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Early Intervention in Unilateral Retinoblastoma: A 2-Year-Old's Journey Through Enucleation and Evidence-Based Care

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Abstract

Retinoblastoma is a neoplasm that arises from the retina and is frequently observed in pediatric patients, with a high degree of morbidity, particularly in underdeveloped nations. The classification of this tumor is based on its spread (intraocular and extraocular) and location (unilateral, bilateral, trilateral, and quadrilateral). Unilateral retinoblastoma is the most prevalent form, accounting for 60–70% of cases. A 2-year-old female patient was brought to the Eye Clinic of the Pediatric and Strabismus Department of Dr. Zainoel Abidin Regional Hospital by her parents with a complaint of a white spot in the center of her left eye, accompanied by decreased visual acuity for 3 months. A subsequent examination, using ultrasound (USG), revealed a mass at the base of the retina, accompanied by calcification and infiltration into the vitreous. An orbital scan revealed intraocular calcification, exclusively in the left eye. The patient was diagnosed with unilateral leukocoria OS et causa retinoblastoma grade E. Subsequent treatment plans included OS enucleation and EUA (Examination Under Anesthesia) procedures. Following the EUA procedure, no mass was identified in the right eye. An anatomical pathology examination revealed no spread to the optic nerve; therefore, chemotherapy was not given.

1. Introduction

Retinoblastoma is an intraocular malignant tumor that most often occurs in children and is caused by a mutation in the RB1 gene, located on chromosome 13q14. The function of the RB1 gene is to act as a tumor suppressor. In the event of a mutation in this gene, it results in the inactivation of the RB1 gene, leading to the uncontrolled proliferation of retinal cells.

The occurrence of such mutations can be either hereditary, accounting for 30% to 40% of retinoblastoma cases, or sporadic/non-hereditary, comprising 60% to 70% of cases [1]. In hereditary retinoblastoma, germline mutations in the RB1 gene, present from birth, are transmitted in an autosomal dominant manner, resulting in the manifestation of the mutation in all cells. Consequently, in addition to retinoblastoma, patients are predisposed to developing secondary non-ocular cancers, including osteosarcoma, leiomyosarcoma, and melanoma.

In contrast, non-hereditary cases involve a somatic mutation that occurs after birth, manifesting exclusively in specific retinal cells, resulting in a unilateral tumor [1, 2]. Retinoblastoma manifests predominantly in pediatric populations, with two-thirds of cases diagnosed before

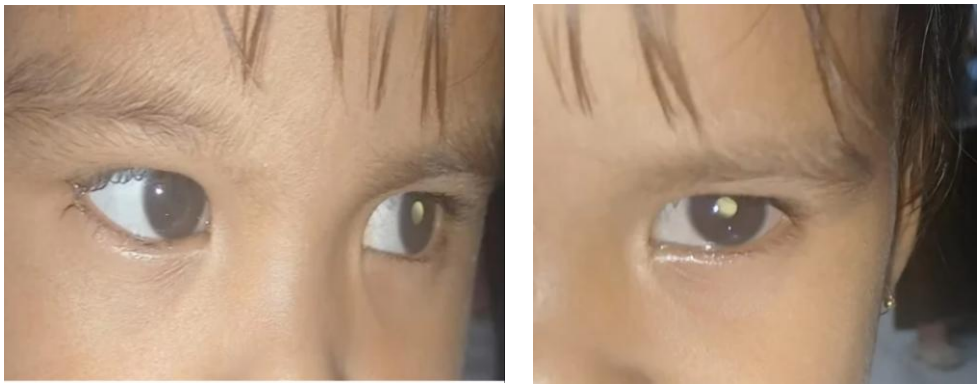

Figure 1. The clinical photograph of the patient's eyes reveals the presence of white spots in both eyes.

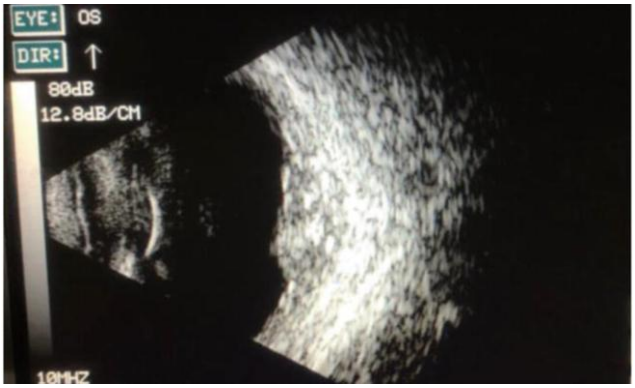

Figure 2. The patient's left eye ultrasound examination revealed a mass at the base of the retina, accompanied by calcification and vitreous infiltration.

the age of two and over 90% of cases diagnosed before the age of five [3].

Globally, the incidence of retinoblastoma exhibits significant variation, ranging from one case per 20,000 live births to one case per 15,000 live births [1]. In Indonesia, retinoblastoma ranks as the second most prevalent childhood cancer, and the country is among the six nations worldwide with the highest incidence rates. In the United States, the incidence of retinoblastoma ranges from 2 to 5 cases per 1 million live births. While retinoblastoma is considered a malignant cancer, the prognosis is favorable in developed countries, particularly when it is detected early and receives proper treatment. Conversely, in developing countries in Asia, the cure rate is lower, with mortality rates ranging from 40% to 70%. The primary factors contributing to this high mortality rate are delayed diagnosis, often exceeding six months, and limited access to healthcare facilities [1, 3, 4].

Patients with retinoblastoma generally present with typical clinical complaints such as white spots on the eyes (leukocoria) or a history of visual impairment. Early detection can be facilitated through red reflex or ophthalmoscopy; however, a significant proportion of retinoblastoma cases in Indonesia are diagnosed at advanced stages, when the tumor has already spread beyond the eyeball (extraocular). The limited accessibility of healthcare facilities, compounded by the lack of public awareness of the early symptoms of retinoblastoma, contributes to the high mortality rate. This case report aims to provide a more in-depth understanding of the symptoms, diagnosis, and management of patients with retinoblastoma.

2. Cases

A 2-year-old female patient was brought to the Eye Clinic of the Pediatric and Strabismus Department at Dr. Zainoel Abidin Regional Hospital by her parents, with a complaint of a white spot in the center of her left eye. The spot, resembling a "cat's eye" when exposed to light, had been present for three months and was accompanied by decreased visual acuity (Figure 1). The patient had no history of strabismus, ocular pain, eye masses, or medication use. There was no family history of similar symptoms, nor was there a history of chemical exposure or infections during pregnancy.

The results of the local status examination demonstrated that both eyes exhibited palpebrae and calm conjunctiva, clear corneas, normal anterior chambers, positive pupillary light reflexes, and both lenses appeared clear. Upon further examination of the lenses using ophthalmoscopy, a white reflex was observed in the pupil of the left eye (OS), confirming the presence of leukocoria. However, the visual acuity of both patients' eyes could not be assessed as the patient was uncooperative. Subsequent ultrasonography (USG) follow-up revealed a mass at the base of the retina with calcification and infiltration into the vitreous, a typical feature of retinoblastoma (Figure 2).

Following an ultrasound examination, an orbital scan was also performed on the child. The result of the orbital scanning examination showed limited intraocular calcification in the left eye. The patient was diagnosed

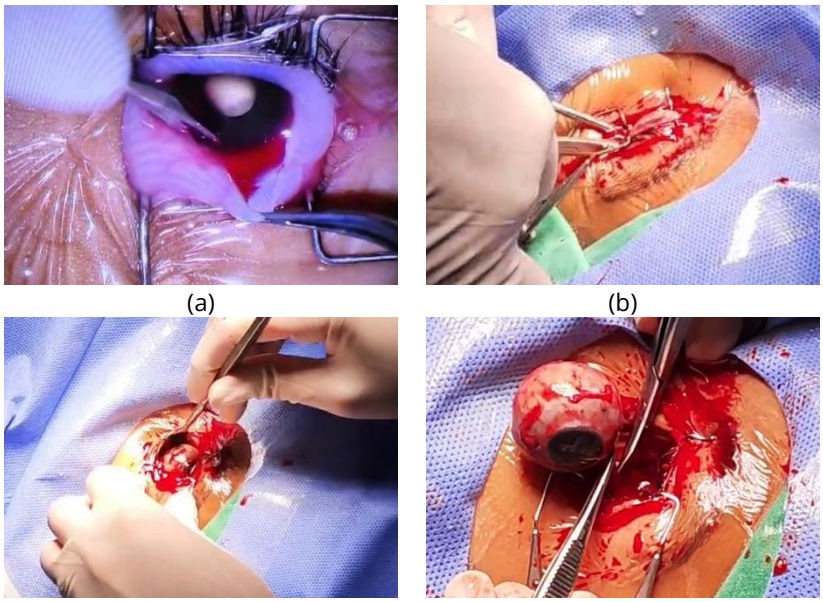

Figure 3. Stages of the left eye enucleation procedure in patients with leukocoria and retinoblastoma: (a) The operator performs a 360° conjunctival peritomy; (b) Anterior tenon dissection is performed and the four rectus muscles are cut; (c) The optic bulb is removed from the socket; (d) Cutting of the optic nerve.

