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Unilateral Retinoblastoma Presentation in a Latin-American Teenager: A Case Report and Literature Review

Erick Andres Quiroz-Gonzalez[1], Miguel Angel Quiroz-Reyes[2, *], Cristina Gonzalez-Gonzalez[3], Roberto Loaeza-Castrejon[2], Luis Haro-Morlett[1], Armando Bautista-Barba[1], Emiliano Fulda-Graue[2], Federico Graue-Wiechers[2]

[1]Ophthalmology Department, Institute of Ophthalmology, National Autonomous University of Mexico, Mexico City, Mexico

[2]Retina Service, Institute of Ophthalmology, National Autonomous University of Mexico. Mexico City, Mexico

[3]Ultrasonographic Department, Institute of Ophthalmology, National Autonomous University of Mexico, Mexico City, Mexico

Email address:

drquiroz@prodigy.net.mx (M. A. Quiroz-Reyes)

[*]Corresponding author

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Abstract: *Background:* Retinoblastoma is the most common intraocular mass in children—typically presenting in infants under 5 years of age—with a mean age of 24 months in unilateral cases, and 12 months in bilateral cases. Late-onset retinoblastoma and its presentation in adults is extremely rare; however, it should always be considered for the differential diagnosis of an intraocular mass originating from the retina. Due to the life-threatening nature of this disease, early diagnosis and prompt treatment are crucial for a good prognosis. *Objective*: A tumor case presentation and multidisciplinary study of a female young adult. *Method:* A case presentation study of a Hispanic teenager with a unilateral retinoblastoma and vitreous exudation resembling a large snowbank. The patient underwent complete ophthalmological examination and subsequent enucleation, with histopathological confirmation of retinoblastoma accompanied by chemotherapy. *Conclusion:* Retinoblastoma presenting as an intraocular mass in a young adult should always be considered as a differential diagnosis. Echography is crucial to obtaining a diagnosis, as well as dictating precise and adequate treatment. We review the literature regarding cases of retinoblastoma, demonstrating that most exhibited differentiated characteristics and were sporadic in nature; in most cases, the eye could not be saved. Review of late-onset retinoblastomas was therefore conducted to enrich our existing knowledge, as well as to prevent making the same mistakes when facing a similar difficult diagnosis.

Keywords: Retinoblastoma, Intraocular Mass, Leukocoria, Echography and Enucleation

1. Introduction

Retinoblastoma is the most common intraocular mass in children—typically presenting in infants under 5 years of age—with a mean age of 24 months in unilateral cases, and 12 months in bilateral cases. This corresponds with 25–35% of all cases, with a global incidence of 1/15,000 to 1/18,000 live births reported. [1] Retinoblastomas have two presentations: the hereditary form, characterized by bilateral or trilateral affection with multifocal infiltration that presents earlier in life; and the sporadic form, usually with a unilateral and unifocal affection that occurs later in life. [2]

In case series including 400 children with retinoblastoma, 34 (8.5%) patients were older than 5 years, while only 3 (0.8%) were older than 15 years. [3, 4] Late presentation is rare; the oldest patient reported was a 74-year-old female, described by Byron. [5, 6] In 1919, Maghy et al. reported the first case of retinoblastoma in an adult, referring to the tumor as a glioma of the retina; in 1929, Verhoeff first coined the term retinoblastoma, describing a 48-year-old patient with

the same tumor. [6]

There are few isolated reports—around 59 within the last century—including patients aged 15 years or older. [7, 8] Retinoblastoma is not usually considered a differential diagnosis for intraocular masses in patients older than 5 years, secondary to the low incidence. This review of late-onset retinoblastomas was therefore conducted to enrich our existing knowledge, as well as to prevent making the same mistakes when facing a similar difficult diagnosis.

2. Case Presentation

A 15-year-old Latin-American teenager presented to the *Institute of Ophthalmology, Conde de Valenciana Foundation, in Mexico City*, with a history of a white dot on her right eye with 1 month of evolution, accompanied by blurred vision. She denied any past medical or family history of cancer. Ophthalmic examination identified best-corrected visual acuity of hand movement in her right eye, and 20/20 in the left eye; intraocular pressure was within the normal range in both eyes (16- and 14-mm Hg, respectively).

