Case Report

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Case Series of Imaging Features of Trilateral and Quadrilateral Retinoblastoma: What Radiologists Need to Know

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Abstract

Objective: To identify the differences between trilateral and quadrilateral retinoblastoma based on radiologic imaging.

Case: This researcher found three cases of retinoblastoma at Sanglah General Hospital. The retinoblastoma patients we found were boys under the age of 5. The first patient presented with swelling, pain, and impaired vision in the right eye. The second and third patients presented with eye protrusion and leukocoria. Computed tomography (CT) imaging revealed a calcified mass in the intraorbital region that extended to the cerebral hemispheres. It may be accompanied by hair-on-end periosteal reaction. In the first patient, the mass extended to the pineal gland. In the second and third patients, the mass extended to the suprasellar and pineal regions. Trilateral retinoblastoma consists of a primordial midline neuroectodermal tumor that originates in the pineal or suprasellar region. It is an uncommon combination of unilateral or bilateral retinoblastomas. Quadrilateral retinoblastoma, on the other hand, presents with bilateral retinoblastoma and tumors in both the suprasellar and pineal regions. The histopathology of trilateral and quadrilateral retinoblastoma shows a different pattern from retinoblastoma.

Conclusion: Retinoblastoma poses one of the most challenging problems due to its distinct patterns of growth, extension, and recurrence. Intracranial metastasis of trilateral and quadrilateral retinoblastoma exhibits a different pattern. The prognosis and diagnosis of retinoblastoma are significantly influenced by clinical examination, radiologic imaging, and histopathology.

Keywords: Pineal gland, quadrilateral, retinoblastoma, suprasellar, trilateral

Introduction

Annually, between 8,000 and 10,000 children under the age of five are diagnosed with retinoblastoma, which is the most common intraocular malignancy in this age group. There are no discernible predispositions based on geography, race, or gender.[1,2] Orbital retinoblastoma is a major cause of death and is associated with a poor prognosis for survival.[3] Inherited retinoblastomas can either occur sporadically or as a result of a germline mutation in the retinoblastoma protein tumor suppressor gene (RB). Bilateral tumors, which account for 30–40% of cases, almost always have a germline mutation, while unilateral tumors account for 60-70% of germline mutations. Trilateral retinoblastoma (unilateral or bilateral retinoblastomas and pineoblastoma), quadrilateral retinoblastoma (trilateral retinoblastoma and suprasellar CNS embryonal tumor), and osteosarcoma are additional conditions that may develop in children with germline mutations. These conditions typically present in early stages, with a median age of diagnosis at 12 months.[4]

The most common initial manifestations of retinoblastoma are white pupillary reflex known as leukocoria, strabismus, and impaired vision. Patients in the advanced

stages of the disease may also experience iris color changes, corneal and globe enlargement, inflammation of the orbits, and exophthalmos. Retinoblastoma is a malignancy that originates from the retina and can exhibit diffuse, infiltrative growth along the retina, endophytic growth into the vitreous chamber, or exophytic growth into the subretinal space.[1] In some cases, retinoblastoma can metastasize to the leptomeninges through direct orbital dissemination, transmission via the optic nerve to the brain, or invasion of the subarachnoid space. It can also metastasize hematogenously, with a preference for the liver, bone marrow, and bone.[4] This case series on retinoblastoma aims to help radiologists distinguish between trilateral and quadrilateral retinoblastoma based on radiologic imaging.

Cases

Case 1

A two-year-old child came to the public health center with swelling in the right eye. The child had a history of itching in the right eye for four months, followed by an enlargement of the eye, impaired vision, redness, and increasing pain. There were no signs of atypical white reflection from the eye. The child had previously undergone multiple examinations at a regional facility but was finally diagnosed with retinoblastoma through a clinical examination.

