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Case Report

Congenital peripheral primitive neuroectodermal tumor: A case treated successfully with multimodality treatment

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KEYWORDS

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Abstract Neonatal tumors comprise less than two percent of childhood malignancies. Most are solid tumors, most common histologies being teratoma and neuroblastoma. We encountered a child who was detected to have a right arm mass on antenatal sonogram, which was diagnosed to be a primitive neuroectodermal tumor involving the triceps on fine needle aspiration cytology performed in the post-natal period. The child was successfully treated with multimodality treatment consisting of surgery, chemotherapy and radiotherapy. We also discuss briefly the problems associated with therapy in neonatal period. A review of all cases reported to have congenital Ewing's sarcoma family of tumors is presented. Novel therapies are needed to improve efficacy and decrease the devastating side effects of treatment in this age group.

Introduction

Ewing's sarcoma family of tumors (ESFTs) is a group of tumors of neural crest origin, consisting of Ewing's sarcoma (ES), Askin's tumors, and peripheral primitive neuroectodermal tumors (pPNETs) [1]. Mean age at diagnosis is 15 years. With current multimodality regimens, five-year survival is 70% [2].

Neonatal presentation is rare, with 35 cases reported in the literature. We report an antenatally detected pPNET of triceps, successfully treated with multimodality therapy.

Case summary

A 13-month child presented to our department with a congenital right arm swelling. An antenatal maternal abdominal ultrasound (USG) at 37 weeks of gestation had shown a single live intrauterine fetus with no structural defects other than a 27 mm cystic subcutaneous right arm swelling (Fig. 1a and b). He was delivered at term by Caesarian section for meconium stained liquor. No other congenital defects were noted. The child's developmental milestones were normal.

At one month, a 5×5 cm non-tender, cystic, freely mobile swelling was noted posterior to the right elbow, with warm but uninvolved skin and dilated superficial veins. No enlarged lymph nodes were noted. Doppler USG showed a hyperechoic mass with vascular periphery, and normal underlying bone and

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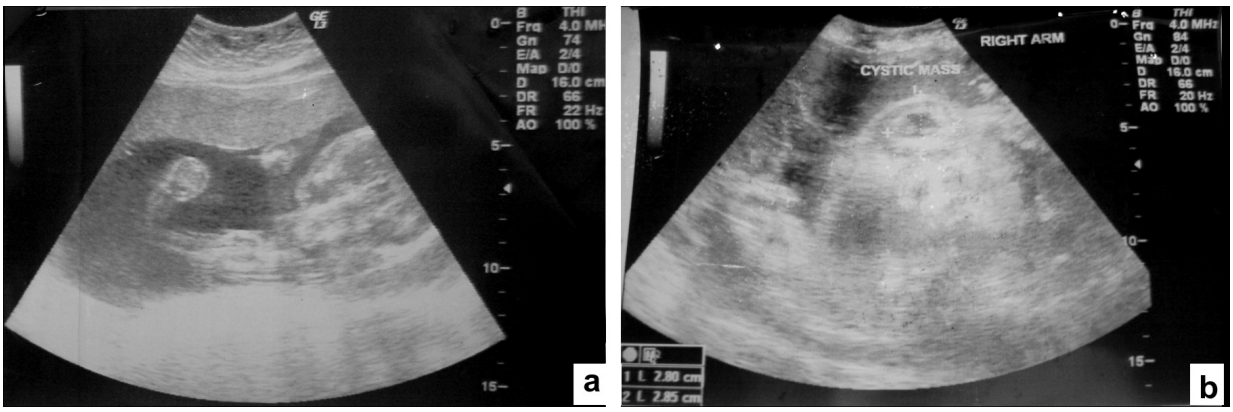

Figure 1 Antenatal ultrasonogram at 37 weeks' gestation showing (a) a single live intrauterine fetus with cephalic presentation, longitudinal lie and flexion attitude. A cystic swelling is seen arising from right arm, (b) the size of the arm swelling measures 2.80 × 2.85 cm.

