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Case Report

# Proptosis is a Pediatric Dilemma

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**Abstract`**

Childhood proptosis is quite different from that of the adult. While thyroid orbitopathy is the most common cause in adults, proptosis among children can be caused by: infection, inflammation, vascular and developmental malformation and finally malignancies. Orbital cellulitis and malignancies are considered the most common causes in children. In the present work we review the common causes of proptosis in children and report a series of four cases with proptosis caused by different malignant lesions retrieved from Pediatric Oncology Unit, Oncology Center of Mansoura University, Egypt in addition to providing an approach to a child with proptosis.

## INTRODUCTION

Proptosis is defined as abnormal protrusion of the eye due to a space occupying lesion in the orbit [1]. Childhood proptosis usually denotes serious problem and requires emergent intervention as it is commonly caused by malignant lesions or at least threatens the vision [2].

Causes of proptosis in children are different from that in adults. While thyroid disorders are the most common causes of proptosis in adults, orbital cellulitis is the most common cause among children [2]. Other causes of proptosis in pediatric age group include: inflammations (e.g. orbital pseudo-tumor and hyperthyroidism), vascularmalformations (e.g. capillary hemangioma), developmental (e.g. dermoid cyst) and neoplasms (e.g. retinoblastoma, optic glioma, rhabdomyosarcoma, leukemia and lymphoma, histiocytosis, Ewing sarcoma and metastases) [3]. In the present work we review four cases of proptosis secondary to different malignant lesions from Pediatric Oncology Unit, Oncology Center Mansoura University, Egypt. A written consent(s) for publication of the patient`sphotos was obtained fromthe parents of each patient.

## CASE (A)

Atwo-month-old female infant, of non consanguineous marriage with uneventful perinatal history suffered from progressive proptosis of her right eye discovered one month after birth. There was noassociation of fever, history of trauma or preceding upper respiratory tract infection. Her 3 years old sister had right suprarenal neuroblastoma which was surgically removed and received post operative chemotherapy. On examination there was no pallor, purpura, ecchymosis, abnormal pigmentation or other body swellings. Her neurological examination was normal as well.The Right eye showed forward proptosis with edematous, red both upper and lower eye lids. Conjunctiva and cornea were edematous and congested with excessive lacrimation and limited mobility of the extra ocular muscles (total ophthalmoplegia) with no palpable pulsations and absent pupillary lightreflex (figure 1A).

Complete blood count (CBC) and bone marrow examination (BME) were unremarkable. Lactate dehydrogenase enzyme (LDH) was elevated (530U/L). Vanillyl mandelic acid (VMA) in 24-hour urine was within normal (2.4mg/day).

Pre and post contrast axial and coronal CT of the orbit showed a well-defined intraconal soft tissue mass in the right orbit with areas of degenerations and no detected calcifications with intact bony walls (figure 1B & 1C). Also CT chest and abdomen was requested searching for a primary lesion but the study wasnormal.

