

Association of Clinical Presentations and Histopathological Features of Retinoblastoma in a Tertiary Eye Care Centre, Eastern Nepal

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Purpose: To assess an association of retinoblastoma with clinical presentations and histopathological features.

Materials and Methods: This is a retrospective analysis of clinical and histopathology records of patients admitted with retinoblastoma in a tertiary care center, Eastern Nepal from May 2009 to June 2017.

Results: Forty-four patients were admitted with the diagnosis of retinoblastoma. Age of the patient ranged from four months to nine years with male: female ratio 1.3:1. Unilateral eye was involved in 43 cases (97.7%), leukokoria being the most common presentation (56.8%), followed by proptosis (20.5%). Using the International Intraocular Retinoblastoma Classification, 75.6% were classified as Group E. The cut end of optic nerve invasion (ONI) was seen in 30.2%. According to the International Retinoblastoma Staging Working Group pathology classification, 60% of tumors were Stage PT1. Statistically significant association was seen between longer duration of presentation with leukokoria, neovascularization of iris and uveitis; older age groups with proptosis and leukokoria. Positive predilection was seen between poorly differentiated cell type and older age groups ($p=0.052$) and proptosis ($p=0.02$). Advance grade of disease was reflected by delayed presentation ($p=0.031$) and older age ($p=0.05$).

Conclusions: Leukokoria was the predominant clinical presentation. Poorly differentiated cell type had positive association with age and proptosis. Advance disease was associated with longer duration and older age.

Abstract

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Keywords: Retinoblastoma, proptosis, leukokoria, intraocular tumor, enucleation.

Introduction

Retinoblastoma is the most common intraocular malignancy during childhood,¹ with two-thirds of cases presenting as unilateral and one-third of cases presenting as bilateral.² The reported average age at diagnosis is at 18 months, with unilateral cases being diagnosed at around 24 months and bilateral cases before 12 months.³ Ninety percent of cases are diagnosed before the five years of age.⁴

Leukokoria, proptosis, squint, red eye and orbital cellulitis have been reported as frequent presentations of the disease,³ with proptosis being more common in developing countries.^{4,5,6}

The prognosis of retinoblastoma depends upon the mode of presentation, duration of symptoms, the site of involvement, histopathological stage and optic nerve involvement. There are few cases reported in the literature describing an association of retinoblastoma with clinical presentations and histopathology features. The aim of this study was to assess an association of retinoblastoma with clinical presentations and histopathological findings.

Materials and Methods

We retrospectively analyzed clinical records and histopathology reports of all the patients admitted with retinoblastoma at a tertiary referral center, BP Koirala Institute of Health Sciences, Nepal over a period of eight years, from

May 2009 to June 2017. In each case, a detailed history was recorded including family history. The parameters studied were, demographic data, presence or absence of anterior segment involvement, vitreous seeding, choroidal invasion and extraocular spread. Treatment options offered to each patient were enucleation, exenteration and a referral for chemotherapy and/or radiotherapy whenever the tumor was found to have extension into the orbit, or infiltration of the cut end of the optic nerve was noted. Each of the eyes was classified according to IIRC (International Intraocular Retinoblastoma Classification). Histopathology slides were reviewed to evaluate cell type, the presence of any optic nerve cut end infiltrations (ONI), choroid and anterior segment invasion. Histopathology staging was done as per the consensus of International Retinoblastoma Staging Working Group (IRSWG)⁷ along with the pathologic tumor staging. Additionally, reports of computed tomography or magnetic resonance imaging of the orbit and brain were recorded. The study was approved by the institutional ethics committee and adhered to the provisions of the declaration of Helsinki.

Statistical Analysis

Data were tabulated in Microsoft Excel 2016 and analyzed using SPSS software, version 16 (SPSS 16- IBM Corp. Armonk, NY). Mean, standard deviation, and percentage

were calculated for the age of the patients and duration at presentation. P-values were calculated for the association of clinical presentation and histopathological findings. The independent samples -test, Mann-Whitney -test, Chi square test or Fisher's exact test were employed for comparison where appropriate. A p value of < 0.05 was considered statistically significant.

