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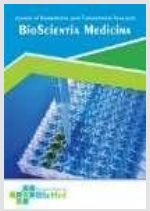

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Systemic Metastase in Late Management of Group D Retinoblastoma: A Case Report

Ernes Erlyana Suryawijaya[1*], I Wayan Eka Sutyawan[2], Ni Made Ayu Surasmiati[2], I Made Agus Kusumadjaja[3]

[1]Resident of Ophthalmology, Faculty of Medicine and Health Science, Universitas Udayana/Prof. Dr. I.G.N.G Ngoerah General Hospital, Denpasar, Indonesia

[2]Pediatric and Strabismus Division, Ophthalmology Department, Faculty of Medicine, Universitas Udayana/Prof. Dr. I.G.N.G Ngoerah General Hospital, Denpasar, Indonesia

[3]Department of Ophthalmology, Faculty of Medicine and Health Science, Universitas Udayana/Prof. Dr. I.G.N.G Ngoerah General Hospital, Denpasar, Indonesia

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***Corresponding author:**
Ernes Erlyana Suryawijaya

E-mail address:
ernesliang92@gmail.com

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A B S T R A C T

Background: Retinoblastoma (RB) is a common malignancy that affects children and is fatal if left untreated. This case report aims to raise awareness the importance of starting therapy immediately in RB patients. **Case presentation:** A girl aged 1 year 9 months, came with complaints that her left eye (LE) appeared white for 2 weeks. Anterior segment examination was normal. On funduscopic examination, optic nerve was difficult to evaluate, covered by a mass, multiple mass scars on the retina, a size of > 6 mm at the posterior pole, and vitreous seeding. Ultrasound examination and CT scan showed an intraocular mass with calcification. The patient was diagnosed with group D intraocular LE RB and was planned for enucleation but was postponed due to cost constraints. The patient came back after 1 year and was diagnosed with extraocular LE RB stage IVB. **Conclusion:** Early diagnosis without adequate therapy leads to tumor spread and reduces patient survival.

1. Introduction

Retinoblastoma (RB) is the most common primary intraocular malignancy of childhood and accounts for 3% of all childhood tumors and is also the second most common intraocular malignant tumor.[1] The number of RB cases ranges from 1 in 14,000 to 1 in 20,000 live births. According to a recent survey, the regions with the highest incidence of RB were Southeast Asia and Africa. In Asia, Saudi Arabia (16.6 in 1 million) had the greatest incidence, while Qatar (0.9 in 1 million) had the lowest incidence.[2] Indonesia is the third country with the most children with RB.[3] The development of RB is initiated by biallelic inactivation of the RB1 tumor suppressor gene located on chromosome 13q14. The majority of patients with germline mutations present with multifocal bilateral RB, usually before the age of 1 year, whereas patients with two somatic mutations always present unilaterally and are usually not diagnosed until around the age of 2 years.[4] A white pupillary reflex called leukocoria is the first sign that is easily observed.[5] RB is a highly curable neoplasm in high-income countries, with

patient survival rates exceeding 99%, making it the most curable pediatric neoplasm. In contrast, in many low-income countries, the majority of patients present with disseminated disease, which is almost always fatal, this occurs due to a lack of awareness and knowledge about the signs and symptoms of RB among the general public and health care providers, late diagnosis, delayed referral, poor access to health services and late initiation of treatment. Socio-economic and cultural aspects, including family health beliefs regarding disease, further worsen treatment compliance and survival. making the situation worse.[2,3,6] Enucleation is usually recommended for eyes with RB classified as The International Intraocular Retinoblastoma Classification (IIRC) group E, some eyes with advanced group D, and eyes with suspected extra-ocular extension.[4] Sometimes enucleation cannot be performed due to rejection by the patient's family, such as one patient who died of brain metastases after persistent rejection of enucleation.[4] This case report aims to raise awareness of the importance of starting therapy immediately in RB patients.

2. Case Presentation

A 1 year 9 months age female, came to the eye clinic, complaining that the patient's left eye (LE) looked white like a cat's eye since 2 weeks ago. Previously, at the age of 2 weeks after birth, the LE was said to be crossed out. After the age of 1 year (after giving vitamin A) the squint complaints improved and appeared again when the patient was 1 year 7 months old. The patient is still said to have eye contact with her parents. The patient was the first child of two siblings. The mother gave birth by cesarean section, had a normal antenatal history, and had no antecedent exposure to teratogenic drugs or substance abuse. Gestational age at term, birth weight 2450 grams. Family history revealed no hereditary disease. The patient's siblings presented with normal growth and development.

The examination found that visual acuity on her left eye (LE) was difficult to evaluate because the patient was uncooperative, anterior segment were within normal limits. On funduscopic examination, it was found that the optic nerve was difficult to evaluate, covered by a mass, multiple mass impressions on the retina, size more than 6 mm in the posterior pole, vitreous seeding, and macula difficult to evaluate. Ultrasound examination showed an echogenic soft tissue mass with calcification, an intraocular mass suggestive of RB. The patient was diagnosed with suspected LE group D intraocular RB and was planned to undergo a CT scan of the head. CT scan showed a hyperdense mass of the left retrolental intra-bulbus oculi which completely filled the vitreous body with a macrocalcified component within which, when contrast was administered, a slight heterogeneous enhancement appeared. The border of the mass with the partial posterior sclera appears indistinct. There was no visible spread of the extraocular mass. No visible pineal body involvement. Multiple subcentimeter lymphadenopathy of the submental, submandibular, and cervical regions supports the diagnosis of RB LE. The patient was then diagnosed with LE RB intraocular group D and was planned to have enucleation but the patient's parents asked to postpone the operation because of costs and would be checked again 1 month later.

Figure 1. Leukocoria in the left eye when first presented.

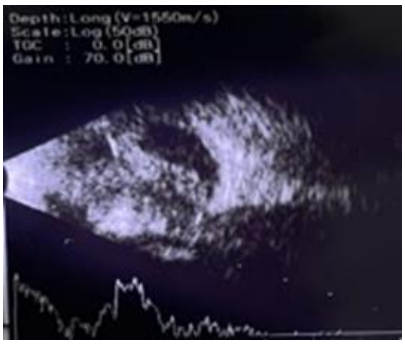

Figure 2. Ultrasound of the LE showed an intraocular mass with calcification.

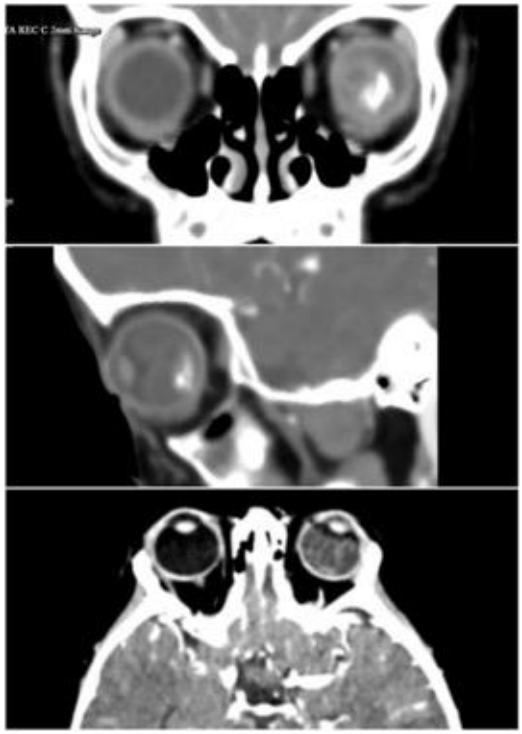

Figure 3. CT scan of the head focused on the orbital showed a solid mass with calcified components filling the left vitreous body.

The patient came back after 1 year, the patient's mother complained that the patient's LE had a lump that was getting bigger in 4 months. The initial complaint was that the LE had a whitish discharge, then it turned black, and over time a lump appeared that was getting bigger and accompanied by purulent discharge since 2 weeks ago. Patients often complain of headaches. Since 4 days both eyes have been moving frequently on their own. The patient was taken to a regional hospital and referred to the central general hospital. The patient did not leave immediately because he was still constrained by costs. The patient was given antibiotics and the anti-pain medication paracetamol and consumed it for 1 week. The patient's mother also gave herbal medicine which was used regularly. Before the mass appeared, the patient's LE was often watered, and eye discharge appeared but not much, sometimes glare. On examination of the LE, visual acuity was difficult to evaluate, the palpebra had a mass measuring 4x3x2cm, soft consistency, fixed, uneven surface, necrotic tissue, crusting, tenderness, yellow mucopurulent discharge, conjunctiva to fundus difficult to evaluate. The patient was diagnosed with LE RB extraocular stage III and