The right eye continued to enlarge until it was the size of a ping-pong ball. The child received one cycle of radiotherapy around two months before, according to allo-anamnesis; however, no medical record exists regarding

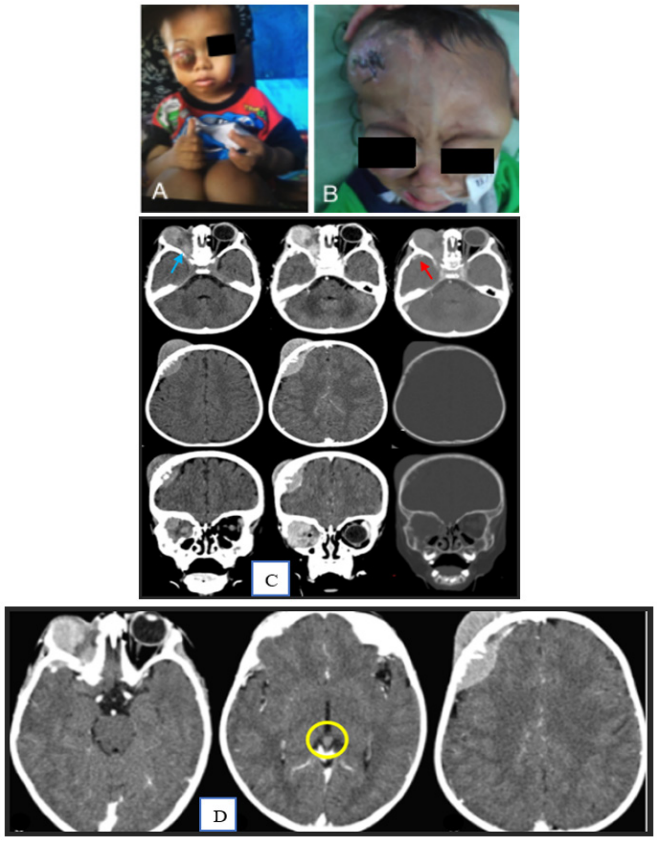

Fig. 1 (A) Swelling of the right eye for the past 4 months, followed by (B) the extension of a mass to the right frontoparietal region. (C) Computed tomography (CT) of the head with axial and coronal contrast revealed a mass in the right frontoparietal region, which also extended to the right optic nerve (blue arrow) and the lateral wall of the orbit (red arrow). Additionally, there was erosion and a hair-on-end periosteal reaction in the adjacent bone, as well as involvement of the meninges and soft tissues. (D) Enlargement of the pineal gland with contrast enhancement (yellow circle)

