RETINOBLASTOMA AND ITS CLINICOPATHOLOGICAL CORRELATION AT A TERTIARY CARE CENTRE*Shruti Chandrakar¹, Ashok Kumar C²*¹Senior Resident, Department of Pathology, Pt. JNM Medical College, Raipur.²Professor and HOD, Department of Ophthalmology, Pt. JNM Medical College, Raipur.**ABSTRACT****BACKGROUND**

Retinoblastoma is the commonest childhood primary malignant intraocular neoplasm that is often characterised by spontaneous regression. They display photoreceptor differentiation. This study provides the clinical presentations and histological profiles of retinoblastoma in a tertiary care centre in Chhattisgarh State, in Central India.

MATERIALS AND METHODS

A retrospective study of clinically and histologically verified retinoblastoma at Pt JNM Medical College, Raipur, Chhattisgarh from January 2010 to December 2011 was undertaken. The clinical and histological features were analysed using the patient's case folder and surgical pathology records.

RESULTS

There were 50 patients, 32 males and 18 females (M:F ratio 1.7:1), age range from 5½ months to 6 years with 42 eyeball tumours histologically confirmed retinoblastoma during the study period. Proptosis with chemosis was the most common clinical presentation (76.1%). Bilaterality was 15% in this study. Enucleation and Exenteration combined with chemotherapy were offered to 31 (75%) and 11(25%) patients respectively.

CONCLUSION

Moderately differentiated type with extensive areas of tumour necrosis was the commonest histological pattern. 27 (65%) of the patients died before completing the course of chemotherapy.

KEYWORDS

Retinoblastoma, Pathology.

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BACKGROUND

Retinoblastoma (RB) is a rare embryonic tumour, but commonest primary malignant intraocular tumour of childhood.^[1,2] In the United States of America, retinoblastoma occurred in 1 of every 15000 live births,^[3] whereas in developing countries of Africa and Asia reports showed that it occurred in 1:18000 live births.^[4,5,6] Retinoblastoma accounted for more than 50% of all ocular and orbital malignancies of all age groups in African series.^[5,6,7,8] However, in Caucasians, it is the second most common tumour following malignant melanoma.^[3,9] The most common and obvious sign of retinoblastoma is an abnormal appearance of the retina as viewed through the pupil, the medical term for which is leukocoria, also known as amaurotic cat's eye reflex.^[1] Other signs and symptoms include deterioration of vision, a red and irritated eye with glaucoma, and faltering growth or delayed development. Some children with retinoblastoma can develop a squint,^[4] commonly referred to as "cross-eyed" or "wall-eyed" (strabismus). Retinoblastoma presents with advanced disease in developing countries and eye enlargement is a common finding.

Depending on the position of the tumours, they may be visible during a simple eye exam using an ophthalmoscope to look through the pupil. A positive diagnosis is usually made only with an examination under anaesthetic (EUA). A white eye reflection is not always a positive indication of retinoblastoma and can be caused by light being reflected badly or by other conditions such as Coats' disease.

The presence of the photographic fault red eye in only one eye and not in the other may be a sign of retinoblastoma. A clearer sign is "white eye" or "cat's eye".

Retinoblastoma occurs in sporadic (60%) – usually unilateral or germline [hereditary] (40%) forms; the later manifesting either as unilateral or bilateral disease and characterised by early onset and predisposition to developing secondary non-ocular, intracranial malignancies termed Trilateral Retinoblastoma.^[10,11] The RB gene is located in the long arm of chromosome 13 (13q14) and the gene is believed to be a recessive suppressor; thus, it requires the loss, deletion, mutation or inactivation of both copies of the gene at the 13q14 locus for RB to develop which correlates with the two "hits" theorised by Knudson.^[12,13,14] Retinoblastoma is a cancer of the retina. When a baby is growing in the womb, the eyes are one of the first things to develop. In the very early stages the eyes have cells called retinoblasts that grow very fast. Later, they stop growing and develop into mature retinal cells that can detect light.

Very rarely, the immature retinoblasts continue to grow very fast and do not turn into mature retinal cells. Instead, they grow out of control and develop into a cancerous tumour called retinoblastoma.

