PHILIPPINE JOURNAL OF
Ophthalmology

VOL. 35 • NO. 1 JANUARY – JUNE 2010

ORIGINAL ARTICLE

A review of pseudoretinoblastoma cases at a tertiary hospital

Rafael M. Valenzuela, MD
Rolando Enrique D. Domingo, MD
Joseph M. Ranche, MD
Lilibeth E. Manganip, RMT

Institute of Ophthalmology
University of the Philippines–National Institutes of Health
Manila, Philippines

ABSTRACT

Objective

To report various intraocular conditions that mimic retinoblastoma.

Methods

A review was conducted of eyeballs enucleated for suspected retinoblastoma between 2003 and 2007, and referred for histopathological confirmation. The slides of cases not histopathologically consistent with the diagnosis of retinoblastoma were reexamined. Clinical records and results of neuroimaging studies were reviewed retrospectively.

Results

Of the 197 eyeballs examined, 182 (92%) proved to be retinoblastoma on histological exam, while 15 (8%) from 13 patients were pseudoretinoblastomas. The age of patients ranged from 4 months to 9 years, with a mean of 35.5 months. The etiologies of the pseudoretinoblastomas were as follows: persistent primary hyperplastic vitreous (PHPV) in 5 eyeballs (33%); retinal dysplasia in 3 (20%); Coats'disease, phthisis bulbi, and vitreous hemorrhage with retinal detachment in 2 (13%) each; and granulomatous endophthalmitis in 1 (8%).

Conclusion

The 8% erroneous diagnosis was lower than the published rates of 10 to 20%. The common etiologies of pseudoretinoblastoma were similar to those reported.

Keywords: *Retinoblastoma, Coats' disease, Persistent primary hyperplastic vitreous, Retinal dysplasia, Granulomatous endophthalmitis*

Correspondence to
Rafael M. Valenzuela, MD
Institute of Ophthalmology
University of the Philippines–National Institutes of Health
Taft Avenue, Ermita
1000 Manila, Philippines
Telephone : +63-2-5247119
E-mail : docralph2000@yahoo.com

No financial assistance was received for this study.

The authors have no proprietary or financial interest in any product used or cited in this study.

PHILIPP J OPHTHALMOL 2010; 35(1): 25-31

RETINOBLASTOMA, considered the most common intraocular neoplasm of childhood, is still relatively rare in Western countries, with an average annual incidence of 8.4 per million children under 5 years of age in the United States.[1] From 1975 to 2004, the incidence of retinoblastoma in the US remained the same.[2] Similar findings were reported in Northern Europe (Sweden and Finland) where the pooled incidence by birth cohort was 6 per 100,000 live births. These data suggested that there was no significant increase in the disease over 40 years (1958 to 1998) as a result of increased awareness and advances in genetic-analysis techniques for predicting retinoblastoma risk, leading to improved genetic counseling and subsequent family planning.[3] Other reports suggested that the prevalence of retinoblastoma may differ by racial groups.[1]

At the University of the Philippines–Philippine General Hospital (UP–PGH), there appeared to be an increase in the number of retinoblastoma cases from 40 new cases per 100,000 during the period 1967 to 1977 to 237 new cases per 100,000 from 1997 to 2001. Espiritu and colleagues attributed this five-fold increase to more survivors of the disease reaching childbearing age and adding gene mutations to the genetic pool.[4]

Given these figures, a child below the age of 5 years who presented with leukocoria and an intraocular mass on ophthalmoscopy was suspected to have retinoblastoma unless proven otherwise. This is based on the fact that almost 90 percent of all patients with retinoblastoma were diagnosed below the age of 5, and the average age at diagnosis was 24 months in unilateral cases and 13 months in bilateral cases. Misdiagnosis became more common in older children who presented with leukocoria, strabismus, and other signs typical of retinoblastoma. Cases of newly diagnosed retinoblastoma have been documented in children between 7 and 18 years old, and in adults as well.[5] But with increasing age of the patient, the chances were greater that suspected retinoblastoma may present in atypical fashion, or turned out to be another condition entirely.

Pseudoretinoblastomas are benign conditions that mimic retinoblastoma and can lead to erroneous diagnosis. They vary in etiology, such as Coats' disease, persistent primary hyperplastic vitreous (PHPV), retinal dysplasia, and endophthalmitis and may present with clinical signs and neuro-imaging findings potentially confusing even to the experienced clinicians. This may lead to the predicament of enucleating an eyeball for suspected malignancy, only to have histopathological diagnosis of a relatively benign condition.