Results

Fortyfour patients were admitted with the diagnosis of retinoblastoma during the study period. The age of the patients ranged from four months to 9 years with the mean ± SD being 2.86± 1.96 years, median 3 years. Majority of the patients were in the age group 1-3 years (61.4%) [Figure1]. There was a slight male preponderance, with a male: female ratio of 1.3:1. Mean age for boys was 2.85±2.23 and girls 2.96±1.74 years. Out of 44 patients, 42 (95.4%) had unilateral eye involvement and two (4.5%) bilateral (total =45 eyes). The mean duration of symptoms to presentation in the hospital was 6.61 ± 8.2 months, median 3.5 years (10 days to 3.5 years). Twenty four patients were Hindus and 17 Muslims, with a history of consanguinity in 10 Muslim families. None of the patients had family history of retinoblastoma. Funduscopy examination of the parents was normal in all the cases.

There was presence of one or more signs in the same patient. The most common presenting sign was leucokoria in 40 patients (90.9%) followed by red eye, 21 (47.7%) and proptosis, 9 (20.5%). All the patients presenting with symptoms either had leucokoria or conjunctival congestion. Leucokoria was the most common only presenting symptom in 25 eyes (56.8%). Figure 2 shows the distribution of modes of presentation.

Table 1 shows an association of clinical features with the duration of symptoms and age at presentation. Statistically significant association was seen between longer duration of presentation with leucokoria, neovascularization of iris and uveitis. Older age at presentation showed positive predilection for proptosis and leucokoria.

Association of clinical presentations of retinoblastoma and histopathological features. According to IIRC classification, 31 eyes (70.5%) presented with Group E tumor, Group D, nine (20.5%) and three Group C (9.1%). Two patients had extraocular extension. None of the eyes were found to have Group A or B tumors.

All the patients underwent examination of the other eye under general anesthesia. Since most of the patients presented with group C (n-3), D(n-9) and E tumor (n-29), the primary choice of treatment was enucleation in 41 eyes (93.2%) and exenteration in two eyes (4.5%) with orbital extension. Oncology facility is not available in our center. One patient with evidence of intracranial extension and the two with orbital extension were further referred for chemotherapy and radiotherapy.

Per the International Retinoblastoma Staging Working Group pathology classification (IRSWG) histopathology staging and pathology tumor staging guidelines, 62.8% of tumors were classified as Stage PT1, 7% PT1a, 2.3% PT2,

9.3% PT2a, 9.3 % PT2b, 7% PT4a and 2.3% were PT4b. Choroidal invasion was seen in 21 eyes (48.8 %), anterior segment involvement in eight (18.6%), sclera in two (4.7%), ciliary body in 12 (27%) and extraocular involvement in two eyes (4.7%). The mean average optic nerve stumped cut was 9.74mm (mode 10 mm). The cut margin of the optic nerve was infiltrated with tumor (ONI) in 13 eyes (30.2%). Undifferentiated cells were noted in 16 eyes (37.2%) and well differentiated in 24 (62.8 %).

When considering mean age and duration of presentation we could not elicit association between histopathology cell type, ONI and choroidal invasion (Table 2).

Extra ocular invasion was associated with ONI ((p-0.028, RR 0.26, 95% CI: 0.16-0.44), proptosis (p-0.031, RR-0.14, CI: 0.7-0.3) and grade of tumor (p-0.048), but not with gender (p-0.306), age (p-0.302), duration at the time of presentation (p-0.37) and cell type (p-0.611). Statistically significant associated was seen between poorly differentiated cell type and older age groups (p-0.052 Fisher's Exact test) and proptosis (p-0.02 Fisher's Exact test, OR-7.5, CI: 1.29 - 43.6), but not with gender (0.189) and duration at presentation (p-0.53). Grade of tumor showed association with duration at presentation (p-0.031) and age (p-0.05), but not with gender (p-0.363).

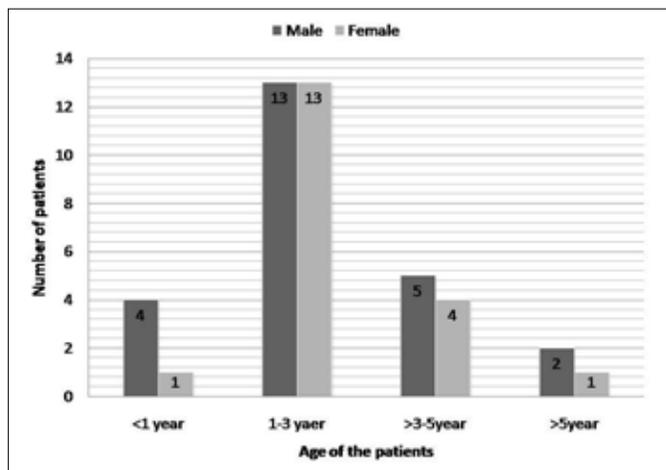


Figure 1: Distribution of age and gender

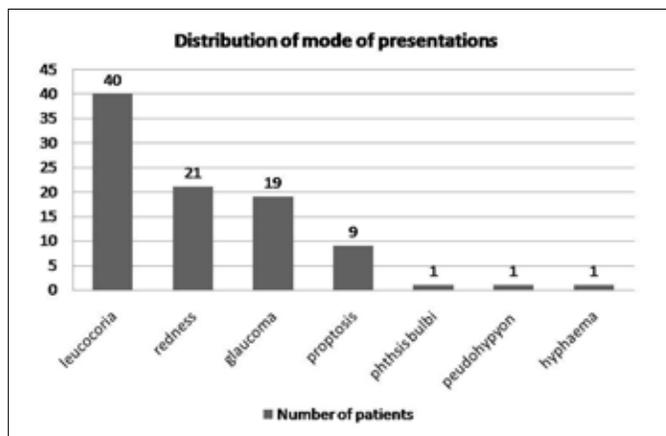


Figure 2: Distribution of mode of presentations of retinoblastoma

Table 1: Association of clinical features with the duration of symptoms and age at presentation

	Presenting symptoms									
	Leucokoria total	Leucokoria only	Proptosis	Red eye	Glaucoma	Pseudohypopyon	Uveitis	Hyphaema	#NVI	Phthisis bulbi
N (%)	40	25	9	21	19	1	2	1	3	1
Mean duration of symptoms (months)	6.61±7.9	4.17±2.73	10±9.68	8.04±9.79	7.86±10.3	5±NA	33±12.72	5±NA	23.33±19	18±NA
*p value	0.26	<0.001	0.66	0.12	0.81	0.049	<0.001	0.049	0.031	0.215
Mean age (years)	2.88±1.69	2.78±1.75	3.8±2.8	3.28±1.94	3.14±2.23	3.5±NA	3.5±0.7	3.5±NA	3.6±0.57	3±NA
*p value	0.005	0.75	0.07	0.95	0.12	0.216	0.31	0.216	0.204	

*Mann Whitney test, *NVI- neovascularization of iris

Table 2: Association of histopathology findings with the duration of symptoms and age at presentation.

Parameters	Histopathology findings					
	Well differentiated cells	Poorly differentiated cells	Optic nerve cut end free	Optic nerve cut end infiltration	Choroid invasion	No choroid invasion
N (%)	24(62.8%)	16(37.2%)	30 (69.8%)	13(30.2%)	21 (48.8%)	22(51.2%)
Mean duration of presentation (months)	6.47±8.29	7.11±8.4	5.41±6.19	7.27±9.06	7.37±10.27	6.08±5.96
*P value	0.53		0.252		0.16	
Mean duration of age (years)	2.63±1.90	3.30±2.08	3.10±2.36	2.78±1.82	3.20±2.37	2.57±1.5
*P value	0.88		0.30		0.28	

*Mann Whitney T test

Advanced histopathological stage of the tumor had positive predilection for older age groups (p=0.49), ONI (p<0.001), poorly differentiated cell type (p=0.05) but not with proptosis (p=0.067), gender (p=0.43) and group of the tumor (p=0.103). Oncology facilities are not available in our institution, so the patients with orbital extension, proptosis, ONI and advanced group D and E were referred for chemotherapy and or radiotherapy. One patient who underwent enucleation was found to have whitish fluffy lesion of >5 disc diameter (DD) on funduscopy examination of the other eye, was too referred for chemotherapy and radiotherapy.

Discussion

In the present study, the mean age of the patients was 2.9 ± 1.96 years (4months to 9 years). In literature, common age of presentation of retinoblastoma ranged from 15 months to 24 months.² Similar data has been reported in Nepal where the mean age was 3.04±1.8 years and 2.5 ± 1.6 years.⁸

There was slight preponderance of male, with a male to female ratio 1.3:1, which is consistent with other studies reported in the literature.^{6,10} Forty-two (95.4%) patients had unilateral involvement and only two had bilateral involvement (4.5%). Previous studies have found the distribution of bilateral cases of retinoblastoma to be around 9.3-40%.^{6,8,9,10,11} The mean duration of presentation in this study was 6.61±8.2 months. Delayed presentation up to 41±14 months has been reported in the literature.^{5,11}

The most common clinical presentation was leucokoria (40 eyes, 90.9%), with leucokoria as only presenting symptom in 25 patients (56.8%) followed by proptosis in 9 eyes (20.5%).

