Enucleated Pseudoretinoblastoma: A Six-year Review from a Philippine Center

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ABSTRACT

Objectives. To evaluate the prevalence, etiologies, demographics, and clinical presentation of enucleated pseudoretinoblastoma.

Methods. This retrospective study reviewed ocular pathology records of enucleated globes with clinically diagnosed or suspected retinoblastoma submitted to a public university ocular pathology laboratory from 2013 to 2018. Hematoxylin-eosin-stained sections of pseudoretinoblastoma cases were reevaluated, and additional clinical data were taken from hospital charts.

Results. Of the 211 enucleated eyes with clinically diagnosed or suspected retinoblastoma, 202 (95.7%) had histologically confirmed retinoblastoma, while 9 (4.3%) had pseudoretinoblastoma. The most common ocular conditions mimicking retinoblastoma were retinal dysplasia (2 eyes) and persistent fetal vasculature (2 eyes). The pseudoretinoblastoma group consisted of 4 females and 5 males, and enucleated were 6 right eyes and 3 left eyes. The mean age at the time of enucleation was 3.65 years, and the mean symptom duration was 17.36 months. Leukocoria, which was noted in 4 patients, was the most frequent initial symptom. No significant difference between the pseudoretinoblastoma group and the retinoblastoma group were found in terms of sex, laterality of the enucleated eye, age at the time of enucleation, and symptom duration.

Conclusion. In this retrospective review, the prevalence of pseudoretinoblastoma in enucleated globes clinically suspected or diagnosed with retinoblastoma was 4.3%. Persistent fetal vasculature and retinal dysplasia were the most common pseudoretinoblastomas. Clinicians should perform a thorough clinical evaluation and judiciously utilize the available diagnostic means to differentiate retinoblastoma from pseudoretinoblastoma.

Keywords: eye enucleation, retinal dysplasia, retinoblastoma

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INTRODUCTION

The diagnosis of retinoblastoma is made based on clinical signs and symptoms supplemented by findings from ocular imaging procedures. Eye conditions that can clinical present like retinoblastoma are called pseudoretinoblastomas. Pseudoretinoblastomas are generally benign lesions and may warrant treatment strategies that differ from those employed in retinoblastoma cases. Reported rates of misdiagnosed retinoblastoma in the clinics or enucleated eyes and the commonly encountered conditions mimicking retinoblastoma vary from center to center and over time.[1-12] These rates range from zero to more than 50%. Information on the most frequent conditions that mimic retinoblastoma could help guide clinicians in their diagnosis and treatment of patients with suspected retinoblastoma. This study evaluated the prevalence, etiologies, demographics, and clinical presentation of enucleated pseudoretinoblastoma submitted

to a public university ocular pathology laboratory over a six-year period. We also compared the demographic and clinical profile of patients with pseudoretinoblastoma with those with histologically confirmed retinoblastoma.

METHODS

This retrospective study was approved by our institution's ethics review board and conducted following the principles of the Declaration of Helsinki. Ocular pathology consultation records of specimens submitted to the Philippine Eye Research Institute from January 2013 to December 2018 were reviewed. Only enucleated globes with clinically diagnosed or clinically suspected retinoblastoma as indicated in the pathology consultation request forms were included in the study. In cases where both globes from the same patient were submitted but on different dates, only the earlier submitted specimen was included in the analysis. Extended enucleation or exenteration specimens were excluded.

After pseudoretinoblastoma cases were identified from the pathology reports, hematoxylin-eosin-stained sections of these enucleated globes were retrieved and reevaluated by an experienced ocular pathologist. Data extracted from ocular pathology records consisted of demographic data, laterality of the specimen, clinical diagnosis, clinical history, and histopathologic findings. When available, additional clinical data such as eye examination findings and ocular imaging results were taken from hospital charts or medical abstracts.

The prevalence rate of pseudoretinoblastoma was computed by dividing the number of histologically confirmed pseudoretinoblastoma by the total number of specimens clinically diagnosed or suspected to have retinoblastoma. Fisher's exact test was utilized when comparing categorical data, while the Welch test was used to compare continuous variables. Post-hoc analyses using the Games-Howell test were done as needed. Statistical analyses were performed using Stata/IC 13.1 (StataCorp LP, College Station, Texas) and R (R Foundation for Statistical Computing, Vienna, Austria).[13,14] The level of significance was set at $\alpha = 0.05$.