Several studies reviewing the diagnostic accuracy of differentiating pseudoretinoblastoma from retinoblastoma primarily involved western eyes. There is a relative paucity of similar studies in Asia. In 2006, Chua and colleagues published a case series of pseudoretinoblastoma in Asian eyes.[6]

This paper reports our experience with suspected retinoblastoma cases that turned out to be pseudoretinoblastomas on histopathological examination. These cases were drawn from the archives of the Institute of Ophthalmology, Section of Ocular Pathology, University of the Philippines–National Institutes of Health, covering the period 2003 to 2007. Clinical findings, neuroimaging details, and histopathologic descriptions typical of the various etiologies encountered are discussed. The features of retinoblastoma are not discussed in detail, but pertinent points of comparison are made where appropriate.

METHODOLOGY

From January 2003 to December 2007, 197 eyeballs that had been enucleated for suspected retinoblastoma were subjected to histologic evaluation. Most of the cases were referrals from the UP–PGH, Department of Ophthalmology and Visual Sciences. A few referrals came from private clinics and other institutions. The referrals were made because of the unavailability of an ophthalmic pathologist. In some cases, a questionable histopathologic diagnosis was submitted to the institute for verification.

In cases where the histopathologic findings were not consistent with retinoblastoma, the hematoxylin and eosin-stained slides were reviewed. Clinical records were reviewed where available, although most of the pertinent clinical data came from the histopathologic request forms submitted along with each specimen. The clinical presentation (leukocoria, strabismus) and the results of imaging studies (B ultrasonography and computed tomography (CT), if available, were recorded (Table 1).

RESULTS

Of the 197 eyeballs examined, 182 (92%) proved to be retinoblastoma while 15 (8%) from 13 patients were pseudoretinoblastomas. Seven of the patients were from the UP–PGH while the other 6 were referrals from other clinics. Of the 13 patients, 8 were male and 5 were female ages ranging from 4 months to 9 years, with a mean of 35.5 months. Eleven of the patients had unilateral disease, while 2 had bilateral pathology. Among the unilateral group, the left eye was affected in 6 cases, the right in 5 cases.

The etiologies of the various conditions mimicking retinoblastoma were as follows: persistent primary hyperplastic vitreous (PHPV), 5 eyeballs (33%); retinal dysplasia, 3 (20%); Coats' disease, phthisis bulbi, and vitreous hemorrhage with retinal detachment, 2 (13%) each; and granulomatous endophthalmitis, 1 (8%).

The most common presenting sign in those with pseudoretinoblastoma was leukocoria, seen in 11 patients

Table 1. **Summary of pseudoretinoblastoma cases (2003–2007).**

Case No.	Age	Sex	Laterality	Clinical Symptoms	Diagnostic Tests	Clinical Impression	Histopathology
03-103	4 yrs	Male	OS	Leukocoria at 4 mos; rupture 4 days PTC[1]		Retinoblastoma	Vitreous hemorrhage; retinal detachment
04-25	6 mos	Female	OD	Leukocoria at 1 mo	USG[2]: no calcification; small globe	Retinoblastoma; r/o PHPV[4]	PHPV
04-100	9 mos	Male	OS	Leukocoria at 2 mos		Retinoblastoma	PHPV
04-126	3 yrs	Female	OD	Leukocoria at 1 yr		Retinoblastoma	Granulomatous endophthalmitis
04-144	2 yrs	Male	OS	Strabismus at 8 mos; leukocoria 2 wks PTC	USG:(+) calcification	Retinoblastoma	Coats' disease
04-178	8 yrs	Female	OD	Leukocoria	USG: retinal detachment	Retinoblastoma	PHPV
04-211	6 yrs	Male	OU	Leukocoria	CT[3]: No calcification	Retinoblastoma	Phthisis bulbi
05-46	1 yr, 7 mos	Male	OD	Leukocoria at 2 mos	CT: inhomogeneous opacity in posterior chamber USG: detached retina, no calcification	Retinoblastoma; r/o[5] Coats' disease	Coats' disease
06-30	2 yrs	Male	OD	Leukocoria		Retinoblastoma	Retinal dysplasia
06-31	9 yrs	Female	OS	Leukocoria at 5 mos; proptosis & rupture	CT: macrophthalmos; proptosis	T/C[6] Retinoblastoma	Vitreous hemorrhage; retinal detachment
06-185	3 mos	Female	OS	Proptosis		T/C Retinoblastoma	PHPV
06-187	2 yrs	Male	OS	Leukocoria at 1 mo		Retinoblastoma	PHPV
07-77	4 mos	Male	OU	Leukocoria at 2mos		Retinoblastoma	Retinal dysplasia

