

Original Article

Pseudoretinoblastoma of 9 enucleated eyes simulating retinoblastoma in 70 enucleated eyes

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Abstract: Objective: To describe pathological features and determine the types and frequency of pseudoretinoblastoma simulating retinoblastoma in 70 enucleated eyes. Materials and methods: Retrospective histopathologic analysis of consecutively enucleated eyes for presumed intraocular retinoblastoma during the past 11 years in the Second People's Hospital of Yunnan Province in China. Results: 9 of the 70 cases were found to be pseudoretinoblastoma on histological analysis. 4 cases were Coat's disease, 2 cases were uveitis and the rest 3 cases were respectively identified as vitreous hemorrhage, toxocariasis and retinal dysplasia. Clinical features and pathological features of these cases were described in detail. Conclusions: Coat's disease accounted for the most common conditions (44.5%) of pseudoretinoblastoma, uveitis (22.2%) accounted for less common conditions, toxocariasis (11.1%), vitreous hemorrhage (11.1%) and retinal dysplasia (11.1%) presented in a sporadic form in our pseudoretinoblastoma series. They have distinctive histopathological features to differentiate from retinoblastoma.

Keywords: Pseudoretinoblastoma, retinoblastoma, coats' disease; pathological features

Introduction

Retinoblastoma is the most frequent primary intraocular malignancy in childhood and infancy. The most common symptom of retinoblastoma was leukocoria and the diagnosis is usually mainly based on retinal mass by indirect ophthalmoscopy, B-scan ultrasonography, computed tomography, MRI and so on clinical and imaging studies. However, a number of cases testified to be other lesions but not retinoblastoma in the follow-up-visit, these lesions clinically mimic retinoblastoma are called pseudoretinoblastoma. In early studies, Howard and Ellsworth reported [1] as much as 53% out of 500 children referred for suspected retinoblastoma were pseudoretinoblastoma, Shields et al reported [2] 42% out of 500 children referred for suspected retinoblastoma were pseudoretinoblastoma. A recent study [3] showed 22% out of 2775 patients referred as retinoblastoma were pseudoretinoblastomas, another study [4] showed 40% out of 331 patients referred as retinoblastoma were pseudoretinoblastomas. There are a few published histopathological

reports of pseudoretinoblastoma served as pathological doctors' reference and guidance until now. This article reviewed the cases of pseudoretinoblastoma from 70 eyes enucleated for presumed retinoblastoma of the Second People's Hospital of Yunnan Province in China in the past 11 years and detailed described pathological features of these cases, which will offer precious pathological materials for pathological doctors to deepen their understandings and make differentiations between similar diseases. An accurate diagnosis even after eye enucleation can avoid unnecessary chemotherapy and guide the subsequent treatment of patients.

Methods

This study was approved by the Second People's Hospital of Yunnan Province in China. 70 cases of formalin-fixed and paraffin-embedded sections of eyes suspected for retinoblastoma by ocular doctors between 2005 to 2015 were retrospectively pathologically. 9 eyes were included for study because no tumors were founded

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Table 1. Demographics and clinical features

	Sex	Age at Enucleation (Years)	Clinical presentation	Ultrasound presentation	Computed Tomography presentation	Magnetic Resonance Imaging presentation
Coats' disease	F	5	Right eyes got to smaller 18 days ago	Suspected hyperecho mass and turbidity of the vitreous body	Diffuse hyperdensity mass in vitreous of the left eye	Not done
	M	8	Loss of vision of the right eye 7 days ago	Intensive banded hyperecho in vitreous and turbidity of the vitreous body	Isodense occupy lesion in the left eye	Not done
	M	6	Left eye went blind when playing 20 days ago	Hyperecho mass and turbidity of the vitreous body	Hyperdensity shadow in vitreous of left eyes	Not done
	F	4	Loss of vision of the right eye 4 months ago	Hyperecho mass and turbidity of the vitreous body	An irregular soft tissue density mass with mild enhancement	Abnormal irregular images in right eye
Uveitis	M	11	Leukocoria of right eye for 1 months	Hyperecho in vitreous	Eye distortion, ocular ball wall thickened and calcium deposition intraocular	Not done
	M	1.8	Leukocoria and left eyes got to smaller 6 months ago	Hyperecho mass and turbidity of the vitreous body	Hyperdensity shadow and soft tissue shadow in vitreous	Not done
Vitreous hemorrhage	M	8	Deterioration of vision of left eyes for 2 years	Diffuse well-distributed hyperechoic mass in vitreous	Not done	Density increased occupy lesion without enhancement in left eye
Toxocariasis	M	5	Loss of vision in the left eye 6 months ago	Hyperechoic to hypotonic mass and turbidity in vitreous	Not done	Not done
Retinal dysplasia	F	1	Left eyes got to smaller 9 months ago	Spots and irregular hyperecho shadow in vitreous and turbidity in vitreous	Isodense occupy lesion	Not done

