JUSINDO, Vol. 8 No. 2, July-December 2026
p-ISSN: 2303-288X, e-ISSN: 2541-7207

Advanced-Stage Retinoblastoma with Systemic Manifestations Due to Delayed Diagnosis of Congenital Leukocoria: A Case Report

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Keywords:
Retinoblastoma; Leukocoria; Optic Nerve Invasion.

Abstract

Background: Retinoblastoma is the most common primary intraocular malignancy in children, with leukocoria as its hallmark clinical sign. Delayed diagnosis may lead to advanced disease, extraocular extension, and a poor prognosis. Case Presentation: A 2-year-4-month-old girl presented to the emergency department with recurrent vomiting, weakness, and decreased activity. Leukocoria of the left eye had been noted since birth but had never been medically evaluated. Ophthalmologic examination revealed no light perception, proptosis, leukocoria, a mid-dilated nonreactive pupil, and restricted extraocular movements in the left eye. B-scan ultrasonography demonstrated a solid intraocular mass suggestive of retinoblastoma. Computed tomography revealed a calcified intraorbital mass with irregular thickening of the left optic nerve and mild cerebral edema, raising suspicion of optic nerve invasion. The patient was classified as Group E retinoblastoma according to the International Intraocular Retinoblastoma Classification and as stage III according to the International Retinoblastoma Staging System. Discussion: This case highlights how nonspecific systemic manifestations may obscure the diagnosis of retinoblastoma and contribute to delayed recognition. Persistent leukocoria that remains unevaluated may progress to advanced disease with possible extraocular extension and a high risk of metastasis. Conclusion: Early recognition of leukocoria and routine red reflex screening are essential for preventing delayed diagnosis and disease progression in children with retinoblastoma

INTRODUCTION

Retinoblastoma is the most common primary intraocular malignancy in children and accounts for a substantial proportion of pediatric ocular cancers (Bentivegna et al., 2024; Chen et al., 2024; Kumari et al., 2025; Virgili et al., 2024). Its incidence is estimated at approximately 1 in 15,000 to 1 in 20,000 live births, with about 80% of cases diagnosed before 3 years of age (Wang et al., 2021a; Zhou et al., 2024). The disease develops through biallelic inactivation of the RB1 tumor suppressor gene, which plays a critical role in cell-cycle regulation through the pRB–E2F pathway. Loss of RB1 function results in uncontrolled proliferation of retinal cells (Zhou et al., 2024).

Clinically, the most common manifestation of retinoblastoma is leukocoria, characterized by a white pupillary reflex, which occurs in approximately 60–80% of cases, followed by strabismus. In advanced stages, patients may develop more severe manifestations, including proptosis, ocular pain, elevated intraocular pressure, extraocular extension, and intracranial involvement (Wang et al., 2021a; Zhou et al., 2024). Optic nerve involvement is one of the most important prognostic factors because the optic nerve

represents a major route of tumor spread toward the central nervous system and is associated with an increased risk of metastasis and mortality (Wang et al., 2021a).

Although advances in diagnosis and treatment have increased survival rates to more than 95% in high-income countries, substantial disparities persist in resource-limited settings, where many patients present with advanced-stage disease because of delayed diagnosis (Ademola-Popoola & Yusuf, 2025; Kaliki et al., 2025). Major contributors to diagnostic delay include limited awareness of early signs such as leukocoria among families and healthcare professionals, as well as inadequate implementation of early screening methods such as the red reflex test (Vempuluru & Kaliki, 2021).

In addition, advanced retinoblastoma may be associated with nonspecific systemic manifestations, such as vomiting, decreased level of consciousness, or other neurologic symptoms, particularly when intracranial involvement, increased intracranial pressure, or cerebral edema is present. Such atypical presentations may contribute to further diagnostic delay because the initial symptoms may not immediately suggest an ophthalmologic disorder (Zhou et al., 2024).