In a study done by Saiju et al, out of 80% cases of leucokoria, eleven patients (36.6%) presented with leucokoria as their only symptom, which is reflected in the literature.^{9,12,13,14} These results contrast with previous studies of retinoblastoma in Nepal in which proptosis and the presence of a fungating mass were the primary presenting symptoms.^{5,9} In a study by Abdu et al, 46% patients presented with fungating orbital mass, leucokoria 22%, proptosis 19%, hyphaema 7%, hypopyon 2%, squint 2% and buphthalmos 2%.¹⁵ In a study done by Saiju et al, out of 80% cases of leucokoria, eleven patients (36.6%) presented with leucokoria as their only symptom, which is reflected in the literature.^{9,12,13,14} This variation in modes of presentations may be due to increased awareness of retinoblastoma in the population and increased likelihood of seeking medical attention for this condition. Phthisis bulbi though is a rare mode of presentation has been reported in the literature.^{16,17} In this study, only one patient had phthisis bulbi. This highlights the need of a detailed evaluation of children presenting with phthisis bulbi to rule out retinoblastoma.

According to IIRC, 9.1% had Grade C, 20.5% Grade D and 70.5% Grade E tumor. This was slightly different than those reported by Fiona et al 2013 in which 6.0% were Group A, 6.0% Group B, 3.0% Group C, 38.8% Group D, and 49.2% were Group E.¹² Similar findings were also reported by Zhao J et al¹⁸ in China, with the majority of eyes (501/595 or 84%) presenting with an advanced stage of the tumor (Group D or E). None of our patients presented with grade A and B, which reflects the late presentation of our patient population compared to other studies.

In our study, optic nerve infiltration was detected in 32.6% of eyes which was less than reported in previous studies from Nepal (38-48%).^{6,8,9}

The delayed presentation showed an association with leucokoria, neovascularization of iris and uveitis; mean age at presentation with proptosis and leucokoria. Statistically significant association was seen between poorly differentiated cell type and older age groups and proptosis, but not with gender and duration at presentation. Grade of tumor was associated with duration of presentation and age, not with gender. Mean age and duration at presentation did not show association between tumor cell type, ONI and choroidal invasion. Extra ocular invasion was associated with infiltration with cut end margin of the optic nerve, proptosis and grade of tumor, but not seen with gender, age, duration and poorly differentiated cell type.

Our findings were similar to findings reported by Shields et al¹⁹ and Khan et al²⁰ where an association of age with optic nerve invasion was also not noted. Khan et al found an association of proptosis, leucokoria, secondary glaucoma and greater size of tumor with optic nerve invasion.²⁰

Chawla et al in their study found a significant association between iris neovascularization, choroidal invasion, IOP, shallow anterior chamber and tumor volume with high risk histopathology. Choroidal invasion was seen in 68%. Our study is unique in that it demonstrates an association of histopathology cell type (well or poorly differentiated cell type) and histopathology stage with the clinical presentations of retinoblastoma.

Most of the patients were in IIRC group D and E; 95.3% of the patients underwent enucleation and 4.7% exenteration. This rate is consistent with previous studies from Nepal^{6,9}, Singapore¹², and Iran²², but is higher than the 75% enucleation and exenteration rate in the United States.¹⁹ Stage PT1 was the most common histopathologic stage, accounting for 62.8% of the cases in our study. Choroidal invasion was seen in 48.8%. In a ten-year retrospective analysis of histopathological records of patients with retinoblastoma done by Smriti et al, found that stage pT1 was seen in 58% of cases followed by pT2a (22%), pT (3a) and pT4b (6%) each and pT3b and pT4a (4% each).²³

Lack of awareness, resources and accessibility to health care, may be the factors for late medical care and hence present with more advanced disease.

The limitation of this study was its retrospective nature, leading to bias in secondary data collection and observational bias. A prospective study exploring risk factors for the outcome is warranted to further explore this relationship.

In conclusion, the most common mode of presentation was leucokoria. A positive association was seen between poorly differentiated cell type with age and proptosis. Advanced disease was associated with longer duration and older age groups.

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