Upon observation, the right-sided leukocoria was remarkable (Figure 1). On anterior segment biomicroscopy, the cornea was clear, while the anterior chamber presented with mild cellularity, a normal iris without neovascularization, and a clear lens with an opacity behind it (Figure 2). Fundus examination revealed a white, mobile, inferior precipitate that filled half of the vitreous cavity—in association with haze—and an elevation of the inferior retina posterior to the exudation zone. Only the upper retina was observed to be attached; the remaining structures were not valuable (Figure 3), and the contralateral eye was unremarkable.

Leukocoria implies a large spectrum of diseases with many differential diagnoses, such as cataracts, retinochoroidal coloboma, toxocariasis infection, Coats disease, intermediate uveitis, chronic retinal detachment, or an intraocular mass. Owing to the exudation, the first diagnosis was intermediate uveitis presenting with a large snowbank and exudative retinal detachment. Echocardiographic examination was performed; on the B-scan, vitreous haze with pinpoint opacities was identified. This was associated with the presence of an intraocular mass at the retina level, filling half the inferior zone of the cavity from the 3 to 9 o'clock meridian, and accompanied by serous retinal detachment along the circumference of the lesion. Additionally, the mass presented internal hyperechogenic condensations with an acoustic shadow, resembling calcifications (Figure 4). On the A-scan, a low-median reflectivity with an internal irregular structure was observed (Figure 5).

Due to the high suspicion of unilateral retinoblastoma, the patient was referred to a third-level institution for integrated management. The patient underwent systemic evaluation to rule out tumor dissemination; however, the patient began to exhibit signs of orbital spreading over a period of 2 months. As a result, neoadjuvant chemotherapy based on carboplatin, etoposide, and vincristine cycles were performed first. Subsequently, enucleation and histopathological examination were performed, accompanied by adjuvant chemotherapy using the same drugs as in the first cycle. The patient is currently being followed-up, and no signs of recurrence have been exhibited.

The histopathologic report confirmed the presence of a differentiated cell type consisting of a retinoblastoma with both exophytic and endophytic growth, as well as 70% necrosis. The neoplasia affected the inferonasal and inferotemporal quadrants, including approximately 50% of the vitreous cavity, with a basal dimension and height of 19 mm and 7 mm, respectively. Multiple foci with choroidal invasions larger than 3 mm were observed, with free margins on the optic nerve. Perivascular invasion of the sclera was identified, and the neoplasia displaced the ciliary body without any contact with the lens. The neoplasia was graded as a Group Vb and Group E retinoblastoma according to the Reese-Ellsworth classification and International Classification of Retinoblastoma, respectively.

Figure 1. *Patient with dilated pupils, showing leukocoria of the right eye.*

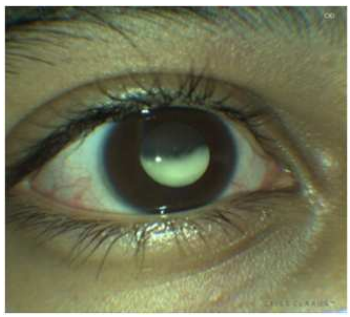

Figure 2. *Anterior segment of the right eye.*

The presence of retrolental exudation was identified, creating a large snowbank.

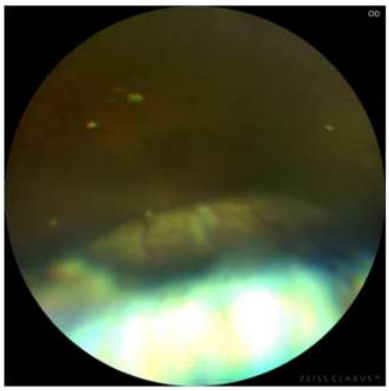

Figure 3. *Ultrawide-field image of the posterior segment.*

Vitreous haze, as well as an inferior retinal detachment posterior to the retrolental exudation, was shown. The superior retina seemed to be attached.