This case is important because it illustrates the clinical progression of retinoblastoma after a prolonged delay in evaluating leukocoria that had been present since early life, with the disease ultimately recognized after the development of severe systemic manifestations and findings suggestive of extraocular extension and optic nerve invasion. This report aims to emphasize the importance of recognizing early signs of retinoblastoma and to increase clinicians' awareness of atypical presentations that may obscure the diagnosis. It also highlights the importance of red reflex screening and early recognition of leukocoria among primary care physicians and pediatricians, provides insight into systemic manifestations of advanced retinoblastoma that may initially resemble non-ophthalmologic conditions, and supports efforts to strengthen early detection and referral systems in resource-limited settings.

METHOD

This case report described a 2-year-4-month-old pediatric patient with advanced retinoblastoma who was treated in the emergency department. Clinical data were obtained from the medical record, including history taking, physical and ophthalmologic examinations, B-scan ultrasonography, and head computed tomography. The diagnosis was established based on clinical and radiologic findings and was classified using the International Intraocular Retinoblastoma Classification (IIRC) and the International Retinoblastoma Staging System (IRSS). The case was presented descriptively and supported by relevant literature for analysis and discussion.

RESULTS AND DISCUSSION

Case Presentation

A 2-year-old and 4-month-old girl was taken by her parents to the Emergency Installation with the main complaint of vomiting since ±6 hours before being admitted to the hospital. Vomiting occurs ±8 times, contains food and fluids, appearing every time you eat and drink. Complaints are accompanied by nausea, heartburn, and headache. Parents also complained that patients seemed increasingly weak, tended to be sleepy since the afternoon,

and the amount of urine decreased with a more intense color. There is no history of fever, diarrhea, cough, runny nose, or shortness of breath.

From further anamnesis, a history of abnormalities in the left eye since birth was obtained in the form of pupils that appeared white and did not shrink when exposed to light. Parents are also aware of a decrease in vision in the left eye and complaints of pain in the eye, but have never had a medical evaluation done before. Family history with similar disorders is denied. The history of pregnancy and childbirth was not abnormal, the patient was born spontaneously with a birth weight of 2500 grams.

On physical examination, it was found that the general state appeared weak with the awareness of compos mentis (GCS 15). Vital signs showed tachycardia (HR 136x/min), 24x/min breathing rate, 37°C temperature, and 99% oxygen saturation without oxygen assistance. Hydration status shows signs of dehydration in the form of cowong eyes, cold acral, and capillary refill time > 2 seconds.

Ophthalmological examination shows the right eye within normal limits with a positive light reflex. In the left eye, 0/NLP visibility, proptosis, pupil mydriasis with negative light reflex, leukoria, and limited eyeball movement. The cornea appears clear with a shallow front eye chamber and the lens appears cloudy. Examination of the posterior segment cannot be assessed.

Figure 1. Clinical picture of the patient's eye
Source: Patient medical records, documented by the authors (2025)

Laboratory examination showed a hemoglobin level of 11.4 g/dL, leukocytes increased by 16.86 x10³/µL with a neutrophil predominance of 88% and a neutrophil-lymphocyte ratio (NLR) of 8.93 leading to an acute inflammatory response. Platelets within normal limits (387,000/µL). Blood glucose was tested for severe hypoglycemia with a level of 41 mg/dL, which then improved to 83 mg/dL after two corrections. Electrolyte examination showed sodium 144 mmol/L, potassium 4.2 mmol/L, chloride 108 mmol/L, and calcium 1.60 mmol/L indicating mild hypocalcemia.

Ophthalmological support examination using a B-scan ultrasound of the left eye showed the presence of a solid intraocular mass with high reflectivity that was highly suggestive of retinoblastoma. A non-contrast head CT scan examination showed left intraorbital mass with multifocal calcification (98–187 HU), thickening and irregularities of the left optic nerve, and a picture of mild cerebral edema in the form of narrowing of the sulcus, girus, and ventricular system. No lesions of intracranial mass or midline deviation were found.