[1]PTC – prior to consult
[2]USG – ultrasonography
[3]CT – computerized tomography
[4]PHPV – persistent hyperplastic primary vitreous
[5]R/O – rule out
[6]T/C – to consider

(84%). Strabismus was the initial presentation in 1 patient that was noted to have leukocoria a few weeks prior to enucleation. Proptosis of the affected eye was seen in 1 patient. In 2 patients, although leukocoria was the presenting sign, there was progression to proptosis and spontaneous rupture of the globe before enucleation could be performed.

In all patients, the affected eyes were blind prior to enucleation. Although the clinical diagnosis of retinoblastoma was presumptive in some cases, enucleation was performed due to considerations such as blindness, pain, and concern over the patient's ability to return for follow-up.

Based on the available clinical data, imaging studies were performed on 7 patients, 3 each by ultrasonography and computerized tomography (CT) of the orbit and 1 both procedures. Calcification in the intraocular mass was reported in 1 case by ultrasonography.

ETIOLOGIES OF PSEUDORETINOBLASTOMA

Coats' disease

This is an idiopathic, non-hereditary disease with no systemic manifestations, first described by George Coats in 1908. It occurs more commonly in male children. Most present with unilateral decreased vision, strabismus, or leukocoria. It is primarily a vascular abnormality characterized by fusiform or saccular venous dilatations in the retina.[7] Leakage of lipoproteinaceous fluid from these vessels leads to accumulation in the subretinal space, and may progress to total detachment.[8]

Differentiating Coats' disease from retinoblastoma may be extremely difficult. Both conditions can present with the triad of total retinal detachment, subretinal mass, or exudate, and abnormal vessels. Clinical features that help distinguish Coats' disease from retinoblastoma include age of presentation. Coats' disease becomes clinically evident in the first decade of life, with a mean age of presentation at 3.03 years.[9] Retinoblastoma presents at a younger mean age of 1.5 years.

Coats' disease is unilateral in 95% of cases, affecting males more commonly (76%), with no family history of the disease. Retinoblastoma is bilateral in 40% of cases, with a 10% chance of positive family history.

Ophthalmoscopy in Coats' may show a clear vitreous, with irregular telengiectasia of retinal vessels (often in temporal retinal quadrants), yellow subretinal exudation, and glistening subretinal cholesterol deposits. In retinoblastoma, the vitreous may have fluffy white seeds. No retinal exudation is seen, but a retinal mass is often visible.[6] The diffuse infiltrative variant of retinoblastoma,

however, may lead to diagnostic confusion. Its placoid tumor growth within the retina, lack of characteristic calcification, and occurrence in older children usually present a dilemma to clinicians. Shields et al. had documented a similar case coexisting with features of Coats' disease in a 44-month-old girl.[10]

Ultrasonography of Coats' disease may show retinal detachment, and the subretinal exudate may show particular echoes due to the cholesterol content of the fluid. Intraocular calcification is rare, but has been occasionally documented.[11] CT may be helpful in advanced cases, showing retinal detachment with overall increased attenuation due to the dense, lipoproteinaceous exudate. MRI shows the distinctive absence of an enhancing mass since subretinal fluid does not enhance; this is in contrast to retinoblastoma, PHPV, and endophthalmitis where an enhancing mass is seen. [12]

Histopathology shows extensive retinal detachment with PAS-positive subretinal fluid, cholesterol clefts, and lipid-laden macrophages. The presence of telengiectatic retinal vessels (Figure 1) serves to differentiate Coats' disease from other causes of retinal detachment.[7]

Persistent hyperplastic primary vitreous (PHPV)

A benign, nonhereditary developmental disorder in which the embryonic hyaloid artery fails to regress normally, resulting in abnormal lens development and secondary changes of retina and globe, PHPV is a congenital condition usually detected at birth in healthy term infants. The 2 most common presenting signs are leukocoria and microphthalmia. Most cases are unilateral (98%); the rare bilateral cases may be associated with Norrie disease, Warburg syndrome, and other neurological and systemic abnormalities.[13]

Other clinical features that may be seen on examination are: a shallow anterior chamber, a smaller-than-normal lens, and the presence of a retro-orbital mass with vessels radiating from a central point, which may be seen when the pupil is dilated. Secondary glaucoma with buphthalmos, corneal opacification, intraocular hemorrhage, or eyeball atrophy may follow.[14]

