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## Ocular retinoblastoma and neuroblastoma: A cytological impression

### Oküler Retinoblastom ve neuroblastoma: Bir sitolojik izlenim

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#### Abstract

Small-round-blue-cell tumor (SRBCT) or a small-round-cell tumor (SRCT) is a group of malignant neoplasms which are seen more often in children (0-20 years-old) than in adults. They generally include Ewing's sarcoma, peripheral neuroectodermal tumor (PNET), rhabdomyosarcoma, synovial sarcoma, non-Hodgkin's lymphoma, retinoblastoma, neuroblastoma, hepatoblastoma, and nephroblastoma or Wilms' tumor as differential diagnoses of small round cell tumors. They have a characteristic appearance consisting of small round cells that stain blue on Hematoxylin and Eosin stained sections. They typically represent undifferentiated cells which are composed of primitive cells with minimal or no differentiation. Accurate diagnosis of these cancers is essential because the treatment options, responses to therapy and prognoses vary widely depending on the diagnosis. A multimodal approach is employed with fine needle aspiration cytology (FNAC) as an important modality of diagnosis for these tumors. We will discuss ocular retinoblastoma and neuroblastoma in our case series which were diagnosed on fine needle aspiration itself and were later confirmed on histopathological examination. This study was also undertaken to determine the utility and safety of intraocular FNAC as a supportive diagnostic tool where clinical features and imaging were found to be inconclusive.

**Keywords:** Fine needle aspiration cytology, Immunohistochemistry, Malignant small round cell tumors, Neuroblastoma, Ocular, Retinoblastoma

#### Öz

Küçük-yuvarlak-mavi hücreli tümör (SRBCT) veya küçük-yuvarlak hücreli tümör (SRCT), çocuklarda (0-20 yaş) yetişkinlerden daha sık görülen bir malign neoplazm grubudur. Bunlar genellikle küçük yuvarlak hücreli tümörlerin ayrıntı tanısı olarak Ewing sarkoması, periferik nöroektodermal tümör (PNET), rabdomyosarkom, sinovyal sarkom, non-Hodgkin lenfoma, retinoblastoma, nöroblastoma, hepatoblastoma ve nefroblastom veya Wilms tümörünü içerir. Haematoksilen ve Eosin ile boyanmış kesitler üzerinde mavi leke veren küçük yuvarlak hücrelerden oluşan karakteristik bir görünüme sahiptirler. Bunlar tipik olarak minimal veya hiç farklılaşma ile ilkel hücrelerden oluşan farklılaşmamış hücreleri temsil ederler. Bu kanserlerin doğru teşhisi önemlidir çünkü tedavi seçenekleri, tedaviye yanıt ve prognozlar tanıya bağlı olarak geniş çapta değişir. Bu tümörlerin önemli bir modalitesi olarak ince iğne aspirasyon sitolojisi (FNAC) ile multimodal bir yaklaşım uygulanmaktadır. Olgu serimizde ince iğne aspirasyonu tanısı konan ve daha sonra histopatolojik incelemede doğrulanan oküler retinoblastom ve nöroblastoma tartışılacaktır. Bu çalışma, klinik özelliklerin ve görüntülemenin sonuçsuz olduğu tespit edilen destekleyici bir tanı aracı olarak intraoküler FNAC'ın kullanımını ve güvenliğini belirlemek için yapılmıştır.

**Anahtar kelimeler:** İnce iğne aspirasyon sitolojisi, İmmünhistokimya, Malign küçük yuvarlak hücreli tümörler, Nöroblastoma, Oküler, Retinoblastom

#### Introduction

Small round blue cell tumors of childhood include neuroblastoma, Retinoblastoma, rhabdomyosarcoma, non-Hodgkin's lymphoma, Ewing's sarcoma and the closely related primitive neuroectodermal tumor (PNET) and the blastemic component of Wilms' tumor. The histologic overlap of small round cell tumors is a challenge to the surgical pathologist. These tumors are characterized both cytologically and histologically by a predominantly small round to oval and relatively undifferentiated cells. The disparity in treatment modalities and clinical outcome in the different subsets of SBRCTs makes the correct diagnosis crucial [1,2].

