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Case Report

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Enucleation for retinoblastoma in a 22-month-old boy

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Abstract: Retinoblastoma is the commonest intraocular tumor in childhood. Management of retinoblastoma is quite complex depending on the stage, visual and globe saving, psychosocial factors, modality of treatment, and health infrastructure. We report a case of retinoblastoma in a child in a limited health facility without a pediatric oncologist or ophthalmology oncologist. A 22-month old boy came with complaints of leukocoria which his parents had known since the previous week. Ultrasonography of the eye shows calcification on the retina that supports Group E retinoblastoma. Bone marrow aspiration and MRI cannot be performed due to limited resources. Even though the parents only noticed the symptoms for a week and immediately brought to the ophthalmologist, the retinoblastoma stage was already in Group E. Enucleation and globe salvage were unavoidable. Enucleation was performed on the patient with histopathology finding the presence of Flexner-Wintersteiner rosette cells. After enucleation, he was referred to the oncologist for adjuvant chemotherapy. Early retinoblastoma detection is crucial in increasing the cure rate while maintaining children's vision.

Keywords: Retinoblastoma, leukocoria, enucleation.

INTRODUCTION

Retinoblastoma malignant tumor that arises from the retina is the most common primary intraocular malignancy in children of primitive neuroectodermal origin.[1,2] However, retinoblastoma is a rare disease with a global incidence of 1 in every 16,000–18,000 live births.[3] The incidence of retinoblastoma is similar in all populations and does not vary according to sex, ethnicity, or socio-economic status. The number of cases of retinoblastoma every year reaches 8,000 children, most of which occur before the age of 5 years.[2] Most cases occur in countries with lower socio-economic-related education levels, and 86.3% are from rural areas.[4,5] As many as 52.3% of retinoblastoma cases came from Asia, and the rest came from Africa (23.5%), Europe (12.0%), America (11.8% and Oceania (0.4%). A total of 56.8 % come from low to middle-income countries.[6]

Management of retinoblastoma in children is quite complex depending on the stage, visual saving, family psychosocial factors, culture, modality of treatment, and health infrastructure.[1] The prognosis in low and middle-income countries is often poor, even though 80% of retinoblastoma cases occur there. Children are diagnosed at an advanced stage where the visual function cannot be maintained at 38.5%, at least at stage II.[5] Although most children survive this cancer, they will lose their vision at intervals of the affected eye or need to have the eye removed.[7,8] Although about 50% of cases are referred to an ophthalmologist within one week after symptoms are detected at the primary care center, one-third of patients still present after eight weeks or even 24 weeks.[7,9] The importance of family awareness of the possibility of retinoblastoma is associated with earlier diagnosis and higher

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rates of globe salvage in patients with retinoblastoma.[10,11] We report a case of retinoblastoma in a child in a limited health facility without a pediatric oncologist or ophthalmology oncologist.

CASE REPORT

ZAH, a 22-month-old boy, was admitted to the Ophthalmologist department of Dr. Ramelan Navy Hospital Surabaya on January 24th, 2023. His parents notice his child's eye looks unusual. His parents complained shiny white spot-like eye cat on the right eye for one week ago (Figure 1). Parents stated if their child had eye complaints. The child has never experienced complaints of red eyes, watery eyes, purulent eyes, and swollen eyes. Parents also never complained of decreased vision. The child has never complained of decreased vision, such as hitting furniture when playing or having difficulty doing activities in the afternoon or less light. Parents stated that the right and left eyeballs movements were balanced or there were no abnormalities. The movement of the right eyeball looks different after a white spot appears in the eye. There was no history of head and eye trauma. Parents never noticed abnormalities in their child's eyes until the last week after a white spot appeared in the middle of the eyeball. Parents also never brought complaints to health workers regarding eye complaints.

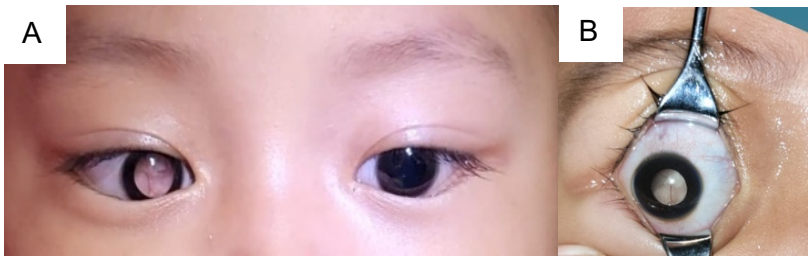

Figure 1. Child's eye looks A) The shiny white spot like eye cat of the right eye on the first visit, B) Leukocoria of the right eye

He was born spontaneously, fully termed, and assisted by a local midwife. His birth weight was 3100 grams. He did not get any prior medication for a specific disease. His family had no history of retinoblastoma or other malignancy. He had complete immunization status according to the government. When a child comes to a health worker in primary health care for immunizations, the officer never says if the child's eyes have abnormalities. The patient never had an eye examination after birth or a vision screening during a visit to primary health care. The patient was given breastmilk and combined formula milk until now. His growth and development were within normal limits until now.

Physical examination revealed good consciousness. Pulse rate was 110 times per minute, and respiration rate was 28 times per minute, axillary temperature was 36.6° C, blood pressure was 100/70 mmHg. His body weight was 11.3 kg. We did not find abnormalities on the ear, nose, throat, or neck examination. There were no palpable lymph nodes or nuchal rigidity. The chest examination revealed no precordial bulging. The Ictus cordis was noticeable on the 5th intercostal space on the left midclavicular line. There was no thrill. The heart sound for first and second heart sounds was normal, without a murmur. The movement of both sides of the chest was symmetrical. Vesicular respiratory sounds were noted, without wheezing or rales. The abdomen examination relieved no hepatomegaly and no splenomegaly. The upper and lower extremities showed no deformity. There was no edema, no cyanosis, and the capillary refill time was normal. The physiological reflexes of the patella and Achilles tendon were normal. Motor strength in the extremities was normal.

The right-eye examination showed orthophoria and normal eyeball movement. The anterior segment of the right eye showed visual activity and had no light perception. There were no abnormalities on the palpebra, conjunctiva, sclera, or cornea. Posterior segment examination of the right eye with direct ophthalmoscope showed positive fundus reflexes (Figure 2). We found leukocoria in the right eye. There were no abnormalities on examination of the left eye, including palpebra, visual field, orbital movement, or anterior and posterior segment. Posterior segment examination of the left eye with direct ophthalmoscope showed fundus reflexes were normal.

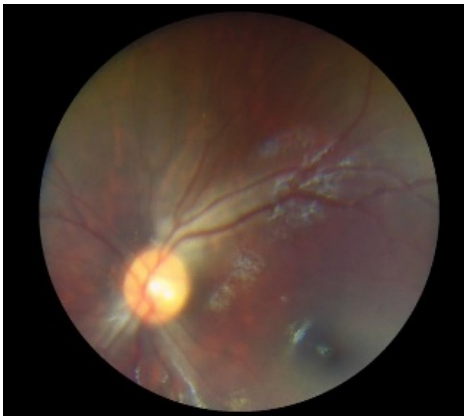

Figure 2. Segment posterior of the left eye

Complete blood count, kidney function, liver function, and albumin levels were within normal limits. The hemoglobin level was 13.5 g/dL, the leukocyte count was $8.6x10^9$/L, and the platelet count was $324x10^9$/L. Ocular ultrasound of the right eye demonstrated a solid mass with calcification in the right eye (Figure 3). The size mass was 1.46 x 1.62 cm. The tumor has occupied more than 50% of the right eyeball. There were no retinal detachment and calcification of the lens. Ocular ultrasound of the left eye showed no retinal detachment or calcification of the lens. Corpus vitreous was normal. We did not perform bone marrow aspiration, head-CT scan and head MRI. Based on anamnesis, clinical manifestation, and ocular ultrasound, the patient was diagnosed with retinoblastoma of the right eye Group E based on International Classification of Retinoblastoma (ICRB). Management of this patient was enucleation of the right eye.