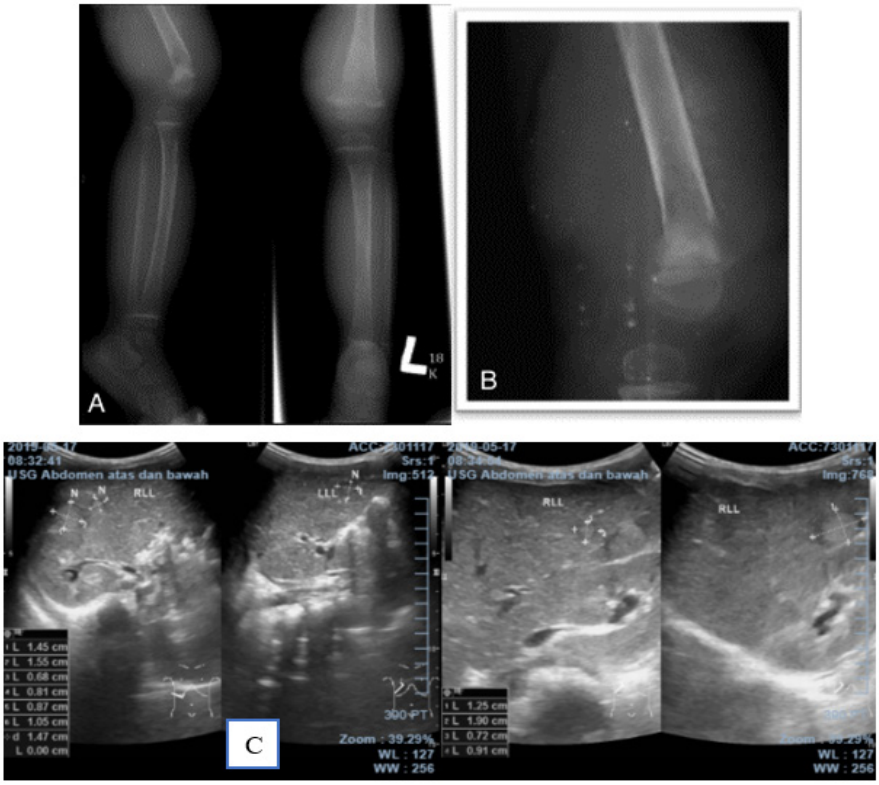

Fig. 2 (A) Cortical destruction was observed on the distal femoral and proximal tibial bones of the left leg. In addition, an interrupted periosteal reaction and diminished trabeculation were seen on the AP and lateral projections of the radiograph. (B) The distal femoral bone showed an interrupted periosteal reaction. (C) A liver ultrasound image revealed numerous hyperechoic nodules on both lobes of the liver.

the radiotherapy. After the eyeball ruptured and started bleeding, emergency enucleation was performed. The histopathology laboratory confirmed that the child had a malignant round-cell tumor based on an analysis of the ocular tissue section. About a month before, the child also began experiencing symptoms of a mass in the right frontal region that extended to the right parietal region. Consequently, the child was referred to our facility for further evaluation and treatment. The initial CT examination did not reveal any symptoms in the left eye.

Additionally, there was progressive weight loss. A broad-based mass was identified in the right lateral orbital wall on the contrast head CT imaging. This mass extended into the right optic nerve and measured approximately 1.9 x 2.0 x 1.8 cm. Another mass was observed in the right frontoparietal region, which was exerting pressure on the right frontal lobe. The surrounding bone exhibited attrition and a hair-on-end periosteal reaction, indicating the involvement of the meninges and soft tissues. The size of the pineal gland was approximately 7.30 x 7.08 x 5.81 mm, which was slightly larger than the normal range of 6.1 mm ± 1.2 x 3.7 mm ± 0.8 x 4.8 mm ± 1.1. The cranial index of the pineal gland was relatively average. Additionally, there was contrast enhancement observed in the pineal gland, suggesting the possibility of a remaining pineal mass.

The destruction of the cortex in the proximal tibia and left distal femoral bone was assessed through lower limb radiography. In addition, there was disruption in the periosteal reaction, leading to a "hair on end" appearance and a reduction in bone trabeculation. Furthermore, we observed multiple hyperechoic lesions of varying sizes in both lobes of the liver. Therefore, it is unlikely that there are retroperitoneal and mediastinal masses present.

During the patient's hospitalization, the mass in the right frontoparietal region grew larger and spread to other areas, including

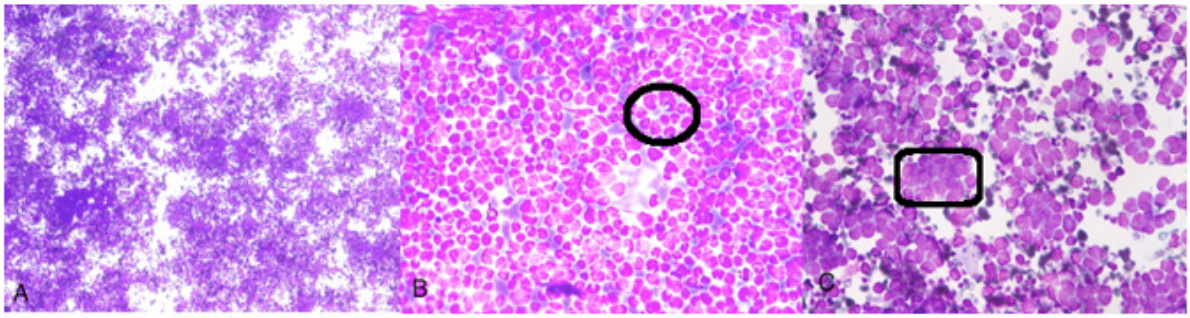

Fig. 3 Malignant round cell tumor was identified by histopathology. (A) Dispersed neoplastic cells amidst tissue hypercellularity (MGG, x100). (B) Rossete structure (MGG, x400) with (C) round-ovoid notched cells arranged in moldings accompanied by an increased nuclear-cytoplasmic ratio, anisocorics. The cells have an irregular core membrane, hyperchromatic and inconspicuous nucleolus. The arrow points to apoptotic cells (MGG, x1000).

the left frontal region, forearm, and foot. The histopathology findings of the right frontal mass indicated a small blue round cell as the second result, while the malignant round cell tumor with a Rosette's component was identified as the third result for the left frontal region, forearm, and foot.