Imaging studies are useful in diagnosis. Ultrasonography shows a heterogeneous hyperechoic mass with high internal reflectivity. The vitreous itself is hypoechoic. Retinal detachment may be present, although rarely severe. Microphthalmos may be obvious. CT shows a generalized increase in attenuation of the vitreous chamber secondary to previous hemorrhage. A tubular or S-shaped retrolental mass may be enhanced by using contrast material. Intraocular calcification is normally not present in PHPV. MRI may show an abnormally hyperintense vitreous, possibly a result of vascular leakage. Images may vary from a well-defined tubular process extending from the posterior lens to the retina, to a triangular or irregular mass with posterior excrescences.

Histologically, PHPV masses are composed of loose, highly vascular connective tissue adherent to the posterior-lens surface, with the lens devoid of its posterior capsule (Figure 2). Dysplastic retina covers the primary vitreous mass.[15] The richly vascular fibrous tissue is prone to episodes of vitreous hemorrhage, and contraction of the mass may cause retinal traction with resulting retinal detachment.[12] A stalk containing the hyaloid artery may be seen to extend from the retrolental mass, attaching it to the optic nerve.

In one of our cases, a 6-month-old girl presented with a small, leukocoric, non-seeing eye. The examining physician noted a shallow anterior chamber with a white retrolental mass. Ultrasound confirmed the presence of the mass with no calcifications. The working impression was PHPV. However, a general pathologist signed out the enucleated eye as a retinoblastoma, citing the presence of small cells forming rosettes. The case was referred to the institute for verification. It was noted that the rosettes were more characteristic of those seen in dysplastic retina that accompanies PHPV. The presence of a hyaloid artery stalk connecting the mass to the optic disc bolstered the diagnosis of PHPV.

Retinal dysplasia

Retinal dysplasia is a poorly understood yet common pathological finding in which tubular "rosette-like" structures are present. The mechanism for its histogenesis has not been fully established. It has been proposed that rosette formation may represent an abortive attempt by retinal tissue to regenerate.[16] The presence of the retinal pigment epithelium (RPE) may be the principal organizing factor in the normal histogenesis of the retina. When the RPE is lacking, or when there is extensive detachment of the retina from the RPE, disorganization and dysplasia of the retina may ensue.[17]

Fulton and associates noted that of 71 eyes obtained at perinatal autopsies, 46 had areas of dysplastic retina. This made retinal dysplasia the most common histopathological diagnosis, and confirmed the prevalence of retinal maldevelopment coexisting with a variety of ocular and systemic disorders. Retinal dysplasia was seen in patients with known chromosomal aberrations (i.e. trisomy 13 and 18, triploidy XXY69), systemic or neurological anomalies evident on physical exam (including hydrocephalus, encephalocele, anencephalus), and gross ocular maldevelopment, as well as those without apparent abnormality on gross exam.[18] It has been suggested that "retinal dysplasia" be used as more of a descriptive term rather than a delineation of a specific clinical condition, due to the nonspecific nature of its development and the

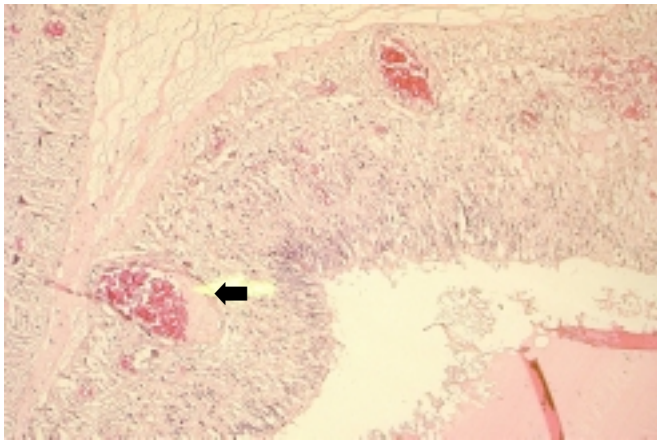

Figure 1. Coats' disease showing telengiectatic retinal vessels (arrow) filled with red blood cells.