Table 1. Pseudoretinoblastomas in a public university ocular pathology laboratory, 2013–2018

Histopathologic diagnosis	Clinical impression	Sex	Age at enucleation	Laterality of enucleated eye	Clinical presentation	Visual acuity	Imaging findings
Retinal dysplasia, retinal detachment	t/c RB	Male	1 mo	Right	Leukocoria 2 wks PTC	No dazzle	UTZ: ill-defined intraocular mass CT scan: Mixed heterogeneity and predominantly hyperdense foci occupying the posterior aspect of the globe
Retinal dysplasia, adherent leukoma	RB	Female	5 yrs	Right	Leukocoria since 3 mos of age	Light perception	UTZ: Retrolental membrane, Consider chorioretinal mass lesion; cannot rule out calcification; CT scan: Calcification noted in the right lens and along the inferolateral wall
Persistent fetal vasculature	RB	Male	3 mos	Right	No response to visual stimuli 2 mos PTC	No dazzle	n.d.
Choroidal hemangioma	RB	Female	12 yrs	Right	Exotropia 7 mos PTC	Light perception	n.d.
Vitreous hemorrhage, uveal prolapse, angle-closure glaucoma	Ruptured globe r/o RB	Female	6 mos	Left	Proptosis noted at birth	No dazzle	UTZ: Choroidal detachment; vitreous, subretinal, and subchoroidal cellularities; no definite intraocular mass seen
Anterior staphyloma, angle-closure glaucoma	RB	Female	5 yrs	Left	Leukocoria since 4 yrs PTC and gradual proptosis	n.d.	n.d.
Persistent fetal vasculature, retinal detachment	RB	Male	1 yr	Left	n.d.	n.d.	n.d.
Hamartoma of the retinal pigment epithelium	RB	Male	1 yr	Left	Leukocoria 1 mo PTC	n.d.	n.d.
Atrophia bulbi, retinal detachment, osseous metaplasia of the retinal pigment epithelium	Retinopathy of prematurity, r/o RB	Male	8 yrs	Left	Diagnosed case of retinopathy of prematurity	n.d.	n.d.

Abbreviations: t/c, to consider; RB, retinoblastoma; PTC, before consult; UTZ, ultrasound; CT, computed tomography; n.d., no data; r/o, rule out.

RESULTS

Of the 211 enucleated eyes from 192 patients with clinically diagnosed or suspected retinoblastoma, 202 eyes (95.7%) from 183 patients had histologically confirmed retinoblastoma, while nine eyes (4.3%) from 9 patients had pseudoretinoblastoma. The ocular conditions mimicking retinoblastoma (see Table 1) consisted of retinal dysplasia (2 eyes), persistent fetal vasculature (2 eyes), choroidal hemangioma (1 eye), vitreous hemorrhage with uveal prolapse (1 eye), anterior staphyloma with angle closure (1 eye), hamartoma of the retinal pigment epithelium (1 eye), and atrophia bulbi with osseous metaplasia of the retinal pigment epithelium (1 eye).

The pseudoretinoblastoma group consisted of 4 females (44%) and 5 males (56%). No patient with pseudoretinoblastoma underwent enucleation of both eyes during the period covered by the study. Age at the time of enucleation ranged from 1 month to 12 years, with 7 out of 9 patients aged five years or younger. Enucleated were six right eyes and three left eyes. Leukocoria, which was noted in 4 patients, was the most frequent initial symptom. Majority of patients started to have ocular symptoms when they were 1 year of age or younger. Five patients had poor vision in the affected eye, while one patient, who was noted to be uncooperative during the ocular examination, had missing visual acuity data. The 3-month-old with persistent fetal vasculature was also found to have small masses in the other eye. Intraocular calcifications or hyperdensities were noted on computed tomography scans for the two patients with retinal dysplasia. For the majority of pseudoretinoblastoma patients, the records that were reviewed contained no data on the imaging studies that were requested and the results of these tests.

Characteristics of patients with pseudoretinoblastoma and retinoblastoma are presented in Table 2. Patients with retinoblastoma are divided into two groups based on the disease stage. Patients with retinoblastoma consisted of 79 females (43%) and 104 males (57%). The female-male ratio in the retinoblastoma group was about the same as that in the pseudoretinoblastoma group. The proportion of enucleated right eyes (or left eyes) with retinoblastoma was similar to that in the pseudoretinoblastoma group ($p = 0.734$).