Case 2

A 17-month-old boy presented with a complaint of swelling and discharge from the left eyeball for 2 days before hospitalization. The eyeball was more prominent than it was 6 months before, appeared more swollen, and had a reddish bulge 5 days before hospitalization. The patient also had a red eyelid and white discharge. The patient sleeps with the left eye not closing completely. The patient was born normal, cried immediately, was full-term, assisted by a midwife, and had a birth weight of 3 kg. The patient is the only child. At the age of three months, the patient presented with a white eye and was evaluated by a pediatrician who diagnosed the condition as a cataract of the left eye. At the age of six months, the patient was evaluated by an ophthalmologist in Sumba who diagnosed the infant with glaucoma and recommended a referral to a hospital in the city.

The patient was admitted to the intensive care unit for 21 days after experiencing recurrent seizures at the age of 13 months, during which time their consciousness did not recover. Following this, they were referred to Sanglah General Hospital. One month later, the patient had another seizure more than 3 times. The patient underwent craniotomy surgery and tumor removal with frozen section and was diagnosed with primary malignant brain tumor ec pilocytic astrocytoma, with a differential diagnosis of brainstem glioma and ependymoma; left orbital proptosis retrobulbar tumor ec neuroblastoma post craniotomy and tumor removal. The histopathology result revealed a small round-cell tumor. One month after being admitted, the patient's condition deteriorated and he passed away.

Case 3

At 7 months of age, a 2-year-old child presented to the hospital with symptoms including lumps in both eyes and head. Initially, a white spot appeared in the right eye and the patient experienced decreased vision. The right eye and the right side of the head became more prominent. The patient was then taken to an ophthalmologist who diagnosed cancer and suggested surgery, but the patient's parents refused at that time. The patient was the third of three children, born normal and full-term, with the assistance of a doctor, weighing 3 kg at birth.

There was no family history of similar complaints. Subsequently, a contrast head CT examination was performed, revealing a heterogeneous solid mass with partially indistinct boundaries measuring approximately 9 x 9.8 x 13.8 cm in the right orbital region. This mass extended to the left-right sphenoidal sinus, left-right ethmoidal sinus, right suprasellar area, and right fronto-parieto-temporal lobe, causing a midline shift of approximately 0.34 cm to the left.