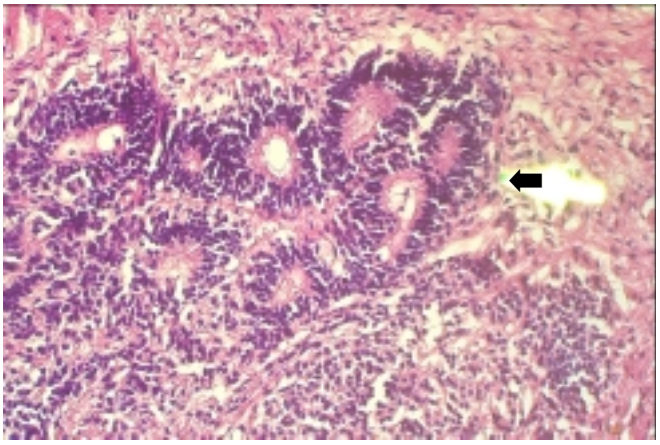

Figure 3. Retinal dysplasia, showing rosette-like structures (arrow) resembling those of retinoblastoma, are present in the retina's photoreceptor layer.

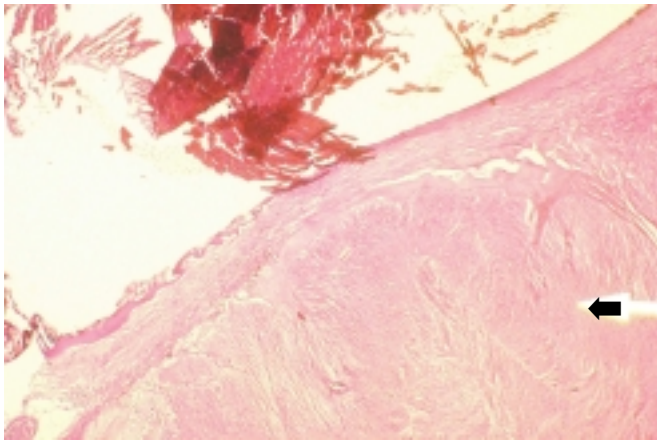

Figure 2. PHPV showing connective tissue mass (arrow) adherent to remnants of the lens. Note absence of lens posterior capsule.

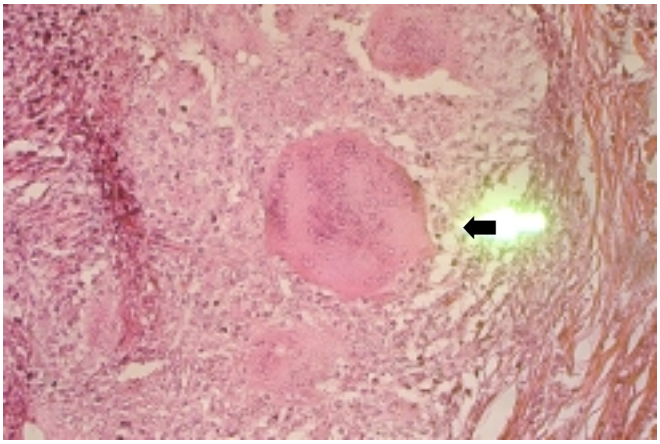

Figure 4. Granulomatous endophthalmitis showing intraocular tissue heavily infiltrated by lymphocytes and numerous Langhans giant cells (arrow).

wide variety of its causes, both hereditary and non-hereditary.[19]

Clinically, retinal dysplasia may vary widely in severity, from simple to massive folding of the retina, central stalks with retinal tissue extending from the optic disk to the lens posterior and complete retinal detachment leading to a disorganized, microphthalmic eye or intraocular proliferation seen as leukocoria. Bilaterally occurring retinal dysplasia is often accompanied by systemic and central nervous sysytem (CNS) abnormalities. Unilateral disease is usually not associated with a specific syndrome.

A noncalcified mass with high reflectivity may be seen on ultrasonography. CT will rarely show calcifications while MRI may show a mass with high signal intensity on T1-weighted and low-signal intensity on T2-weighted images. A normal-appearing vitreous may be combined with a tent-shaped retinal detachment and subretinal exudate. Aplasia of the optic nerve of the affected eye may be present.[20]

Histopathologically, an intraocular mass consisting of disorganized retina with abnormal differentiation, proliferation and rosette formation in the photoreceptor layer is typical (Figure 3). In contrast to the Flexner-Wintersteiner rosettes of retinoblastoma, the rosettes of retinal dysplasia may contain a variety of differentiated cell types. The better differentiated rosettes usually occur in association with systemic abnormalities, while the primitive single-layer rosettes generally occur in infants without systemic disease. Unlike their malignant counterpart, dysplastic rosettes do not represent a neoplastic or pre-neoplastic process.[21]

Granulomatous endophthalmitis

Among conditions that mimic retinoblastoma, endogenous endophthalmitis is considered a rarity. In a large series of 500 patients thought to have retinoblastoma on preliminary exam, endophthalmitis was seen in only 2 cases (0.4%).[5] Tubercular endophthalmitis is even rarer, but there are documented cases in the literature of orbital

TB mimicking retinoblastoma.