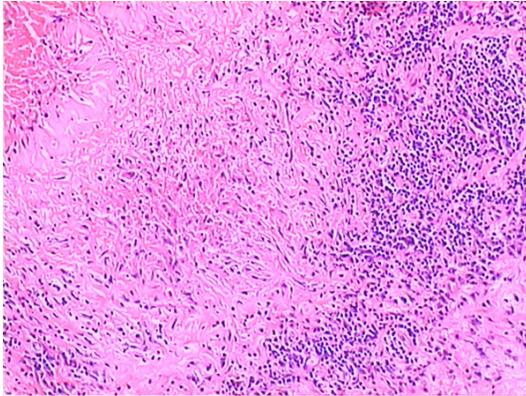


Figure 1. Toxocariasis: larval coagulative necrosis and granuloma (HE, $\times 10$).

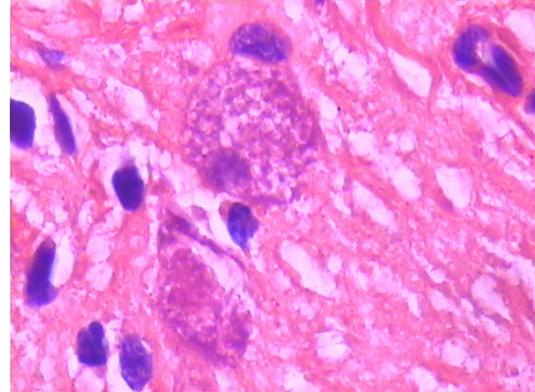


Figure 2. Toxocariasis: toxocariasis cyst, with basophil granules in cytoplasm (HE, $\times 100$).

by pathological examination after surgical enucleation. Important patient medical records were reviewed for demographic information, including age at nucleation, sex, and race, family history and laterality. Clinical patient follow up was limited in our study since a large member of patients had lost contact because of mobile phone number had been changed. Pathological characteristics and definitions: Haematoxylin and eosin stained sections were carefully reviewed on an Olympus BX51 microscope with regular pathological diagnosis process.

Results

61 (87.1%) out of 70 enucleated eyes were identified as retinoblastoma histopathologically, 9 (12.9%) were found to be pseudoretinoblastoma but not retinoblastoma. 4 eyes were identified as Coats' disease, 2 cases were uveitis and the rest 3 cases were respectively identified as vitreous hemorrhage, toxocariasis and retinal dysplasia. The detailed information of these patients was showed in **Table 1** as follows. The mean age of pseudoretinoblastoma at presentation was 3.1 years in 61 retinoblastoma patients while was 5.6 years in 8 pseudoretinoblastoma patients in our series. Demographics and clinical features of pseudoretinoblastoma patients were described in detail in **Table 1**.

Pathologic features

Coats' disease (4 cases)

The retinal layers were being thickened especially the outer layer because of intensive exu-

dation. Exudated materials always were eosinophilic proteinaceous materials, with needle-like cholesterol deposited in some areas. Foamy histiocytes phagocytosised with lipid always aggregates around cholesterol deposited areas, sometimes with brown pigment in cytoplasm, polykaryocytes also existed. Ossification occurred in dense fibrosis tissues in 2 cases. Abnormal telangiectatic vessels were seen in the retina in 3 cases. Retinal detachment was seen in 3 cases.

Uveitis (2 cases)

Case 1: Fungal Uveitis: The retinal pigment epithelium and fibrous tissue were hyperplasia distinctively, with large amount of calcium deposited in uveal. Further more, numerous yeasts were perceived, obscure filamentous fungi also founded. In addition to, a few yeasts with a small nucleus were found in PAS stain to testify the diagnosis. Besides lymphocyte and plasma cell, much eosinophilia were found to infiltrate around blood vessels.