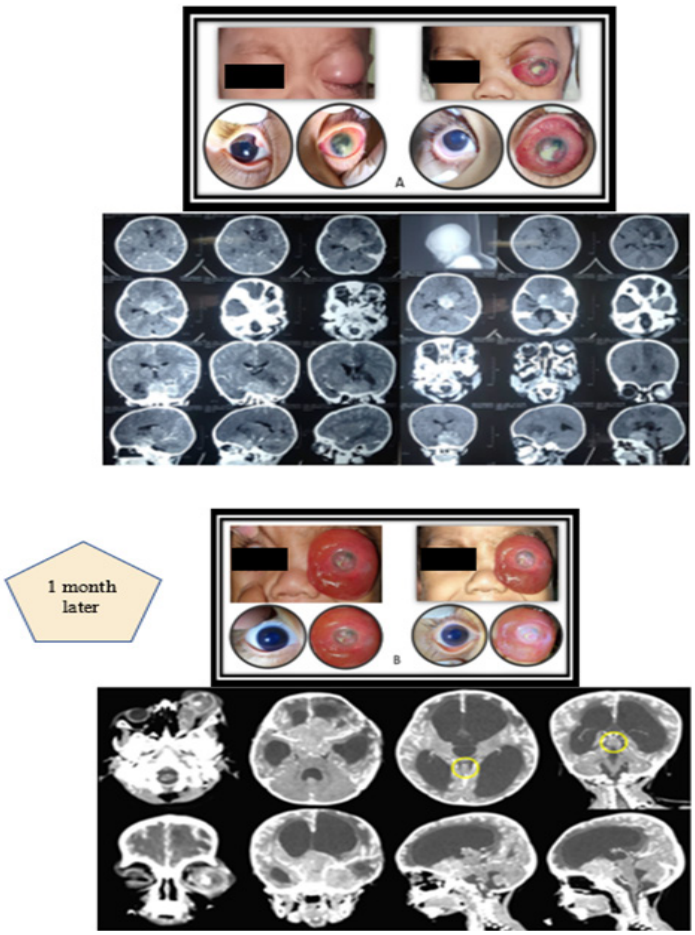

Fig. 4 (A) At 2 months of age, there was swelling in the left eyeball and a reddish bulge. Contrast head CT imaging showed an endophytic mass with a calcified component on the right orbital, extending to the suprasellar gland and causing pineal gland enlargement. (B) One month after craniotomy surgery, the left eye became more prominent and swollen, with a reddish bulge that persisted for the last 5 days. Contrast head CT imaging showed an enlarged suprasellar mass (axial diameter ± 6.23 cm) that had extended to the pineal gland, resulting in pineal gland enlargement (±10.6 x 16.4 x 15.5 mm) with contrast enhancement (indicated by the yellow circle) and communicating hydrocephalus.

Additionally, it exerted pressure on the anterior horn of the right lateral ventricle and encouraged leftward movement of the right-side midbrain. The mass also extended to the sinus cavernous, left retrobulbar to infiltrate the left orbital causing left proptosis oculi accompanied by left intraorbital calcification, extended to the right maxillary sinus to the right mandible and eroding the left right fronto-parieto-temporal osseus, clivus, greater wing and right sphenoid osseus, ethmoidalis osseus, lamina papiracea, right mastoid osseus, right zygomaticus osseus, right maxillary osseus, right mandibular osseus, with surrounding hair-on-end periosteral reaction and pineal gland enlargement measured ± 7. 4 x 8.1 x 7.8 cm with slight contrast enhancement. The patient had undergone chemotherapy for several months but in the 9th month, the patient's condition worsened and later died.

Discussion

11% of all cancers diagnosed in infants within the first year of life are retinoblastomas, which are the most common malignant intraocular

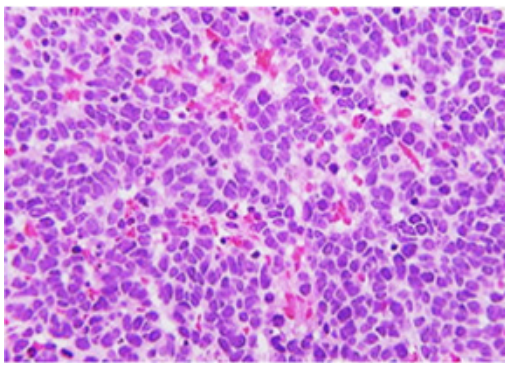

Fig. 5 As determined by histopathology, a small round cell tumor was identified. The tumor mass consists of neoplastic cell proliferation arranged in a solid nest pattern, which is partially molded and partially resembles pseudo rosette formation. The cellular features include a narrow eosinophilic cytoplasm, an elevated N/C ratio, an irregular nuclear membrane, an ovoid-round nucleus, and hyperchromaticity. There were 3 mitoses observed in 10 large fields of view.

tumor in this age group. Approximately one-third of cases are bilateral. Retinoblastomas are most commonly observed in early infancy, with 95% of cases manifesting before the age of five. The average age of diagnosis is 13 months. The effects of retinoblastoma are equally experienced by boys and girls, with no racial bias.[5] In this case series, all patients were boys aged 1–2 years.