One report from New Delhi described a five-year-old boy presenting with leukocoria and proptosis. A globular mass, 8 mm in diameter and having a central necrotic area, was noted in the upper nasal quadrant of the sclera. The preoperative diagnosis was retinoblastoma with extraocular involvement. Post-enucleation histopathology showed a panophthalmitis with granulomas composed of histiocytes, epitheloid cells, and Langhans giant cells.[22]

Another case from New Delhi involved an eight-year-old girl who presented with leukocoria, pain, and redness of the affected eye. Complete blood count (CBC) and chest X-ray were unremarkable. Ultrasound of the orbit showed a diffuse mass in the vitreous cavity with foci of calcification. CT confirmed the presence of the mass and a hyperintense foci suggesting calcification. Because of the pain and lack of vision in the eye, and because imaging studies could not rule out retinoblastoma, enucleation was performed. Histologically, the choroid and retina were heavily infiltrated by lymphocytes, epitheloid cells, and Langhans giant cells. Foci of calcification were scattered throughout the mass. Special stains demonstrated the presence of acid-fast TB bacilli.[23]

In our case series, a three-year-old girl presented with leukocoria. Ultrasonography was suggestive of calcification in the intraocular mass. Histopathology showed extensive granulomatous inflammation of the intraocular tissues, with numerous Langhans giant cells present (Figure 4). Although confirmatory staining with Ziehl-Neelsen stain or other special stains for the demonstration of acid-fast bacilli would have been ideal, these were unavailable at the time. The submitted patient data did not include details of diagnostic work-up for systemic TB. However, the histopathologic features seen on microscopic examination of the eyeball were distinctive enough to support a presumptive diagnosis of TB endophthalmitis.

Ocular involvement is usually secondary to a primary focus in the lung or alimentary tract, or may spread contiguously from adjacent structures such as the paranasal sinuses, or through the bloodstream. Rarely, the eye may be the portal of entry for bacilli, as in primary ocular tuberculosis.[24] The manifestations of ocular tuberculosis may be protean, but choroiditis is the most common.[25]

A six-year-old boy with orbital tuberculosis masquerading as a malignancy has been reported in Australia.[26] A high index of suspicion must be maintained for tuberculosis as a possible differential diagnosis for retinoblastoma, especially, but not limited to places where the disease is endemic.

DISCUSSION

A number of studies have documented the various etiologies of pseudoretinoblastoma, as well as the percentage of error in distinguishing suspected retinoblastoma from a benign intraocular lesion. Until recently, many eyes with pseudoretinoblastoma were enucleated erroneously for suspected malignancy.

In 1962, Kogan and colleagues revealed an error rate of 30%.[27] Subsequent studies using mostly western data showed that 10 to 20 % of enucleated eyes proved to be pseudoretinoblastoma, and it has been suggested that this error rate is rather unavoidable, despite advances in diagnostic modalities.[28]

In 1991, Shields et al. found that out of 500 patients, 212 (42%) had pseudoretinoblastoma. The most common etiologies were: PHPV (28%), Coats' disease (16%), and ocular toxocariasis (16%).[29]

In a retrospective study of 486 patients in France referred for suspected retinoblastoma, 78 (16%) had another lesion: Coats' disease (25%); congenital malformations including PHPV, coloboma, microphthalmia; isolated or associated with retinal dysplasia (30%); and inflammatory disorders including toxocariasis and toxoplasmosis (8%).[30]

In what is believed to be the only published study involving Asian eyes, Chua et al. presented a case series of 28 enucleations for suspected retinoblastoma between 1991 and 2002. Of these, 3 (10.7%) were pseudoretinoblastomas—2 cases of Coats' disease, and 1 case of presumed ocular toxocariasis.[6] While acknowledging the small sample size, this study suggested that the causes of pseudoretinoblastoma were consistent with those seen in Caucasian eyes.