**Figure 1a** Severe forward proptosis of the right eye.

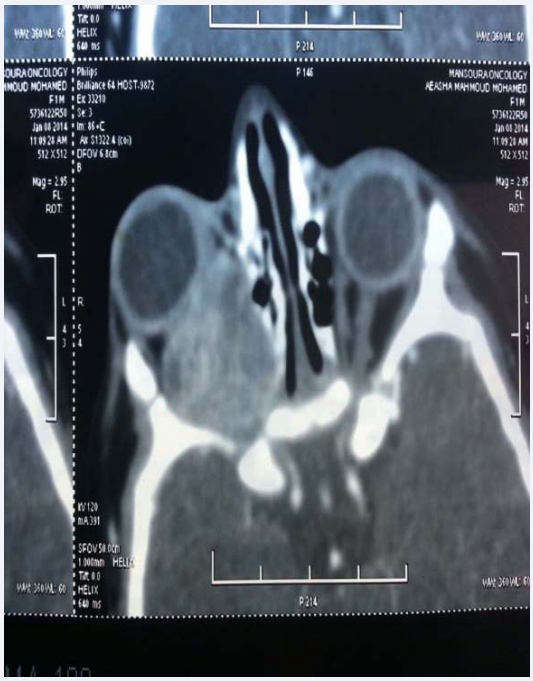

**Figure 1b** CT orbit (Axial plane).

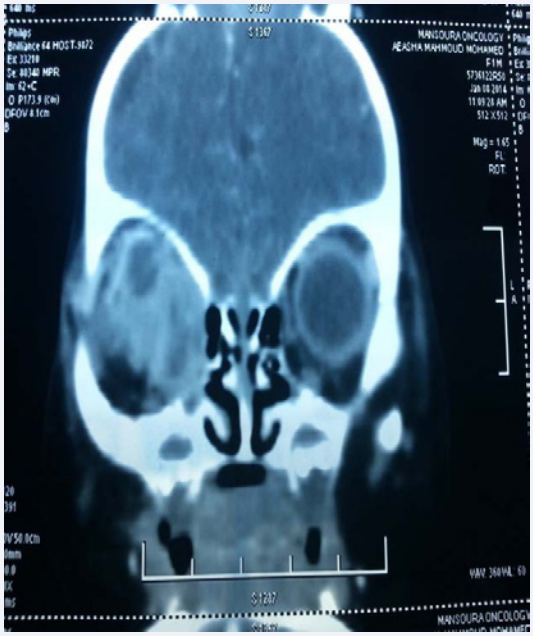

**Figure 1c** CT orbit (Coronal plane).

A biopsy was done through a trans-orbital approach.It revealed a malignant round cell tumor (figure 1D) and immune histochemistry for final diagnosis was mandatory. Synaptophysin and chromogranin were negative [not Neuroblastoma], (Desmin was negative [not Rhabdomyosarcoma], CD99 was negative [not Ewing sarcoma or PNET], S100was negative [not Langerhans cell histiocytosis], LCA was positive [consistent with Lymphoma], CD3, CD19 and CD20 all were negative [Not T or B lymphoma], but CD56 was positive so it is consistent with natural killer (NK) cell lymphoma (figure 1E).Case A was diagnosed as primary NK cell lymphoma of the orbit.

## CASE (B)

A7-year-old girl had a history of fever and bone aches that lasted for 2 weeks followed by pallor and bilateral proptosis with swelling of both cheeks. Her examination revealed pallor, gum hypertrophy, swollen non tender both maxillae with downward displacement of the hard palate more on the right side. Her eyes were proptotic (more on the right), with normal pupillary light reflex and normal movement of the extra ocular muscles (figure 2A). No palpable peripheral lymph nodes. Her abdominal examination showed hepatosplenomegaly.

Blood picture showed normocytic and normochromic anemia together with thrombocytopenia. Bone marrow aspiration revealed blast cell infiltration (56%) with a morphologic (FAB) classification of acute myeloid leukemia (AML-M5) (figure 2B) which was confirmed by flow cytometric analysis (CD64=97%, CD11b=50%, CD11c=50%, CD36=40%).Post contrast MRI of the brain, orbit and paranasal sinuses showed a well-defined soft tissue lesion in the posterior ethymoidal, sphenoidal and maxillary air sinuses extending to both orbits (figures 2B & 2C).

Case B was diagnosed as Granulocytic sarcoma of the orbit.

## CASE (C)

A 5-year-old girl presented with history of progressive

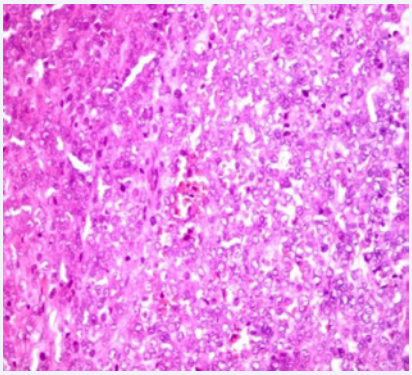

**Figure 1d** Malignant round cell tumor.

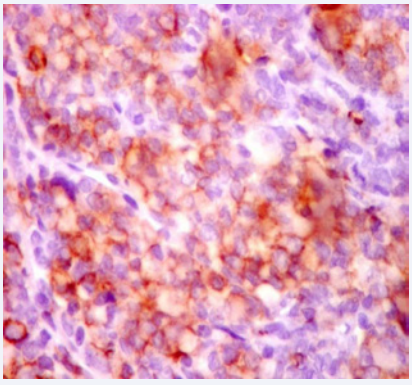

**Figure 1e** CD56-positive cells (H&E) (consistent with NK Lymphoma).

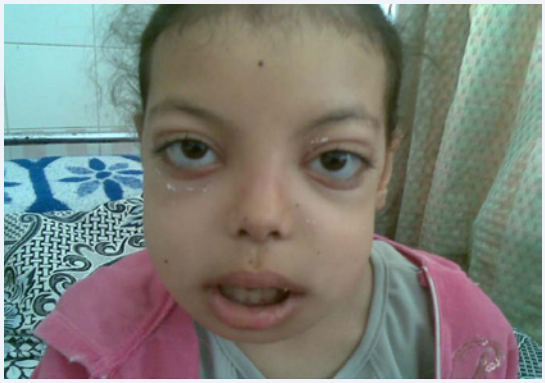

**Figure 2a** Proptosis with swollen both maxillae.

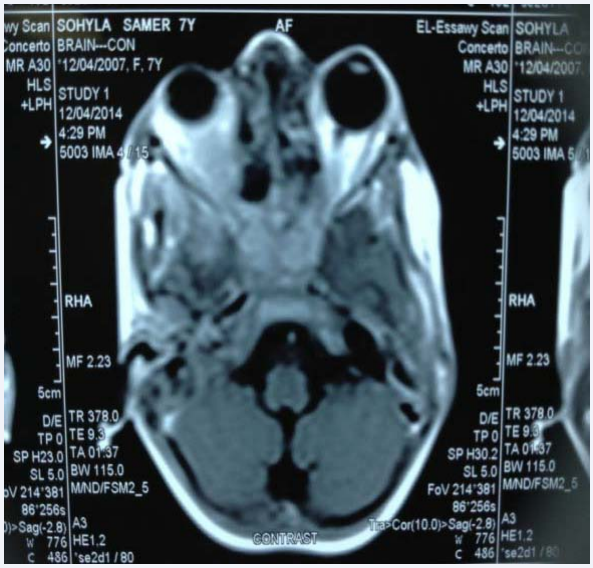


**Figure 2b** Soft tissue lesion infiltrating the RT orbit.

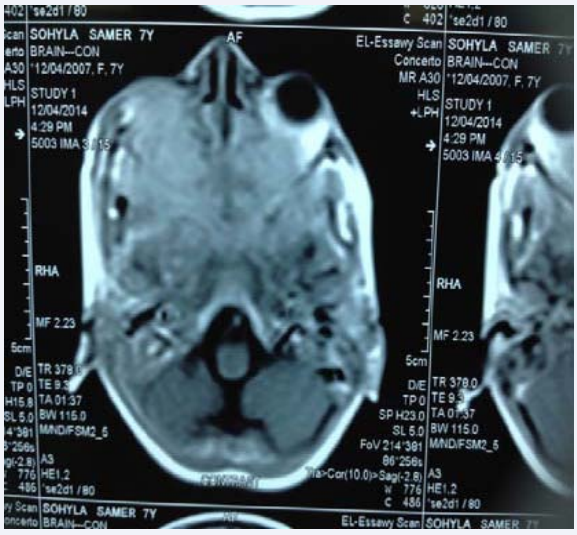


**Figure 2c** Soft tissue lesion infiltrating both the Lt orbit & maxillary sinuses.

superolateral proptosis of the right eye. The condition was not associated with fever, bone aches or other body swellings. Examination revealed lateral proptosis of the right eye with limited movement to the medial and downward gaze and intact pupillary light reflex (figure 3A). There was no purpura, ecchymosis or palpable peripheral lymph nodes. Her abdominal examination was normal with no palpable masses.

Blood picture, bone marrow aspiration and acute phase reactantswere within normal.Post contrast MRI of the brain and orbit showed a well-defined soft tissue mass between the retro-orbital muscles and optic nerve (figure 3B).CT chest and bone scan were normal without detected metastases. A trans-orbital biopsy was done that revealed a malignant round cell tumor consistent with embryonal rhabdomyosarcoma with characteristic "tad pole" cells (figure 3C). Immune histochemistry showed positive tumor cells for Desmin (figure 3D).Case C was diagnosed as Embryonal Rhabdomyosarcoma of the orbit.

## CASE (D)

A5-year-old girl suffered from fever and abdominal pain lasting for 1 month followed by appearance of left abdominal

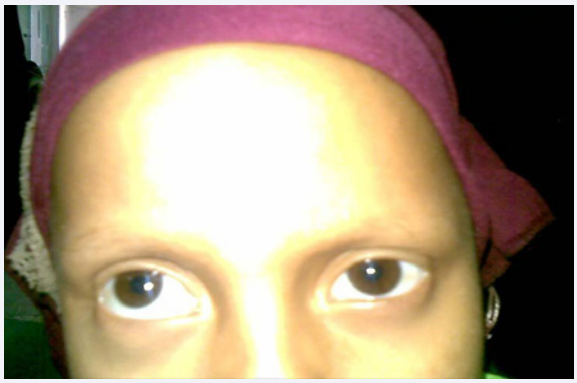

**Figure 3a** Superiolateral proptosis of RT eye.

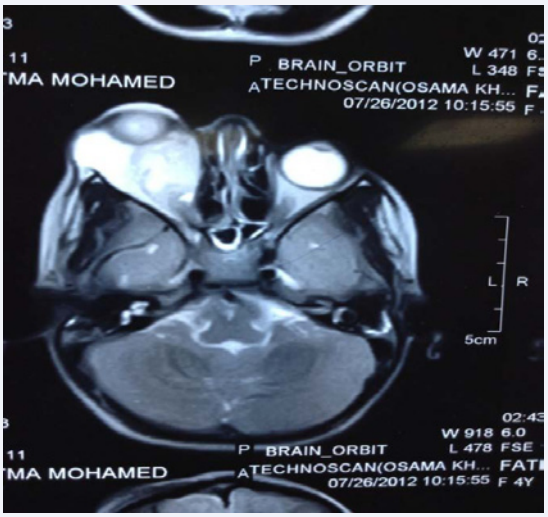


**Figure 3b** The mass occupying the medial aspect of the RT orbit (red arrow).

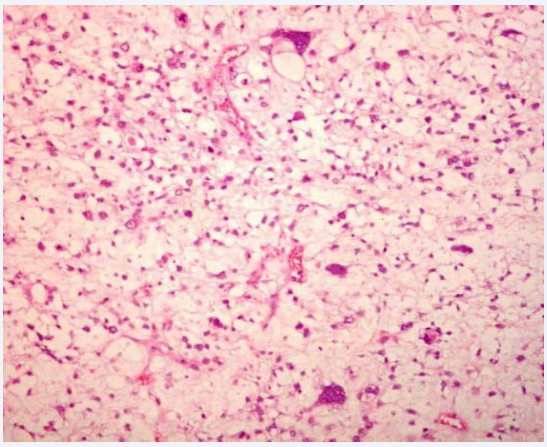

**Figure 3c** Rhabdomyosarcoma (H&E).

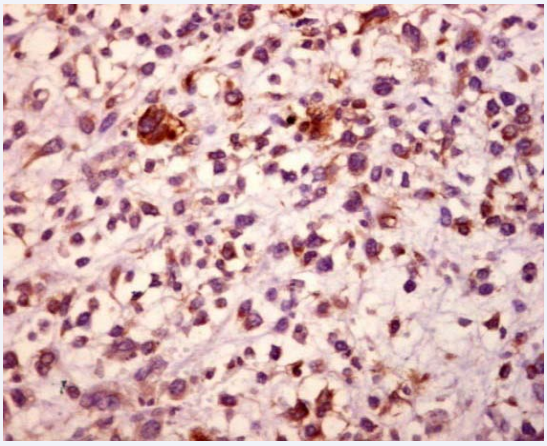

**Figure 3d** Positive cells for Desmin.

**Figure 4a** RT forward proptosis.

swelling. One week later she developed progressive proptosis of the right eye. On examination the right eye showed forward proptosis with no lacrimation or discharge, no limitation in the movement of the extra ocular muscles, preserved visual acuity and pupillary light reflex (figure 4A). Her abdominal examination revealed a huge mass occupying the left hypochondrial, lumbar and iliac regions crossing the midline, ovoid in shape, hard in consistency, ill-defined border, irregular surface and not tender. Her neurological examination was normal.

Blood picture showed normocytic and normochromic anemia together with thrombocytopenia (Hb= 6.3gm/dl normocytic normochromic, platelets=52x$10^3$/$mm^3$). Bone marrow aspiration revealedinfiltration with sheets of non hematopoietic cells (figure 4B) and VMA in 24-hour urine was elevated (32mg/day)(normal up to 13.5mg/day).

Post contrast CT abdomen describeda huge well-defined soft tissue mass displacing the left kidney anteriorly and medially, crossing the middle line with areas of cystic degeneration (figure 4C).