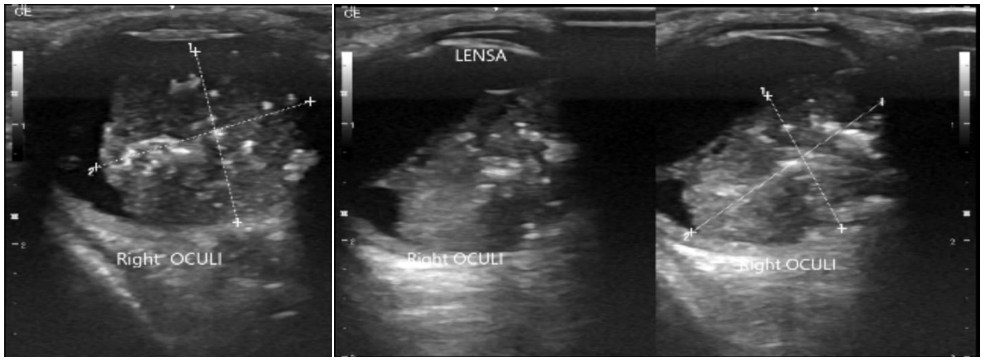

Figure 3. A solid mass in the posterior segment of the right eye

The patient had enucleation on January 27th, 2023, with the removal of the entire globe of the right eye and its intraocular contents, with preservation of all other periorbital and orbital structures (Figure 4). The right eye globe has been taken by anatomical, pathological examination.

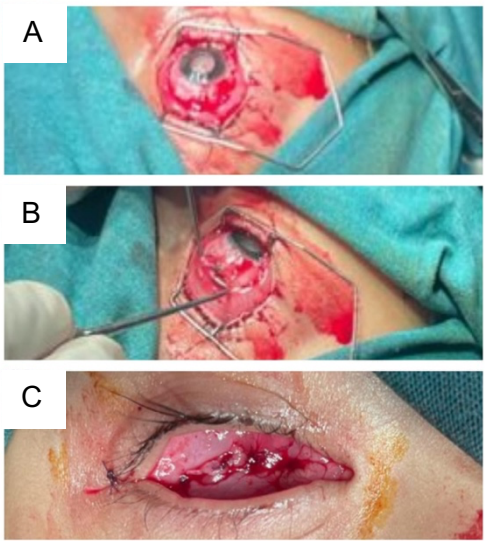

Figure 4. Enucleation A) Eyelids are retracted with a lid speculum, B) Tenon's fascia away from the globe using curved Stevens scissors in the four quadrants between the rectus muscles, C) Conjunctiva was closed and sutured (bottom)

January 31st, 2023, the patient was controlled to the ophthalmologic department. The physical examination showed a palpebral hematoma of the right eye. We give amoxicillin, paracetamol, eye ointnment, and a warm compress. The patient was controlled for two more weeks.

February 14th, 2023, the patient was controlled to the ophthalmologic department with histopathology examination result. Histopathology finding showed that the tumor tissue was a proliferation of anaplastic cells with a monotonous round nucleus, small size, hyperchromatic, thin cytoplasm, and slightly formed Flexner-Wintersteiner rosette (Figure 5). Retinoblastoma was also found at the end of the optic nerve and was therefore referred to the pediatric oncologist for adjuvant chemotherapy.

