Recent Trends in Management of Retinoblastoma

An Essay

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Abstract

Retinoblastoma is a neuroblastic tumor. Retinoblastoma originates from the retinal neuroepithelium that can differentiate into almost any type of outer or inner retinal cell, including photoreceptors. It is the most common primary intraocular malignancy of childhood.

The clinical manifestations of retinoblastoma vary with the stage of the disease at the time of recognition. In its earliest clinical stage, a small retinoblastoma, i.e., less than 2 mm in basal dimension, appears ophthalmoscopically as a subtle, transparent or slightly translucent lesion in the sensory retina. Slightly larger tumors lead to dilated retinal blood vessels that feed and drain the tumor. Some larger tumors show foci of chalk-like calcifications that resemble cottage cheese. Any retinoblastoma of any size can produce a white pupillary reflex; what we call (leukocoria).

Key Words:

Definition, clinical picture and classification of retinoblastoma, Pathology, Differential diagnosis of retinoblastoma

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To My Wife Who Participate By Great Effort In This Assay

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Introduction

Retinoblastoma is the commonest primary eye tumor of the eye in childhood. Most children diagnosed with retinoblastoma are younger than 3 years old. Retinoblastomas are extremely rare in older children and in adults. This tumor may involve one (75% of cases) or both (25% of cases) eyes in a child. Untreated, retinoblastoma is almost always fatal, hence the importance of early diagnosis and treatment. Retinoblastoma occurs about equally in boys and girls and in different races and ethnicities. It also occurs equally in the right or left eye. It is now known that retinoblastoma can be inherited as a familial tumor in which the affected child has a positive family history of retinoblastoma or as a nonfamilial (sporadic) tumor in which the family history is negative for retinoblastoma. Most congenital or hereditary retinoblastomas are found during the first year of life, while non-inherited retinoblastomas tend to be diagnosed in the first and second-years olds (Abramson et al, 2008).

As the child does not complain of any poor vision, the tumor may remain undetected. The most common way of presentation is a white reflex (leukocoria) behind the pupil. This is sometimes called the cat's eye reflex. It may also present as squint, poor vision, painful red eye, inflammation of the tissue surrounding eye, protrusion of the eye ball (proptosis) etc. Occasionally it is detected on a routine eye checkup by an ophthalmologist, especially in a child with family history of this disease (Hurwitz et al, 2006).

Once a retinoblastoma is diagnosed, other tests may be done to check the exact position and size of the tumor, and whether it has begun to spread into surrounding structures. This is known as staging that will assist in deciding the best treatment option for the patient. Example of these tests includes ocular and orbital ultrasonography, computerized tomography, and magnetic resonance imaging (National Cancer Institute, 2008).

The management of retinoblastoma has gradually changed over the past few decades. There is a trend away from enucleation and radiotherapy toward chemoreduction and focal conservative treatments. Such conservative methods are vision saving and are known as salvage modalities (Abramson et al, 2008).

Aim of work

The aim of the work is to review the literature about recent trends in management of retinoblastoma.

DEFINITION, CLINICAL PICTURE AND CLASSIFICATION OF RETINOBLASTOMA

Retinoblastoma is a neuroblastic tumor. Retinoblastoma originates from the retinal neuroepithelium that can differentiate into almost any type of outer or inner retinal cell, including photoreceptors. It is the most common primary intraocular malignancy of childhood, with an incidence of approximately one in every 20,000, and affects males and females equally. The median age at diagnosis is 12 months in those with bilateral tumor and 24 months in those with unilateral disease (usually before the age of five years). Onset after five years of age is rare (Abramson et al, 2008).

The commonest presentation of retinoblastoma is white pupillary reflex (leucocoria). The child also may be presented with strabismus, occasionally by acute red eye and rarely by buphthalmos or pseudohypopyon. Untreated, retinoblastoma will grow and produce seeding in the eye, leading to retinal detachment and invasion of the orbit, optic nerve invasion, and central nervous system invasion. Metastases generally occur within 12 months. Most commonly, metastases occur through direct invasion of the central nervous system via the optic nerve. The tumor also may spread through the subarachnoid space to the contralateral optic nerve or through the cerebrospinal fluid to the central nervous system, as well as hematogenously to the lungs, bone, and brain (Hurwitz et al, 2006).