Post contrast CT brain showeda well-defined soft tissue lesion infiltrating the posterolateral aspect of the left orbit (intra orbital extra conal) with cystic degeneration (figure 4D).

Ultrasound guided Tru-cut biopsy from the abdominal mass showed a malignant round cell tumor consistent with neuroblastoma (figure 4E). Immune histochemical stain showed positivity of synaptophysin (figure 4F) and chromogranin (figure 4G). Case D was diagnosed as metastatic Neuroblastoma of the orbit.

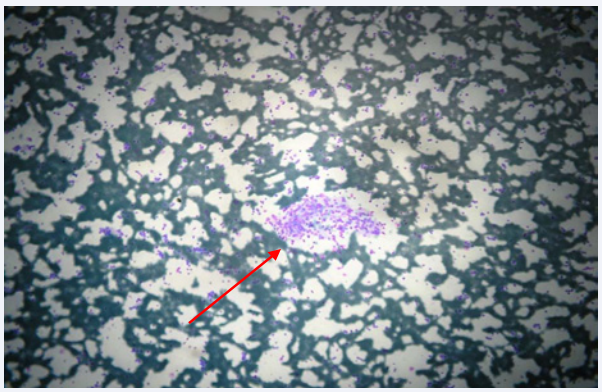

**Figure 4b** Sheets of non hematopoietic cells infiltrating BM.

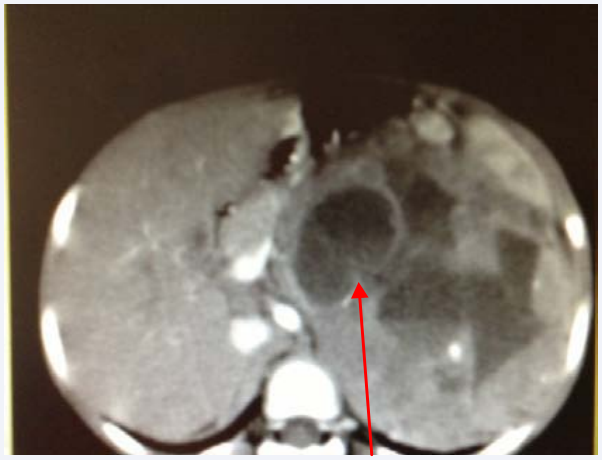

**Figure 4c** CT abdomen.

## DISCUSSION

Childhood proptosis is quite different from that of the adult.While Grave's disease and other thyroid disorders are the most common causes of proptosis in adults, orbital cellulitis and malignancies e.g. retinoblastoma, optic glioma, rhabdomyosarcoma, leukemia and lymphoma, histiocytosis, Ewing sarcoma and metastasesare the most common causes among children [2]. Other causes of proptosis in pediatric age group include inflammations (e.g. orbital pseudo-tumor and hyperthyroidism), vascular malformations (e.g. capillary hemangioma) and developmental anomalies (e.g. dermoid cyst) [3].