was planned for repeat orbital-focused head MRI with axial, sagittal, and coronal contrast and pediatric hematology medical oncology (HOM) consultation for chemotherapy planning. MRI results showed a heterogeneous solid mass with minimal necrotic components in the left ocular bulb which extended to the peri and left retro-orbital and infiltrated the left optic nerve resulting in proptosis, pressing on the left lamina papyracea, orbital floor, and lateral orbital wall, pressing on and infiltrating the left extraocular muscle, extending to the left periorbital cutis-subcutis, extends along the left optic nerve to the optic chiasm, suprasellar, pushes the pituitary gland inferiorly and the midbrain posteriorly, abuts and pushes the pars clinoid, supraclinoid and right communicating internal carotid arteries to the lateral and anterior cerebral arteries right and left cranially supports the picture of RB. The patient was diagnosed with left eye retinoblastoma extraocular stage III. HOM Pediatrics diagnosed the patient with LE RB extraocular stage IVB with bone marrow aspiration (BMA) results showing metastases with increased megakaryocyte activity. The patient planned to administer a high-dose chemotherapy protocol with a combination of carboplatin 28/mg/kg (restriction 25%), vincristine 0.05 mg/kg (restriction 25%), and etoposide 12 mg/kg.

After the eighth chemotherapy, the patient LE was phthisis and scheduled to have another MRI with the result compared with previous MRI results, which showed the impression of a heterogeneous solid mass, partly indistinct boundaries, lobulated edges, endophytic left bulbus oculi accompanied by extension to the retrobulbar, optic nerve to the left optic chiasm, and sticking in the left superior and lateral rectus muscles, according to the description of RB, reduced impression size, left sphenoid sinusitis, right and left inferior turbinate hypertrophy, minimal deviation of the nasal septum to the left. After the 10th chemotherapy, the patient experienced seizures, desaturation, fever, and decreased consciousness. The patient died due to severe acute respiratory distress syndrome, sepsis, epilepsy general onset motor tonic impaired awareness et causa central nervous system metastases comorbid RB extraocular stage IVB.

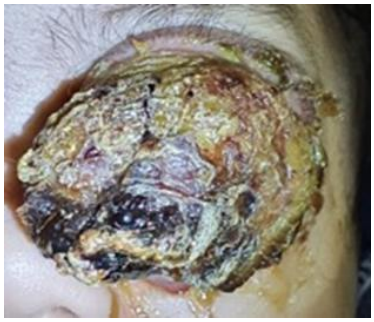

Figure 4. LE after 1 year without therapy.

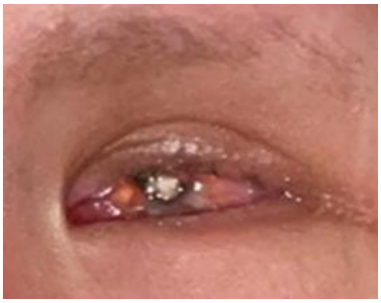

Figure 5. LE After the 8th chemotherapy.

3. Discussion

Retinoblastoma is the most common malignancy in children throughout the world with an incidence rate in the entire population of 1 in 15,000–20,000 live births or the equivalent of 9000 new cases each year.[7] RB is caused by mutations in RB1 which is a tumor suppressor gene.[8] 90% of RB cases are diagnosed in children aged less than 3 years. The average age at diagnosis of unilateral disease is approximately 24 months.[8] Prognosis and survival depend on early diagnosis and appropriate treatment. More than 90% of RB children living in underdeveloped countries die from potentially curable tumors with high survival rates. In developed countries, the goal of treatment has shifted from saving the eyeball to preserving vision. However, preventing death is a major challenge in underdeveloped countries where the majority of children already have advanced diseases.[7]

Early diagnosis of RB can improve the survival rate and visual prognosis of patients.[9] The most frequent signs are leukocoria (white pupillary reflex), strabismus, and eye inflammation. Other features, such as spontaneous hyphema, iris heterochromia, and orbital inflammation, are less common and associated with more advanced tumors. In rare cases, RB may present with pain and inflammation and have features similar to endophthalmitis, uveitis, preseptal, or orbital hemorrhage, or cellulitis.[9] Vision problems rarely occur in some patients because they are still so small that they cannot yet express their vision loss.[8] RB can show local spread along the optic nerve directly to the orbit and can also metastasize hematogenously to the liver, bones, brain, and other organs.[9] To improve early detection of RB, professionally trained nurses have an important role in this disease, several research programs recommend evaluation of RB1 gene mutations at the fetal stage, which will increase the possibility of early detection of Rb and other non-eye tumors and thus the possibility of successful treatment. Centralizing services in one health center in developing countries with telemedicine can achieve patient outcomes comparable to developed countries.[2,10]