Retinoblastoma can occur unilaterally,

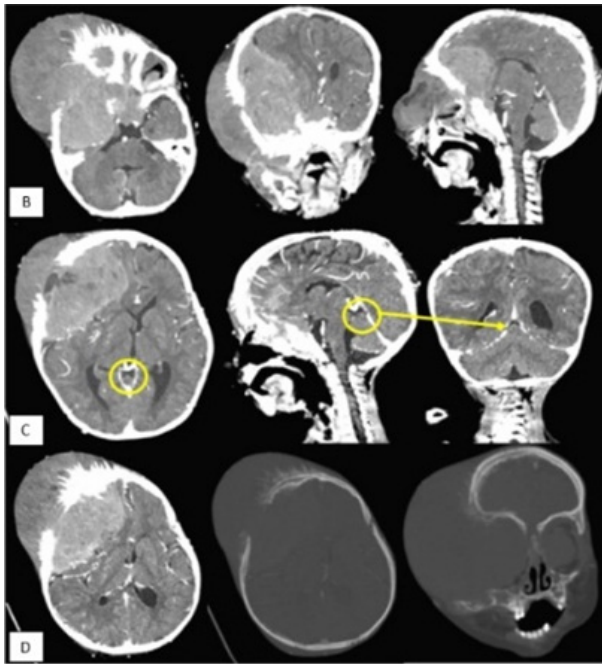

Fig. 6 (A) The patient has had lumps in both eyes and the right side of the head since she was 7 months old. Contrast head CT imaging revealed a calcified mass extending from the right orbital into the paranasal sinus and left orbital. (B) It also showed compression of the right cerebral hemisphere in the right fronto-parieto-temporal and suprasellar regions. (D) This was characterized by periosteal reaction, resulting in a hair-on-end appearance in the adjacent bone. (C) Additionally, there is an extension to the pineal gland, measuring approximately 7.4 x 8.1 x 7.8 cm, with slight contrast enhancement.

bilaterally, trilaterally, or quadrilaterally.[6] It has been estimated that 0.5-6% of patients with bilateral retinoblastoma will develop trilateral retinoblastoma.[2] The incidence of quadrilateral retinoblastoma is even lower than that of trilateral retinoblastoma. Trilateral retinoblastoma was first described by Jacobiec *et al*. It refers to the formation of a primary intracranial primitive neuroectodermal tumor in a patient who already has intraocular retinoblastoma. Trilateral retinoblastomas are typically located in the pineal gland, suprasellar region, or parasellar region, although there have been a few exceptional cases.

Quadrilateral retinoblastomas involve a tumor and bilateral ocular retinoblastomas in both the suprasellar and pineal regions. Rather than being a metastasis, the presence of an associated midline intracranial tumor indicates multifocal disease. The cause of intracranial lesions in patients with retinoblastoma is still unknown. There are two possible sources of intracranial tumors: pineal photoreceptors, which resemble retinal photoreceptors in both function and appearance, and ectopic foci of retinal cells on the floor of the third ventricle. One possible explanation for this coexistence of diseases is the shared photoreceptor origin shared by the retina and pineal gland. In the first case, there was right unilateral retinoblastoma with intracranial extension and involvement of the pineal gland, as confirmed by histopathological examination showing small round blue cells. This establishes the diagnosis of trilateral retinoblastoma. In the second case, there was right unilateral retinoblastoma with involvement of the suprasellar and pineal glands.

Histopathological examination revealed a small round cell tumor, leading to the diagnosis of quadrilateral retinoblastoma. In the third case, the retinoblastoma was bilateral and extended to the paranasal sinuses, with involvement of the suprasellar region and pineal gland. Based on CT imaging, it was suspected to be quadrilateral retinoblastoma. Typically, patients with retinoblastoma exhibit a white pupillary reflex. Retinoblastoma is responsible for up to 50% of cases of pediatric leukocoria. In addition to symptoms such as strabismus, ocular irritation, vision loss, and redness of the eyes, retinoblastoma can also cause orbital inflammation that resembles cellulitis. The presence of leukocoria is often assessed using CT imaging. In our case series, all patients exhibited leukocoria, as well as lumps and orbital pain. Retinoblastoma is a malignant tumor known for its invasive properties, often leading to metastasis in distant organs via the circulatory system. Metastasis and invasiveness can occur early in the development of retinoblastoma.[2]