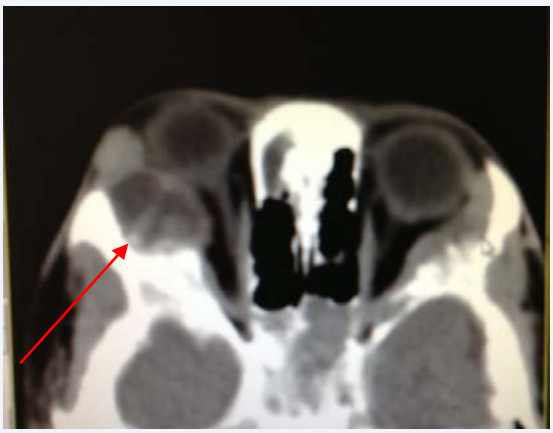

**Figure 4d** CT brain.

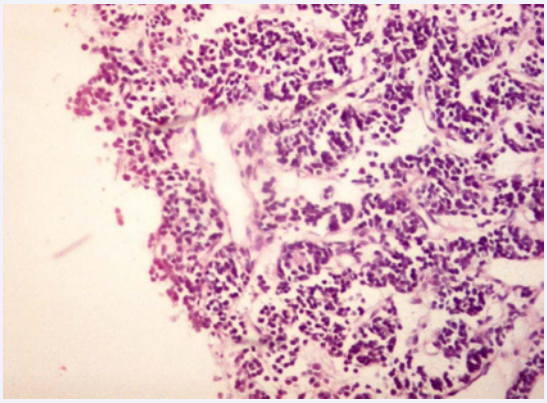

**Figure 4e** Malignant round cell tumor (H&E).

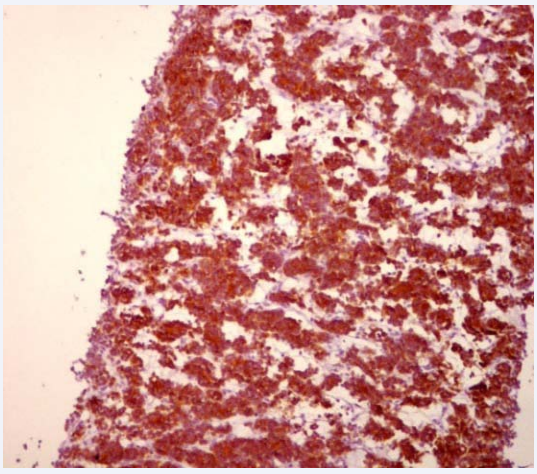

**Figure 4f** Diffuse positive tumor cells for chromogranin.

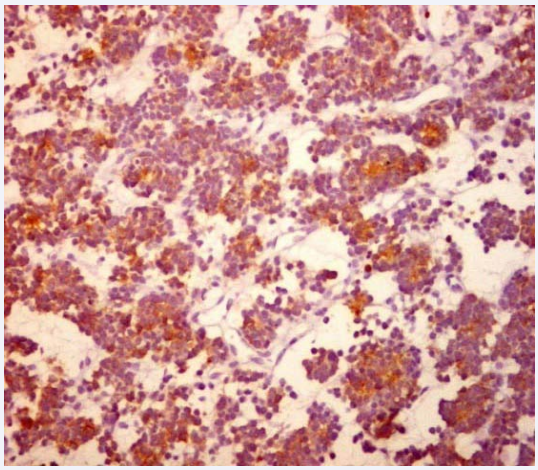

**Figure 4g** Positive cells for synaptophysin.

Common associating ocular symptoms and signs include leukocoria (white pupil), strabismus, (restriction of ocular motility) (ophthalomplegia), asymmetric eye position within the orbit, decreased vision, high pressure in the eye, inflammation of the eyelids or conjunctiva, pseudohypopyon (inferior whitish layer in the anterior chamber of tumor cells), vitreous hemorrhage or inflammation, and an afferent pupillary defect [3].

### Orbital cellulitis

The most common cause of proptosis among children. Usually it is preceded by upper respiratory tract infection, sinusitis or penetrating trauma of the eye. Patients commonly complain of pain when moving the eye, bulging of the infected eye, and limited eye movement. Along with these symptoms, the eye is red, swollen and discharges pus. Organisms that are commonly responsible for orbital cellulitis include: Staphylococcus aureus, streptococcus pneumoniae and β hemolytic streptococci [4].

### Inflammatory orbital pseudo tumor

It refers to a marginated mass-like enhancing soft tissue involving any area of the orbit. Although it is the most common painful orbital mass in adult population, pediatric cases represent only 17%. The exact etiology is unknown, but infectious and immune-mediated mechanisms have been postulated. Orbital pseudo tumor has been observed in association with Crohn's disease, systemic lupus erythematosus, rheumatoid arthritis, diabetes mellitus, all of which strengthen the basis of being an immune-mediated disease. The most common sign is proptosis, but redness and pain are also experienced. Bilateral presentation may have a higher incidence of systemic disease [5].

### Capillary hemangioma

It is a hamartoma of capillary endothelial cellsand the most common vascular tumor in children. It is commonly unilateral superonasal eyelid or eye brow lesion and typically blanches on pressure. Most cases are diagnosed within the first weeks to months of life, after which the hemangioma begins a proliferative phase for up to 10 months. After the first year of life, the lesion involutes and follows a regressive course up to 10 years [6].

### Dermoid cysts

They are the most common orbital cystic tumor of childhood. Usually present in the first few years of life. When growth is outward into the eyelid, cysts present in early childhood, and when they grow inward into the orbit they present later in life. Typically they are smooth, well-circumscribed, subcutaneous, painless mass located in the superolateral aspect of the orbit at the frontozygomatic suture and when deep they may present with proptosis [7].

