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CASE REPORT / OLGU SUNUMU

An extremely rare case of a pediatric peripheral primitive neuroectodermal tumour: Orbital primitive neuroectodermal tumour

Çok nadir bir pediatrik periferik primitif nöroektodermal tümör vakası: Orbital primitif nöroektodermal tümör

Hacer BAL, Cennet ŞAHİN, Erkin ARIBAL

ABSTRACT
Primitive neuroectodermal tumours (PNETs) are a group of malignant soft tissue tumours of neuroepithelial origin that arise from primitive neural crest cells. Most of the PNETs occur in the central nervous system (CNS). If the origin is outside the CNS it is called peripheral primitive neuroectodermal tumour (pPNET). Histopathologically, PNETs consist of small round cells with a hyperchromatic nuclei, high nuclear-cytoplasmic ratio and varying degrees of neural differentiation detectable by immunohistochemical or ultrastructural techniques. pPNETs occur predominantly in children and young adults and show no gender difference. Occurrences of pPNETs in the orbit are infrequent and to the best of our knowledge only eighteen cases have been reported in the literature up to now. In this study, we present clinic, radiologic and histopathologic features of an orbital mass in an 8-year-old boy, which was diagnosed as a primary orbital pPNET confirmed by immunohistochemistry.

Key words: Pediatric, Peripheral primitive neuroectodermal tumour, Orbita

ÖZET
Primitif nöroektodermal tümörler (PNET) primitif nöral krest hücrelerinden köken alan bir grup malign yumuşak doku tümörleridir. Tümör, santral sinir sistemi ya da beyin dışındaki yumuşak dokulardan köken alırsa, periferik primitif nöroektodermal tümör (pPNET) adını almaktadır. Histopatolojik olarak PNET hiperkromatik nükleuslu, yüksek nükleus/stoplazma oranına sahip, immünohistokimyasal ve/veya ultrastrüktürel teknikler ile saptanabilen değişik derecelerde nöral diferansiasyona sahip küçük yuvarlak hücrelerden oluşmaktadır. pPNET genellikle genç erişkin ve çocuklarda ortaya çıkmakta olup cinsiyet ayrımı göstermez. Orbital yerleşim nadir izlenmektedir ve şimdiye kadar, literatürde yalnızca on sekiz vaka bildirimine ulaşılmaktadır. Biz, bu çalışmamızda immunohistokimyasal olarak pPNET tanısı onaylanmış 8 yaşında erkek çocuğun gözünde saptanan kitlenin klinik, radyolojik ve histopatolojik özelliklerini sunmayı amaçladık.

Anahtar kelimeler: Pediatrik, Periferik primitif nöroektodermal tümör, Orbita

Hacer Bal, Erkin Arıbal
Department of Radiology, School of Medicine, Marmara University, Istanbul, Turkey

Cennet Şahin (✉)
Radiology Clinic, Tekirdağ State Hospital, Tekirdağ, Turkey
e-mail*: cennetsahin@yahoo.com*

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Introduction

Primitive neuroectodermal tumours (PNETs) are rare tumours originating from cells of primitive neural crest. The majority of PNETs arise in the central nervous system (CNS). PNETs seen outside the CNS are called periferal primitive neuroectodermal tumors (pPNET)s [1-3]. pPNETs are commonly present in the thoracopulmonary region, abdomen, pelvis and the extremities but infrequently in the head and neck. Orbital location is infrequent and seen mostly secondary to metastatic spread of PNETs [1-5]. Only eighteen orbital pPNET cases have been reported in the literature up to now [5]. In the differential diagnosis of orbital pPNET, other small blue round cell tumours like Ewing's sarcoma, rhabdomyosarcoma, lymphoma, neuroblastoma and metastatic retinoblastoma of the orbit should be considered (Table I) [4,5]. pPNETs occur predominantly in children and young adults and show no gender difference [1,6,7]. The treatment for pPNET usually involves a combination of surgery and chemotherapy with or without radiotherapy [3,6].

Table I. The sarcomas relevant to the differential diagnosis of primary pPNET

pPNET	HIC-2 gene (+), NSE (+), synaptophysin (+), glial fibrillary acidic protein (GFAP) (+), MIC2 gene (+)
Ewing's Sarcoma	PGP9.5 antibody (+), MIC2 gene (+)
Rhabdomyosarcoma	Actin (+), Vimentin (+), Desmin (+), S-100 (-)
Lymphoma	LCA (+),CD45 (+),CD20 (+),CD3 (+)
Neuroblastoma	PGP9.5 antibody (+), MIC2 gene (-)
Osteogenic Sarcoma	Osteoid (+)

pPNET: Peripheral primitive neuroectodermal tumour

Case Report

An 8-year-old boy was brought to our hospital with complaints of progressive protrusion of the left eye ball for two months and visual lost for one week. On external ocular examination there was a localized, tender, firm, fixed, non-pulsating globular mass in the superolateral orbit. There was an inferior and medial deviation of the left eye, restriction of ocular movements superolaterally and total visual loss.

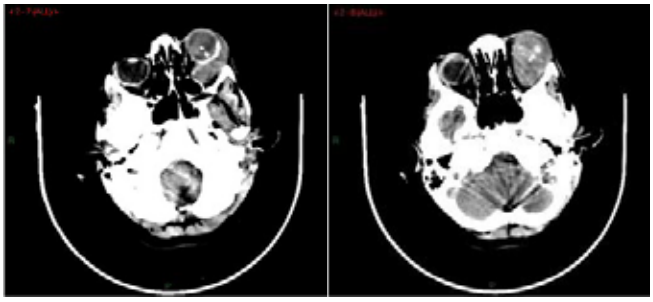

Figure 1. On preoperative non-contrast enhanced cranial CT images; the left eye is hyperdense compared to the right. There is a 36x20 mm mass in the left lateral orbital region, causing inferomedial and anterior deviation of the left eye. Also there are calcifications on posterolateral wall of the eye. No bone invasion is seen.

He had minimal ptosis and he had no ocular pain. There was no history of injury, fever, chronic cough or other systemic symptoms. The patient had magnetic resonance imaging (MRI) and computed tomography (CT) with a prediagnosis of an ocular mass. On non-contrasted cranial CT images there was a 36x20 mm space-occupying lesion in the left lateral orbital region, causing inferomedial and anterior deviation of the left eye (Figure 1). Also there were calcifications on posterolateral wall of the eye. On contrast enhanced cranial MRIs, an extention of the lesion along the left optic nerve, optic chiasm and optic tract was seen clearly (Figure 2). There was also a persistent primary hyperplastic vitrea on the left eye. A neoplastic process was suggested. Extensive systemic investigations were done subsequently to rule out any other foci of tumour; these included a complete hemogram, CT of thorax-abdomen-pelvis, spinal MRI and bone marrow biopsy. These were all normal and therefore a diagnosis of a primary orbital malignancy was made. The patient had a left craniotomy, excision of the orbital rim and the mass, a duroplasty three days after the diagnosis. Histopathologic examination of the tumour revealed a diffuse collection of small malignant round to oval cells with high mitotic activity. Immunohistochemically, the majority of the tumour cells were positive for CD99 (MIC2 gene), neuron specific enolase (NSE) and the synaptophysin gene. Periodic acid-Schiff (PAS) reaction which rules out Ewing's sarcoma was negative. Based on the above findings the patient was diagnosed as having pPNET of the left orbit. Cytogenetic studies showed the characteristic t(11;22) chromosomal translocation that confirmed the pPNET diagnosis. Following the operation, the patient had chemotherapy and radiotherapy treatments. Cranial CT and MRI were performed during postoperative 24 hours (Figure 3), and control images were obtained two months later, showing no recurrence and a total resection of the mass (Figure 4).