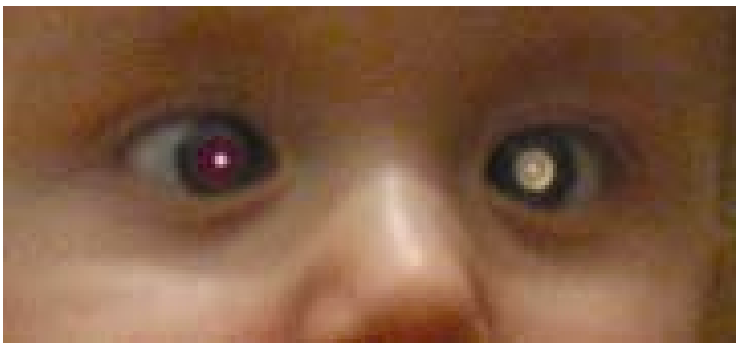

Fig (1) child with left leucocoria (Chuah et al, 2006).

Several classifications of retinoblastoma have been developed to assist in prediction of globe salvage. The most popular grouping and the mostly used in practice is the Reese-Ellsworth classification. This classification currently being developed to simplify the grouping scheme and allow a more practical

approach to judging results of chemoreduction and radiotherapy. Reese-Ellsworth classifies the tumor according to its response to chemoreduction and radiotherapy as follow:

Group I: very favorable

(a) Solitary tumor, less than 4 disc diameters in size, at or behind the equator.

(b) Multiple tumors, none over 4 disc diameters in size, all at or behind the equator.

Group II: favorable

(a) Solitary tumor, 4 to 10 disc diameters in size, at or behind the equator.

(b) Multiple tumors, 4 to 10 disc diameters in size, behind the equator.

Group III: doubtful

(a) Any lesion anterior to the equator.

(b) Solitary tumors larger than 10 disc diameters behind the equator.

Group IV: unfavorable

(a) Multiple tumors, some larger than 10 disc diameters.

(b) Any lesion extending anteriorly to the ora serrata.

Group V: very unfavorable

(a) Massive tumors involving over half the retina.

(b) Vitreous seeding (Abramson et al, 2008).

The most recent classification system for retinoblastoma is known as the international classification. The international classification for intraocular retinoblastoma that is used in the current Children's Oncology Group treatment studies, as well in some institutional studies, has been shown to assist in predicting those who are likely to be cured without the need for enucleation or external beam radiotherapy.

1-Intraocular retinoblastoma: there is cancer in one, or both, eyes but it has not begun to spread to other parts of the eye or into the tissues surrounding the eye. Intraocular retinoblastomas are sub-divided by means of the

international classification into five grades (A to E) depending upon the size and position of the tumor, and the extent of any damage to the eye. It gives the doctor more information to help them to plan appropriate treatment.

Group A: small intraretinal tumors away from foveola and disc.

* All tumors are 3 mm or smaller in greatest dimension, confined to the retina and

* All tumors are located further than 3 mm from the foveola and 1.5 mm from the optic disc.

Group B: all remaining tumors confined to the retina.

* All other tumors confined to the retina not in Group A.

* Tumor-associated subretinal fluid less than 3 mm from the tumor with no subretinal seeding.

Group C: discrete local disease with minimal subretinal or vitreous seeding.

* Tumor(s) are discrete.

* Subretinal fluid, present or past, without seeding involving up to one-fourth of the retina.

* Local fine vitreous seeding may be present close to discrete tumor.

* Local subretinal seeding less than 3 mm (2 DD) from the tumor.

Group D: diffuse disease with significant vitreous or subretinal seeding.

* Tumor(s) may be massive or diffuse.

* Subretinal fluid present or past without seeding, involving up to total retinal detachment.

* Diffuse or massive vitreous disease may include “greasy” seeds or avascular tumor masses.

* Diffuse subretinal seeding may include subretinal plaques or tumor nodules.

Group E: presence of any one or more of these poor prognosis features.

* Tumor touching the lens.

* Tumor anterior to anterior vitreous face involving ciliary body or anterior segment.

* Diffuse infiltrating retinoblastoma.

* Neovascular glaucoma.

* Opaque media from hemorrhage.

* Tumor necrosis with aseptic orbital cellulites.

* Phthisis bulbi (National Cancer Institute, 2008).

2-Extraocular retinoblastoma: the cancer has spread beyond the eye and into the tissue surrounding it or to other parts of the body.

3-Recurrent cancer: if the cancer comes back after initial treatment. It may come back in the eye, the tissue surrounding the eye, or in other parts of the body (National Cancer Institute, 2008).