Case 2: There were large number of inflammatory cells (lymphocytes most prevalent) infiltrated the urea, retina, optic nerve and vitreous. Fibrovascular tissue were hyperplasia distinctively that indicated this case was the late stage of chronic uveitis. Extensive ossification had occurred in these fibrovascular areas. There were expanding hyperaemia blood vessels with a large number of blood red cells exudated around them. In addition to a thick-wall vessel and a few fibrous tissue. With inflammatory cells infiltrated went through the optic nerve (S100 is positive by Immochemistry) which indi-

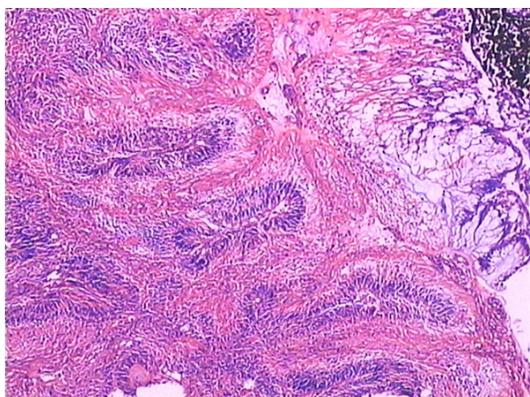


Figure 3. Retinal dysplasia: hyperplasia retina was composed of multiple retinal layers, with branching tubules and acinus communicated with the subretinal space (HE, $\times 4$).

cated the central retinal artery also had involved with inflammation.

Vitreous hemorrhage (1 case)

The eyeball was filled with erythroblasts, erythrocyte ghost cells, hemoglobin spherules, and macrophages. Macrophages were laden with ghost cells and golden-brown granules of the blood pigment hemosiderin. Some areas showed massive inflammatory cells infiltrated. Retina was thinned by pressure from hemorrhage.

Toxocariasis (1 case)

Larval coagulative necrotic fragments were surrounded by many lymphocyte, a few plasma cell, epithelioid histiocytes and polykaryocytic histiocytes to compose of granuloma (**Figure 1**). Cysts with 8-100 μm in diameter and numerous basophil granules in cytoplasm appeared in the retina. These basophil granules were cystozoites which is crescent shaped and 2-7 μm in diameter in cyst (**Figure 2**). CD68 immunohistochemical staining testified a positive expression in histiocytes in granuloma while a negative expression in cysts. In addition to, a cyst lined with flat epithelium also was founded and retinal detachment was accompanied. Some areas of the retina were thickened because of exudation and slightly fibrosis.

Retinal dysplasia (1 case)

There was irregular geographic hyperplasia in the retina. Hyperplasia retina was composed of multiple retinal layers, with branching tubules

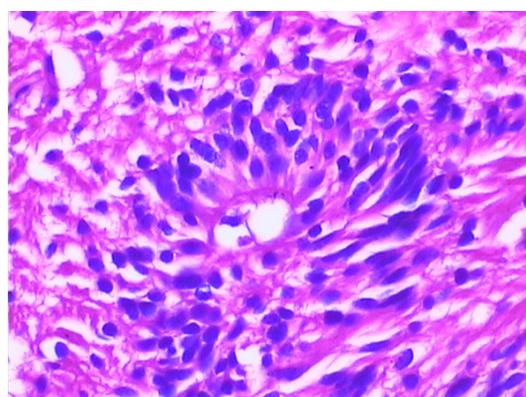


Figure 4. Retinal dysplasia: dysplastic rosettes which was much larger than the neoplastic Flexner-Wintersteiner rosettes and with multiple retinal layers (HE, $\times 40$).

and acinus communicate with the subretinal space (**Figure 3**). Some tubules resembled as dysplastic rosettes, however it was much larger than the neoplastic Flexner-Wintersteiner rosettes of retinoblastoma and with multiple retinal layers (**Figure 4**). There were not any cellular atypia in all cells in the retina.

Discussion

The rate of clinical misdiagnoses of retinoblastoma had been reported in some articles. This figure was much higher in the last century, despite this possibility has improved significantly with the development of clinical and imaging diagnostic techniques in the recent years, eyes enucleation in clinical misdiagnoses condition testified to be pseudoretinoblastoma can't be avoided. In a report by Chuah C T et al [5] in 2006, 3 (11%) out of 28 enucleated eyes referred to retinoblastoma were pseudoretinoblastoma. Huang S et al [6] in 2010 showed 5% out of 355 eyes enucleated for presumed retinoblastoma found no evidence of retinoblastoma. In our hospital with key ophthalmological disciplines and specialties in our province, this figure was 9 (11.9%) out of 70 enucleated eyes in the past 11 years.