### Malignant neoplasms

They are considered the second most common cause of proptosis in children. They may be primary or secondary. Primary orbital tumors include: rhabdomyosarcoma, retinoblastoma, lymphomas, histiocytosis optic glioma and Ewing sarcoma. Metastatic (secondary) orbital tumors include: neuroblastoma, leukemia (granulocytic sarcoma) and bone tumors. In this paper we reviewed four cases of proptosis secondary to four different malignant neoplasms: Case (A) represents a case of **Natural killer cell lymphoma** which is extremely rare with unusual age and clinical presentation. Natural killer cell lymphoma is rare and aggressive type of lymphoma. It is rare in pediatric age group. Moreover, NK lymphoma is more common among Asia and Latin America while rare among the Caucasians. It is almost exclusively extra nodal with the nose and nasopharynx as the most common sites [8]. However, in this patient it was retro orbital.

The first clinical suspicion in this case was neuroblastoma (from the age and positive family history) with orbital metastasis as 42% of patients presenting at less than one year of age [9]. Moreover, it has specific predilection to metastasize to the orbits [10] but her abdominal examination was normal without palpable masses, also chest and abdominal CT were free from suprarenal, paraspinal or mediastinal masses. Also VMA was within normal range. The second clinical suspicion was granulocytic sarcoma (previously known as choloroma), however it can occur with lymphoid origin as well but it is much more rare [11]. In this case, both CBC and BME were unremarkable in addition to the biopsy which did not reveal granulocytic sarcoma even as isolated lesion without marrow involvement although it is extremely rare [11].

Case (B) represents a case of AML with granulocytic sarcomas in the orbits and paranasal sinuses. Granulocytic sarcoma describes extra medullary collections of blastcells, it can occur, however rarely as the only manifestation of leukemia without marrow involvement with better outcome than marrow involvement. It is interesting to note that in one study AML patients with orbital granulocytic sarcoma and CNS granulocytic sarcoma may behave better than patients with marrow disease and granulocytic sarcoma at other sites and AML patients without any extra medullary disease. This is may be referred to the increased incidence of t (8; 21) in patients with orbital granulocytic sarcoma, which has been associated with a favorable prognosis [11]. Patients with granulocytic sarcoma may achieve complete remission after chemotherapy without radiation therapy, however it may be necessary for lesionswhich fail to respond completely to chemotherapy alone [12].

Case (C) represents a case of orbital rhabdomyosarcoma originating from the right medial rectus muscle. Rhabdomyosarcoma is the most common primary orbital malignancy in childhood, accounting for 10% of all rhabdomyosarcoma cases [13]. There are two major subtypes of orbital rhabdomyosarcoma: the more aggressive, less common alveolar type and the less aggressive, more common embryonal type (89%) [14] which is compatible with the current case. Orbital rhabdomyosarcoma presents as a rapidly growing, painless mass that leads to proptosis, most commonly in the medial quadrant of the orbit for embryonal type [15] similar to this case and the inferior quadrant for the alveolar type.

Case (D) represents a case of left suprarenal neuroblastoma with orbital metastasis. This case had typical presentation for neuroblastoma (the age at diagnosis was below 7 years, in a common primary site which was suprarenal, associated with common sites for metastases which were the bone marrow and the orbit, together with high urinary catecholamines, typical pathologic findings and positive tumor cells to the special stain for neuoblastoma including synaptophysin and chromogranin). Neuroblastoma is the most common extra cranial solid tumor of childhood originating from the neural crest. It is the most common primary cancer among children to metastasize to the orbits [10]. The orbital neuroblastoma metastases commonly present with unilateral or bilateral proptosis and periorbital or eyelid ecchymosis (raccoon eyes) albeit not found in this case. Orbital neuroblastoma metastases tend to occur in the posterolateral orbital wall [7] which is consistent with the current case. The survival and outcomes of neuroblastoma have improved over the last 30 years with the use of multimodality approach including chemotherapy, radiation therapy, surgery, myeloablative therapy with stem cell transplantation, immunotherapy, and differentiation therapy [15]. However, it is still a challenge for disseminated disease.

## CONCLUSION

Although proptosis is not a common complaint in children, its presence usually reflects a serious problem and needs emergent intervention. The risk of malignancies should be considered especially in subacute and chronic courses. Thorough general and regional examinations with special importance to the abdominal examination all are mandatory as they may be the clue for diagnosis. Moreover, non invasive investigatory tools as CBC, LDH, VMA and imaging studies should precede the invasive ones as they may direct the diagnosis properly.

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