CASE REPORT

Retinoblastoma: A Curse to Childhood

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ABSTRACT

Retinoblastoma is a cancer of the retina, the innermost layer of the eye that receives the light and images necessary for vision. About 300 children are diagnosed with retinoblastoma each year, making it the most common eye cancer in children under the age of 5. Every year, thousands of babies and children in low- and middle-income countries lose their sight and their lives to a treatable childhood eye cancer called retinoblastoma; usually because it was not recognized and treated in time.

Keywords: Retinoblastoma, germinal mutations, ophthalmoscopy, chemotherapy, tumor

Retinoblastoma is the most common intraocular malignancy in children. The current incidence ranging from 1 in 15,000 to 1 in 18,000 live births.[1] The average age at diagnosis is 18 months, with unilateral cases being diagnosed at around 24 months and bilateral cases before 12 months. Out of the newly diagnosed cases of retinoblastoma only 6% are familial while 94% are sporadic. It is bilateral in about 25-30% of cases. Bilateral retinoblastomas involve germinal mutations in all cases. Out of the unilateral cases, approximately 15% are caused by germinal mutations while the 85% are sporadic.[2] With the improvement in diagnostic and treatment modalities, early diagnosis and prompt treatment has remarkably improved the survival and salvageable vision in retinoblastoma patients, which otherwise would have succumbed to death in pre-revolutionary era in medical science.

GENETICS

Only 6% of retinoblastoma cases are found to be familial while remaining 94% are sporadic in origin. All bilateral cases are thought to be hereditary. Knudson proposed two-hit hypothesis for the occurrence of retinoblastoma.[3] According to this, two chromosomal mutations are required for the occurrence of retinoblastoma. Those having familial disease inherit one germinal mutation from the parents (first hit), while another mutation occurs sporadically while development of retina (second hit). Sporadic cases encounters both the mutations while retinal development. Familial cases because of underlying germinal mutation are also predisposed to other nonocular malignancies like osteosarcoma.

CLINICAL PRESENTATION

The clinical presentation of retinoblastoma depends on the stage of the disease.[4] Early lesions are likely to be missed, unless an indirect ophthalmoscopy is performed. Leukocoria (56%) is the most common clinical presentation of retinoblastoma followed by strabismus (20%). Leukocoria is observed mainly in endophytic growth of tumor that has gained substantial size to be observed through the pupil as grayish white reflex. Strabismus occurs when the tumor is involving fovea thus interfering with the normal fixation pattern of child. Other clinical presentations include diminished vision, red painful eye, asymptomatic, hyphema, vitreous hemorrhage, proptosis or orbital cellulitis.

Three types of tumor growth patterns are observed:

- Endophytic: Extension into vitreous cavity.
- Exophytic: Extension into subretinal space.
- Infiltrating: Diffusely involving retina causing placoid thickening. This type is diagnosed late and usually seen in older children.

Retinoblastoma may spread locally via scleral emissary veins to involve orbital tissues and central nervous system (CNS) involvement through optic nerve or hematogenous spread. Distant metastasis may involve pre-auricular or cervical lymph nodes and bone marrow.

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DIAGNOSIS

A child with suspected retinoblastoma must undergo complete ophthalmic evaluation including a dilated fundus examination under anesthesia. Diagnosis is usually clinical, aided by ultrasonography (USG) B-scan of the eye revealing tumor extension and intralesional calcification.[4] Computed tomography (CT) scan and magnetic resonance imaging (MRI) are reserved in cases with atypical presentation, extraocular extension or those having diagnostic dilemma. CT scan helps to delineate tumor extension and co-existent pinealoblastoma can be detected (trilateral tumor). MRI is useful when optic nerve or intracranial extension is suspected. Intralesional calcification on CT scan or USG B-scan is highly suggestive finding for retinoblastoma.

On histopathology, poorly differentiated tumor consists of small to round cells having scanty cytoplasm and hyperchromatic nuclei. Well-differentiated tumors show rosettes and fleurettes formation, which is highly suggestive of photoreceptor differentiation of tumor cells. Flexner-Wintersteiner rosettes consist of columnar cells arranged around a lumen are highly characteristic of retinoblastoma.