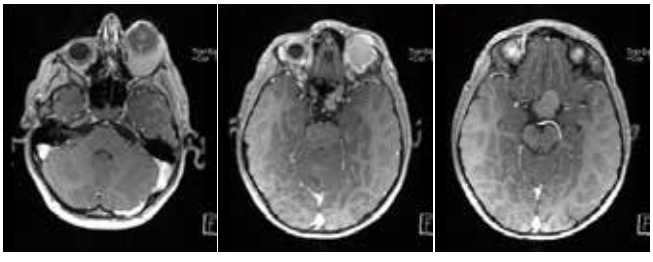

Figure 2. Preoperative contrast enhanced T1-W axial (a, b, c) images. There is a mass in 36x20 mm diameter that shows marked homogeneous enhancement on the left lateral orbital region, causing inferomedial and anterior deviation of the left eye. Extension of the lesion along the left optic nerve, optic chiasm and optic tract is seen clearly. Also a persistent primary hyperplastic vitrea is seen on the left eye.

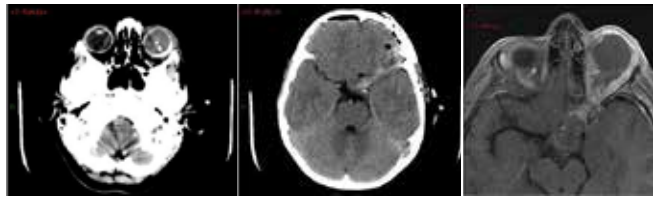

Figure 3. On postoperative same day control non-contrast enhanced cranial CT (a, b) and contrast enhanced axial T1-W MR (c) images; there are postoperative (left craniotomy, mass excision, duroplasty) changes on the left frontotemporal bone and left frontal lobe after the resection of the mass.

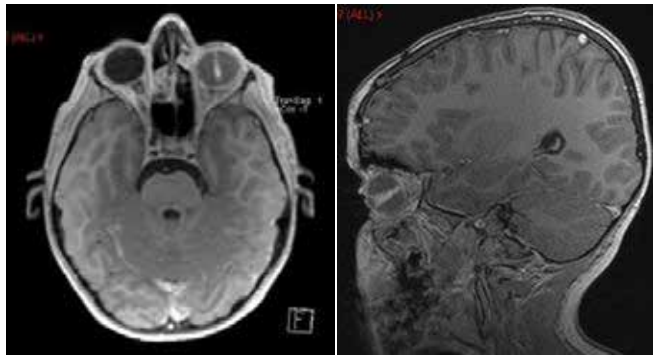

Figure 4. Control contrast-enhanced cranial MRIs, two months after the treatment. On axial and sagittal T1-W images there was no recurrence.

Discussion

PNET cells are derived from neuroectoderm which appears primitive. There are two types based on the tumour location: (1) PNETs in the CNS; (2) pPNETs outside the nervous system [1-3]. Primary orbital location which is a type of pPNET, as we present in our case, is extremely rare[1,3]. pPNET occurs predominantly in children and young adults and show no gender difference [1,6,7]. Imaging and histopathology, though supportive, do not confirm the diagnosis. Immunohistochemical and cytogenetic studies help in the confirmation of diagnosis. Microscopically, primary pPNETs are cellular tumours with small round cells that have hyperchromatic nuclei, and a high nuclear–cytoplasmic ratio. pPNETs differ in their degree of neuroectodermal differentiation. They are classified under Ewing's family of tumours (extraosseous type), with which they share histopathological and cytogenetic similarity [1,3,8]. Immunohistochemical and cytogenetic