Retinoblastoma can extend into the suprasellar region through the optic nerve.[7] The incidence of metastatic retinoblastoma ranges from 4.8% to 11%. Typical sites for extraocular retinoblastoma include the orbit, preauricular nodes, skeleton, central nervous system (CNS), and liver. Trilateral retinoblastoma is associated with an elevated risk of second primary malignancies in skeletal and soft tissues, such as osteosarcoma, leiomyosarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, angiosarcoma, Ewing sarcoma, PNET, and spindle cell sarcoma. The involvement of multiple bones and tissues indicates the presence of metastases rather than multifocal second primary malignancies. Bone metastases, which most commonly occur in the cranium and long bones, can cause symptoms such as atypically low blood counts, pain, and fever in patients with trilateral retinoblastoma.[3] In our case series, two cases of trilateral retinoblastoma with bone metastases in the head were observed, as well as one case with metastases in the long bones and liver. The diagnosis of retinoblastoma typically involves specialized ophthalmologists using funduscopy (conducted under general anesthesia) and ultrasound.

The primary distinguishing feature of retinoblastoma, intratumoral calcifications, can be detected using ultrasound (US). However, while ultrasound is specifically designed to detect superficial ocular masses, it is less sensitive than CT and MR imaging in detecting deeper tumor extensions such as optic nerve invasion and intracranial disease. CT is highly specific and sensitive in detecting calcifications.[8] It is the preferred method for detecting intraocular calcifications. MR imaging is used to detect leptomeningeal enhancement and parenchymal metastases, as well as assess primary midline intracranial lesions. Unilateral retinoblastoma is typically treated with surgical enucleation, while bilateral cases often require superior eye preservation. Enucleation alone is not sufficient for treating more advanced cases; additional treatments such as radiation (EBRT=external beam radiation therapy, plaque radiation), consolidation therapies (cryotherapy and transpupillary

thermotherapy), and chemotherapy (IVC=intravenous chemotherapy, IAC=intra-arterial chemotherapy, IvitC=intravitreal chemotherapy, intracameral chemotherapy) are necessary. Untreated retinoblastoma is usually fatal in the majority of the cases.[1,9]

The combination of high-dose chemotherapy and stem cell rescue is an alternative therapeutic strategy for the management of metastatic and advanced retinoblastoma.[9] Metastasis indicates a poor prognosis. Trilateral retinoblastoma, which occurs when the tumor has spread to the subarachnoid space, is associated with an unfavorable prognosis. Those who receive treatment for a detected pineal or sellar mass have an average survival time of 9.7 months, compared to 1.3 months for those who do not receive treatment.[5] An analysis using histopathology can identify neuroepithelial-derived small round cell tumors. Under a microscope, Homer-Wright pseudorosets (also present in other PNETs) and Flexner-Wintersteiner rosettes (which are relatively specific to retinoblastoma) are visible.[4] A subset of round cell tumors with an increased nuclear-cytoplasmic ratio are highly aggressive malignancies characterized by their monotonous, undifferentiated, and relatively small size.

Peripheral neuroectodermal tumor, rhabdomyosarcoma, non-Hodgkin's lymphoma, neuroblastoma, hepatoblastoma, Wilms' tumor, desmoplastic small round cell tumor, and synovial sarcoma are all neoplastic tumors that fall into this category. Malignant small round cell tumors are tumors composed of malignant round cells that are marginally larger than or double the size of red blood cells in air-dried smears. These neoplasms are defined by small, spherical, relatively undifferentiated cells.[10] In the first case, a histopathological examination revealed a malignant round cell tumor in the right frontal region, as well as Rosette components in the forearm, leg, and left frontal region. The second case showed the presence of a small round-cell tumor with partial formation of a pseudorosette during histopathological examination.

A comprehensive understanding of retinoblastoma requires a multidisciplinary team of specialists for proper treatment, long-term monitoring, and optimal survival while preserving vision, as well as a meticulous examination for precise diagnosis. Radiology plays a crucial role in distinguishing between trilateral and quadrilateral retinoblastoma cases.

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