INTERNATIONAL CLASSIFICATION SYSTEM FOR RETINOBLASTOMA

The International Classification System includes grouping and staging of retinoblastoma (Box 1). Grouping is done preoperatively to plan lines of management and prognosticate organ salvage while grouping is done post-enucleation to prognosticate the survival of the patient.[5]

CASE REPORT

A 14-month-old female child presented to us with intermittent deviation of both eyes and white reflex in both eyes for last 3 months, along with redness and photophobia in right eye for last 15 days. On examination, child resisted occlusion of left eye signifying poor vision in right eye. Right eye conjunctiva was congested, cornea was hazy and edematous, and anterior chamber was full of fluffy clumps with hypopyon of approximately 1 mm (Fig. 1). Fundus details could not be seen due to hazy media. Intraocular pressure was unrecordably low. Patient had leukocoria in left eye with mid-dilated pupil, which was not reacting to light (Fig. 1). On fundus examination, yellow white mass with dense vitreous seeding was seen in left eye. Intraocular pressure was

Grouping and Staging of Retinoblastoma

Grouping (Shields)

Group A Small tumor
- Retinoblastoma <3 mm in basal dimensions

Group B Larger tumor
- Retinoblastoma >3 mm in basal dimensions
- Macular location (<3 mm from foveola)
- Juxtapapillary location (<1.5 mm from optic disc)
- Clear subretinal fluid <3 mm from tumor margin

Group C Focal seeding
- C1 Subretinal seeds <3 mm from retinoblastoma
- C2 Vitreous seeds <3 mm from retinoblastoma
- C3 Both subretinal and vitreous seeds <3 mm from retinoblastoma.

Group D Diffuse seeding
- D1 Subretinal seeds >3 mm from retinoblastoma
- D2 Vitreous seeds >3 mm from retinoblastoma
- D3 Both subretinal and vitreous seeds >3 mm from retina

Group E Extensive retinoblastoma
- Occupying >50% globe or
- Neovascular glaucoma
- Spontaneous vitreous hemorrhage or hyphema
- Invasion of optic nerve, choroid (thickness >2 mm), sclera, orbit, anterior chamber

Staging

Stage 0 No enucleation

Stage I Enucleation, tumor completely resected

Stage II Enucleation, microscopic residual tumor

Stage III Regional extension
- Overt orbital disease
- Pre-auricular or cervical lymph node involvement

Stage IV Metastatic disease
- Hematogenous metastasis
  - Single lesion
  - Multiple lesions
- CNS extension
  - Prechiasmatic lesion
  - CNS mass
  - Leptomeningeal disease

Figure 1. Leukocoria in left eye with mid-dilated pupil, not reacting to light.

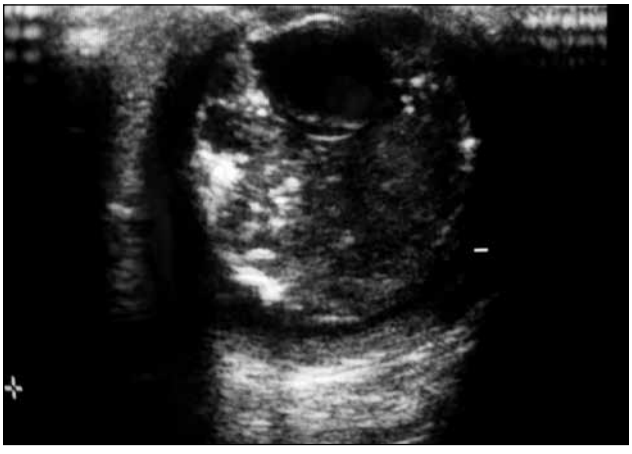

Figure 2. USG showing diffuse vitreous seeding in right eye.