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Retinoblastoma is the most common primary malignant intraocular tumor in children that develops from the immature cells of the retina which are the light-detecting cells of the eye. Children with retinoblastoma have a hereditary genetic defect associated with retinoblastoma, in other cases it is caused by a congenital mutation in the chromosome 13 gene, 13q14 [1]. It is almost exclusively found in young children with mean age of 5 years. It equally affects both the sex and the tumor has no predilection for left or right eye. Most common presentation is leucocoria with typically white papillary reflex (amaurotic cat's eye reflex) or proptosis in late stages of the disease in some developing countries as classic manifestation [2]. Other clinical features are strabismus, uveitis, hyphema, red eye, secondary glaucoma, panophthalmitis and orbital cellulitis [3]. It is necessary to differentiate retinoblastoma from pseudoretinoblastomas presenting with similar ocular conditions. Although, in rare circumstances pseudoretinoblastoma and retinoblastoma can coexist in a patient [4]. There are very few studies on the safety and efficacy of diagnostic FNAC in RB cases due to the risk of tumor dissemination and extraocular spread associated with the procedure [5]. As a less invasive procedure, fine needle aspiration (FNA) cytology has a definite advantage over surgical excision to arrive at a tissue diagnosis before initiation of therapy.

Neuroblastoma is an infrequent tumor of childhood, usually located at any site containing neural tissue specifically immature cells of sympathetic nervous system - retroperitoneum and adrenal gland are the most common locations followed by thoracopulmonary region, mediastinum, head and neck, and pelvis. The symptoms vary depending on the location of the tumor. More than 50% of the cases present with signs and symptoms of metastatic disease. Children with metastasis to retrobulbar region present with proptosis [6,7]. In neuroblastoma, the raccoon eye appearance is due to obstruction of the palpebral vessels that are branches of ophthalmic and facial vessels by the tumor tissue in and around the orbit [8].

## Case presentation

### Case 1

A 4-year-old boy presented to the Ophthalmic clinic with a history of leucocoria in the right eye. On ophthalmological examination, visual acuity was absence of light perception in the affected eye. Fundus details could not be visualized due to advanced disease. The left eye was within normal limits. Imaging features on B-scan ultrasonography, CT scan and MRI of the orbit was inconclusive, but retinoblastoma could not be ruled out. Possible differentials were Coats' disease, endogenous endophthalmitis and retinoblastoma. To establish the diagnosis, intraocular FNAC was planned after taking an informed consent under general anesthesia. A 26-G needle mounted on a 5 ml syringe was introduced through the conjunctiva and the sclera into the intraocular mass. Careful controlled aspiration was done and cryotherapy was applied at the site of entry after the needle was withdrawn. The puncture fluid was very thick with a significant amount of white floccular exudates, as shown by the slit-lamp examination. Smears were prepared from the aspirated material and stained by Hematoxylin and Eosin stain. Cytology revealed a malignant round cell tumor,

with round to oval, small and uniform cells, with scanty cytoplasm; in closely packed clusters of variable sizes, compatible with retinoblastoma (Figure 1). Enucleation surgery was performed. Histopathologic findings in enucleated eyes were consistent with the diagnosis of retinoblastoma showing the tumor composed of undifferentiated cells along dilated blood vessels with a large ischemic necrosis around it. Homer-Wright rosettes were present. Immunohistochemical staining showed cytoplasmic positivity with synaptophysin in the tumor cells. The child was followed-up for ophthalmic and systemic evaluation for 6 months with no evidence of local recurrence or systemic metastasis.

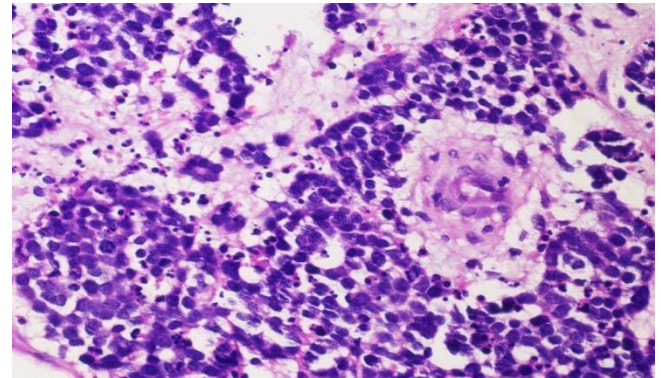


Figure 1: Retinoblastoma: Cytology revealed a malignant round cell tumor, with round to oval, small and uniform cells, with scanty cytoplasm, in closely packed clusters of variable sizes. Hematoxylin and Eosin x 40X.