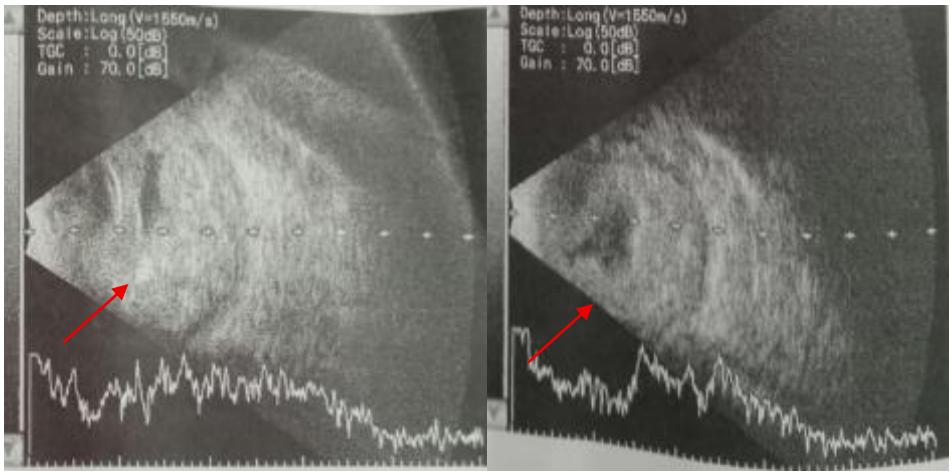

Figure 2. B-scan ultrasound – intraocular solid mass indicated by a red arrow

Source: Patient medical records, processed by the authors (2025)

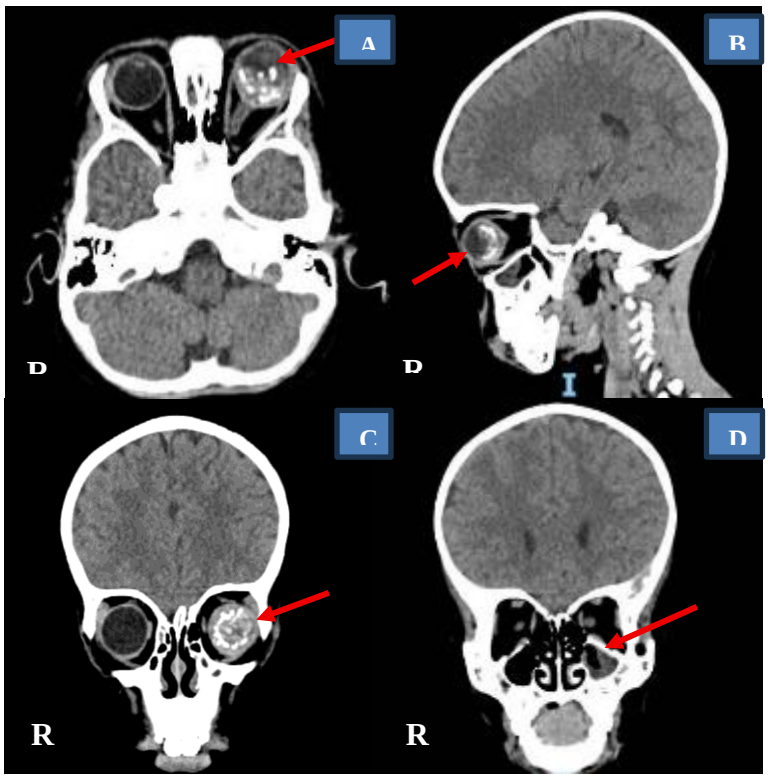

Figure 3. A. Axial Cut – CT, there is a thickening of the irregularity of the left optic nerve, B. Sagittal Cut – CT shows the presence of an intraorbital solid mass, C. Coronal Cut – CT shows the intraorbital period with multifocal calcification, D. Coronal Cut – CT shows thickening of the left maxillary sinus mucosa

Source: Patient medical records, processed by the authors (2025)

Based on clinical and supporting findings, the patient was diagnosed with advanced stage retinoblastoma sinistra with suspicion of optic nerve invasion, accompanied by cerebral edema, profus vomiting with severe dehydration, hypoglycemia, and mild hypocalcemia. Based on the International Intraocular Retinoblastoma Classification (IIRC), this condition belongs to group E, characterized by loss of visual function (NLP), the presence of leukocoria with suspicion of extraocular invasion, and opacity media that inhibits fundus visualization.

Meanwhile, based on the International Retinoblastoma Staging System (IRSS), this case is included in stage III because there is a suspicion of orbital involvement in the form of an invasion of the optic nerve based on imaging examination.