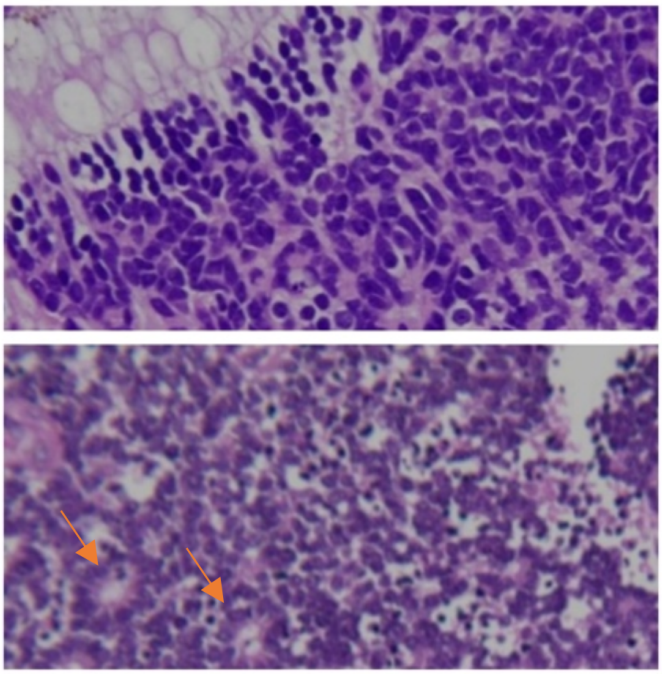

Figure 5. Anatomical pathological of the right eye after enucleation showed Flexner-Wintersteiner rosette (arrow)

RESULTS AND DISCUSSION

Retinoblastoma is a tumor that develops in the retina. In this case, the patient was a 22-month-old boy, whose parents complained of a shiny white spot like a cat's eye on the right eye a week ago. A cohort study of 4351 cases in 153 countries reported that the median age at diagnosis was 30.5 months, and 54.6% were male.[8] The cumulative incidence of Retinoblastoma was higher in boys than girls. The mortality rate in boys was 3.4 times more than in girls.[12] The incidence and mortality rates for Retinoblastoma and other malignant cancers in children are higher for boys than for girls, including acute lymphoblastic leukemia, lymphoma, renal carcinoma, and rhabdomyosarcoma.[13] After all confounding variables, including social aspects controlled, sex differences in the incidence, mortality, and survival of retinoblastoma were associated with the X-linked chromosome in boys.[12] The X chromosome in women plays a role in apoptosis, especially in the activation of p53 as a tumor suppressor gene[14] and estrogen elaboration).[15]

In this case, from ocular examination showed leukocoria of the right eye. Thus, the patient has unilateral leukocoria without family history of retinoblastoma or other malignancies. Once the tumor develops, a white pupillary reflex known as leukocoria is the first readily observed sign, which is noticed by the family and described as a glow, glint, or cat's-eye appearance. The main symptoms of retinoblastoma from large-scale studies were leucoria (62.8%), strabismus (10.2%), and proptosis (7.4%).[8] However, in this case we found no other symptoms other than leukoria. In this case, the parents started to panic and stress when the child had leukoria. However, primary healthcare professionals may have difficulty detecting the most common symptom (leukoria). They may not be aware that retinoblastoma is the underlying pathology of eye symptoms that are more common in infants and young children.[7] About 20% of cases of retinoblastoma in Argentina are diagnosed within 24 weeks of the onset of symptoms.[9] A one-third of patients were diagnosed at an advanced stage, 29.5% at stage II and 4.2% at stage III/IV.[9] About 50% of children were referred to an ophthalmologist within one week from the first consultation with primary healthcare professionals; a quarter of delayed referral was more prolonged than eight weeks.[7] The proportion of parents presenting to a retinoblastoma treatment center at an early stage with leukocoria or strabismus alone mainly comes from low-income countries.[6] There is a significantly increased risk of delayed diagnosis in younger patients, those with squint rather than leukoria, and those who first present to a health visitor rather than a general practitioner. The risk of local tumor invasion increases significantly with diagnostic delays.[6,7,9] Primary health professionals need education about the importance of ocular symptoms, especially squint, in pediatric patients.