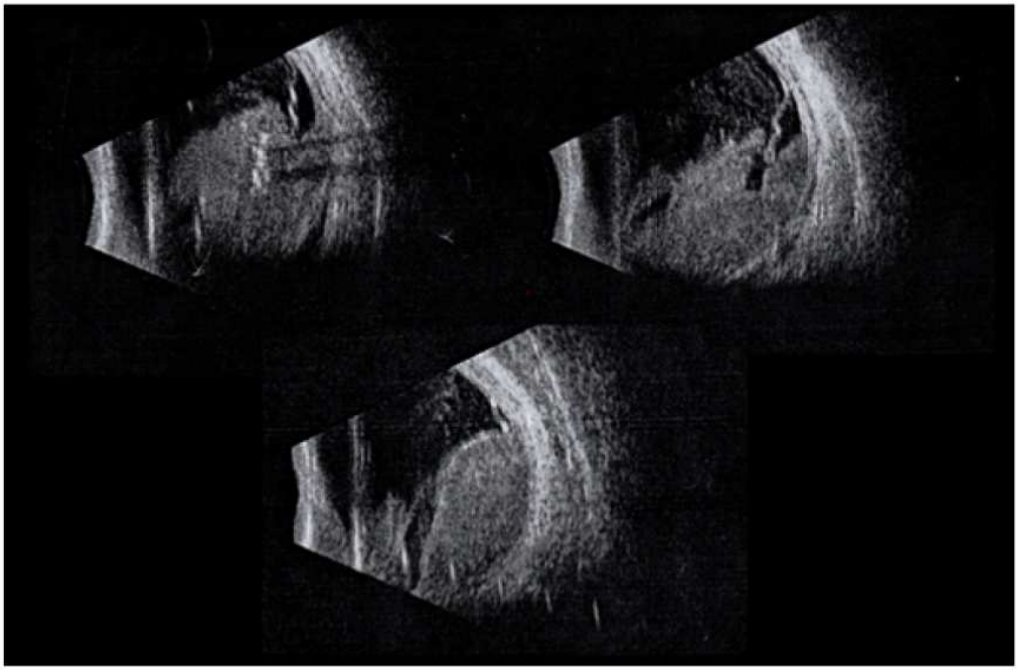

Figure 4. *B-Mode echography showing vitreous opacities.*

A tumor associated with retinal detachment in the surrounding areas, as well as hyperechoic condensations with acoustic shadows, consistent with calcifications, are seen at the level of the retina.