with unilateral leukocoria OS ec retinoblastoma grade E, and a surgical procedure of enucleation was scheduled for February 22, 2025, using general anesthesia. Before

the surgical intervention, a comprehensive laboratory evaluation was conducted. This included a chest X-ray and consultation with the anesthesia and pediatrics departments. Following the completion of the enucleation procedure, an EUA (Examination Under Anesthesia) is performed on the patient's right eye, with the administration of 1% mydriatic eye drops. At this point, an examination of the posterior segment of the right eye is performed with an indirect fundoscope, and no masses are found in the posterior segment of the right eye. Subsequently, the tissue extracted during the enucleation procedure is transferred to the anatomical pathology laboratory for further examination (Figure 3). Postoperatively, the patient is prescribed an oral antibiotic twice, half a teaspoon per day, paracetamol three times, half a teaspoon per day, a combined antibiotic eye drop three times, one drop per day, and an antibiotic eye drop six times, one drop per day, to reduce the risk of infection. Anatomical pathology laboratory examination results showed that there was no spread to the optic nerve, so chemotherapy was not administered.

3. Discussions

Retinoblastoma is a neoplasm that originates in the retina and primarily affects children. It is associated with a high morbidity rate, particularly in developing countries. Leukocoria, a characteristic sign of retinoblastoma, can also be observed in several other ocular conditions, including Coats disease, persistent fetal vasculature, cataracts, ocular toxocariasis, and retinopathy of prematurity. Therefore, a thorough understanding of the signs and symptoms is essential for accurate differential diagnosis [5, 6]. Under normal conditions, most of the light entering through the pupil is absorbed by the retinal cells, including photoreceptors and blood vessels. A small portion is reflected by the vascular layer located behind the retina, producing the characteristic red reflex seen during funduscopic examination. In patients with retinoblastoma, light transmission to the retina is disrupted by the presence of a tumor mass. This mass reflects incoming light, resulting in a white pupillary reflex. In retinoblastoma, leukocoria typically appears bright white. In contrast, conditions such as Coats disease may produce a yellowish reflex, while cataracts often cause a blue-gray reflex [7–9].

Several signs and symptoms are commonly observed in patients with retinoblastoma, including leukocoria (60%), strabismus (20%), ocular inflammation (5%), proptosis, hyphema, decreased vision, and glaucoma [3, 10, 11]. In this case, the patient experienced leukocoria and decreased vision, with no other signs or symptoms. Following a physical examination and the identification of signs and symptoms indicative of retinoblastoma, a diagnostic examination was conducted to confirm the diagnosis. A variety of supportive examination modalities can be used, including ultrasound, wide-field photography, contrast-enhanced MRI, and histopathologic examination. Of these, ultrasonography stands out for its multiple important functions and its routine use in patients with retinoblastoma. Specifically,

it is used to assess the presence of subretinal fluid, calcification, or implantation in the subretina or vitreous. Furthermore, ultrasound is instrumental in quantifying tumor dimensions and assessing its invasion of surrounding structures, including the optic nerve, choroid, sclera, and orbit. Additionally, it can be used to assess the possibility of lymphadenopathy, which may occur in patients, and help select the appropriate therapy modality according to the patient's clinical condition [3, 11]. In the patient's case, an ultrasound examination revealed a mass at the base of the retina, accompanied by calcification and infiltration into the vitreous, thus confirming the diagnosis of retinoblastoma.

A general classification of retinoblastoma is based on three things: spread, location, and classification scheme. The initial classification is determined by the extent of the lesion's spread, which is further categorized into two distinct forms: intraocular, which remains confined to the retina, and extraocular, which has spread into the tissues surrounding the retina. The classification of retinoblastoma is further based on the location of the tumor: unilateral, bilateral, trilateral, and quadrilateral. The most prevalent form of retinoblastoma is the unilateral type, which affects a single eye and is estimated to occur in approximately 60-70% of patients diagnosed with retinoblastoma. Bilateral retinoblastoma, which affects both eyes, has a lower prevalence of approximately 5% of retinoblastoma cases. Rare forms of retinoblastoma include trilateral and quadrilateral retinoblastoma, which are characterized by the presence of a tumor in both eyeballs and the pineal gland (trilateral) or in all brain tissue (quadrilateral). Patients with these rare forms of retinoblastoma typically present with unilateral leukocoria. In cases where unilateral retinoblastoma is suspected, as is the case here, an examination of the contralateral eye is necessary to confirm the presence of retinoblastoma growth.

