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SUMMARY

Peripheral primitive neuroectodermal tumors (pPNETs) are a group of soft tissue tumors of neuroepithelial origin, that arise outside the central and sympathetic nervous system. Orbital location is infrequent, to the best of our knowledge only sixteen cases have been reported in the literature. With this article we would like to report the demographics and clinical characteristics, diagnostic features, differential diagnosis, prognosis and therapeutic options of primary orbital peripheral primitive neuroectodermal tumor, based on our patients and on the cases reported in the literature up to now. Differential diagnosis should be made with other small round cells tumors, immunohistochemical and ultrastructural techniques are essential for this purpose. Although bone invasion and extraorbital extension are possible, systemic metastases are uncommon in the cases of orbital pPNETs. Surgery has been the initial treatment in most cases; chemotherapy +/- radiotherapy is considered the best additional treatment. The orbital variety seems to be less aggressive than other forms of pPNETs since most of the patients reported were alive after the follow up period (at least 6 months).

MAIN TEXT

INTRODUCTION

Peripheral primitive neuroectodermal tumors (pPNETs) are a group of malignant soft tissue tumors of neuroepithelial origin that arise outside the central and sympathetic nervous system, and occur predominantly in children and young adults.

Histopathologically, pPNET consists of small round cells with hyperchromatic nuclei, high nuclear-cytoplasmic ratio and varying degrees of neural differentiation detected by immunohistochemical and/or ultrastructural techniques.

The first case of pPNET was reported by Stout in 1918 located in the ulnar nerve¹. In 1973, Hart and Earle introduced the term primitive neuroectodermal tumor (PNET) to describe embryonal neoplasms of the central nervous system that did not fulfil the diagnostic criteria for other entities², and it was not until the late 1970s that pPNET was admitted as an own entity.

Orbital location is unusual, to the best of our knowledge only 16 cases have been reported in the literature up to April' 10^{3,4,5,6,7,8,9,10,11,12,13,14,15,16,17}. We describe one case of primary orbital pPNET and discuss its clinical, histopathologic, radiologic, and therapeutic features based on our patients and on the cases reported in the literature.

MATERIALS AND METHODS

We reviewed the clinical record of one patient diagnosed with orbital pPNET in the Department of Paediatric Ophthalmology of University Hospital La Paz, Madrid, a tertiary referral centre in Spain. Recorded data included the following characteristics: demographic (age, gender), clinical (signs and symptoms, orbital location, recurrences, metastases, follow up), histopathologic, radiologic, and therapeutic.

An intensive online literature search was made in order to find all the orbital pPNET cases reported up-to-date. The sources used for the literature search included PubMed (<http://www.pubmed.com>) and The Cochrane Library (<http://cochranelibrary.com>) and the terms utilized for the search were: “Orbital peripheral primitive neuroectodermal tumor”, “Orbit peripheral primitive neuroectodermal tumor.”, “Orbital primitive neuroectodermic tumor”, “Orbit primitive neuroectodermic tumor”, “Orbital peripheral primitive neuroectodermal tumour”, “Orbit peripheral primitive neuroectodermal tumour.”, “Orbital primitive neuroectodermic tumour”, “Orbit primitive neuroectodermic tumour”, “Orbit neuroepithelioma”, “Orbital neuroepithelioma”.

CASE REPORT

A previously healthy 22-month old boy with proptosis of the right eye for the last week was referred to our hospital in February 2006.

External ocular examination showed mild eyelid inflammation and proptosis with diminished retropulsion of the right eye. The mentioned eye was displaced laterally and inferiorly with restriction of ocular movements superiorly. Apparently there was no pain. Visual acuity could not be measured because of lack of collaboration. Biomicroscopy found a 2 millimetres (mm), round, superficial, inferior ulcer in the right eye. Funduscopy of both eyes was unremarkable and intraocular pressures were normal. A computed tomography (CT) scan of the right orbit found a poorly-defined, extraconal orbital mass, superomedially located, with lateral and inferior displacement of the globe. The mass enhanced after contrast administration and measured 15x18x18 mm. There was no evidence of extraorbital extension or bone erosion (Figures 1A, 1B). A non-homogeneous lesion with some cystic spaces was described in the B-scan orbital ultrasonography performed.