### Case 2

A 3-year-old female child presented to the Ophthalmic clinic with rapid onset of proptosis of the right eye. On ocular examination, she had proptosis of 29 mm with lid edema and ciliary congestion with total restriction of extraocular movements. There was a 1.5 cm × 1 cm firm nodule on the sclera with foci of hemorrhage. The anterior chamber was filled with exudate. The intraocular pressure was raised to 27.1 mm Hg in the right eye by schiotz tonometry. On general examination, the child was febrile. There was no palpable abdominal mass. The chest was clear and the cardiovascular system was normal. Computed tomography of orbit and brain revealed a 5 cm × 3.5 cm × 2.0 cm heterogenous mass filling the right orbit with areas of coarse calcification. The optic nerve was encased within the mass with perineural spread up to optic chiasma, with thinning of the floor of the orbit. Based on the tomography findings, retinoblastoma was suspected. Fine needle aspiration cytology of the mass showed varying numbers of small primitive cells with scanty cytoplasm, poorly to well-formed pseudorosettes, cell processes and a fibrillary matrix (Figure 2).

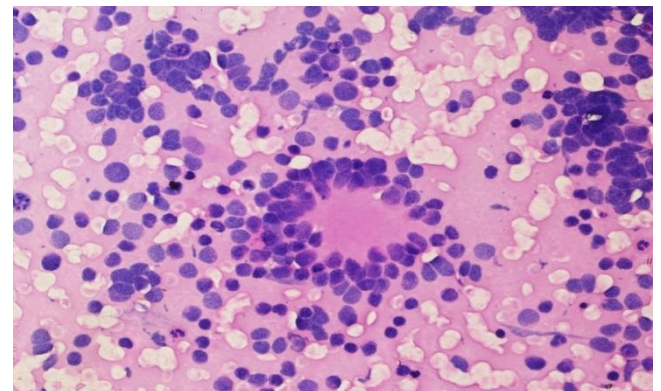


Figure 2: Neuroblastoma: Fine needle aspiration cytology of the mass showed varying numbers of small primitive cells with scanty cytoplasm, poorly to well-formed pseudorosettes, cell processes and a fibrillary matrix. Hematoxylin and Eosin x 40X.

Histopathological examination of incisional biopsy of orbital mass showed small round tumor cells in sheets separated by incomplete fibrous septa under low power. Examination at higher magnification revealed round to polygonal cells with high nucleocytoplasmic ratio, palisading of nuclei, and delicate cytoplasmic processes. Few foci with central fibrillary material with tumor cells around giving vague appearance of rosettes (Homer Wright) were seen. Immunohistochemistry was positive for neuron specific enolase and chromogranin and negative for both epithelial membrane antigen (EMA) and cytokeratin AE1/AE3, suggestive of neuroblastoma.

## Discussion

Irrespective of the age and site, four common types of round cell tumors are Hematopoietic: lymphoma and leukemia, Neuroblastoma, Rhabdomyosarcoma and Ewing's sarcoma. Types of small cell tumors occurring primarily in bone are poorly differentiated chordoma, melanotic neuroectodermal tumor, mesenchymal chondrosarcoma and small cell osteosarcoma. Those occurring mostly in specific sites include desmoplastic small round cell tumor, germ cell tumors, NUT translocation carcinoma. Some of the organ-specific blastomas are Wilm's tumor (nephroblastoma), Hepatoblastoma, Sialoblastoma, pancreatoblastoma, pleuropulmonary blastoma.

Several genetic factors have also been proposed such as constitutional mutations, deletions, single nucleotide substitutions (truncated protein), Epigenetic factors like Loss of imprinting, Loss of heterozygosity, Methylation, Histone acetylation, sRNAs, siRNAs.

Retinoblastoma is a neuroectodermal tumor of primitive cells of retina. A "benign" variant of retinoblastoma is known as retinoma or retinocytoma which is a differentiated tumor with no growth potential. It is the commonest intraocular malignancy in children. More than 90% of cases are diagnosed before the age of 5 years with the average age of diagnosis at 1 year in bilateral cases and 2 years unilateral cases [9]. The presentation of retinoblastoma in adults is extremely rare [10]. In adults, it always present with atypical manifestations such as decreased vision, floaters, and pain. It rarely presents with classic manifestations [11].

Retinoblastoma gene was the first tumor suppressor gene identified, a recessive gene located on chromosome 13q and thus both the genes must be inactivated before their functional derangement. Retinoblastoma gene produces Rb protein which can be inactivated by mutation or deletion, thus leading to loss of cell cycle control and genomic instability.

Clinical presentation and indirect ophthalmoscopic examination are insufficient for the diagnosis. CT scan is still the study of choice in the diagnosis of retinoblastoma showing intraocular calcification, but when MRI is available it should be performed for better differentiation from lesions such as Coat's disease. In doubtful cases, FNAC is performed. Cytological smears show predominantly discrete population of small round cells with occasional rosette-like structures as Flexner-wintersteiner rosettes and homer wright rosettes. Flexner-Wintersteiner rosettes are seen as cells around the lumen whereas in case of Homer-Wright rosettes, the cells are arranged around cobweb-like material. The nuclei are round, monomorphic and

hyperchromatic with fine nuclear chromatin. Occasional prominent nucleoli are also seen. The distinct cytological features of retinoblastoma are tight cohesion and nuclear molding among the tumor cells.

