Retinoblastoma in an Adult

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Abstract

Retinoblastoma is a rare malignant tumor of the retina usually seen in children before 5 years of age. The tumor is extremely rare in adults. We report here an unusual case of retinoblastoma in a 55-year-old adult female who presented to us with an orbital mass at a late stage of the disease. Detailed laboratory investigations and imaging studies could not make a precise diagnosis. The treating ophthalmologist suspected primary intraocular tumor, metastatic carcinoma, malignant melanoma, or lymphoma and referred the patient for fine needle aspiration cytology (FNAC). Cytopathological examination of Giemsa-stained FNAC smear was consistent with that of retinoblastoma and established the diagnosis.

Keywords: Fine needle aspiration cytology, noncontrast computed tomography scan, retinoblastoma

Introduction

Retinoblastoma is the most common ocular malignancy of childhood usually presenting in children before 5 years of age with an incidence rate of 1 in 15000 to 18000 live births.[1] This tumor is extremely rare in adults. Ever since the first case of retinoblastoma reported in an adult in 1929 by Verhoeff[2] there have been only 30 case reports of retinoblastoma in adults.[3,4] We report a rare case of unilateral retinoblastoma with cytopathological confirmation in a 55-year-old woman.

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**Case Report**

A 55-year-old female presented to the ophthalmology department of the hospital with complaints of a painful swelling in the left eye. The swelling had been gradually increasing in size over the last 8 months with dull continuous pain in the eye and periocular area. There was progressive diminution of vision for the last 6 months in the affected eye, and at the time of presentation in the hospital, the affected eye was completely blind. The progressive increase in the size of the swelling and pain in and around the eye compelled the patient to avail hospital services. The treatment history was not significant. The patient was being treated by a local doctor with eye drops and certain oral medicines the records of which were not available with her. She did not have any history of significant ocular disease or any ophthalmic surgery. There was no history of similar disease in the family.

On examination, an intraorbital mass protruding from the left eye was visible. Axial proptosis with stretched out sclera along with dilated blood vessels covering the entire exposed part of the eye ball was seen. The underlying cornea was barely visible through the widened palpebral aperture with hyperemic keratinized conjunctiva tissue. The swelling was more prominent in the region superior to the upper eye lid. The skin appeared stretched along with dilated vessels in the superior part of the eye ball [Figure 1a]. On palpation, the mass was tender and soft in consistency. Fundus examination was not possible because of overlying vascularized keratinized tissue over cornea. The intraocular tension was also not recorded because of these reasons. The status of the pupil of the diseased eye could also not be commented upon, even though it appeared slightly dilated. The patient had no perception of light in the left eye. Ophthalmological examination of the right eye did not show any abnormality both in the anterior as well as in posterior chamber. The fundus examination of the right eye was normal. The intraocular tension of right eye was also normal.

Systemic examination of the patient was normal. Breast examination and gynecological examination were also normal. Clinically, at that stage, differential diagnoses of metastatic carcinoma, astrocytoma, and adult-onset retinoblastoma were considered by treating ophthalmologist and investigations were planned.

Blood examination was within normal limits. This included hemoglobin values, total leucocyte count, differential leucocyte count, and erythrocyte sedimentation rate. Peripheral blood smear was normal. The kidney function tests, liver functions tests, serum alkaline phosphatase, serum calcium, and serum phosphorus were normal. Urine examination was also normal. Electrocardiogram was also normal.

Noncontrast computed tomography (NCCT) scan off the orbit and Para Nasal Sinuses (PNS) revealed marked left proptosis with markedly expanded left ocular globe by a hyperdense mass, few cystic components with extension into left anterior cranial fossa, left anterior ethmoid, left frontal sinus, left frontal fossa soft tissues with destruction of left orbital walls, and great wing of sphenoid bone [Figure 1b]. A precise diagnosis was not possible based upon CT findings. The radiologist considered provisional diagnosis of primary intraocular tumor, metastatic carcinoma, malignant melanoma, or lymphoma and advised further investigations. Chest CT and abdomen ultrasonography were carried out and found to be normal. The patient was referred to us for fine needle aspiration cytology (FNAC) at this stage.

FNAC was done using a 22-gauze needle. Smears were prepared, air dried, and stained with Giemsa stain and Periodic Acid Schiff’s stain (PAS stain). The microscopic examination of Giemsa-stained smears showed small, round cells in cluster and rosettes formation, suggestive of retinoblastoma [Figure 2a]. PAS positive granules in the cytoplasm of tumor cells were seen in PAS-stained smears, consistent with the diagnosis of retinoblastoma [Figure 2b].