A few days after the first examination, the patient was seen in the emergency department of our hospital because of acute worsening of proptosis and periorbital hematoma. An excisional biopsy of the mass, via transconjunctival orbitotomy, was then performed removing most of the tumor. The tissue was formalin fixed, processed for paraffin embedding and subsequently stained with hematoxylin-eosin and periodic acid-Schiff (PAS). Microscopically the tumor had several hemorrhagic and necrotic areas and was composed of small round blue cells with scant clear cytoplasm, inconspicuous nucleoli and high mitotic activity (Figure 1C). No rosettes or pseudorosettes were found. The PAS reaction was positive (Figure 1D). Sections were studied immunohistochemically using the following antibodies: neuron-specific enolase (code no. IR612, Dako), synaptophysin (code no. IR776, Dako), CD99 (MIC2 gene) (code no. IR057, Dako), glial fibrillary acid protein (code no. IR524, Dako), neurofilaments (code no. IR607, Dako), chromogranin (code no. IR502, Dako), S100 protein (code no. IR504, Dako), vimentin (code no. IR630, Dako), CD57 (LEU-7/HNK-1) (code no. IR647, Dako), common actin (clone HHF35, Dako), desmin (code no. IR606, Dako), CD45 (code no. IR751, Dako) and low molecular weight cytokeratin (NCL-L-CK8-TS1, Novocastra). The antibodies were applied synchronously with appropriate positive control slides. The tumor cells were positive for synaptophysin, neurofilaments (Figure 1E), CD99 (Figure 1F), chromogranin, S100 protein, vimentin and CD57. No cells were stained with antibodies against neuron-specific enolase, glial fibrillary acidic protein, desmin, common actin, CD45 and low molecular weight cytokeratin. After these histopathological and immunohistochemical findings the diagnosis of primitive neuroectodermal tumor was made.

The extensive systemic evaluation (bone marrow biopsy, cranial magnetic resonance imaging (MRI), and CT scans of thorax, abdomen, pelvis and extremities) was negative and the diagnosis of orbital pPNET was established.

The patient was successfully treated with additional radiotherapy and chemotherapy (vincristine, ifosfamide, doxorubicin, etoposide, cyclophosphamide, actinomycin), according to the Spanish Society of Paediatric Oncology (SEOP) 2001 recommendations for Ewing's sarcoma¹⁸, and he is in remission up to February'10. Consecutive orbital imaging techniques performed over these years have not detected tumoral pathology (Figures 2A, 2B).

Although very infrequent, another case of orbital pPNET was diagnosed in our department a few years ago⁷. While reviewing this case, the tumor samples were recovered and new and more complete histopathological studies, including immunohistochemical stains, were performed obtaining new results. Paraffin sections of the tumor were stained with hematoxylin-eosin and PAS. Histopathologic examination demonstrated a proliferation of small, round blue cells with scant clear cytoplasm and without nucleoli. There were some foci of necrosis and frequent mitotic figures. No rosettes or pseudorosettes were identified. The PAS stain was negative. Sections were studied by immunohistochemistry for the list of antibodies mentioned in the previous case. These antibodies were applied synchronously with appropriate positive control slides. Immunohistochemically the tumor cells expressed synaptophysin, neurofilaments, CD99 and vimentin. All other stains (neuron-specific enolase, glial fibrillary acid protein, chromogranin, S-100 protein, CD57, common actin, desmin, CD45, low molecular weight cytokeratin) were negative.

RESULTS

PPNETs located in the orbit are extremely rare, only sixteen cases were found after an intensive online literature search. The most important data of these sixteen cases are summarized in table 1.

	Age/ Gender	Inicial signs/ symptoms	Orbital location	Bone invasión/ Extraorbital extension	Rosette	Inmuno histo chemistry	Electron microscopy	Metastases/ Recurrence	Treatment	Status/ Follow Up
CASE 1 Kim et al ³	2 years/ male	Proptosis right eye	Infero medial	No	+	NSE CD99	N/A	No/No	CHT RT	Alive/ 30 months
CASE 2 Das et al ⁴	8 years/ female	Proptosis left eye	Supero lateral	No	+	CD99 (pseudo rosette)	N/A	No/No	Surgery	Alive/ 6 months
CASE 3 Romero et al ⁵	10 months/ female	Proptosis right eye	Infero medial	No	+	CD99 S100 Vimentin	N/A	No/No	Surgery CHT RT	Alive/ 17 months
CASE 4 Tamer et al ⁶	10 years/ male	Proptosis, deviation right eye. Diplopia	Infero lateral	No	-	NSE S100	Cytoplasmic filaments Neurosecretory granules	No/No	Surgery RT	Alive/ 8 months
CASE 5 Romero et al ⁷	6 years/ male	Proptosis right eye	Medial	No	-	CD 99 Vimentin NF	N/A	Yes (Lungs)/ Yes	Surgery CHT RT	Dead/ 8 years