Grossly, retinoblastomas are usually creamy white with chalky areas of calcification and yellowish necrotic regions. They may grow inward toward the vitreous cavity (endophytic retinoblastoma) presenting as one or more isolated or coalesced tumors of variable size or may grow outward towards the choroid (exophytic retinoblastoma) causing retinal detachment, or in a mixed pattern. Thus, vitreous and subretinal seeding along with calcifications are virtually pathognomonic of retinoblastoma. Rarely, retinoblastomas thicken the retina diffusely without forming a discrete mass (diffusely infiltrative retinoblastoma). Whereas retinocytoma (retinoma) is characterized by homogenous, more or less translucent greyish masses, calcifications, with pigment migration and proliferation bordering the tumor with spontaneous remission. Tumor may invade the optic nerve and extend along it towards the brain or individual neoplastic cells may reach the CSF by penetrating into the subarachnoid space surrounding the optic nerve. Thus, the resection margin of optic nerve in an enucleated eye should be given careful attention [10].

Retinoblastomas infrequently spread extraocularly through sclera channels that contain blood vessels and nerves (emissarial canals), but the spread mainly occurs through the optic nerve and choroid. A risk of trilateral involvement is seen in the hereditary form of retinoblastoma. There is association of retinoblastoma, usually bilateral (90%) but not exclusively, with an intracranial neuroblastic tumor commonly in the region of the pineal gland (pinealoblastoma). Since these cells are being linked to the RB1 gene and of the same phylogenetic origin as retinal tissues. Under the St. Jude's staging system, intraocular retinoblastoma is classified into four stages: Stage I: the tumor is confined to the retina. Stage II: it is confined to the eyeball. Stage III: the cancer has spread to areas in the region around the eye. Stage IV: the cancer has spread through the optic nerve to the brain, or through the blood to soft tissues, bone, or lymph nodes [11].

Persistent hyperplastic primary vitreous (PHPV) and Coats' disease are the most common conditions (benign) to mimic retinoblastoma. Coats' disease also known as primary (congenital) retinal telangiectasia is a rare non hereditary probably congenital exudative retinopathy. The exudates are responsible for a luminous leukocoria but in the presence of retinal detachment, it takes on a greyer hue. Clinically, coat's disease shows three major features: retinal telangiectasia in the form of strings of fusiform dilatations of the retinal vessels; massive yellowish exudates within and underlying an edematous retina, sometimes giving a pseudo-tumoral appearance; exudative, sometimes leading to total retinal detachment.

PHPV is a non-hereditary, congenital malformation. Normally, regression of the embryonic vascular connective tissue (hyaloid artery, vasa hyaloidea propria, tunica vasculosa lentis) occurs after 4 months of gestation. The arrest of this normal regression leads to PHPV. It is almost always unilateral often presenting with moderate microphthalmia and other associated

malformations such as failure of cleavage of the anterior segment or uveal coloboma.

Retinoblastoma should also be differentiated from various small round cell tumors, such as lymphoma or leukemia and metastatic neuroblastoma involving the orbit. Fundus examination does not enable diagnosis to be made with certainty. Ultrasonography is the next method of choice which is an inexpensive and is highly specific means of detecting the calcifications [12]. Other methods of diagnosis include ocular coherence topography (commonly used for macular lesions) and CT scan (involves X rays and thus is potentially dangerous). Immunocytochemistry is helpful in the differential diagnosis of small blue round cell tumors [13]. Treatment strategies aim to salvage the eye and preserve vision. Currently, the methods available for treatment include laser treatment, cryotherapy, radiotherapy, chemotherapy and enucleation. Enucleation is the treatment of choice for advanced unilocular retinoblastoma or the worse eye in bilateral cases [12].

Neuroblastoma is an undifferentiated malignant tumor of the primitive neuroblasts. Neuroblastoma is a pediatric neoplasm which is the most common cancer diagnosed during infancy [13]. It represents second most common orbital tumor in children after rhabdomyosarcoma. It arises from the sympathetic system and ganglia and represents the peripheral nervous system counter part of retinoblastoma. Neuroblastoma occurs primarily in abdomen in 60% cases but in only 8% cases the tumor arises in the orbit from ciliary ganglion [14]. Most of the cases are reported before the age of 4 years.