**Discussion**

Retinoblastoma is a rare malignant neoplasm originating from the photoreceptor precursor cells of the eye, presenting usually in early childhood with an incidence rate of 1 in every
| Author/year         | Clinical Presentation                                      | Age/sex | CT scan/USG/MRI | FNAC                          | Biopsy/IHC                                      |
|-------------------|-----------------------------------------------------------|---------|----------------|-------------------------------|------------------------------------------------|
| Verhoeff, (1929)  | Snowflakes before left eye, loss of vision for one week, no pain but feeling of numbness on left side of head | 48/M    | NA             | NA                            | Abundance of rosettes in the growth IHC- NA     |
| Biswas et al. (2000) | All 3 patients presented with endophytic tumors with vitreous seeds | 32/M, 21/M, 25/F | USG showed calcification in one and no calcification in two cases | NA               | Retinoblastoma, which was endophytic, well-differentiated, with Homer-Wright rosettes IHC with neuron specific endolase used in two cases on biopsy sample |
| Singh et al. (2011) | Sudden painless diminution of vision in the right eye, of three days’ duration Unilateral endophytic retinoblastoma | 29/F    | On CT scan, Endophytic soft tissue mass emanating from the retina, with foci of calcification without any optic nerve or extraocular involvement | NA               | Histopathological examination confirmed the diagnosis of retinoblastoma, which was endophytic, well-differentiated, with Homer-Wright rosettes, and no choroidal or optic nerve invasion IHC- NA |
| Nag (2014)        | Study was to assess the role of FNAC in Orbital lesions  | All age group | CT showed intraocular tumors | CT/USG-guided FNAC done | Comparison with Histopathology, FNAC has sensitivity of 86.6%, specificity 100%, and positive predictive value 100% |
| Sharifzadeh et al. (2014) | History of diminished vision in left eye since 7 months along with redness which did not respond to topical medications | 29/F    | MRI showed an enhancing nodular mass lesion in the posterior aspect of the left globe protruding into the vitreous and associated with exudative or nearby hemorrhagic retinal detachment | FNAC Sample inadequate for reporting | Flexner-Wintersteiner rosette formation IHC stains positive for neuron-specific enolase (NSE), retinoblastoma protein and synaptophysin and negative for human melanoma black 45 (HMB45) and leukocyte common antigen in the tumor cells |
| Yacoub (2014)     | Gradual painless visual loss in the right eye associated with floaters for one month | 23/M    | CT revealed an inferior solid mass with intratumoral calcifications, with no signs of extra ocular extension | NA              | Histopathology of the enucleated eye showed differentiated retinoblastoma, displaying Homer-Wright rosettes and Flexner-Wintersteiner rosettes with no choroidal or optic nerve invasion IHC-NA |
| Zhang (2015)      | floaters in the left eye 1 year before, and was diagnosed with “glaucoma OS” Then the patient’s visual acuity began to decrease | 45/M    | USG showed vitreous opacities and intraocular elevated lesions with moderate reflective echoes and absence of calcification | Vitreous cytology showed small malignant cells. | Small cell neuro endocrine carcinoma of the left eye. IHC staining: CgA (+), Syn (+), NSE (+), CD56 (NK-1) (+), S-100 (−), GFAP (−), HMB45 (−), LCA (−), Melan-A (−), p53 (−), Ki-67 (index 20%). The final diagnosis was undifferentiated retinoblastoma |
| Present case (2015) | History of gradually increasing swelling in left eye with pain in the eye and peri-orbital area. Progressive loss of vision over for last six months leading to complete blindness | 55/F    | CT revealed marked left eye proptosis with extension of tumor into left anterior cranial fossa, left anterior ethmoid, left frontal sinus, left frontal fossa soft tissues with destruction of left orbital walls and great wing of sphenoid bone | Giemsa Stain smears showed small, round cells in cluster and rosettes formation. PAS positive granules in the cytoplasm of tumor cells were seen | Surgery was not performed due to very advanced disease. Biopsy sample/IHC were not possible |

*CT: Computed Tomography, MRI: Magnetic Resonance Imaging, USG: Ultrasonography, IHC: Immunohistochemistry, PAS: Periodic Acid Schiff’s reagent, NA: Not available
15000 to 18000 live births. The tumor can be either heritable with a germline mutation of the \textit{RB1} gene or nonheritable. Heritable mutations typically present in the first year of life with bilateral disease. In comparison, the nonheritable form typically presents slightly later and is primarily unilateral.\textsuperscript{[5]} The retinoblastoma gene was the first tumor suppressor gene discovered in the human genome.\textsuperscript{[6]}