*Prognosis:

Poor prognostic factors include a delay in tumor diagnosis, larger tumor, greater age, evidence of optic nerve involvement, and extraocular extension. Extraocular spread is the main factor that determines the prognosis. Almost all untreated patients die of intracranial extension and disseminated disease within two years. Survival rate is also affected by the development of second tumor especially osteogenic sarcoma. Reese-Ellsworth's classification is useful in predicting the tumor response to treatment but does not predict the survival rate (Hurwitz et al, 2006).

PATHOLOGY OF RETINOBLASTOMA

Retinoblastoma arises from primitive neuroectodermal cells exhibiting retinal differentiation. The tumor starts in any of the nucleated retinal layers. Early, the tumor is limited to the substance of the retina and then grows exhibiting one of the following growth patterns:

1-Endophytic retinoblastomas: grow mainly from the inner surface of the retina into the vitreous. As endophytic tumors grow large and become friable, tumor cells are shed into the vitreous. Tumor cells in the vitreous may seed onto the inner surface of the retina and invade into the retina. It is important to distinguish multicentric retinoblastoma from retinal seeding because the presence of multiple tumors indicates a germinal mutation. If the tumor lies mainly on the inner surface of the retina rather than within it, or if the tumor cell clusters are seen within the vitreous, retinal seeding is suggested. Tumor cells in the vitreous may also spread into the posterior chamber and then into the anterior chamber by aqueous flow. Secondary deposits on the lens, zonular fibers, ciliary epithelium, iris, corneal endothelium, and trabecular meshwork may be observed and tumor cells may follow the aqueous outflow pathways out of the eye (Apushkin et al, 2005).

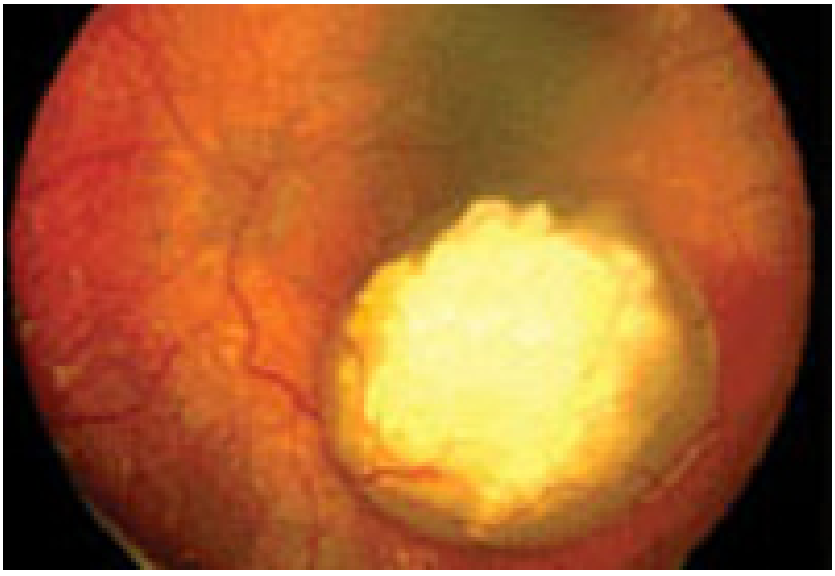

Fig (2) fundus picture of classic endophytic retinoblastoma (Mafee, 2006).

2-Exophytic retinoblastomas: grow primarily from the outer retinal surface towards the choroid, producing first an elevation and then a detachment of the retina. As the tumor grow lager, it may give rise to total retinal detachment and tumor cells may form subretinal exudate. Secondary implants then develop on the outer retinal surface where they can invade into the retina or the inner surface of the RPE. The implants then replace the RPE and eventually infiltrate through the Bruch membrane into the choroid. From the choroid, tumor cells escape along ciliary vessels and nerves into the orbit and conjunctiva. From there they gain access to blood vessels and lymphatics and metastasize (Hurwitz et al, 2006).

3-Mixed endophytic-exophytic tumors: are probably more common than either type alone, especially among larger tumors. The combined features of both endophytic and exophytic growth characterize these tumors.

4-Diffuse infiltrating retinoblastomas: are the least common. These tumors grow diffusely within the retina without greatly thickening it and without forming elevated mass. Tumor cells are discharged into the vitreous, often seeding the anterior chamber and producing a pseudohypopyon.