						SYTPH				
CASE 6 Lezrek et al⁸	13 years/ male	Proptosis right eye	Retro bulbar	Intracranial and sinusal extension	-	CD99 S100	N/A	No/ Yes	CHT RT	Alive/ 11 years
CASE 7 Sen et al⁹	13 years/ female	Mass in left lower lid	Inferior	Extension to the lower lid and left maxilla	-	NSE CD99 SYTPH	Cytoplasmic filaments Neurosecretory granules	No/ No	CHT	Dead/ 3 months
CASE 8 Hyun et al¹⁰	34 years/ female	Pain, blurred vision right eye	Retro bulbar	No	+ (pseudo rosette)	NSE S100 CD57	Cytoplasmic filaments Cytoplasmic microtubules Neurosecretory granules Synaptic-like junctions	Yes (Liver)/ Yes	Surgery CHT RT	Alive/ 35 months
CASE 9 Alyahya et al¹¹	5 years/ female	Proptosis, pain, swelling right eye	Retro bulbar	No	+ (pseudo rosette)	CD99 SYTPH	Neurosecretory granules	No/ No	Surgery CHT RT	Alive/ 34 months
CASE 10 Kiratli et al¹²	28 years/ male	Visual loss right eye	Lateral	No	+ +	NSE Vimentin	N/A	No/ No	Surgery	Alive/ 15 months

CASE 11 Singh et al¹³	10 years/ female	Painful lump in right eyebrow	Supero lateral	Bone invasion	-	NSE	Cytoplasmic filaments Neurosecretory granules	No/No	CHT RT	Alive/9 months
CASE 12 Arora et al¹⁴	13 years/ female	Proptosis left eye	Lateral	No	-	-	Neurosecretory granules	N/A/ N/A	Surgery	N/A/ N/A
CASE 13 Arora et al¹⁴	4 years/ male	Proptosis left eye	Lateral	No	-	-	Neurosecretory granules	N/A/ N/A	Surgery	N/A/ N/A
CASE 14 Wilson et al¹⁵	7 years/ female	Proptosis left eye	Supero medial	Intracranial extension	+	NSE	Cytoplasmic microtubules Neurosecretory granules	No/No	Surgery CHT RT	Alive/ 45 months
CASE 15 Shuangshoti et al¹⁶	52 years/ male	Proptosis right eye	Lateral	No	+	GFAP	N/A	No/No	Surgery RT	Alive/6 months
CASE 16 Howard et al¹⁷	8 months/ male	Swelling right lower lid	Inferior	Bone invasion	+	N/A	N/A	Yes (Lymph node)/ Yes	Surgery RT	Dead/ 14 months

Present	22	Proptosis	Supero	No	-	CD 99	N/A	No/No	Surgery	Alive/ 4
case	months/ male	right eye	medial			S100			CHT	years
						Vimentin			RT	
						NF				
						SYTPH				
						CD57				
						Chromogranin				

+: present. -: absent. N/A: non available.

NSE: neuron-specific enolase. S100: S100 protein. NF: neurofilaments. SYTPH: Synaptophysin. GFAP: glial fibrillary acid protein.

CHT: chemotherapy. RT: radiotherapy.

Orbital pPNETS mainly affect patients in paediatric ages, thirteen of the sixteen reviewed cases were younger than sixteen years of age. No sex predilection was detected.

Proptosis was the initial sign reported in the majority of cases. The most frequent orbital locations were the lateral wall (seven cases) and the inferior wall (four cases). In more than two thirds of the patients the tumor appeared in the right orbit.

Immunohistochemical techniques are the histopathologic diagnostic tool more often used to establish the diagnosis of pPNET. Neuron-specific enolase and CD99 are the immunohistochemical markers more commonly detected in the published cases, followed by S100 protein, synaptophysin, and vimentin. Ultrastructural techniques were used in eight patients, in two cases to make the histopathologic diagnosis and in the rest to confirm the results obtained by immunohistochemistry.