Neuroblastoma commonly spreads via lymphatics to regional lymph nodes, often in the para-aortic chain, and less commonly to the next echelon of lymphatics, such as the left supraclavicular fossa (Virchow node) in patients with abdominal tumors. Hematogenous spread often occurs to bone marrow, bone, and liver. Neuroblastoma appears to have a proclivity for the bones of the skull and especially the posterior orbit, which can cause the clinical presentation of "raccoon eyes" from periorbital ecchymosis within three months after diagnosis. 40% of orbital metastasis is bilateral. Other possible ophthalmic manifestations of metastatic neuroblastomas are Horner's syndrome, papilledema, retinal striae, anisocoria, nystagmus and cranial nerve paralysis.

The typical neuroblastoma is composed of small, uniform cells containing dense, hyperchromatic nuclei and scant cytoplasm. The presence of neuritic processes (neuropil) is pathognomonic. Numerous markers have been used for the diagnosis of neuroblastomas including NE markers, cytoskeletal proteins, catecholamine-synthesizing enzymes, and neuroblastoma-"specific" antibodies (such as NB84, that is raised to neuroblastoma cells) to differentiate from common possible differentials such as desmoplastic small round cell tumor, Ewing's sarcoma/primitive neuroectodermal tumor, rhabdomyosarcoma, ganglioneuroblastoma [15].

Desmoplastic small round cell tumors grow and spread uninhibited within the abdominal cavity. First symptoms of the disease often include abdominal distention, abdominal mass, abdominal or back pain, gastrointestinal obstruction, lack of appetite. They reveal well circumscribed solid tumor nodules with areas of central necrosis within a dense desmoplastic

stroma. Cells have hyperchromatic nuclei with increased nuclear/cytoplasmic ratio. On immunohistochemistry, these cells have trilinear coexpression- epithelial marker cytokeratin, the mesenchymal markers- desmin, vimentin and the neuronal marker- neuron-specific enolase. A multi-modality approach of high-dose chemotherapy, aggressive surgical resection, radiation, and stem cell rescue improves survival for some patients but prognosis remains poor [16,17].

Rhabdomyosarcomas (RMS) of the orbit are usually found in children. Majority of these tumors are of the embryonal followed by alveolar subtype developing from primitive mesenchymal cells that go on to differentiate into striated muscle cells. They are found in the orbit, eyelid, conjunctiva and uveal tract [18]. Orbital RMS should be considered in the differential diagnosis of any child with a progressive unilateral proptosis [18]. These tumors typically present with a rapid enlarging mass, often in the upper inner quadrant of orbit. It is usually painless but causes proptosis and diplopia. Often the mass invades the eyelid causing marked edema. CT scan shows homogeneous soft tissue masses isodense to normal muscle. The mainstay of treatment is a combination of radiotherapy and chemotherapy.

Ewing's sarcoma rarely occurs in children under 5 years and the peak incidence is between 10 and 15 years. Earlier it was thought that Ewing's sarcoma only occurred in the bone, however other tumors were found within the soft tissues and is thought to be similar microscopically. These include extraosseous Ewing's sarcoma and peripheral primitive neuroectodermal tumor (PNET) and are now grouped together as the Ewing's sarcoma family of tumors. They primarily occur in non head and neck sites. Only 2-10% develops in head and neck sites, most commonly involving skull and jaw, other less common sites includes the sinonasal tract, orbit and various mucosal sites. There is reciprocal translocation between chromosome 11(FLI1 gene) and chromosome 22(EWSR1 gene). HPE shows uniform small cells with round to oval nuclei, fine chromatin (powdery) with pale to clear cytoplasm and indistinct cell borders. These tumors give diastase sensitive PAS positive reaction and express CD99. Prognosis depends on the extent of the disease at initial presentation, size of the tumor and response to therapy [19].

Ganglioneuroblastomas are neuroectodermal in origin and is the fourth most common tumor in childhood within first 4 years of life. They occur anywhere in anatomic distribution of sympathoadrenal neuroendocrine system. They behave in a benign fashion are composed primarily of mature ganglion cells, neuropil, and Schwann cells. Ganglioneuroblastomas have histopathologic characteristics of both neuroblastomas and ganglioneuromas [20].

#### Conclusions

Accurate diagnosis of pediatric small round cell tumors has become crucial, as disparate approaches to therapy are used for distinct tumor types. Immunohistochemistry can be helpful in narrowing the differential diagnosis of small-round-cell tumors. Despite recent advances in immunohistochemistry and molecular pathology, some cases of small-round-cell tumors of childhood remain diagnostically problematic.

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