Retinoblastoma in adults is an extremely rare tumor. Only about 30 cases have been reported in the world literature till date.\textsuperscript{[3-5,7,8]} Almost all these adults were sporadic and unilateral cases aged between 20 and 74 years. Characteristic manifestation of adult retinoblastoma was whitish, elevated, vascularized retinal mass, and diminution or loss of vision. Our patient was an adult female who reported at a very late stage of the disease with a significant degree of proptosis and extra propulsion of the whole ocular globe with hyperemic keratinized conjunctiva over the entire exposed part of the sclera and cornea. The affected eye was blind and it was not possible to examine the posterior chamber and retina.

CT is considered to be the best imaging modality for detection of intraocular calcifications.\textsuperscript{[9,10]} Arrigg et al.\textsuperscript{[11]} in their retrospective study of 21 cases of retinoblastoma using high-resolution CT found intraocular calcification in 83% of the cases. The degree of calcification appeared to depend on tumor size and only small tumors were devoid of calcification. The amount and distribution of calcification was similar on both histological study and CT scan. In patients less than 3 years of age in whom a retinoblastoma is suspected, the presence of calcification on CT is virtually diagnostic of it. The calcification which is a characteristic of retinoblastoma in children is usually not found in adults. Among most of the case reports of adult retinoblastoma available in the literature, only a few patients showed calcification in imaging studies. Our patient also did not show any calcification on NCCT. In a majority of cases of adult retinoblastoma reported in the literature [Table 1], the diagnosis was made at a fairly advanced stage. Our patient also reported to us at a very late stage of the disease.

Various case reports of adult retinoblastoma emphasize the role of clinical diagnosis and confirmation by biopsy to be the most important tool in final diagnosis. However, in the last three decades, the role of additional modalities such as CT scan, ultrasonography, magnetic resonance imaging (MRI) scan, FNAC, and immunohistochemistry (IHC) has become very important.\textsuperscript{[7,11]} IHC can be performed on biopsy samples, cytological smears, and cell blocks prepared from FNA sample. To differentiate retinoblastoma from malignant melanoma and malignant lymphoma, IHC stains used are NSE (neuron-specific enolase), synaptophysin, GFAP (glial fibrillary acidic protein), S-100, LCA (leucocyte common antigen), and HMB45 (human melanoma black 45).\textsuperscript{[3]} Retinoblastoma cells show positivity for NSE, synaptophysin, GFAP, and S-100 whereas malignant melanoma cells are positive for S-100 and HMB-45. The LCA is positive for lymphoma and is regarded as an excellent marker to distinguish lymphomas from poorly-differentiated tumors of epithelial, mesenchymal, or neural derivation. Char and Miller in 1984 studied the role of FNAC in retinoblastoma in 3 patients and established its role in the correct diagnosis of the disease.\textsuperscript{[12]} Over the last three decades, especially with the advent of imaging studies, the role of FNAC in the diagnosis of retinoblastoma and other orbital malignancies has gained importance. It has a sensitivity of 86.6%, specificity 100%, and positive predictive value 100%, as reported by Nag et al.\textsuperscript{[13]} They carried out FNAC under direct vision or under ultrasonography/CT guidance a using 22-gauze needle without anesthesia. The final diagnosis in our patient was also established after FNAC. FNAC was carried out transcutaneously on the palpable mass in the superior part of the swelling. The cytological examination was consistent with the diagnosis of retinoblastoma. In our patient, the CT scan findings established that the tumor had breached the orbital wall and had locally spread out of the orbit to the neighboring areas. Unlike our case, most other case reports did not have adequate sample on FNAC.\textsuperscript{[5,14]} Diagnosis in most cases was based on the enucleated orbital mass on histopathology, which supplemented by IHC in many case reports.\textsuperscript{[5,7,14]} However, in our patient, surgery was not done due to extension of tumor into the anterior cranial fossa and other adjoining areas.

**Conclusion**

Retinoblastoma should be considered as one of the uncommon differential in the diagnosis of an intraocular mass in adults despite its low frequency compared to other tumors including metastasis, melanomas, lymphomas, astrocytomas, etc. Clinical diagnosis is often possible unless the patients reports very late, as was in our case. When the diagnosis is not established clinically and by other noninvasive techniques, FNAC is indicated. It is a cheap, cost-effective, and simple procedure and helps in establishing the diagnosis with a very high degree of accuracy.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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