We did not find a family history of cancer including retinoblastoma in either the paternal or maternal families. Retinoblastoma could be familial or sporadic, bilateral or unilateral, and heritable or nonheritable. The incidence of retinoblastoma is related to the interaction of many factors, for example, where the parents live in city, the presence of pets during pregnancy mainly cat and dog, and exposure to hazardous chemicals from the father six months before pregnancy (paint, leather equipment, decoration, electronic accessories, benzene, formaldehyde and other heavy metals.[16] Cases of nonheritable retinoblastoma have unilateral tumors, unlike heritable retinoblastoma, which often develops bilaterally and multifocally. The most cases about two-thirds of all cases were unilateral retinoblastoma.[17]

The diagnosis of retinoblastoma is established based on clinical examination, ophthalmology, and support and confirmed by histopathology. In this case, USG showed a solid mass with calcification in the right eye without retinal detachment, calcification of the lens, or vitreous seeding. Based on anamnesis, clinical manifestations, and USG, the patient was diagnosed with unilateral

retinoblastoma stage E of the right eye. The first classification for intraocular retinoblastoma was Reese and Ellsworth (RE) in the 1960s to predict eye survival after external beam radiotherapy. The R-E classification system was no longer appropriate and substituted by an International Intraocular Retinoblastoma Classification (IIRC) in 1990 after introducing intravenous chemotherapy.[17] The IIRC classification categorizes tumors from the A-E group, depending on size, location, and additional features, including the presence of 'seeded' retinoblastoma (small colonies of cancer cells in the vitreous) and/or retinal detachment. The Minister of Health of the Republic of Indonesia has issued National Guidelines for Medical Services for the Treatment of Retinoblastoma in 2022. The retinoblastoma classification system refers to the International Classification of Retinoblastoma (ICRB), which divides retinoblastoma into Groups A to Group E.

Ultrasonography, CT-scan, and MRI are imaging modalities for head and neck tumors in children. The currently recommended diagnostic evaluation for retinoblastoma is ultrasonography and MRI.[18–20] However, in this patient, Ct-scan and MRI were not performed. The examination supplementing the diagnostics is the ultrasound (USG) of the eyeball.[18,21,22] USG of the eyeball assessing the size or location of the tumor, internal features of the malignant tumor (including the presence of calcifications), and possible extra-ocular propagation. Pathognomonic ultrasound for retinoblastoma is a retinal mass with hyperechoic calcification.[18] The growth pattern of retinoblastoma can be endophytic, exophytic, and infiltrative. Endophytic retinoblastoma is a white mass penetrating the internal limiting membrane and may be accompanied by vitreous seeding.

The initial step in these patients was enucleation, followed by histopathological examination to identify high-risk histopathological features and tumor differentiation. The treatment chosen for retinoblastoma depends on the type of retinoblastoma (intraocular or extraocular) and globe involvement (unilateral or bilateral). In addition to primary management, supportive therapy should be given, including nutritional support and infection management. The objective of managing a child with retinoblastoma is the survival of the patients, globe salvage, and vision salving.[23] In 2006, the Intraocular Classification of Retinoblastoma scheme successfully predicted the outcome of intravenous chemotherapy.[17] For retinoblastoma in groups A–C, the globe salvage in ≥ 90% of eyes. Group E retinoblastoma underwent primary enucleation.[17] Enucleation is the surgical procedure that involves removing the entire globe and its intraocular contents, preserving all other periorbital and orbital structures.[24] The management of retinoblastoma has experienced rapid development, but enucleation is still the main choice at an advanced stage. Enucleation is usually performed for advanced Group D and Group E retinoblastoma. Enucleation was also indicated for extraocular extension (orbital cellulitis, neovascular glaucoma, intraocular hemorrhage, tumor in the anterior chamber, optic nerve or choroid involvement).[23] Globe salvage is an eyeball rescue that does not require enucleation.[25] The average globe salvage reached 93% in Group A and only 19% (95% CI 5-50%) in Group E.[25] In this case, globe salvage is no longer possible because retinoblastoma is already in stage E. We must explain to the parents that vision cannot return.

