

## Unilateral Leukokoria (White Puppillary Reflex) in a Four Year Old Male Child

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### CASE REPORT:

A young boy, Qamar Abbas four years old, presented at Sheikh Zayed Hospital Eye O.P.D. with white pupil in the right eye on 19th January, 1988.

Examination revealed no perception of light in the right eye. Biomicroscopy revealed a few cells in the anterior chamber and a yellowish-white exudative mass in the lower temporal quadrant of the anterior chamber. In addition there was rubeosis iridis of the temporal half of iris and a dilated, non-reacting pupil with marginal ectropion uveae. The lens was clear and retrolental space displayed a yellowish-white mass. There was no red reflex. The left eye was normal.

Ultrasonography (B-Scan) of the right eye revealed total retinal detachment with echogenic areas suggestive of intra-ocular calcification.

A firm clinical diagnosis of retinoblastoma was made. On further questioning, the father admitted that the patient had visited Lahore in October, 1987 and was advised enucleation by various Ophthalmic Surgeons. But there was a grievous delay of 3 months due to parental hesitation. Enucleation of the right eye was carried out on 20-01-1988. The growth was confined to the globe which was enlarged, hence we were unable to get sufficient excision of optic nerve.

The specimen was sent for histopathology. Grossly on section, there was total retinal detachment with pus in the posterior segment. Optic nerve length was 0.3 cm. Microscopically, there were Flexner-Wintersteiner rosettes typical of well differentiated retinoblastoma. Distal and of rotsettes optic nerve was heavily infiltrated with tumor cells. The patient was referred to INMOL for Radiotherapy which was carried out after the wound had healed.

A total dose of 4,000 Rads was given in ten divided doses, three times a week.

Followup lumbar puncture and bone marrow exami-

nation revealed no tumor metastasis. We plan to keep following the case.

Family members were also examined and we found no clinical evidence of tumor in the siblings.

Leukokoria or white pupillary reflex in a child is a challenging situation for an ophthalmologist.

Retinoblastoma is the most common intra-ocular malignancy of childhood, followed by leukemia and neuroblastoma. It comprises 3% of all malignant tumors of childhood. After uveal malignant melanoma (40%) and metastatic carcinoma, it is the most common intra-ocular malignancy (30%) in all age groups.

It has a frequency of 1:17000 to 1:34000 live births and an incidence of 250-300 new cases/year in the U.S. There is no predilection for sex, and if any there is a slight male preponderance. There is no particular racial preference, though coloured races are rarely affected.

The tumor is bilateral in 20-30% of cases, with an average age of detection 18 months. 42% are detected in the first 2 years of life and 64% in the first 3 years, and rarely after 7 years of age (range 1mo-48 years). The 2nd eye is involved after several months to years.

Retinoblastoma is familial in 6% of cases and sporadic in 94%; it represents a genetic mutation in 25% of cases and a somatic mutation in 75%.

Bilaterality of the tumor is a pointer to its hereditary nature and of genetic mutation and transmissibility. The inheritance is autosomal dominant with 80% penetrance.

There are a host of associated neoplasms, e.g. leukemia, lymphoma, osteogenic sarcoma etc. Certain chromosomal anomalies like trisomy-13 and trisomy-21 are also

documented associations.

Basically the tumor cells in retinoblastoma arise from neurosensory retina, Hence there is a tendency to return to the parent tissue architecture.

The degree of differentiation of the tumor has no prognostic significance. However, it does determine the regression pattern. The histologic hall-mark of differentiation is Flexner-Wintersteiner Rosette, composed of columnar or cuboidal tumor cells, arranged in a radial fashion around a central lumen which contains an acid muco-polysaccharide substance. This substance is similar to the one which surrounds the rods and cones in normal tissue.

There is electron-microscopic evidence of minute processes which protrude into the lumen of the rosette representative of outer photo receptor elements.

A pseudo-rosette is in contrast an aggregation of tumor cells around a blood vessel; cells distant from the core show necrosis.

A Homer-White rosette of neuroblastoma has no acid muco-polysaccharide in the lumen.

There can be secondary calcification in those tumor areas which undergo ischemic necrosis. This is a much sought clinical clue displayed radiologically or on B-Scan Ultrasonography.