Extraocular retinoblastoma is staged using the International Retinoblastoma Staging System (IRSS), which classifies it into five stages. Stage 0 indicates patients who receive conservative treatment without surgical intervention. Stage I is characterized by enucleation, accompanied by complete tumor removal and histological examination to ensure no residual tumor is present. Stage II involves enucleation of the eye, but a microscopic tumor remains after removal. Stage III indicates tumor spread to the periorbital area, which is further categorized into two distinct forms: invasion that passes through the orbit, or spread to the pre-auricular or cervical lymph nodes. Stage IV describes metastatic spread, which is further divided into two subcategories. The first subcategory is hematogenous metastasis, which is the spread of the tumor through the blood without involving the central nervous system. The second subcategory involves the spread of the tumor to the central nervous system [12].

Based on the International Classification of Retinoblastoma (ICRB), intraocular retinoblastoma can be classified into several groups based on the size and spread of the tumor, which helps to determine the management and prognosis of the patient. Grade A includes retinoblastoma with a tumor size ≤ 3 mm in width or thickness, indicating a relatively small and limited tumor. Grade B involves retinoblastoma with a tumor size > 3 mm or a tumor located in an important location, such as the macula or around the juxtapapillary area (≤ 1.5 mm from the optic disc). Additionally, the presence of subretinal fluid within 3 mm of the tumor's boundary is classified under this category. Grade C indicates that the retinoblastoma has metastasized to subretinal and/or vitreous tissue within < 3 mm of the primary tumor. Grade D signifies a more advanced stage, with tumor spread > 3 mm to subretinal and/or vitreous tissue. Grade E includes very extensive retinoblastoma, with tumors involving more than 50% of the eyeball, or accompanied by serious complications such as neovascular glaucoma and invasion into deeper structures, such as the postlaminar optic nerve, choroid (> 2 mm), sclera, orbit, or anterior chamber of the eye [3, 12]. Based on this classification, Grade A patients are advised to undergo local therapy with cryotherapy or transpupillary thermotherapy (TTT). Patients classified as grade B and C are recommended to undergo local treatment in conjunction with chemotherapy. For patients diagnosed with grade D unilateral retinoblastoma, enucleation is recommended, or they may receive the same therapy as those classified as grade B and C. For patients with grade E, enucleation is strongly recommended, followed by chemotherapy administration [13].

In this patient, unilateral leukocoria OS, ec retinoblastoma grade E was diagnosed, and enucleation was performed. Following enucleation, an EUA (Examination Under Anesthesia) was performed on the patient's right eye, and no mass was found. The tissue removed during the enucleation procedure was then sent to the anatomic pathology laboratory for histologic examination. The anatomical pathology examination revealed no evidence of tumor extension into the optic nerve. To enhance the prognosis of patients following enucleation, the administration of adjuvant chemotherapy is strongly recommended in cases where the histological examination reveals massive choroidal

invasion (>3 mm), evidence of tumor cell spread beyond the eyeball through the optic nerve, extra-scleral invasion, and orbital invasion. On the other hand, if the histologic examination shows only prelaminar optic nerve invasion and intraretinal tumor spread, chemotherapy is not performed, as in this case [14].

4. Conclusions

Early detection of retinoblastoma and prompt, appropriate management according to the stage of the disease are critical to reduce morbidity and mortality rates in patients. In cases that are limited to the intraocular cavity, enucleation can be an effective and immediate treatment option. However, when the cancer has metastasized beyond the eye, a more complex treatment approach is required before further action can be considered. This approach incurs higher treatment costs and prolongs the duration of treatment, which undoubtedly has both economic and emotional impacts on patients and their families. In this case, the patient underwent enucleation on her left eye and EUA (Examination Under Anesthesia) on her right eye. Since no tumor extension was found, chemotherapy was not performed. Therefore, recognizing the significance of early detection and selecting appropriate treatment based on the stage of the disease is key to improving patient prognosis and reducing long-term complications.

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