Before enucleation, the patient or parents must be given informed consent to explain the indications, risks, benefits, and possible complications.[24,26] In this case, Histopathology finding refers to retinoblastoma, with a monotonous round nucleus and Flexner-Wintersteiner rosette. Retinoblastoma on microscopic examination reveals small hyperchromatic cells, a high nuclear-to-cytoplasmic ratio, necrosis, and multifocal calcification. Tumor differentiation was classified as well differentiated (>50% known as Homer- Wright rosette) or poorly differentiated (<50% known as Flexner-Wintersteiner rosette).[21,27] The incidence of high-risk retinoblastoma in eyes that have undergone primary enucleation reaches 77.5%,

especially in poor and undifferentiated cells, more in children over two years of age.[28]

We plan chemotherapy after enucleation in our patient. Primary enucleation followed by adjuvant chemotherapy will improve survival, reducing the occurrence of metastasis in children with locally advanced retinoblastoma and histopathologic high-risk characteristics.[29–33] This patient will be given adjuvant chemotherapy with a regimen of vincristine, etoposide, and carboplatin by a pediatric oncologist. Systemic chemotherapy for retinoblastoma is chemo reduction of large tumors (neoadjuvant chemotherapy) or reduces the risk of relapse, metastasis, or recurrence after surgical enucleation (adjuvant chemotherapy).[34] The patient requires adjuvant chemotherapy. Retinoblastoma requires combination therapy which is not only with enucleation but can be followed by chemotherapy and/or radiotherapy.[23,30,31,35] Combination therapy can provide more effective results and a better prognosis. Meta-analyses report that overall survival in children with retinoblastoma is 79% (74-84%), and globe salvage is 22% (14-32%).[8] Poor prognosis (lower globe salvage, metastasis related mortality, treatment failure) are more common in countries with low incomes and in rural areas, and access to health services is limited, including in Southeast Asia.[8,36]

The World Health Organization (WHO) Guide for Effective Programs in Cancer Control emphasizes the early diagnosis of retinoblastoma, with the target population being children with white reflexes and strabismus as early symptoms. Screening for early detection of retinoblastoma has developed in various developing countries, but it is necessary to emphasize screening newborns through examination of the red reflex.[10,35,37] Early retinoblastoma detection is crucial in increasing the cure rate while maintaining children's vision.[38] The late referral will delay diagnosis, although retinoblastoma may be more aggressive at an older age. Health workers, especially pediatricians, and ophthalmologists, need to educate and increase parents' understanding of retinoblastoma's early signs and symptoms. Parents can have symptoms of depression (73%), anxiety (64%), and stress (100%) as a psychological impact of retinoblastoma and a decrease in the child's quality of life.[11]

Retinoblastoma is a cancer in children which is still a challenge in terms of globe salvage and chemotherapy.[11] Early detection of retinoblastoma should have been carried out earlier by parents and first-line health workers. Identification failure will cause the child to come with an advanced condition. Delay in diagnosis will result in globe salvage failure, and the child must lose his sight. A general ophthalmologist can perform surgery. The limitations of this case report are the absence of head imaging examinations such as MRI and bone marrow aspiration. The next step is adjuvant chemotherapy. However, cancer service centers are unavailable everywhere, so he must be referred immediately.

CONCLUSION

In our case, a 22-month-old boy with a shiny white spot-like cat eye on the right eye (unilateral leukocoria) without a family history of retinoblastoma. Ocular ultrasound showed a solid mass with calcification in the right eye, which refers to intraocular retinoblastoma stage E of the right eye. The management is enucleation, and the histopathology finding refers to retinoblastoma (Flexner-Wintersteiner rosette). He was sent to the pediatric oncologist for further chemotherapy to provide a better prognosis.

AUTHORS' CONTRIBUTIONS

All authors contributed equally from conception, design, data extraction, and statistical analysis to interpretation of data.

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DATA AVAILABILITY STATEMENT

The utilized data to contribute in this research are available from the corresponding author on reasonable request.

DISCLOSURE STATEMENT

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors. The data is the result of the author's research and has never been published in other journals.

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