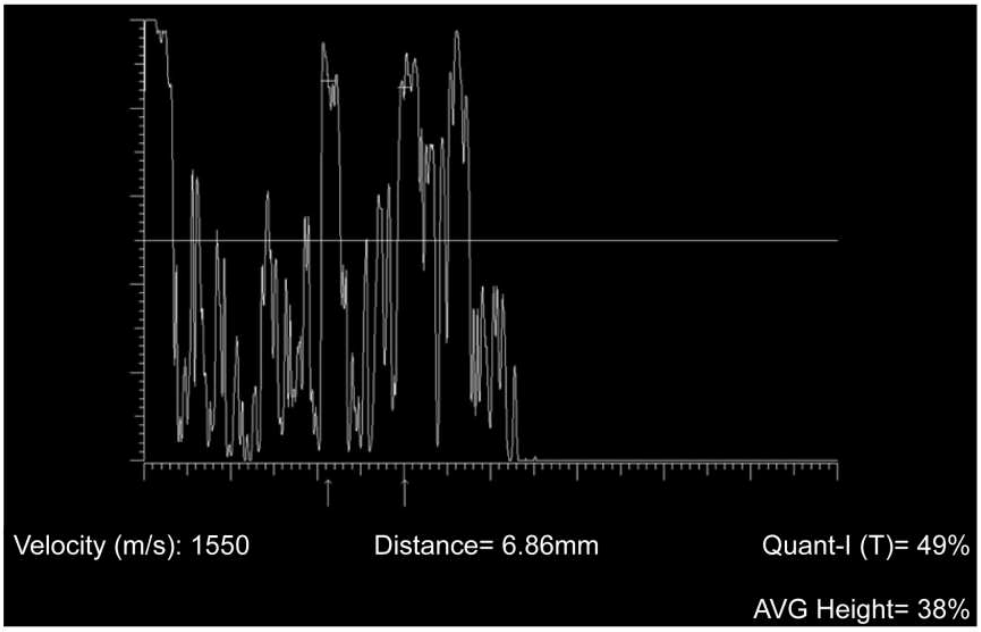

Figure 5. *A-mode scan demonstrating the low-medium reflectivity of the tumor and irregular internal reflectivity.*

3. Discussion

This case report describes a young female outside the range of normal retinoblastoma presentations. Globally, retinoblastoma is most prevalent in children under 5 years of age, comprising 90% of cases. As previously mentioned, there are few adult cases reported in the literature, and only two represent Latin-American patients. [9, 10]

Herein, we review retinoblastoma in adults and young adults reported over the years. A literature search based on the Cochrane, PubMed, CrossRef, Embase, and Google Scholar databases reported 59 cases of histopathologically verified late presentation retinoblastoma; four cases in which the eyes were saved were excluded. Tumor extension, initial treatment, and histopathological characteristics of the tumor are presented in Table 1.

Table 1. *Tumor extension, initial treatment, and histopathological characteristics of the tumor.*

Author	Year	Country of publication	Age/gender	Tumor extension	Primary treatment	Histopathology
Maghy, et al.	1919	United Kingdom	20/F	Intraocular	Enucleation	FW
Verhoeff, et al.	1929	USA	48/M	Intraocular	Enucleation	FW
McCrea, et al.*	1943	NM	20/M	NM	Enucleation	NM
Rasmussen, et al.*	1944	NM	48/M	NM	Enucleation	None
Rychener, et al.	1948	USA	33/F	Intraocular	Enucleation	FW
O'Day, et al.*	1948	NM	29/M	NM	Enucleation	NM
Arseni, et al.*	1959	NM	53/M	NM	Enucleation	FW
Mehra, et al.	1961	India	45/M	Orbital metastases	Enucleation	FW
Finlay, et al.*	1962	NM	74/F	NM	Enucleation	NM
Makley, et al.	1963	USA	52/M	Intraocular	Enucleation	FW
Ohara, et al.*	1963	NM	43/F	NM	Enucleation	HW
Perz, et al.*	1964	NM	56/M	NM	Enucleation	NM
Laschi, et al.*	1968	NM	40/F	NM	Enucleation	None
Kremlicka, et al.*	1975	NM	42/M	NM	Enucleation	FW
Berkeley, et al.*	1977	Butan	60/M	Orbital Metastases	Enucleation	None
Takahashi, et al.	1983	Japan	26/F	Intraocular	Enucleation	HW
Neronova, et al.*	1986	NM	46/F	NM	Enucleation	NM
Shields, et al.	1991	USA	16/F	Intraocular	Enucleation	NM
Shields, et al.	1991	USA	17/M	Intraocular	EBRT	NM
Shields, et al.	1991	USA	18/F	Intraocular	Enucleation	NM
Biwas, et al.	1996	India	32/M	Intraocular	Enucleation	HW
Biwas, et al.	1996	India	21/M	Intraocular	Enucleation	NM
Mietz, et al.	1996	USA	26/F	Intraocular	Cryotherapy and EBRT	HW
Nork, et al.	1996	USA	29/F	Intraocular	Enucleation	None
Park, et al.	1999	Australia	16/F	Intraocular	Enucleation	HW and fleurettes
Biwas, et al.	2000	India	25/F	Intraocular	Enucleation	None
Odashiro, et al.	2005	Brazil	21/F	Intraocular	Enucleation	FW and Fleurettes
De jong, et al.	2006	Netherlands	27/M	Intraocular	EBRT	FW
Orellan, et al.	2009	Canada	23/M	Intraocular	Enucleation	None
Shrestha, et al.	2010	Nepal	37/M	Intraocular	Enucleation	None
Nandedkar, et al.	2010	India	22/F	Orbital Metastases	CT	None
Mehdizadeh, et al.	2010	Iran	16/F	Intraocular	TTT	HW
Wells, et al.	2011	USA	48/F	Intraocular	EBRT	HW
Singh, et al.	2011	Oman	29/F	Intraocular	Enucleation	HW
Zhang, et al.	2012	China	20/M	Intraocular	Enucleation	HW
Goel, et al.	2012	India	50/M	Intraocular	Enucleation	FW
Khetan, et al.	2013	India	33/F	Intraocular	EBRT	None
Zafar, et al.	2013	Pakistan	25/M	Orbital metastasis	CT and EBRT	None
Chawla, et al.	2013	India	24/M	Orbital metastasis	CT and EBRT	NM
Khetan, et al.	2014	India	30/F	Intraocular	TTT and CT	NM
Yousef, et al.	2014	Oman	23/M	Intraocular	CT	FW + HW
Sharifzadeh, et al.	2014	Iran	29/F	Intraocular	Enucleation	FW
Zhang, et al.	2015	China	45/M	Intraocular	Enucleation	None
Kaliki, et al. (8)	2015	USA/India	Mean age 30, 50% M	6 Intraocular 2 Orbital metastases	2 EBRT 1 CT 1 IAC 4 Enucleation	NM
Raj, et al.	2015	India	32/M	Orbital Metastases	Enucleation and CT	None
Magan, et al.	2016	USA	32/M	Intraocular	EBRT + IAC + IVC	NA
Hernandez, et al.	2016	Mexico	17/M	Intraocular	Enucleation	NM
Vasudha, et al.	2018	India	55/F	Orbital metastases	NM	NM
Rashaed, et al.	2019	Saudi Arabia	21/M	Orbital metastases	Enucleation	None
McMahon, et al.	2019	USA	23/M	Intraocular	IAC + IVC	NA
Zhou, et al.	2020	China	34/F	Intraocular	Enucleation	Fleurettes
Riazi, et al.	2021	Iran	22/M	Intraocular	IAC + CT	NA