The spectrum of pseudoretinoblastoma is changing with years going on. In the earliest large series report of pseudoretinoblastoma in 1965 [1], the leading simulators included PFV (19%), ROP (14%), posterior cataracts (14%), choroidal coloboma (12%) and uveitis (10%), while Coats' disease (4%) only accounted a small proportion in this article. In the recent

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years, a report of 604 patients found [3] Coats' Disease (40%), persistent fetal vasculature (28%), vitreous hemorrhage (5%) and ocular toxocariasis were the most common simulating lesions, another report disclosed [8] Coats' disease (40%) and persistent fetal vasculature (26%) were the most common condition of pseudoretinoblastoma, ocular toxocariasis (4%), vitreous hemorrhage (5%), familial exudative vitreoretinopathy (3%), rhegmatogenous retinal detachment (3%), coloboma (3%), astrocytic hamartoma (2%), combined hamartoma of retina and retinal pigment epithelium (2%) also is presented in pseudoretinoblastoma. Another study [5] also found Coat's disease (66.7%) is the most common mimickers and ocular toxocariasis also is perceived in their series. In our series, Coat's disease also accounted for the most common conditions (44.5%), uveitis accounted for 22.2%, toxocariasis, vitreous hemorrhage, and retinal dysplasia respectively accounted similarly for 11.1% in our study. We have got the same tendency that Coats' Disease was the dominate simulators of retinoblastoma, other disease such as uveitis, vitreous hemorrhage, persistent fetal vasculature, toxocariasis also was presented but affected in a sporadic form.

Retinoblastoma is showed as a yellow-white retinal tumor in ophthalmoscopy and presented as masse in vitrella and subretinal, always with intraocular calcifications in sonography. The median age of retinoblastoma was 2.5 years old in a large series report of China [7] while it was 3.1 years old in our series. More slightly late diagnosis age may be related to most patients come from remote areas in our province and the disadvantage economic condition of them. The more elderly diagnoses age in our hospital may be partly responsible for ocular doctor's misdiagnosis of pseudoretinoblastoma as retinoblastoma.

The most important differentiation of retinoblastoma is Coats' disease. Coats' disease can mimic retinoblastoma because of proteinaceous fluid exudates and cholesterol deposits in retina, so formed the hyperechoic mass or soft tissue shadow ultrasoundly. In addition to, ossification also appeared in Coats' disease, which will add additional testimony for retinoblastoma. If leukocoria is presented as the main clinical symptoms, a ocular doctors most possibly will diagnosis a child with these manifestations

as retinoblastoma. However, Coats' disease usually affects older child with mean age of presentation at five years, on the other hand, retinoblastoma always affects younger child with mean age of presentation at three years. Abnormal leaky retinal vessel is a distinctive feature of Coats' disease which will causes exudative retinal detachment. While retinoblastoma showed as a yellow-white retinal tumor with a dilated retinal artery and vein in indirect ophthalmoscopy. Histopathologically, Coats' disease showed as eosinophilic proteinaceous materials exudated, with cholesterol deposited. Foamy histiocytes and polykaryocytes loaded with lipid appeared, a prolonged lesion will case fibrosis tissues proliferate and tissue ossification. Abnormal telangiectatic vessels is characteristic in Coats' disease.

"Uveitis" is a general term not only means the inflammation affects the uvea of the eye, but also affects the lens, retina, optic nerve, and vitreous [8]. The onset of uveitis always considered as a failure of the ocular immune system. Uveitis is categorized into four types: anterior uveitis, intermediate uveitis, posterior uveitis and diffuse uveitis which depends on the portion of the uvea that is affected. In this case it showed as diffuse uveitis type and the late stage of the disease since fibrovascular tissues had hyperplasia seriously, so formed a mass in ultrasound. Histopathologically, uveitis showed as inflammatory cell infiltrated (uvea, lens, retina, optic nerve, and vitreous can be involved), protein contents exudated, expanding blood vessels, fibrovascular proliferation and so on.