Diagnosis of RB is made clinically.[8] Monocular visual acuity and afferent pupillary defects should be assessed.[8,9] Examination under anesthesia (EUA) needs to be carried out. Examination includes intraocular pressure and corneal diameter and evaluation for iris neovascularization with a portable slit lamp.[8-11] Fundus photography and ultrasonography should also be performed to document findings and allow serial comparisons. RB begins as a round, translucent, gray-to-white tumor on the retina, as the tumor enlarges, necrotic foci with calcification appear, giving the tumor a characteristic chalky white appearance. larger tumors contain dilated and tortuous intratumoral vessels.[9,12] Magnetic resonance imaging (MRI) is often performed to evaluate optic nerve involvement, and extraocular extension, and to consider the possibility of concomitant primitive neuroectodermal tumor (trilateral RB with pinealoblastoma). Bone marrow examination or lumbar puncture may also be performed in patients who have concerns about the extent of the disease, especially with extraocular extension to rule out the possibility of cerebrospinal fluid (CSF) or bone marrow metastases.[9,13]

Retinoblastoma may invade the optic nerve head and spread through the lamina cribrosa into the central nervous system (CNS).[8] RB cells may escape the eye by invading the optic nerve and extending into the cerebrospinal fluid. Tumor cells may invade the choroid before traversing emissary canals, thereby spreading hematogenously or eroding through the sclera to enter the orbit. Extraocular extension may result in proptosis as the tumor grows in the orbit. Tumor cells may penetrate the trabecular meshwork in the anterior chamber and enter the conjunctival lymphatics. Subsequently, palpable preauricular and cervical lymph nodes may develop.[8] Metastasis to the CNS can occur in advanced, untreated cases. Central nervous system (CNS) metastasis was the most common cause of relapse and death.[11-14]

Enucleation is usually recommended for RB classified IIRC with advanced group D, group E, and eyes with extra-ocular spread.[15-17] Delayed eye

removal can increase mortality. Patients diagnosed with RB at 1 year of age or older were more likely to have a somatic RB1 mutation with unilateral RB classified in a higher IIRC stage, had a higher proportion of optic nerve invasion, and had a higher need for enucleation. Enucleation remains the treatment of choice in low- and middle-income countries, where approximately 55% of eyes with RB are enucleated and there is an increased risk of treatment failure and less frequent globe salvage.[18] Enucleation is the least conservative treatment and therefore is only intended for cases where the eyeball cannot be saved, otherwise, enucleation should be avoided if rescue can be achieved with other treatment modalities in an effort to maintain vision and improve conservation. During the first 2 years after surgery, all patients undergoing enucleation should be carefully monitored for the risk of recurrence. Overall, enucleation is widely used and continues to be used in cases where other treatment modalities have not helped.[19,20] Intravenous chemotherapy (IVC) is used for extraocular RB. This treatment usually consists of two, three, or four medications each month that are inserted into the bloodstream through a catheter for six to nine months. Systemic chemotherapy is widely used for the treatment of RB in combination with additional local treatment. The most commonly used regimen is vincristine, etoposide, and carboplatin (VEC). Intravitreal chemotherapy (IVitC) focal vitreous seeding is considered a precision intra-vitreal chemotherapy and is an emerging technique. Often used as an adjunct therapy to IAC, in IVitC, the drug is administered directly into the vitreous cavity in advanced stages of RB where vitreous seeding occurs. Thermotherapy, treatment method which is often used for small tumors, not only for the eyes. The dimensions usually indicated are a maximum diameter of 4 mm. Cryotherapy is an adjuvant and is used in conjunction with other treatments with RB tumors up to 3.5 mm in diameter and 2 mm in thickness. This therapy is contraindicated in cases with vitreous seeding and any tumor that is larger than normal. External beam radiation (EBR) External beam radiation is in the management pathway for the treatment of RB after enucleation in an effort to save the remaining eye.[12,13]

4. Conclusion

Important to note that the main goal of current therapy for RB is to protect the patient's life, followed by preserving the globe, and finally saving vision. In high-income countries, patient survival rates exceed 99%, making RB the most curable childhood cancer. In contrast, in many low-income countries, the majority of patients present with disseminated and metastatic disease that is almost always fatal. Prognosis and survival depend on early diagnosis and appropriate treatment. In low and middle-income countries globally, survival rates decrease significantly due to overall low detection and intervention resulting in the spread of RB. It is important to increase early detection of RB, by training medical personnel or cadres at the community level, evaluating RB 1 gene mutations in fetuses, using telemedicine, especially in areas with limited health facilities, and improving the referral system. RB is a curable malignancy with good survival if treated promptly, but the disease is fatal if left untreated. Rapid initial diagnosis without adequate therapy leads to the spread of the tumor mass and reduces patient survival.

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