5-Complete spontaneous regression: is believed to occur more frequently in retinoblastoma than in any other malignant neoplasm. Typically, there is a severe inflammatory reaction followed by phthisis bulbi. The mechanism or mechanisms by which regression occurs are unknown (Abramson et al, 2008).

The tumor produces seeding in the eye and causes retinal detachment. As the tumor grows, it spread through invasion of the orbit, optic nerve invasion, and central nervous system invasion. Metastases generally occur within 12 months. Most commonly, metastases occur through direct invasion of the central nervous system via the optic nerve. The tumor also may spread through the subarachnoid space to the contralateral optic nerve or through the cerebrospinal fluid to the central nervous system, as well as hematogenously to the lungs, bone, and brain (Hurwitz et al, 2006).

Microscopically, retinoblastoma composed of dense masses of small round cells (dark blue) with hyperchromatic nuclei and scanty cytoplasm. Trabecular and nesting formation are common. Mitotic figures are typically numerous. As the tumor cells usually outgrow their blood supplies, necrosis and haemorrhage are common within the tumor. A sign of differentiation

toward retinal structure (although this is of little prognostic value) is provided by the presence of so-called Flexner Wintersteiner rosettes, Homer Wright rosettes and fleurettes. Flexner Wintersteiner rosettes are clusters of cuboidal or short columnar cells arranged around a central lumen. The nuclei are displaced away from lumen. Homer Wright rosettes show radial arrangements of cells around a central tangle of fibrils (pseudorosette). Fleurette are tumor cells with photoreceptor differentiation. The following features are commonly seen in retinoblastoma:

- Necrosis and haemorrage.
- Staining of the blood vessels (from the release of the DNA from necrotic retinoblastoma).
- Calcification (Apushkin et al, 2005).