FW: Flexner-Wintersteiner, NM: Not mentioned, HW: Homer-Wright, EBRT: External beam radiotherapy, CT: Chemotherapy, TTT: Transpupillary thermotherapy, IAC: Intra-arterial chemotherapy, IVC: Intravitreal chemotherapy, NA: Not applicable.
*Information collected from Sengupta, et al.

There are different theories regarding the development of retinoblastoma in adults. It is known that retinoblastoma arises from photoreceptor precursors [11]; thus, it is believed that the persistence of embryonal retinal cells may lead to malignant transformation in older adults. Another theory considers the formation of a rare tumor—benign in nature and linked to the RB1 gene mutation—referred to as retinocytoma. [12] This was previously believed to be a type

of spontaneously regressed tumor; however, it may be the precursor to retinoblastoma in adults. According to the theory proposed by Knudson, this is a tumor exhibiting a single mutation, with a "second hit" that occurs later in life; this culminates in a malignant transformation due to genomic instability, and the stimulus causing the mutation is often unknown. [9] The last theory arose from the belief that the retinoblastoma may have developed early in life with an asymptomatic and undiagnosed course, undergoing a spontaneous regression that reactivates later in life. [13]

In adults, retinoblastoma usually manifests as a white intraocular mass with subacute progression—typically complicated by vitreous hemorrhage, vitreous seeding, or lens displacement—manifesting as low vision or pain due to the development of a neovascular glaucoma. This contrasts with the presentation in children, where the most common manifestations are leukocoria and strabismus. In the B-mode scan in adults, retinoblastoma appears as a mass, usually posterior to the eye equator, in association with an exudative retinal detachment; additionally, most presentations lack intralesional calcifications, unlike retinoblastoma in children where this is a classic sign.