studies suggest that these tumours have a common origin. pPNETs occur in soft tissues of the body, resembling soft tissue sarcomas (small, round blue-cell tumours) but have the same chromosome translocation as soft tissue Ewing's sarcoma. PNETs and Ewing's sarcomas commonly have a t (11; 22) (q24; q12) translocation [9]. In PNET, there are varying degrees of neuronal differentiation, beginning with the expression of the neuron-specific enolase (NSE), followed by Homer-Wright rosette formation, phenotypic ganglion cell differentiation, and finally by the expression of neurofilament protein. The presence of Homer-Wright rosettes is associated with these tumours but it is not diagnostic for these tumours [6]. Ewing's sarcoma family includes Ewing's sarcoma, pPNET, neuroepithelioma, atypical Ewing's sarcoma and Askin's tumour (tumour of the chest wall). pPNETs are commonly present in the thoracopulmonary region (Askin's tumour), abdomen, pelvis or the extremities [1, 3]. In PNET, immnunohistochemical studies can be positive for one or several neural or glial markers: synaptophysin, CD99 (MIC2 gene), glial fibrillary acid protein, neurofilaments, chromogranin, S100 protein, CD57 (LEU-7/HNK-1), and vimentin. Expression of the MIC2 gene produces a glycoprotein antigen MIC2 (CD99), which consistently identifies pPNETs/Ewing's sarcoma. These sarcomas typically co-express CD99 (MIC2) and vimentin, but central nervous system PNETs (that is, not meningeal PNETs) lack the expression of CD99. Positive staining for the cited neural markers is very suggestive of pPNETs, but it is important to consider the lack of specificity of most neural markers and the variable immunohistochemical features of pPNET. Ultrastructural studies show the presence of neurosecretory granules, cytoplasmic filaments, cytoplasmic microtubules and synaptic-like junctions. Electron microscopy is a very useful technique but it is not available in many centers [3, 4,6,9-11]. CD99 (MIC2 gene), NSE and synaptophysin were positive in our case, and this confirmed the diagnosis of pPNET. PAS reaction rules out Ewing's sarcoma as in our case. The majority of sarcomas that are a part of the differential diagnosis of primary pPNET of the orbit are shown in Table I [4,6,11].

pPNETs that occur in the head and neck region are uncommon in most published case series [7, 11]. The incidence of pPNETs is likely to be underreported in the literature. However, Romero [11] reported 16 cases, Hemalatha et al. [5] reported 17 cases with orbital pPNET. According to Hemalatha's study, only 18 cases have been reported in the literature.

Orbital pPNETs tend to occur in younger patients when compared with other pPNETs. Only 3 of the 18 published cases were older than 13 years at the time of diagnosis [3,5,11]. The clinical features of pPNETs depend on the site of presentation and mass effect. pPNETs are highly aggressive, and metastasis may be the first presentation. The most common sites of pPNET metastasis include the lung, bone and bone marrow [5,11-13]. The lack of metastasis in the orbital form of pPNET could be explained by the poor lymphatic system of the orbit [11].

The treatment for pPNET usually involves a combination of surgery and chemotherapy with or without radiotherapy [3,6,11]. The modality of treatment depends on the type, site and size of tumour, extent of metastasis as well as the age and general health status of the patient. Surgery has been the initial treatment for orbital pPNET in most cases and has been the initial therapeutic approach used in our patient, althoug some of the published cases have been treated with chemoteraphy and radiotherapy without surgery, with good results [6]. Our case was managed with successful resection of the mass, chemotherapy and external beam radiotherapy. There was no recurrence on the control investigation performed two months after the operation.

Conclusion

When a primary hypercellular small round cell tumour of the orbit is encountered, the recently recognized rare pPNET of the orbit should be considered in the differential diagnosis although the orbit is an extremely rare site for such a tumour. Accurate diagnosis of these tumours is of paramount importance. Immunocytology helps to confirm the diagnosis. Management should be aggressive using multimodality treatment approaches given at the appropriate time. These patients should be followed up for life to rule out recurrence, metastasis and treatment-related malignancies.

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