Bone invasion +/- extraorbital extension was detected in five cases but only three patients developed metastases (liver, lungs and lymph node). Just one of these three

patients, the one with lymph node involvement, showed bone invasion or extraorbital extension.

Multi-discipline treatment, including different combinations of surgery, chemotherapy and radiotherapy, has been used to treat most of the orbital pPNETs reported. Four patients were managed only with surgery without additional radiotherapy or chemotherapy.

Survival time was longer than thirty months in seven of the seventeen patients. Five of these seven patients with longer survival time were treated with surgery, chemotherapy and radiotherapy, the remaining two patients received chemotherapy and radiotherapy without surgery.

DISCUSSION

PNETs are a group of heterogeneous malignant neuroepithelial tumors that presumably origin from the neural crest⁹. According to the third edition of International Classification of Childhood Cancer¹⁹ and to the 2007 World Health Organization²⁰, PNETs are embryonal neoplasms that occur predominantly in children and young adults.

The majority of PNETs arise in the central nervous system and in the sympathetic nervous system. When they occur outside these locations they are called pPNETs being the thoracopulmonary region the most common primary site of pPNET, followed by the head and neck^{21,22,23}.

There is considerable controversy concerning the histogenesis of pPNET. Different hypotheses have been postulated to explain the presence of PNET out of the central nervous system and the sympathetic nervous system: spread out of undifferentiated

neuroepithelial cells to the peripheral tissues from the neural tube; migration of neuroepithelial cells in association with peripheral nerves^{16,17}.

PPNET represents 4-17% of all paediatric soft tissue tumors and appears more often in adolescents and young adults with no sex predilection^{25,51}.

Primary orbital pPNET is very infrequent, only 16 cases have been reported in the literature. There is an additional article published as an orbital pPNET²⁴ but this case corresponds to a melanotic neuroectodermal tumor with distinct clinical and histopathological features.

Orbital pPNET tend to occur in younger patients in comparison with other pPNET, only 3 of the 16 published cases had more than 13 years of age at the diagnosis.

Histopathologically pPNETs are composed of small, round, hyperchromatic cells with varying degrees of neural differentiation. Differential diagnosis should be made with other small round cell tumors as: Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, lymphoma, osteogenic sarcoma and mesenchymal chondrosarcoma. In the past, pPNETs have been included within Ewing's sarcomas because they share microscopic, molecular and genetic abnormalities. Many authors consider that pPNET and extraosseous Ewing's sarcoma represent opposite ends of the same spectrum of malignancy²⁵. Both tumors present the same genetic aberrations, that is, translocation (11;22)(q24;q12)^{26,27,28} and less common, translocation (21;22)(q22;q12)^{29,30}.

Translocation (11;22)(q24;q12) results in the fusion of EWSR1 gene (Ewing's sarcoma gene) with the FL1 gene while in translocation (21;22)(q22;q12) the fusion occurs between EWSR1 gene and ERG gene. Other chromosomal rearrangements: translocation (7;22)(p22;q12)³¹, translocation (2;22)(q33;q12)³¹, translocation (17;22)(q12;q12)²⁹, and translocation (4;19)(q35;q13)³² are rare. PPNET can be distinguished from Ewing's sarcoma and other small round cell tumors by establishing

neural differentiation. Immunohistochemical and/or ultrastructural techniques are essential for this purpose. Ewing's sarcoma has a better prognosis than pPNET, making necessary the distinction between these two entities. Schmidt et al reported a disease-free survival rate in Ewing's sarcoma patients at 7.5 years follow-up of 60% compared with 45% in pPNET patients³³.

As mentioned above, histopathologically, pPNET demonstrates varying grades of neural differentiation. Microscopically we can see Homer-Wright rosette formation; identification of Homer-Wright rosettes is associated with these tumors but it is not diagnostic of pPNET. Immunohistochemical studies can be positive for one or several neural markers: neuron-specific enolase, synaptophysin, CD99 (MIC2 gene), glial fibrillary acid protein, neurofilaments, chromogranin, S100 protein, CD57 (LEU-7/HNK-1), and vimentin. Positive staining for the cited neural markers is very suggestive of pPNET, but it is important to consider the lack of specificity of most neural markers and the variable immunohistochemical features of pPNET.