Table 2. Profile of patients with pseudoretinoblastoma and retinoblastoma, 2013–2018

Characteristic	Group			
	Pseudoretinoblastoma (n = 9)	Retinoblastoma		
		All (n = 183)	Intraocular (n = 97)	Extraocular (n = 86)
Sex				
Female	4 (44%)	79 (43%)	43 (44%)	36 (42%)
Male	5 (56%)	104 (57%)	54 (56%)	50 (58%)
Laterality of enucleated eye				
Right	6 (67%)	81 (44%)	38 (39%) [a]	43 (50%)
Left	3 (33%)	82 (45%)	48 (49%)	34 (40%)
Both	0 (0%)	20 (11%)	11 (11%)	9 (10%) [b]
Age at enucleation *(years)*				
Range	0.083 – 12	0.167 – 11	0.167 – 6	0.417 – 11
Mean ± SD	3.65 ± 4.19	2.23 ± 1.63	1.87 ± 1.35	2.64 ± 1.83
Duration of symptoms *(months)*				
Range	0.5 – 57	0.1 – 60	0.1 – 48	0.75 – 60
Mean ± SD	17.36 ± 24.27	11.13 ± 10.38	9.00 ± 8.94	13.37 ± 11.33
Initial signs/symptoms [c, d]	n = 7	n = 173	n = 92	n = 81
Leukocoria	4 (57%)	137 (79%)	73 (79%)	64 (79%)
Strabismus	1 (14%)	20 (12%)	15 (16%)	5 (6%)
Blurred vision	1 (14%)	9 (5%)	4 (4%)	5 (6%)
Redness	0 (0%)	14 (8%)	4 (4%)	10 (12%)
Proptosis	0 (0%)	4 (2%)	1 (1%)	3 (4%)
Pain	0 (0%)	5 (3%)	1 (1%)	4 (5%)
Tearing	0 (0%)	6 (3%)	1 (1%)	5(6%)
Swelling	1 (14%)	3 (2%)	0 (0%)	3 (4%)
Brownish discoloration	0 (0%)	5 (3%)	1 (1%)	4 (5%)
Mass	0 (0%)	4 (2%)	2 (2%)	2 (2%)

[a] *Column percentages do not add up to 100% due to rounding.*
[b] *Disease stage in the more advanced eye, if applicable.*
[c] *Most frequent signs and symptoms.*
[d] *Multiple signs and symptoms per patient are possible.*

Abbreviation: SD, standard deviation.

Twenty patients with retinoblastoma underwent surgical removal of both eyes.

The mean age of pseudoretinoblastoma patients at the time of enucleation was 3.65 years, which was 1.42 years more than the mean age of those with retinoblastoma, almost two years more than the mean age of the subgroup with intraocular retinoblastoma, and about one year more than mean age of the subgroup found to have extraocular retinoblastoma histopathologically. The mean age of patients with pseudoretinoblastoma was found not to be significantly different than that of those with retinoblastoma (p = 0.5047). Pairwise comparisons showed no significant difference between the pseudoretinoblastoma cohort and the intraocular retinoblastoma subgroup (p = 0.451) or the extraocular RB subgroup (p = 0.761) in terms of age at the time of surgery. The ages at time of surgery of those with intraocular retinoblastoma were significantly lower than those with extraocular retinoblastoma (p = 0.005).

Symptom duration or the length of time from the appearance of symptoms to around the time of surgery of those with pseudoretinoblastoma ranged from 0.5 to 57 months with a mean of 17.36 months, while the symptom duration of those with retinoblastoma ranged from 0.1 to 60 months with a mean of 11.13 months. No difference in the mean symptom duration of the pseudoretinoblastoma and retinoblastoma groups was found (p = 0.5238). However, statistical significance was reached when the pseudoretinoblastoma group and two retinoblastoma subgroups were compared (p = 0.0429). Post-hoc testing revealed that those with intraocular retinoblastoma had shorter symptom duration than those with extraocular disease (p = 0.018). No significant difference between the pseudoretinoblastoma group and either the intraocular retinoblastoma group (p = 0.656) or the extraocular retinoblastoma group (p = 0.904) was seen.

Leukocoria, seen in 79% of patients, was the most commonly observed initial symptom or sign among those with histologically confirmed retinoblastoma. Other common symptoms in this patient group included strabismus, blurred vision, and eye redness.