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If the tumour is not treated, the cells continue to grow and the cancer fills most of the eyeball. It can also spread to other parts of the eye and begin to block the flow of fluid inside the eye. This leads to a build-up of pressure and can cause loss of vision.

Fortunately, most retinoblastomas are found early and successfully treated before they spread outside the eyeball. If they do spread, they can go to anywhere in the body including the brain, bones and lymph nodes. They can be difficult to treat once they have spread.

Prenatal and postnatal prediction of susceptibility to inherited RB using recombinant DNA markers is now possible.^[15] Somatic amplification of the MYCN oncogene is responsible for some cases of non-hereditary, early-onset, aggressive, unilateral retinoblastoma. Although MYCN amplification accounted for only 1.4% of retinoblastoma cases, researchers identified it in 18% of infants diagnosed at less than 6 months of age. Median age at diagnosis for MYCN retinoblastoma was 4.5 months, compared with 24 months for those who had non-familial unilateral disease with two RB1 gene mutations. This would make genetic counselling for familial (Hereditary) RB more accurate, leading to an earlier tumour detection and effective therapy. The clinical presentation of RB includes leucocoria, strabismus, conjunctival chemosis, proptosis, and even blindness, which are attributed to late presentation and diagnosis.^[2,16] In spite of the treatment modalities such as enucleation, radiotherapy, photocoagulation, chemotherapy and even exenteration as in extraocular involvement, the mortality from RB in our environment is very high.^[2,5,6,16,17,18]

Endophytic Growth

Endophytic growth occurs when the tumour breaks through the internal limiting membrane and has an ophthalmic appearance of a white-to-cream mass showing either no surface vessels or small irregular tumour vessels. This growth pattern is typically associated with vitreous seeding, wherein small fragments of tissue become separated from the main tumour. In some instances, vitreous seeding may be extensive and allow tumour cells to be visible as spheroid masses floating in the vitreous and anterior chamber, simulating endophthalmitis or iridocyclitis, and obscuring the primary mass. Secondary deposits or seeding of tumour cells into other areas of the retina may be confused with multicentric tumours.

Exophytic Growth

Exophytic growth occurs in the subretinal space. This growth pattern is often associated with subretinal fluid accumulation and retinal detachment. The tumour cells may infiltrate through the Bruch's membrane into the choroid and then invade either blood vessels or ciliary nerves or vessels. Retinal vessels are noted to increase in calibre and tortuosity as they overlie the mass.

Diffuse Infiltrating Growth

This is a rare subtype comprising 1.5% of all retinoblastomas. It is characterised by a relatively flat infiltration of the retina by tumour cells but without a discrete tumour mass. The obvious white mass seen in typical retinoblastoma rarely occurs. It grows slowly compared with typical retinoblastoma.

MATERIALS AND METHODS

A total of 42 ocular surgical specimens from 50 patients with clinical diagnosis of retinoblastoma at the Ophthalmology Department of Pt. JNM Medical College, Raipur, Chhattisgarh from January 2010 to December 2011 and registered at the pathology department for histological verification were retrospectively studied. The age, sex, presenting symptoms, duration of symptoms, site, management and other adjunct treatment were obtained from the patient's case notes and analysed. Paraffin sections stained by standard haematoxylin and eosin (H & E) were retrieved and reviewed by one of the Authors. Special stains, Methyl green-pyronin (MGP) for calcium deposition and pearl blue reaction for haemosiderin pigments were employed where necessary. Each optic nerve was examined for involvement in tumour spread up to the line of transection. The histological diagnosis was based on cell morphology, degree of differentiation, presence of Flexner-Wintersteiner rosettes, optic nerve infiltration by tumour cells to the cut end of the optic nerve and tumour necrosis. Clinical photographs of some of the patients as well as photomicrographs were also included for illustration.

