Study of conjunctival changes following treatment of retinoblastoma by radiotherapy and chemotherapy

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By
MUHAMMAD WAHID El-HAWARY
M.B.B.Ch.

Supervised by

Prof. Dr. OTHMAN ALI ZIKO
Professor of Ophthalmology
Faculty of Medicine
Ain Shams University

Lecturer Dr. MOMEN HAMDY
Lecturer of Ophthalmology
Faculty of Medicine
Ain Shams University

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بِسْمِ اللّهِ الرَّحْمـــَنِ الرَّحِيمِ

"قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ
الْعَلِيمُ الْحَكِيم"

"البقرة – آية ٣٢"

صدق الله العظيم

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Muhammad Wahid

To my mother who spent her lifetime just to see me in this place…

May her soul rest in peace.

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List of Abbreviations

®	Registered mark
µg	Microgram
ANOVA	Analysis Of Variance
CEV	Carboplatin, etoposide and vincristine
cGy	Centigray
CT	Computerized Tomography
ED	Eye drops
EUA	Examination under anesthesia
F	Fischer exact test
Fig.	Figure
GCD	Goblet cell density
gm	Gram
Gy	Gray
HPF	High power field
HS	Statistically Highly-Significant
IC	Impression cytology
LM	Light microscope
mg	Milligram
ml	Milliliter
mm	Millimeter
MRI	Magnetic Resonance Imaging
n	Number

N/C	Nucleus to cytoplasm ratio
NS	Statistically Non-Significant
P	Probability index
PAS	Periodic acid-Schiff
PFV	Persistent Fetal Vasculature
RB1	Retinoblastoma gene 1
ROP	Retinopathy of prematurity
SD	Standard deviation
SPSS	Statistical Package for Social Science
SS	Statistically Significant

REVIEW OF LITERATURE

Retinoblastoma is the most common primary intraocular malignant tumor of childhood; representing approximately 4% of all pediatric malignancies, second only to uveal melanoma as the most common primary intraocular malignant tumor in all age groups. The frequency of retinoblastoma ranges from 1 in 14,000 to 1 in 20,000 live births, depending on the country. There is no sexual predilection, and the tumor occurs bilaterally in 30%-40% of cases. Approximately 90% of cases are diagnosed in patients younger than 3 years. The mean age at diagnosis depends on family history and the laterality of the disease. Over 95% of children with retinoblastoma in the United States and other medically developed nations survive their malignancy, whereas about 50% survive worldwide. The reason for the poor survival in undeveloped nations relates to late detection of advanced retinoblastoma, often presenting with orbital invasion or metastatic disease. **(Rodrigues et al, 2004 and Rosa et al, 2011)**

Retinoblastoma is typically diagnosed during the first year of life in familial and bilateral cases and between ages 1 and 3 in sporadic unilateral cases. Onset later than age 5 is rare but can

occur. A retinoblastoma is a neuroblastic tumor, biologically similar to neuroblastoma and medulloblastoma. Diagnosis of retinoblastoma can usually be based on its ophthalmoscopic appearance. Intraocular retinoblastoma can exhibit a variety of growth patterns; like intraretinal growth, endophytic growth, exophytic growth or occasionally diffuse infiltrating growth pattern. **(Raab et al, 2011)**

Retinoblastoma results from malignant transformation of primitive retinal cells before final differentiation. Because these cells disappear within the first few years of life, the tumor is seldom seen after 3 years of age. The gene predisposing to retinoblastoma (retinoblastoma gene RB1) is found at location 13q14. **(Kanski et al, 2011)**

It is 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. Approximately 6% of newly diagnosed retinoblastoma cases are familial and 94% are sporadic. All patients with familial retinoblastoma are at risk to pass the predisposition for the development of the tumor to their offspring, but the manifestations are only 80% penetrant. Retinoblastoma is generally classified into: familial or sporadic, bilateral or unilateral, and hereditary or non hereditary. **(Shields et al, 2006)**

An association of neuroblastic intracranial malignancy exists in patients with the hereditary form of retinoblastoma, most often manifesting as pineoblastoma or other parasellar tumors. The pineoblastoma is identical to retinoblastoma from an embryologic and pathologic standpoint. This association of midline intracranial pineal tumors and suprasellar or parasellar neuroblastic tumors with bilateral retinoblastoma has been termed "trilateral" retinoblastoma. **(Bader et al, 1980**)

Spontaneous regression of retinoblastoma is also possible and can be asymptomatic, resulting in the development of a benign retinocytoma, or it can be associated with inflammation and, ultimately, phthisis bulbi. **(Raab et al, 2011)**

CLINICAL PRESENTATION

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 **(Fig. 1)**. Some larger tumors show foci of chalk-like calcification that resemble cottage cheese. A retinoblastoma of any size can produce leukocoria. **(Shields and Shields, 1999 b)**

Figure 1: Medium sized retinoblastoma **(Lorenz and Moore, 2006)**

The most common presenting sign is leukocoria (white pupillary reflex), which is usually first noticed by the family and described as a glow, glint, or cat's-eye appearance **(Fig. 2 and 3)**. Approximately 25% of cases present with strabismus (esotropia or exotropia) **(Fig. 2)**. It may also present with ocular inflammation. The diagnosis of retinoblastoma can generally be suspected on the basis of an office examination with documented visual acuity. An examination under anesthesia (EUA) is needed in all patients suspected of having retinoblastoma to permit a complete assessment of the extent of ocular disease prior to treatment. **(Rosa et al, 2011)**