Retinoblastoma has four clinical stages according to progression of the disease. There is an initial quiescent stage which lasts for about 6 months, followed by glaucoma and buphthalmos. Next there is extraocular local spread by extension to orbital bones, regional lymph nodes, optic nerve and brain. Lastly blood borne metastasis takes place, mainly skull bones (50%), viscera (50%) and lymph nodes (33-50%) of cases.

Grossly, the tumor can stay confined to or grow out of the globe i.e. have endophytic or exophytic type of growth, respectively.

The tumor may spread to the choroid by invasion along subretinal space. Volume of choroidal invasion has prognostic significance, and this carries a mortality of 62%; or else the tumor can grow along the optic nerve and invade the sub arachnoid space and thereby gain access to the central nervous system.

The tumor presents most frequently as a Leukokoria in a young child. Other presentations include an esotropia, loss of vision and secondary glaucoma. The tumor necrosis can present as orbital cellulitis, exophthalmos, eyelid edema, conjunctival chemosis and conjunctivitis. Corneal involvement presents as photophobia. There can be heterochromia iridis and granulomatous uveitis leading to phthisis bulbi. The role of E.U.A. with well dilated pupils can not be over emphasized. Both eyes should be thoroughly examined.

The tumor when visible has a creamy colour, smooth or irregular surface, with overlying yellow fatty exudate or superficial stromal hemorrhage. Stromal calcification has a gray white translucent appearance while that on surface has a cottage cheese pattern.

In case the tumor cannot be visualized due to overlying inflammation, vitreous hemorrhage or retinal detachment, ancillary diagnostic methods can be employed.

X-ray Orbit can reveal intra-ocular calcification which can also be documented sonographically by B-Scan ultrasound. The latter can reveal the cystic or solid nature of the growth. Serial B-Scans can help document progression of the tumor.

C.T. scan is even more precise in this context.

Anterior chamber paracentesis for examination of cells and estimation of aqueous/serum LDH ratio is also helpful, but is mainly a research tool.

P[32] uptake which is based on increased uptake of radioactive material by the metabolically highly active malignant cells, carries a risk of radiation exposure.

FFA can help in case the tumor is being followed after local treatment.

Bone marrow and CSF examination are meant to establish the metastatic status of the tumor.

## TREATMENT

Various treatment modalities available are listed in Table-1. The choice depends on the stage at which the case presents. A correlation of presentation of the case to prognosis with the type of treatment is listed in Table-2.

It is to be remembered that most of the cases presenting early have a family history and are hereditary;

those presenting late, comprising about 95% are of sporadic nature.

**TABLE-1  
THERAPEUTIC MODALITIES**

-	Enucleation/Exenteration
-	Radiotherapy
-	Chemotherapy
-	Photo-coagulation
-	Cryotherapy
-	Cobalt-60 Plaques/Radon Seeds

Group 4 and Group 5 patients are treated by enucleation. A sufficiently long portion of optic nerve, approximately 100 mm, should be excised, as it is of prognostic significance.

**TABLE-2  
PROGNOSIS FOR SUCCESSFUL TREATMENT  
(REESE AND ELLSWORTH)**

Group-I	Very Favourable
	A. Solitary tumor less than 4 disc diameter (DD) in size, at or behind equator.
	B. Multiple tumors, none over 4 DD in size, all at or behind equator.
Group-II	Favourable
	A. Solitary tumor 4 to 10 DD in size, at or behind equator.
	B. Multiple tumors 4 to 10 DD in size, behind equator.
Group-III	Doubtful
	A. Any tumor anterior to equator
	B. Solitary tumor larger than 10 DD behind equator.
Group-IV	Very Unfavourable
	A. Multiple tumors, some larger than 10 DD in size.
	B. Any lesion extending anteriorly to the ora serrata.
Group-V	Very Unfavourable
	A. Massive tumors involving over half the retina
	B. Vitreous seeding.

In addition, if there is orbital involvement exenteration has to be carried out as well.

Radiotherapy plays a significant role, both as primary as well as an adjunctive modality. Primary radiotherapy can be utilized in Group-1,2 and possible 3. Usual dose is 400 Rads, thrice a week, for 3 weeks i.e. a total dose of 3600 Rads delivered through alternating temporal and nasal portals.