During initial hospital treatment, patients receive comprehensive management that focuses on stabilizing general conditions prior to referral. Fluid resuscitation was carried out by administering Ringer Lactate as much as 220 mL as a loading dose, followed by an infusion of D5 1/4 NS with a total of 1000 mL of fluid per 24 hours. Hypoglycemia is managed by administering a 10% dextrose bolus of 22 mL, with periodic monitoring of blood glucose levels until it reaches normoglycemia values. To overcome cerebral edema, 20% mannitol was given with a loading dose of 50 mL followed by a maintenance dose of 15 mL 6 times, and dexamethasone of 1.5 mg four times a day. Other supportive therapies include the administration of ondansetron as an antiemetic, omeprazole for the protection of the gastrointestinal mucosa, and empirical antibiotics in the form of ampicillin-sulbaktam given the presence of leukocytosis and possible systemic inflammatory processes. Correction of hypocalcemia is carried out by intravenous administration of calcium gluconate.

From the ophthalmological side, patients receive topical therapy in the form of Cendo Tonor (betaxolol) eye drops twice a day in the left eye to help lower intraocular pressure. Once the patient's general condition is stable, the patient is planned to be referred to a tertiary hospital with an eye oncology facility for further definitive management, including evaluation of possible ennucleation measures and adjuvant therapy according to the stage of the disease.

Retinoblastoma is the most frequent primary intraocular malignancie in children that generally occurs due to biallelic inactivation of the RB1 gene through the two-hit hypothesis mechanism, resulting in uncontrolled retinal cell proliferation (Shields & Shields, 2010; Zhou et al., 2024). The disease is most commonly found in children under five years of age and most unilateral cases are diagnosed before the age of three, according to the patient profile in these case reports (Donica et al., 2025; Zhou et al., 2024). In molecular pathogenesis, retinoblastoma develops through a spectrum of diseases that can be initiated by premalignant lesions in the form of retinoma, where loss of RB1 function has occurred but is still controlled by cellular senescence mechanisms. The transformation into aggressive malignancy occurs when the mechanism fails due to the accumulation of additional mutations that allow the progressive and invasive proliferation of tumor cells (Toumasis et al., 2025). Understanding the course of this pathogenesis suggests that there are early phases of the disease that are actually still possible to detect before progressing to advanced retinoblastoma with a worse prognosis.

Leukocoria is the most frequent clinical manifestation in retinoblastoma, while proptosis and neurological manifestations are generally found in advanced stages with extraocular involvement (Cruz-Gálvez et al., 2026; Vempuluru & Kaliki, 2021). In this case, the history of leukobacteria from birth was never evaluated until the patient presented with profus vomiting, lethargy, and signs of severe dehydration due to impaired oral intake. Such systemic presentations are relatively rarely reported in retinoblastoma and have the potential to lead to early suspicion of acute metabolic or gastrointestinal disorders, thus masking classic ophthalmological symptoms and prolonging the delay in diagnosis. Studies show that delayed diagnosis correlates with increased disease stages, the need for eucleuation, and patient mortality (Kaliki et al., 2025; Soliman et al., 2017). The causative factors are multifactorial,

including low family awareness, delay in recognizing danger signs by health workers, and limited access to tertiary health services (Ademola-Popoola & Yusuf, 2025). The uniqueness of the clinical presentation in this case provides important educational value that advanced retinoblastoma can present with dominant systemic manifestations that resemble non-ophthalmological disorders.

Retinoblastoma has a rapid growth progressivity so that in a short time the tumor can develop from intra-retinal lesions to diseases with vitreous, choroidal, sclera, and extraocular tissue involvement (Kaliki et al., 2025; Zhou et al., 2024). In this case, the presence of proptosis, limited eyeball movement, loss of visual function, and cloudy refractory media indicate advanced stage retinoblastoma with a poor visual prognosis. Based on the International Intraocular Retinoblastoma Classification (IIRC), the condition is included in Group E with a high risk of extraocular spread and the need for euclysis (Shields & Shields, 2010). Studies show that patients in developing countries are more likely to come at an advanced stage due to delays in diagnosis and referral, which is associated with increased ennucleation needs as well as patient mortality (Ademola-Popoola & Yusuf, 2025; Donica et al., 2025).

