Bilateral Retinoblastoma: Early detection and treatment with intraarterial chemotherapy of a six-month-old  
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Abstract:
A six-month-old female presents with leukocoria and is diagnosed with bilateral retinoblastoma. The patient is ultimately treated with intraarterial chemotherapy within one week of diagnosis with expected good vision in the least affected eye.

I. Case History
   a. Demographics: A six-month-old of mixed ethnicity (Caucasian, Jewish, and Asian) female presented to the University Eye Center.
   b. Chief Complaint: First eye exam through an InfantSee referral because her mother was worried about a picture taken a few days/weeks prior that showed unequal red reflexes. (image1) Her pediatrician’s evaluation of the eyes nine days prior to our examination was unremarkable.
   c. Ocular and Medical History: The patient had no prior medical problems. She was born full term and weighed 7 lbs. 5 oz. She received an MRI shortly after birth due to a fall she suffered during home delivery. The findings of that MRI were unremarkable. There is a family medical history of melanomas (paternal grandmother and paternal great-grandfather) and lung cancer (maternal great-grandmother). She has a positive family ocular health history of esotropia and amblyopia (father) and glaucoma (maternal grandmother). There is no family history of retinoblastoma. She was not conceived through IVF and presented with no developmental delays.
   d. Medications: none

II. Pertinent Findings
   a. Initial clinical examination findings:
      i. Bruckner: Leukocoria OS
      ii. Dry Retinoscopy OD: +0.75DS, OS: +14.00DS
      iii. Hirschberg: No strabismus/aligned
      iv. 10 prism diopter test: No alternating fixation
      v. Dilated fundus examination: OD: flat posterior pole OS: large elevated white mass posterior pole
   b. Clinical examination findings at Memorial Sloan Kettering Cancer Center (MSKCC) under anesthesia:
      i. OD: Reese Ellsworth classification Ib; Two small tumors in right eye in the superior arcades. (image2) ERG: near normal levels.
      ii. OS: Reese Ellsworth classification Vb: 5 masses with inferior temporal subretinal seeding. (image 3) ERG: 25-30% of normal.

III. Differential Diagnosis
   a. Primary: Coats Disease
b. Others: ROP, Toxocariasis, PHPV, Astrocytic Hamartoma, Norrie’s Disease, Coloboma, and Congenital Cataract

IV. Diagnosis and Discussion:

a. Retinoblastoma

Retinoblastoma (Rb) is the most common primary ocular malignancy in childhood and yet it accounts for only 4% of pediatric malignancies (4). The incidence in the US is one per 18,000 live births, or 350 cases per year of which 30% are bilateral (2). The average age of diagnosis is 12 months for bilateral disease and 24 months for unilateral disease (3). Left untreated, the condition is fatal, but with modern treatments, the survival rate is over 90% (3). Only about 10% of patients have a previous family history meaning 90% of patients are thought to be new mutations (2).

In the early 1970’s Kundson first proposed a “two hit” theory of Rb development. In Rb, both alleles of RB1, the Rb gene, are mutated. Hereditary tumors are more likely to result in bilateral or multifocal tumors. The bilateral tumors usually present with one large tumor and smaller tumors in the other eye. Also, the hereditary form is more likely to be accompanied by retinomas, second nonocular malignancies, and ectopic intracranial retinoblastoma, which is why the infant should not be exposed to radiation at an early age. Nonheritable retinoblastomas are usually single and found later in childhood. The latest unilateral Rb has been found is 44 months old (3).

Extensive research is always ongoing concerning the RB1 gene since it is the first tumor suppressor gene to be cloned. Knudson’s “two-hit” theory has been widely accepted, but current research shows that the process going on is far more complicated and is being studied in detail. Current research claims that horizontal cells may be the cells of origin and that they can clone after differentiation (4).

In the past, patients with extensive ocular involvement limited to the globe were either enucleated or treated with extensive radiation. Enucleation creates huge psychological trauma for the patient and parents, but it is very successful at preventing the metastasis of the malignancy. External beam irradiation is effective at curing retinoblastoma, but it causes a very high rate of primary tumors elsewhere which give a poor prognosis of survival, especially when administered at less than twelve months old (3).

Currently, direct treatment of the tumor with intraarterial chemotherapy, used concurrently with laser coagulation and cryotherapy, gives an excellent prognosis of survival and eradication of the tumor for many cases (4).

Intraarterial chemotherapy involves catheterization of the femoral artery under anesthesia. The catheter is then guided into the ipsilateral carotid artery and subsequently into the ophthalmic artery using a micro catheter. Once in place, a dose of chemotherapy is infused for 30 minutes. The catheters are then
withdrawn and the child is awakened from anesthesia, observed for six hours, and typically discharged the same day (1).

Treatment involves multiple applications of the chemotherapy and exams under anesthesia every 4-6 weeks for up to a year after signs of active tumor. This allows the infant to keep his/her eye and have a lower chance of tumors later in life, while minimizing unwanted side effects of treatment (3).

The standard management for an eye with advanced Rb with a Reese-Ellsworth classification of Va and Vb is enucleation. However, intraarterial chemotherapy is now being used successfully to treat these eyes and salvage globes, which prevents compromise in orbital bone growth and improves the overall cosmetic appearance in these patients (2).

V. Treatment and Management

a. Plan:
After the initial examination, the patient’s parents were apprised of the findings and referred the same day to New York Eye and Ear Infirmary. They were consequently referred to Memorial Sloan Kettering Cancer Center where the infant was examined three days later under anesthesia. After the examination at MSKCC, a diagnosis of bilateral retinoblastoma was made, and the patient’s parents were presented with the treatment options. The standard management for an eye with advanced retinoblastoma with a Reese-Ellsworth classification of Vb is enucleation; however, the parents were presented with the option to treat with intraarterial chemotherapy in both eyes—potentially salvaging the left globe. That same day the small masses OD were treated with laser (A10 nm) and the subretinal seeding OS was treated with cryo-therapy to prevent ciliary body invasion. An MRI was ordered and they were scheduled to begin intraarterial chemotherapy in both eyes within the next few days. MRI has since come back normal without signs of metastasis. Intraarterial chemotherapy was successfully administered to the left eye. The right eye had complications and the intraarterial chemotherapy was aborted. The patient was brought back to attempt the right eye a second time. The results of that treatment are unknown to the authors at this time.

b. Prognosis:
The patient has an excellent chance of survival with intraarterial chemotherapy and has the potential for salvaging the left globe. It is also predicted that she will retain good vision in the right eye.

VI. Conclusion

There are many aspects that the optometrist must take away from this case. InfantSee is a worthwhile program that provides a comprehensive eye assessment
within the first year of life at no cost to the family (5). All infants should be given a full exam including dilation. Once a suspected finding of retinoblastoma is found, the referral should be urgent and scheduled for within a week of seeing the patient. The optometrist should always have a current referral list for rapid referral once retinoblastoma or other emergent conditions are suspected.

VII. Image Index

a. Image 1: Leukocoria OS noted by mother.

b. Image 2: Two small lesions superior arcades OD.
c. Image 3: Mass OS with inferior subretinal seeding.

References:


