate cell that has features both spindle B and epitheliod cells. Currently malignant melanoma of uvea are divided into 3 cell types 1) Spindle (admixture of spindle A and spindle B).2) Epitheloid cells and 3) Mixed cell types. There is no general consensus among pathologist regarding the number of spindle and epitheloid cell required for the diagnosis of mixed cell melanoma. In general tumors with a few epitheloid cells (3-5%) are classified as mixed[7].

Material and Method:

A retrospective study of patients admitted at M & J Institute of Ophthalmology, Western Regional Institute, Civil Hospital, Ahmadabad was done. Cases studied were received over a period of 12 years from 2001 to 2012.A detailed history of each patient regarding age, sex, clinical features and radiologic investigation was taken.

The surgically resected specimen were fixed in 10%formalin, gross examination was done and representative areas were taken for processing .H & E staining was done.IHC was done using whenever required mainly HMB-45,S100 protein .

Fig-1:Malignant Melanoma with pigmentation and detached retinal Epithelium.

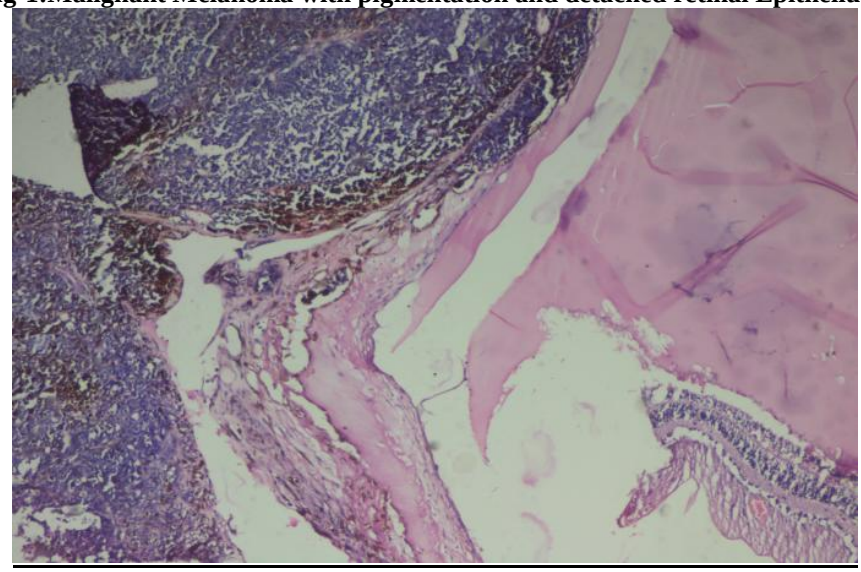


Fig-2Mixed Variant. Pigment laden cells with high N:C ratio and prominent nucleoli.

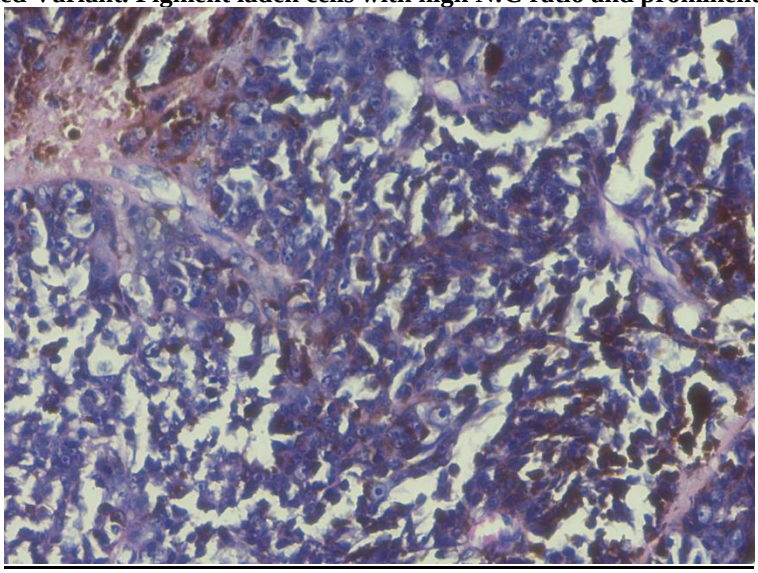


Fig-3 Highly pleomorphic cell with frequent atypical mitosis.

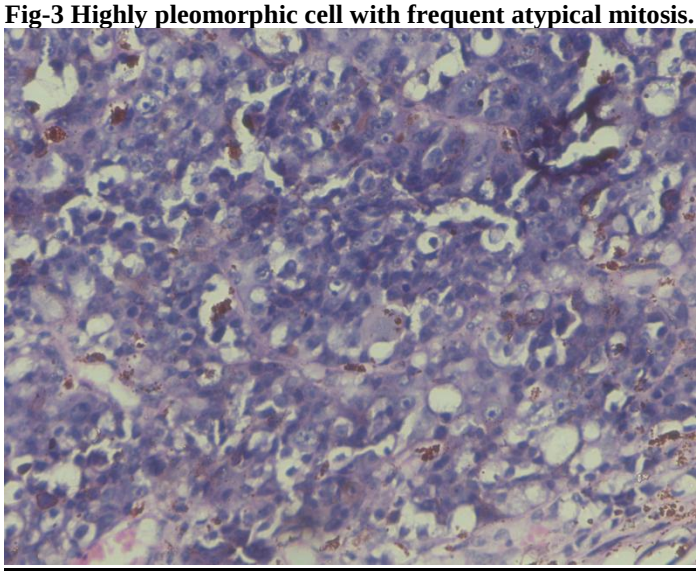
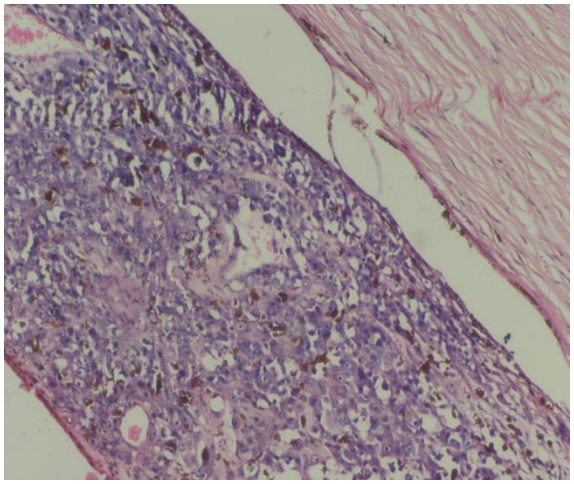