The diagnosis of retinoblastoma in this case is established through a combination of clinical and radiological findings. B-scan ultrasound examination showed intraocular mass with high reflectivity due to intratumoral calcification, while head CT scan showed intraorbital heterogeneous mass with multifocal calcification accompanied by thickening and irregularity of the left optic nerve. These findings are typical characteristics of retinoblastoma and help distinguish them from other comparative diagnoses such as persistent fetal vasculature, Coats disease, endophthalmitis, and congenital cataracts (Zhou et al., 2024). The suspicion of optic nerve invasion in this case is an important prognostic finding because it is the main pathway for the spread of the tumor to the central nervous system. Feng et al. (2025) reported that post-laminar invasion of the optic nerve was associated with an increased risk of metastasis and a decrease in survival rates (Feng et al., 2025), while Wang et al. (2021) showed that patients with optic nerve involvement generally present with severe clinical manifestations such as proptosis, orbital pain, and total vision loss (Y. Z. Wang et al., 2021b).

Systemic manifestations of profus vomiting, hypoglycemia, lethargy, and severe dehydration in patients indicate that advanced retinoblastoma not only has a localized impact on the eye but can also cause significant systemic disorders. The condition may be related to acute metabolic disorders due to persistent vomiting aggravated by the progression of intraorbital disease as well as mild cerebral edema on CT scans. Initial management in the form of hypoglycemic correction, rehydration, administration of dexamethasone, and mannitol in this case is appropriate to stabilize the systemic condition before definitive therapy is performed.

The current approach to retinoblastoma management is multimodal with the main goal of life salvage, followed by efforts to maintain the eyeball and visual function whenever possible (Kritfuangfoo & Rojanaporn, 2024; Shields & Shields, 2010). In this case, the left eye no longer has visual potential (no light perception) accompanied by proptosis and suspicion of optic nerve invasion so that eulation becomes the most rational main therapy. Research shows that timely ennucleation followed by adjuvant therapy can provide a good survival rate in advanced retinoblastoma (N. Wang et al., 2022). Nevertheless, this action can

lead to orbital growth disorders and facial deformities in early childhood (N. Wang et al., 2025). The development of modern therapies such as intra-arterial chemotherapy (IAC), intravitreal chemotherapy, and combination focal therapy has increased eyeball rescue rates in early-to-mid-stage retinoblastoma, although its implementation is still limited in developing countries due to the need for specialized facilities and resources (Kritfuangfoo & Rojanaporn, 2024).

In addition to the therapeutic aspect, retinoblastoma also has long-term genetic and ophthalmological implications. Kamihara et al. (2025) explain that retinoblastoma is a cancer predisposition syndrome related to RB1 gene mutations, so genetic evaluation is important to determine hereditary risk, the possibility of bilateral tumors, and the need for long-term surveillance. Patients with BR1 germline mutations have a higher risk of developing second primary malignancy such as osteosarcoma and soft tissue sarcoma (Kamihara et al., 2025). Abdallah et al. (2025) also reported that advanced retinoblastoma can cause anterior segment changes in the form of siltation of the anterior eyepiece, changes in lens curvature, and neovascular glaucoma due to the effect of intraocular tumor mass (Abdallah et al., 2025). Overall, this case illustrates how a delay in diagnosis of leukoria can lead to advanced progression of retinoblastoma with optic nerve involvement and severe systemic manifestations. Therefore, early detection through red reflex screening, increased public awareness and health workers, and an effective referral system are crucial factors in improving prognosis and reducing retinoblastoma mortality in children.

CONCLUSION

This case describes advanced unilateral retinoblastoma associated with delayed recognition and evaluation of leukocoria early in life, resulting in presentation with loss of visual function, suspected optic nerve invasion, and systemic manifestations suggestive of significant disease progression. Delayed detection and treatment likely contributed to disease progression and a poorer prognosis; therefore, management focused primarily on life-saving definitive therapy. Early recognition of leukocoria, routine red reflex screening, and increased awareness among clinicians and the public are crucial for preventing diagnostic delays and improving clinical outcomes in patients with retinoblastoma.

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