RESULTS

42 cases of retinoblastoma were diagnosed from 50 patients during the 2-year interval which accounted for 33.3% of the total number of ocular and orbital tumour cases seen at the eye clinic and 10.5% of childhood malignancies during the same period at Pt JNM Medical College. There were 32 males and 18 females, giving a male to female ratio of 1.7:1. The ages of the children ranged from 5½ months to 6 years with a mean age of 29 months (SD 0.78). The commonest clinical presentation in our experience was proptosis with associated conjunctival chemosis (76.1%). This was followed by leucocoria 61.9%, and hypopyon 42.8%. Eyelid swelling and blindness were observed in approx. 30% of the cases each - Table 1.

Signs and Symptoms	No. of Cases	Percentage
Proptosis and conjunctival chemosis	32	76.1
Leucocoria	26	61.9
Hypopyon	18	42.8
Eyelid swelling	13	30.9
Blindness	12	28.5
Eye discharge	6	14.2
Pain	4	9
Globe perforation	4	9
Table 1. Clinical Signs and Symptoms		

Histological Features	No. of Cases	Percentage
Poorly differentiated	15	35.7
Moderately differentiated	22	52.3
Well differentiated	5	11.9
Table 2. Characteristic Histological Features of Retinoblastoma Differentiation		

Flexner-Wintersteiner	13	30.9
Pseudorosette	29	69.0
Rosette		

Optic nerve	16	38
Skeletal muscle	1	2.3
Lacrimal gland	2	4.7
Vascular emboli	2	4.7
Microscopic Spread		

Necrosis	34	80.9
Dystrophic calcification	11	26.1
Haemorrhage	10	23.8
Siderosis	4	9.5
Cholesterol slits	3	7.1
Basophilia	3	7.1
Others

Gross **Flexner-Wintersteiner** **Retinoblastoma**

In this study, Retinoblastoma accounted for 33% of all cases of ocular and orbital malignancies in our centre that compares well with the findings in other studies where the incidence varies from 34 – 55 percent.^[6,19,20] Similarly, our present experience of Retinoblastoma accounting for 10.5% of all childhood cancer and the commonest childhood intraocular tumour corroborates findings in African series^[19,20,21,22] but high when compared with developed countries where 2.4 – 4% has been reported.^[2,23] We reported a male to female sex ratio of 1.7:1. This differs with the observation of no sex predilection in other studies.^[14,17,23,24] Our patients appeared to present very late as the average age of the children at the time of diagnosis was 29 months. This is comparable to similar findings in the developing countries,^[6,8,17,19] it is high when compared with the reports of western countries.^[14,23,24,25] The late presentation in our study could be due to among other causes like lack of awareness of the disease, delayed referral prompted by consultation with traditional medical practitioners and poor affordability and accessibility to available medical facilities.

No single case of RB was reported in an adult in this series which agrees with the findings of Olurin et al.^[19] Proptosis with conjunctival chemosis was the commonest clinical presentation manifesting in 76.1% of our patients. This is at variance with findings in other studies where leucocoria and strabismus were observed.^[16,17,23] This picture is attributed to delay in presentation of the patients for diagnosis and treatment. This opinion is supported by the claim that proptosis is the result of orbital involvement.^[16] Also Erwenne et al concluded in their study of 158 consecutive cases of RB that extraocular disease was strongly dependent on the age at diagnosis and lateness of referral.^[25] The incidence of bilateral RB in this series is 15% that agrees with the findings in some African series.^[17,19] In Zambia it is 4% whereas in the western countries such as Germany, England and Wales, the incidence is higher.^[22,23] The disparity may be associated with incomplete data or due to higher incidence of unilateral (sporadic) RB over bilateral cases in India. Histologically, the two characteristic arrangements of cells that are pathognomonic of RB are Flexner-Wintersteiner rosette and fleurette representing an attempt to differentiate into photoreceptor cells. Well-differentiated tumours are characterised by the presence of Flexner-Wintersteiner rosettes. In this communication, 22 eyes (52.3%) were of moderately differentiated type; compared with other studies the above findings are comparable.^[17,23]

CONCLUSION

Retinoblastoma is the commonest malignant intraocular tumour of childhood, mostly of moderately differentiated type histologically and characterised by high mortality in our centre. There is need for improved accessibility to health facilities and the importance of genetic counselling should be emphasised.

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