Here the over all prevalent dilemma of a well differentiated tumor being localized but radio resistant is faced i.e. cases showing F-W rosettes show a poorer response.

Complications of radiotherapy include skin damage, vascular necrosis, secondary tumors, intra-ocular hemorrhages, secondary glaucoma, endophthalmitis and cataract. But with supervoltage radiotherapy, due to accurate placement and delivery, the danger of these complications is relatively less. However risk of secondary tumors, especially osteogenic sarcoma is increased.

Well differentiated tumors should lose their pink colour and elevation; while poorly differentiated ones should have a cottage cheese appearance as evidence of regression.

Cryotherapy, photocoagulation, Radon seeds and Cobalt plaques are meant either as primary treatments for Group 1 or 2 tumors, or prior to second dose of radiotherapy. They have the disadvantage of sparing microscopic metastases. The tumor must disappear after successful treatment and be replaced by fibro-calcific areas.

In short, cases with unilateral involvement in Group 1 or 2 have a positive family history and respond to local treatment by radiation, photo coagulation or cryotherapy, but need careful followup. Unilateral Group 4 or 5 cases need enucleation.

In bilateral assymetric cases, the more involved eye should be enucleated, while the less involved one, if in group 1 or 2 should have local treatment, initially.

In bilateral symmetrical cases, with advanced growth, bilateral enucleation or crossed temporal and nasal portal irradiation should be tried; although the latter needs extreme caution regarding detection of spread beyond the globe. In cases of microscopic involvement of excised end of optic nerve, about 5000 Rads are to be delivered to orbital apex.

In case of gross involvement, in addition to above, 3000 Rads to the brain should also be administered.

In either case, intrathecal methotrexate 0.5 mg/kg should also be given.

## PROGNOSIS

The prognosis depends on optic nerve, orbital and systemic involvement. Involvement of optic nerve upto lamina cribrosa carries a mortality of 8%, that of lamina cribrosa 15%, of retrolaminar portion 44% and it rises to 65% in case distal cut end is involved. Orbital spread has a survival rate of 9% and necessitates exenteration or radiotherapy and chemotherapy. Systemic metastases carries a 100% mortality.

Careful & meticulous followup of retinoblastoma cases can never be over-emphasized. Initial followup of 4-6 weeks twice and then every 4-6 months for 3 years is the minimum. After age 5, yearly followup is to be continued for life.

Family members should also be screened at the earliest; not only the siblings but also the parents for evidence of healed scars of regressed tumors. If any other family members have suggestive histories these should be taken into consideration for the purpose of genetic counseling.

Q. What are the considerations in followup of this case. (Dr. Pervaiz Iqbal, Department of general surgery),

A. After the patient had enucleation and orbital radiotherapy, we did a lumbar puncture and bone-marrow examination to rule out metastasis.

We plan to keep a close watch on the other eye of the patient. This will involve clinical examination of left retina under full mydriasis. Frequency of visits initially will be 4-6 weeks twice, then six months and yearly follow-up afterwards. Such patients also have an increased tendency of secondary neoplasms especially after radiotherapy which is an important clinical consideration.

Q. In case of inadequate optic nerve excision i.e. distal end infiltration with tumor cells which can be confirmed by frozen section is it possible to go for the optic nerve through craniotomy.

(D. Attique-ur-Rehman, maxillo-facial surgeon).

A. Adequate optic nerve excision was difficult in our case because of a enlarged globe which hindered good exposure. Professor Naeem-ur-Rehman from Dept. of Neurosurgery commented that it is possible to dissect the optic nerve upto the optic chiasma via a trans-frontal craniotomy approach.

## REFERENCES

1. Puklin, J.E. and Apple, Dj. In *Principles and practice of Ophthalmology*, W.B. Saunders and company Philadelphia, 1980. 1136-48.
2. Ellsworth, RM: Treatment of retinoblastoma *AMJ. Ophthalmol* 1986; 66:49-51.
3. Tso mom, Zimmerman LE, Fine BS: The nature of retinoblastoma: I. Photoreceptor differentiation: A clinical and histopathologic study. *Am J ophthalmol* 69:339-359.