Fig -4Epitheliod variant of tumor cell.Sclera is free from tumor.



Results:

A total number of 42 cases of malignant melanoma received over a period of 12 years from 2001 to 2012 were studied.

Among these 42 cases received, 31 patients were male and 11patients were female.

Age distribution:

Years	10-20	20-30	30-40	40-50	50-60	60-70	70onwards
No.of cases	-	2	8	10	12	9	1
Percentage	-	4.7%	19%	23.8%	28.5%	21.4%	2.3%

All the cases were unilateral. Most of the cases were posteriorly located only 1 case(2.38%) of anterior uvealmelanoma,arising from iris was noted. Scleral invasion was found in 3 cases(7.14%) and extraocular spread was seen in 2 cases(4.76%).None of the cases showed optic nerve invasion.

Morphological types and their incidence:

Types	Epitheloid	Spindle	Mixed
No.of cases	6	5	31
Percentage	5%	9%	86%

Out of 42 cases only one patient came back with recurrent malignant melanoma of orbit,so the rate of recurrence was 2.3%.

Discussion:

Total 215 cases of intraocular tumors were studied over a period of 12 years,out of which 42 cases were diagnosed as intraocular malignant melanoma and 172 cases were of retinoblastoma.

Table: Incidence of Intra ocular tumors.

	Type of tumour	Total no.of cases	Percentage
ADULTS	Malignant melanoma	42	19.5%
	Lymphoma	nil	-
Children	Retinoblastoma	172	80%
	Medulloepithelioma	1	0.3%

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In Australia ocular melanoma shows higher rates, with incidence of 8 per million in men, and 6.1 per million in women [7].In the present study higher incidence of melanoma was found among male patient. i.e 31 cases(73.8%),and the male to female ratio was 2.81. In a study done by PredragJovanovicet al similar results were observed, with incidence of 6.8 per million in men, compared with 5.3 per million in women (male to female rate ratio 1.29) .[7] In Australia ocular melanoma shows higher rates, with incidence of 8 per million in men, and 6.1 per million in women [8].

In our study highest incidence of ocular melanoma was found in 50-60 years age group(28.5%). Most of the cases were found between 40-70 years age.Similar findings were observed in other studies.Most patients with uveal melanoma are aged between 50 and 80 years, with peak in seventies [1], and mean age at diagnosis 58 years [4].In a study at the Armed Force Institute of Patholog ,1.6% of uveal melanoma were seen in patient under 20 years of age. At our institute earliest age of presentation was years with 4.7% patients presenting between 20-30 years of age.

Among the three microscopic variants i.eepithelioid, mixed and spindlecell ,in the present study most of the cases are of mixed cell type(73%) and this finding corresponds to study done by COMS which also shows higher prevalence of mixed variant (86%).Among the three variants of melanoma epithelioid type is associated with poor prognosis.In our study incidence of epithelioid variant was 15%.

Table: incidence and comparision of variants of intraocular malignant melanoma.

Microscopic type:	Present study	COMS[9]
Spindle cell	12%	9%
Mixed cell	73%	86%
Epithelioid	15%	5%

All cases in our study were unilateral tumor which corresponds to the standard reference[4].Only one case of melanoma arising from iris was observed which corresponds with refrences from different series that melanomas of iris represent 3.3-16.6% of uvealmelanoma.Iris melanoma shows better prognosis compared to posterior uveal melanoma.

Scleral invasion was seen in 6 patients i.e 14.2% while other studies shows higher rates of sclera invasion upto 55.7%[9]. Extrascleral extension was observed in 2 cases(4.76%) which is comparable to COMS study which shows incidence of 8.2%.[9] In a study of COMS optic nerve invasion was seen in less than 10% cases of enucleated eyes and is usually associated with large tumor size,but in our study not a single case of optic nerve invasion was noted.[4]

Conclusion:

Ocular melanoma is the second most common type of melanoma after cutaneous and the most common primary intraocular malignant tumor in adults. Diagnosis is in most cases established by clinical examination with great accuracy. .Clinical risks for survival are older age and sex of the patients (prognosis being worse in males).
The variables that are best predictive of poor patient survival are epitheloid cell types,largesttumourdimension,extrascleral extension and mitotic activity followed by location of the tumor.Patients with massive extraocular orbital invasion at the time of diagnosis have a poor survival rate.Althoughenucleation is the primary treatment for most large uveal melanoma and for tumors that have produced severe secondary glaucoma,a variety of alternative treatments have been introduced in an effort to preserve the eyes and save vision. These include use of radioactive plaques such as cobalt60. Orbital exenteration is only justified for very advanced uveal melanoma with massive extraocular extension.

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