In Tehran, a review of 453 patients between 1986 and 2000 showed 53 cases (11.7%) were pseudoretinoblastomas. In their setting, the most common etiology was endophthalmitis (22.7%). The next most common etiologies were: phthisis bulbi, vitreous hemorrhage, and retinal detachment (17% each). Coats' disease (11.3%), PHPV (7.5%), and retinal dysplasia (7.5%) were less commonly seen. The mean age of patients with pseudoretinoblastoma was 44.7 months, as compared to those with retinoblastoma who presented at a mean of 33.23 months.[31]

In our series of 197 submitted enucleated eyeballs from 2003 to 2007, 16 eyes (8%) were pseudoretinoblastomas. This rate is close to the 10 to 20% diagnostic-error range reported in western studies. Leukocoria was the most common presenting sign. The patients' mean age at diagnosis was 36.38 months, younger than that of the pseudoretinoblastoma patients in the Tehran study. Three of our patients were older than the norm (6, 8 and 9 years old) for retinoblastoma, and 4 patients were less than 1 year old, with leukocoria evident at 1 to 2 months prior to consultation. The unusual age of presentation may

increase the index of suspicion that a pseudoretinoblastoma is present.

Our findings may reflect the increasing number of retinoblastoma cases being referred to the UP–PGH as reported by Espiritu and associates.[4] In contrast to other countries where retinoblastoma is considered a rare entity, perhaps there is a higher rate of contact between Philippine ophthalmologists and patients with retinoblastoma. As to etiology, our results showed that PHPV, retinal dysplasia, and Coats' disease were the most common causes of pseudoretinoblastoma similar to previous studies.

The presence of calcification detected by ultrasonography in one of our patients with granulomatous endophthalmitis underscores the contention that although intraocular calcification is a useful marker for retinoblastoma, it exists in benign conditions as well. The accuracy of ultrasonography in detecting intraocular-tumor calcification has been estimated at only 80% as compared to CT or MRI which are much more accurate.[32] All our pseudoretinoblastoma patients who had CT scans showed no calcifications, even though they had a demonstrable intraocular mass on indirect ophthalmoscopy.

Patients' records and results of ancillary studies were not always accessible, and these missing data may have hampered us in arriving at a more accurate interpretation of the underlying pathologic condition.

In our cases with bilateral eye disease, more clinical information would have helped establish whether the ocular pathology (i.e. retinal dysplasia, phthisis) was part of a genetic disorder or syndrome. As for our patient with granulomatous endophthalmitis, investigations as to whether the three-year-old child had preexisting tuberculosis would have been helpful. The importance of pertinent clinical data that can aid the ocular pathologist in arriving at a precise diagnosis cannot be over emphasized.

Although the primary clinical impression of all the referring physicians in our series was "retinoblastoma," 2 referrals listed a secondary differential diagnosis of PHPV (Case 04-25) and Coats' disease (Case 05-46). The histopathology proved to be consistent with the secondary diagnosis in these cases. In some cases, the diagnosis of retinoblastoma was a qualified one, with the referral written as "consider retinoblastoma" or "rule out retinoblastoma."

In dealing with suspected retinoblastoma, it is advisable for clinicians to be as thorough as possible, with extra effort put into examining the patient. Diagnostic studies may be necessary, but should be used judiciously. When an exhaustive evaluation still yields doubt in the diagnosis, the old dictum of enucleating a blind, leukocoric eye may well be the most justifiable course of action.