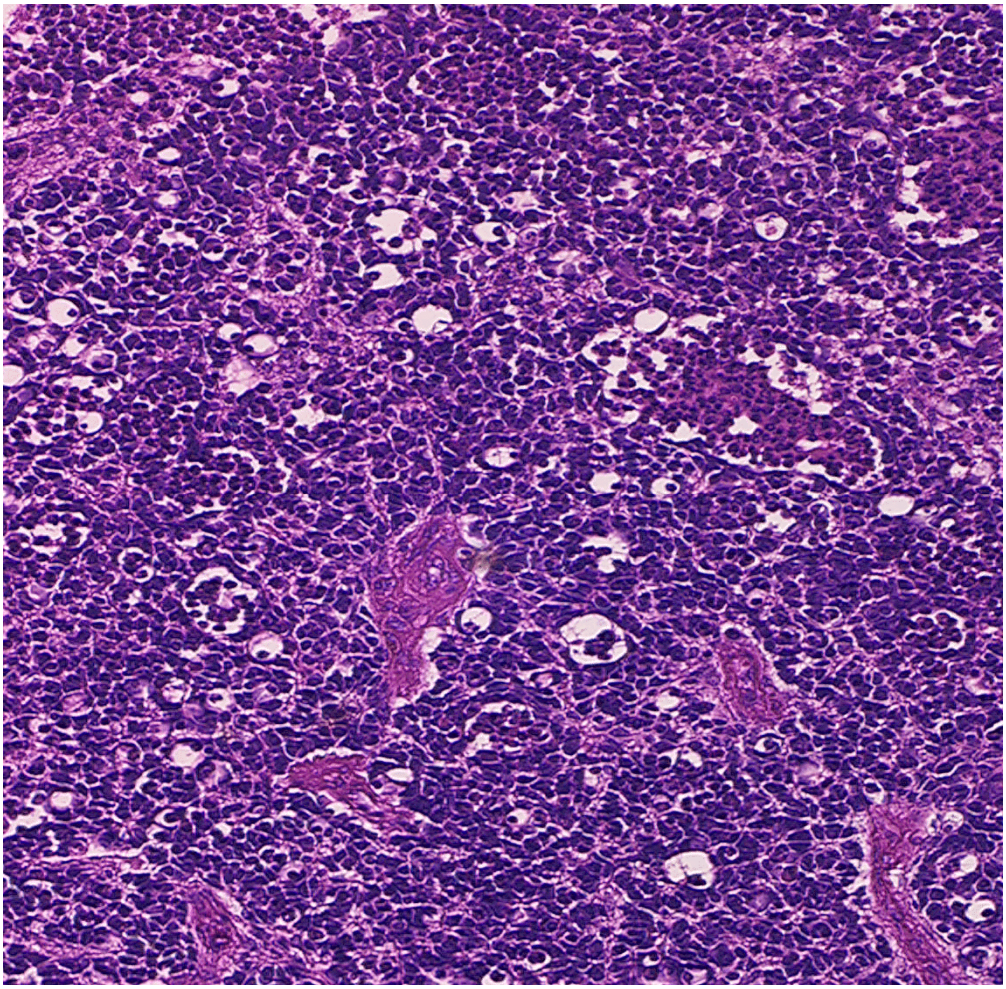

Fig (3) microscopic appearance of retinoblastoma (Hurwitz et al, 2006).

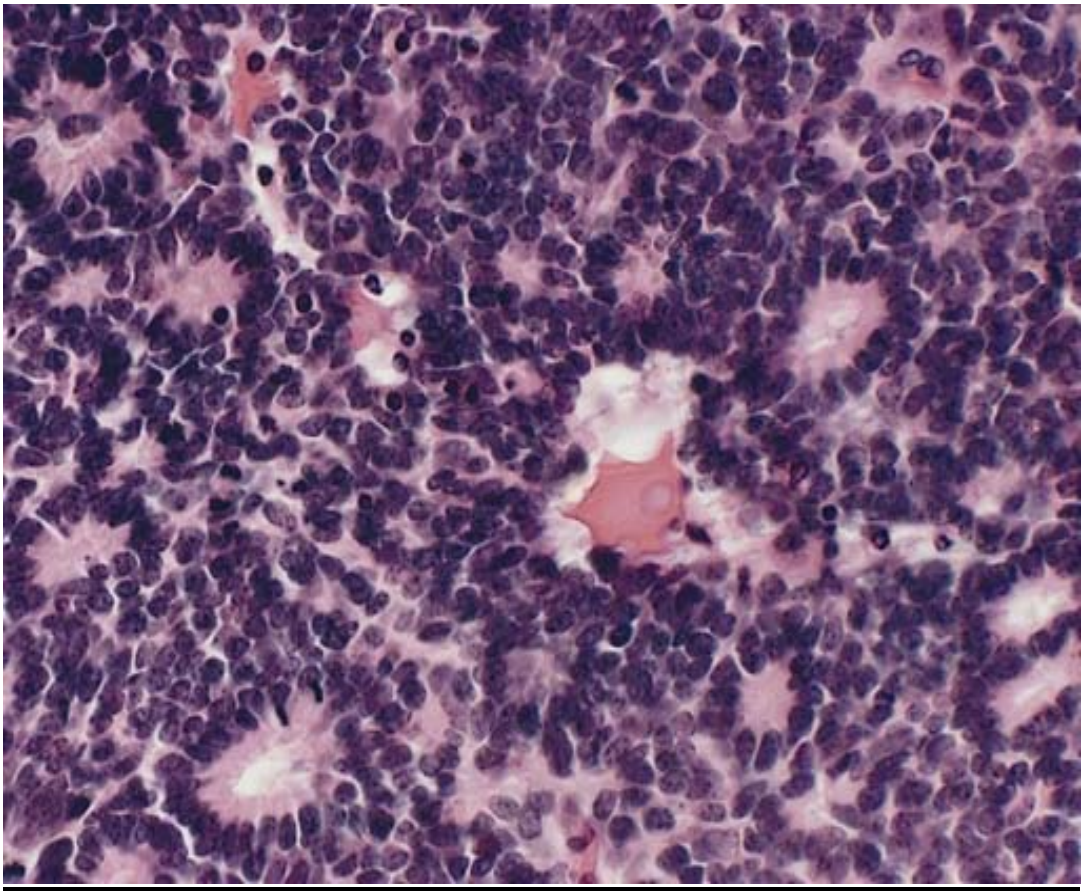

Fig (4) Flexner Wintersteiner rosettes (Hurwitz et al, 2006).

Pathologic Staging of Retinoblastoma:

1-Primary tumor:

*pT0: no evidence of primary tumor.

*pT1: tumor confined to retina, vitreous or subretinal space.

*pT2: minimal invasion of optic nerve and/or optic coats.

-pT2a: tumor invades optic nerve up to level of lamina cribrosa.

-pT2b: tumor invades choroids focally.

-pT2c: tumor invades optic nerve up to level of lamina cribrosa and invades choroids focally.