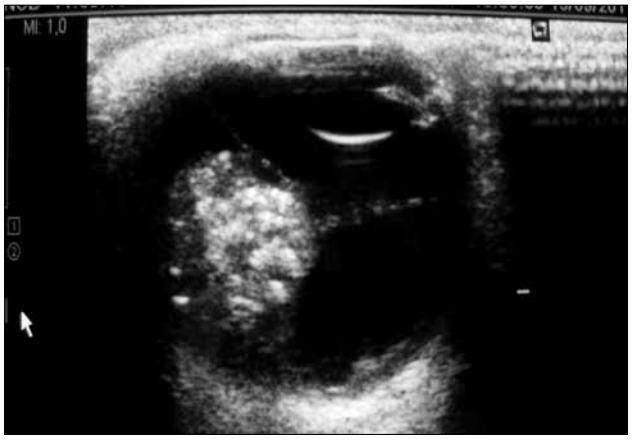

Figure 3. USG showing well-defined hypoechoic endophytic lesion with calcific foci and overlying retinal detachment in posterior segment in left eye.

17.3 mmHg with Schiotz tonometer in left eye. On USG, diffuse vitreous seeding is seen in right eye (Fig. 2) and well-defined hypoechoic endophytic lesion with calcific foci and overlying retinal detachment in posterior segment was seen in left eye (Fig. 3). Choroidal thickness of 1.4 mm in right eye and 1.6 mm in left eye was seen. On CT scan soft tissue mass with calcification was seen in both eyes (Fig. 4). No retrobulbar extension was seen. Family history was negative for retinoblastoma. After observing history, examination and finding on USG and CT scan diagnosis of retinoblastoma Group E in right eye and retinoblastoma Group D in left eye was made and child was referred to higher center for further management.

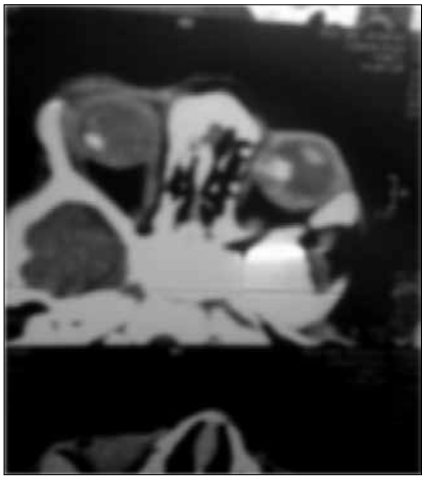

Figure 4. CT scan showing soft tissue mass with calcification in both eyes.

MANAGEMENT

The management of retinoblastoma needs a multidisciplinary team approach including an ocular oncologist, pediatric oncologist, radiation oncologist, radiation physicist and an ophthalmic oncopathologist. The primary aim is to save the life of a child. Management of retinoblastoma is highly individualized and depends upon age at presentation, laterality, tumor location, tumor staging, visual prognosis, systemic condition and socioeconomic status. Genetic counseling is an important aspect in the management of retinoblastoma.[6]

Current protocol suggests management of small intraocular tumors, unilateral or bilateral, by focal cryotherapy alone or in combination with standard dose 6 cycle chemotherapy with vincristine, etoposide and carboplatin. Focal therapy should be deferred until 6 cycles of chemotherapy for tumors located in visually crucial areas and residual disease is treated with transpupillary thermotherapy or plaque brachytherapy (iodine-125 [^{125}I] or ruthenium-106 [^{106}Ru] for 36-72 hours). Extensive disease described under Group D and E of International Classification System is managed by high-dose chemotherapy followed by aggressive focal

therapy. Primary enucleation should be considered in overt disease without salvageable vision. External beam radiotherapy using linear accelerator is delivered after high-dose chemoreduction in cases with residual orbital disease.[7] Cases with metastatic disease are usually managed on palliative grounds. CNS metastasis can be managed with high-dose chemotherapy along with intrathecal chemotherapy.[8] The recent advances such as identification of genetic mutations, early diagnosis and improved treatment modalities like chemoreduction with adjuvant focal therapy have contributed to better survival, improved eye salvage and potential for optimal visual recovery.

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