References

1. Tamboli A, Podgor MJ, Horm JW. The incidence of retinoblastoma in the United States: 1974 through 1985. *Arch Ophthalmol* 1990; 108: 128-132.
2. Broadus E, Topham A, Singh AD. Incidence of retinoblastoma in the USA: 1975–2004. *Br J Ophthalmol* 2009; 93: 21-23.
3. Seregard S, Lundell G, Svedberg H, Kivela T. Incidence of retinoblastoma from 1958 to 1998 in Northern Europe: advantages of birth-cohort analysis. *Ophthalmology* 2004; 111: 128-132.
4. Espiritu RB, De Jesus AA, Valera EC, Mercado GV. Epidemiological pattern of retinoblastoma at the Philippine General Hospital. *Philipp J Ophthalmol* 2004; 29: 136-139.
5. Shields CL, Shields JA, Shah P. Retinoblastoma in older children. *Ophthalmology* 1991; 98: 395-399.
6. Chua CT, Lim MC, Seah LL, et al. Pseudoretinoblastoma in enucleated eyes of Asian patients. *Singapore Med J* 2006; 47: 617-620.
7. Fernandes BF, Odashiro AN, Maloney S, et al. Clinical-histopathological correlation in a case of Coats' disease. *Diagnostic Pathology* 2006; 1:24.
8. Chang MM, McLean IW, Merritt JC. Coats' disease: a study of 62 histologically confirmed cases. *J Pediatr Ophthalmol Strabismus* 1984; 21: 163-168.
9. Haik BG. Advanced Coats' disease. *Trans Am Ophthalmol Soc* 1991; 89: 371-476.
10. Shields CL, Uysal Y, Benevides R, et al. Retinoblastoma in an eye with features of Coats' disease. *J Pediatr Ophthalmol Strabismus* 2006; 43: 313-315.
11. Pe'er J. Calcifications in Coats' disease. *Am J Ophthalmol* 1998; 106: 742-743.
12. Smirniotopolous JG, Bargallo N, Mafee MF. Differential diagnosis of leukocoria: radiologic-pathologic correlation. *Radiographics* 1994; 14: 1059-1079.
13. Chung EM, Specht CS, Schroeder JW. Pediatric orbit tumors and tumor-like lesions: neuroepithelial lesions of the ocular globe and optic nerve. *Radiographics* 2007; 27: 1159-1186.
14. Francois J. Neonatal or juvenile leukocoria. *Ophthalmologica Basel* 1979; 179: 129-141.
15. Kaste SC, Jenkins JJ, Meyer D, et al. Persistent hyperplastic primary vitreous of the eye: imaging findings with pathologic correlation. *Am J Radiol* 1994; 162: 437-440.
16. Lahav M, Albert DM, Craft JL. Light and electron microscopic study of dysplastic rosette-like structures occurring in disorganized mature retina. *Albrecht Von Graefes Arch Klin Exp Ophthalmol* 1975; 195: 57-68.
17. Silverstein AM, Osburn BI, Prendergast RA. The pathogenesis of retinal dysplasia. *Am J Ophthalmol* 1971; 72: 13-21.
18. Fulton AB, Craft CL, Howard RO, Albert DM. Human retinal dysplasia. *Am J Ophthalmol* 1978; 85: 690-695.
19. Hunter WS, Zimmerman LE. Unilateral retinal dysplasia. *Arch Ophthalmol* 1965; 74: 23.
20. De Graaf P, VanderValk P, Moll AC, et al. Retinal dysplasia mimicking intraocular tumor: MR imaging findings with histopathologic correlation. *J Neuroradiol* 2007; 28: 1731-1733.
21. Chan A, Lakshminrusimha S, Heffner R, Gonzalez-Fernandez F. Histogenesis of retinal dysplasia in trisomy 13. *Diagnostic Pathology* 2007; 2: 48.
22. Ghose S, Seth V, Singhal V, et al. Diagnostic problems in leukocoria. *Indian J Ophthalmol* 1983; 31: 233-237.
23. Raina UK, Tuli D, Arora R, et al. Tubercular endophthalmitis simulating retinoblastoma. *Am J Ophthalmol* 2000; 130: 843-845.
24. Kaur A, Agrawal A. Orbital tuberculosis: an interesting case report. *Int Ophthalmol* 2005; 26: 107-109.
25. Helm CJ, Holland GN. Ocular tuberculosis. *Surv Ophthalmol* 1993; 38: 229-256.
26. Chin PK, Jacobs MB, Hing SJ. Orbital tuberculoma masquerading as orbital malignancy. *Aust NZ J Ophthalmol* 1997; 25: 67-69.
27. Kogan L, Boniuk M. Causes for enucleation in childhood with special reference to pseudo-gliomas and unsuspected retinoblastoma. *Int Ophthalmol Clin* 1962; 2: 507.
28. McLean IW. Retinoblastomas, retinocytomas and pseudoretinoblastomas. In: Spencer WH, Green WR, eds. *Ophthalmology: An Atlas and Textbook*. 4th ed. Philadelphia: WB Saunders 1996: 1332-1380.
29. Shields JA, Parsons HM, Shields CL. Lesions simulating retinoblastoma. *J Pediatr Ophthalmol Strabismus* 1991; 28: 338-340.
30. Vahedi A, Lumbroso LeRouic L, LevyGabriel C, Doz F. Differential diagnosis of retinoblastoma: a retrospective study of 486 cases. *J Fr Ophthalmol* 2008; 31: 165-172.
31. Assadi Amoli F, Piri N, Shamus H. Etiologies of pseudoretinoblastomas in histopathologic specimens of enucleated or exenterated eyes with clinical diagnosis of retinoblastoma. *Acta Medica Iranica* 2005; 43: 105-109.
32. Kaufman LM, Mafee MF, Song CD. Retinoblastoma and simulating lesions: role of CT, MR imaging and Gd-DTPA contrast enhancement. *Radiol Clin North Am* 1998; 36: 1101- 1117.