To obtain a precise diagnosis of retinoblastoma, histopathological analysis is essential. Flexner-Wintersteiner rosettes—as well as higher differentiated cells that have photoreceptor characteristics in a bouquet-like cluster, called fleurettes—present in well-differentiated retinoblastomas and are associated with a better prognosis. Flexner-Wintersteiner rosettes and fleurettes are primarily composed of red and green cones, lacking blue cones. [10] These can appear in the same retinoblastoma, demonstrating various grades of differentiation; however, when fleurettes appear, they may be classified as retinocytomas. When blue cones or rods are the dominant features, they are referred to as bacillettes, which are also well differentiated. [10] Conversely, undifferentiated retinoblastomas lack fleurettes and Flexner-Wintersteiner rosettes, instead containing Homer-Wright rosettes that are less differentiated neoplastic cells associated with a poor prognosis. [10]

Immunohistochemical techniques complement the diagnoses; by staining tumor cells with monoclonal antibodies specific to neuron-specific enolase—not retinoblastoma—the techniques could be used to identify other neuron-derived neoplasias, such as medulloblastoma. [10] Almost all reports initially treat patients via enucleation; still, attempts to salvage the globe have been described in some cases. Khetan et al. [14] described a patient initially treated with chemotherapy and transpupillary thermotherapy, leading to tumor regression for two years; later, recurrence was reported, culminating in enucleation. Mietz et al. [11] presented a case initially treated using cryotherapy and radiotherapy. Partial regression occurred; however, the patient required enucleation 14 months later. There are only four reports wherein the eye was successfully saved, including a report by Kalikili et al. [15] where an intraocular tumor was treated via external beam radiotherapy. In the same study, they tried to salvage the eyes of other patients using radiotherapy and systemic chemotherapy; however, their efforts were unsuccessful and eventually resulted in enucleation. [16-18]

Riazi et al. [16] reported a patient with a Group D retinoblastoma, treated and saved using intra-arterial chemotherapy based on two cycles of melphalan and topotecan. The option to undergo conservative treatment may be contemplated; however, owing to the aggressive nature of the tumor and late diagnosis, this would eventually lead to enucleation. It is important to note that there are few reported deaths due to retinoblastoma in adults; this may be due to the prevention of metastasis through enucleation, or a bias secondary to the absence of adequate follow-up. [9] Additionally, it should be considered that these patients are predisposed to the formation of other tumors, such as osteosarcoma.

There will always be complications regarding the diagnosis of retinoblastomas in adults, as malignancies are not expected to appear in this age group. Generally, it is not considered in the differential diagnosis, often leading to a delay in treatment following a prognostic error; thus, retinoblastomas should always be considered for amelanotic masses originating from the retina.

4. Conclusion

The diagnosis of retinoblastoma is often not considered in adulthood, but before any tumor in adolescence and due to the poor prognosis for vision and for life, it should be studied and ruled out in a multidisciplinary way.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Availability of Data and Materials

Photos, composite figures, datasets, and histopathologic studies supporting the findings of this study may be released upon written application to the Photographic Laboratory and Clinical Archives Department at the Institute of Ophthalmology Fundacíon Conde de Valenciana (non-profit organization), Chimalpopoca 14, Colonia Obrera, Mexico City, Mexico 06800, and the corresponding author upon request.

Code Availability

Not applicable.

Authors' Contributions

All authors contributed to the study description of the case. The Material preparation, data collection, and analysis were performed by Erick A. Quiroz-Gonzalez, Miguel A. Quiroz-Reyes, Cristina Gonzalez-Gonzalez, Roberto Loeza-Castrejon, Luis Haro-Morlet. The first and main draft of the

manuscript was written by Erick A. Quiroz-Gonzalez, and all authors commented on the previous versions of the manuscript. All authors have read and approved the final manuscript for publication.

Ethics Approval

All procedures in this study involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki (1964) and its later amendments or comparable ethical standards. This clinical case report received full ethical approval from the research ethics board and was approved by the institutional review committee and the teaching department of the institution enrolled (no reference number is provided for a clinical case report by this institution).

Consent to Participate

Informed consent was obtained from the parent/guardian for the minor to anonymously participate in the publication.

Consent for Publication

The authors affirm that the parent/guardian provided informed consent for the publication of all images, as well as the images in the online resources, if any.

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