DISCUSSION

In this review, the prevalence of pseudoretinoblastoma in eyes clinically diagnosed or suspected to have retinoblastoma was 4.3%. This figure is in the middle range of reported rates from other Asian centers. In a tertiary hospital in Iran, pseudoretinoblastoma was seen in 53 (11.7%) of 453 enucleation or exenteration specimens over a 14-year period, and endophthalmitis was the most frequent etiology.[6] Pseudoretinoblastoma was found in 3 (10.7%) of 28 eyes enucleated for possible retinoblastoma in a Singapore center over an 11-year period, and 2 of these eyes were diagnosed with Coats disease.[7] In a study from an eye institute in India, 9 (14%) of 64 eyes with clinically diagnosed or suspected retinoblastoma enucleated over a 3.5-year period had pseudoretinoblastoma, and proliferative vitreoretinopathy with gliosis was the most frequent histologic finding.[8] In a different series from India that had magnetic resonance imaging results as part of the inclusion criteria, pseudoretinoblastoma was found in 4 (1.4%) of the 280 eyes enucleated over a 4-year period.[9] The etiologies were granulomatous endophthalmitis, astrocytic hamartoma, Coats disease, and persistent fetal vasculature. Evaluation of 70 eyes from a 10-year period in a hospital in China found 9 eyes (12.9%) to have pseudoretinoblastoma, and Coats disease as the most frequent lesion.[10] In a review of enucleations over a 4-year period in another Chinese center, the misdiagnosis rate was 0.48%, and the one eye with pseudoretinoblastoma was found to have Coats disease on histologic examination.[11]

The computed prevalence rate of 4.3% is 3.3 percentage points lower than the previously reported figure from our center for the 2003 – 2007 period.[12] Although this difference is not statistically significant (p = 0.11), we consider the observed reduction in enucleated pseudoretinoblastoma of about 3 per 100 enucleations to be clinically meaningful, especially given our setting where lack of resources and equipment preclude the carrying out of diagnostic tests such as magnetic resonance imaging for most patients. Possible reasons for this decrease include better clinical recognition of conditions that simulate retinoblastoma and a lower prevalence of pseudoretinoblastomas. Determining the prevalence of pseudoretinoblastomas among referrals to ocular oncology clinics and analyzing their clinical and imaging features are suggested for future study.

Seven ocular conditions simulated retinoblastoma, with persistent fetal vasculature and retinal dysplasia accounting for 44% of pseudoretinoblastoma cases. These two etiologies were also the most common ones in the previous series from our center. Unlike in that last review and those from other centers, no Coats disease or endophthalmitis cases were seen among the enucleated eyes with pseudoretinoblastoma. In two specimens in our study, retinoblastoma was not the primary diagnosis but rather a secondary consideration or a condition to be ruled out, possibly out of an abundance of caution. Enucleation and histopathologic examination of a blind eye may be a reasonable course of action to resolve a diagnostic dilemma after other available diagnostic means have been utilized.

Patients with pseudoretinoblastoma were on average older by about 1.5 years at the time of surgery than those with histologically confirmed retinoblastoma. That pseudoretinoblastoma patients tended to be older was also reported by Asadi Amoli et al. In contrast to our study, the mean age difference of 1 year that they found in their cohort was statistically significant. Moreover, the mix of pseudoretinoblastoma etiologies in their series differed from ours.

The mean duration of symptoms was longer by six months in pseudoretinoblastoma patients than in those with retinoblastoma, but this difference was not significantly different from zero. The ages and symptom duration of

those in the pseudoretinoblastoma group, who had diverse ocular conditions, were more spread out around the mean than those in the retinoblastoma group.

Due to its retrospective nature, our study is limited by the lack of clinical data due to incomplete documentation or missing charts. For instance, majority of the pseudoretinoblastoma patients had no data on the imaging studies that they underwent prior to the surgery, if done at all, thus precluding a comparative analysis of imaging findings in pseudoretinoblastomas and retinoblastoma cases. For future similar studies, a prospective approach can be considered.

CONCLUSION

In this retrospective review, 4.3% of enucleated globes clinically suspected or diagnosed with retinoblastoma were found to have ocular conditions other than retinoblastoma on histologic examination. Persistent fetal vasculature and retinal dysplasia were the most common pseudoretinoblastomas. The pseudoretinoblastoma group and the retinoblastoma group did not differ significantly in terms of sex, laterality of the enucleated eye, mean age at the time of enucleation, and mean symptom duration. Clinicians should endeavor to perform a thorough clinical evaluation and judiciously utilize the available diagnostic means to differentiate retinoblastoma from pseudoretinoblastoma.

Statement of Authorship

Both authors contributed in the conceptualization of the study, acquisition and analysis of data, and manuscript drafting and revising, and approved the final version submitted.

Author Disclosure

Both authors report no conflicts of interest in this work.

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