Ultrastructural studies by electron microscopy 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. Although in the case we present, no rosettes were identified on light microscopy, neural differentiation was established immunohistochemically. Unluckily we could not access to studies with electron microscopy in order to confirm ultrastructurally the diagnosis. With the improvement of the diagnostic techniques, probably more cases of pPNET will be reported in the future and it is possible that some so-called extrasosseous Ewing's sarcoma, today would have been diagnosed as pPNET.

PPNET are aggressive tumors. Bone invasion and extraorbital extension have been described in the published cases of orbital pPNET^{8,9,13,15,17}, but only two cases showed

systemic metastases^{7,10}, and regional lymph node involvement was found in another case¹⁷. None of the two cases with systemic metastases showed local bone invasion or extraorbital extension. Common locations for metastases from pPNETs include bone marrow, bone, brain, and lungs. The lungs⁷ and the liver¹⁰ are the sites of the metastases reported in the two cases of orbital pPNET. The lack of metastases in the orbital form of pPNET could be explained by the poor lymphatic system of the orbit.

There is no general consensus for the best therapeutic strategy for pPNET and a therapeutic approach similar to that utilized for Ewing's sarcoma has been used because of similarities between the two tumors^{18,34,35,36}. Surgery has been the initial treatment for orbital pPNET in most cases and has been the initial therapeutic approach used in our patients, although some of the published cases have been treated with chemotherapy and radiotherapy without surgery, with fairly good results^{3,8,13}. When performed, surgery should remove the tumor completely but this might be technically difficult.

Chemotherapy +/- radiotherapy is considered by many authors as the best additional treatment^{3,5,8,10,11,13,15,37}. Recent studies suggest that multi-discipline treatment including systemic chemotherapy and surgery could prolong survival in patients with Ewing's sarcoma family tumors³⁸. The mentioned study reports that CAV/IE (Cyclophosphamide, Adriamycin, Vincristine/ Ifosfamide, Etoposide) scheme might be better than other chemotherapy schemes. This chemotherapy modality has been used with good results in some of the latest cases of orbital pPNET published^{3,5}, and it is very similar to the chemotherapy protocol used in our patient following the Spanish Society of Paediatric Oncology (SEOP) 2001 recommendations for Ewing's sarcoma¹⁸. Other authors defend the role of radiotherapy in the treatment of these tumors. Laskar et al suggest that radiation remains an important component in the multimodality management of Ewing's sarcoma family tumors, recommending the use of post-

operative radiotherapy when gross or microscopic positive margins are reported and when there are clear margins but there is a poor histopathological response to chemotherapy³⁹; according to the Cooperative Ewing Sarcoma Study (CESS) and to the European Intergroup Cooperative Ewing Sarcoma Study (EICESS) a poor histopathological response is considered when necrosis is less than 90%⁴⁰ however other authors show better results when the necrosis threshold is 95% or even 99%^{35,41}.

The timing of post-operative radiation is an issue to be solved, some authors recommend the radiation after surgery within 6-10 weeks of surgery^{39,42}, while others report no significant difference with further delay⁴³.

The best survival results in the orbital pPNET patients, have been obtained in those treated with surgery, chemotherapy and radiotherapy. Five of the published patients, and the present case, have been treated with such therapeutic combination and the survival time has been longer than thirty months for all of them^{7,10,11,15}, except for one patient that was seventeen months⁵.

New therapeutic approaches based on Ewing's sarcoma biology, such as anti-vascular endothelial growth factors^{44,45}, anti-insulin-like growth factors^{46,47} retinoic acid derivatives^{48,49}, and agents that interfere with the mTOR (mammalian target of rapamycin)⁵⁰ are on study and represent promising future therapeutic options.

PPNETs have rapid progression and bad prognosis, metastases and local extension are often found during initial diagnosis. The overall survival rate of pPNET is poor, Kushner et al documented a progression-free survival of localized tumors greater than 5 centimetres of 25% at 24 months⁵¹. Orbital variety seems to be less aggressive than other forms of pPNET since most of the patients reported were alive after the follow up period (at least 6 months), and since seven of the seventeen patients (41.2%) have been

alive for at least 30 months. Longer follow-up of the patients is needed to evaluate the long-term prognosis of orbital pPNET.

In conclusion, management of these tumors must be aggressive using multi-discipline treatment and a regular follow-up is mandatory to rule out recurrences and metastases.

Further studies are necessary to determinate the best therapeutic guideline.

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