Fungal endophthalmitis usually is indolent clinically, and multiple vitreous microabscesses are a characteristic finding in fungal endophthalmitis. GMS fungal stain discloses fungal hyphae within a microabscess. This case is not so typical because of late delayed diagnosis or presentation since it showed large amount of deposited calcium, hyperplasia fibrous tissue and retinal pigment epithelium in uveit. Histopathologically, hyaline branched hyphae or yeast cells in PAS stain is very important to make a definite diagnosis.

Vitreous hemorrhage is the extravasation or leakage of blood into the vitreous humor or around the vitreous humor of the eye. Many condition such as diabetes, hypertension, trauma can cause vitreous hemorrhage. Blood can

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break through the hyaloid membrane into the substance of the formed vitreous, can be exist persistently and can undergoes degeneration gradually. The vitreous body is filled with fresh or remote hemorrhage, and numerous erythrocyte ghost cells or other blood breakdown products are present. Then macrophages will aggregate to digest hemorrhaged red blood cells.

Ocular toxocariasis can mimic retinoblastoma because of endophthalmitis will simulates endophytic neoplasm in retina. Toxocariasis occurs in slightly older children toward the end of the first decade, with a history of contacts with puppies or a prior history of visceral larva migrans. Human toxocariasis is caused by the larvae (immature worms) of the dog roundworm, the cat roundworm, the fox roundworm and so on, very scarcely the bird's roundworm [9]. The girl in this case always played with throstles since his family had bred throstles for years before her onset. His toxocariasis most possibly cased by ingesting throstle roundworm eggs when playing with these birds. Organizing vitreoretinal traction and signs of inflammation is very characteristic in ocular toxocariasis to help us differentiated it from retinoblastoma. Histopathologically, cysts with numerous basophil granules in cytoplasm appeared in retina is very important to make the diagnosis, a positive ELISA test result can make a definite diagnosis of toxocariasis.

Retinal dysplasia is a type of retinal malformation. Patients have congenital microphthalmia and most have trisomy 13. It resembles retinoblastoma and must be distinguished from retinoblastoma because the retina is proliferated markedly and rosettes can be observed pathologically. Retinal dysplasia showed as mass of disorderly dysplastic retina consisted of aberrant proliferated retina with branching tubules which communicated with the subretinal space [10]. Most tubules is much larger which is sized in hundreds of ums than Flexner-Wintersteiner rosettes which is sized in 30-60 ums mostly. But some small tubules sized in dozens of ums also resembled Flexner-Wintersteiner rosettes of retinoblastoma. However, these rosettes were composed of multiple retinal layers while Flexner-Wintersteiner rosettes were composed of simple tumor cell layer sometimes with bistratified tumor cell layer. The most important key lines in no cellar

atypia is perceived in retinal dysplasia while dramatical cellar malignant features is presented in retinoblastoma. Retinal dysplasia can be focal, multifocal or geographic. Retinal detachment occurs with complete retinal dysplasia, in this condition blindness is accompanied in that eye.

Retinoblastoma has some mimickers and sometimes it is rather challenging to distinguish them because the decision is based on findings of the clinical examination and radiologic studies, the diagnosis can't be confirmed by biopsy until the enucleation is carried out. Ocular doctors always depend on B-ultrasound, CT and MRI to exclude simulated diseases of retinoblastoma after ophthalmoscope examination. Retinoblastoma appears as a solid echogenic mass with high echogenic foci of calcifications on ultrasound studies. Calcium deposition intraocular is considered as a key element to identify retinoblastoma, in this aspect, CT is sensitive in detecting intraocular calcium deposition. Magnetic resonance imaging (MRI) is most sensitive to evaluate the extension of the tumor, so MRI plays an increasingly important role for initial diagnosis, extension, staging and treatment planning of retinoblastoma. However, some patients in our hospital (as much as 75% in our pseudoretinoblastoma series) will give up MRI because of its highly cost, so decreased the possibility to get a more accurate diagnosis for patients. In our series, most misdiagnoses cases (5 out of 9) showed calcium deposition histopathologically, so appeared in CT as hyperattenuating intralaminar areas, so even though calcium deposition is an important sign for retinoblastoma, but also can be seen in many pseudoretinoblastoma. Ocular doctors should pay more attention and make more evaluation to patient so as to make an accurate diagnosis and avoiding undue diagnostic or therapeutic procedures, especially for these patients older than 3 years.

One case in this paper-the toxocariasis one was presented in Chinese Journal of Pathology in February 2017 [11].

Disclosure of conflict of interest

None.

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