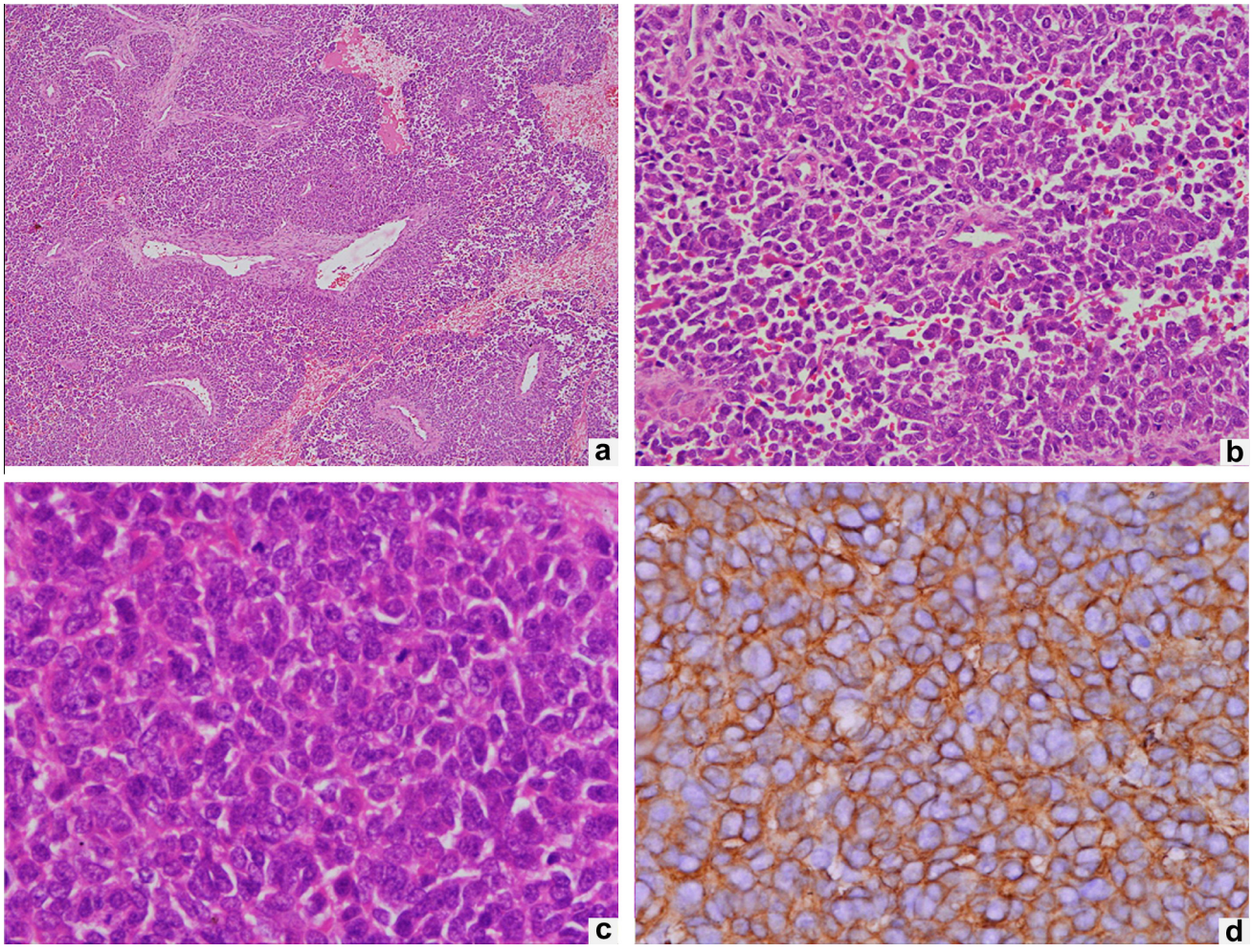

Figure 2 Photomicrographs showing a cellular tumor with rich vascularity (a) H&E ×40. Higher-power view showing predominant round cells with perivascular arrangement (b) H&E ×200. The tumor cells have scant cytoplasm, hyperchromatic nucleus without nucleolus and brisk mitotic activity (c) H&E ×400. Immunohistochemical staining for CD99 (MIC-2) demonstrates strong diffuse membranous positivity in the tumor cells (d) ×400.

brachial artery. Fine needle aspiration cytology suggested malignant round cell tumor. The tumor was excised with clear resection margins. Intraoperatively, the mass was adherent to triceps and cut section showed hemorrhage and necrosis.

Table 1 Cases of congenital pPNET reported in world literature.

S.No.	Author	Diagnosis	Site	Size	Mets	Surgery	Chemotherapy	Radiotherapy	Follow up	Overall survival
1	Angervall [3]	pPNET	Paravertebral (D10)	6 cm	NA	None	None	None	Lost to follow up	NA
2	Das L, Med Pediatr Oncol 1982 [5]	pPNET	Left chest wall	16 cm	Skin nodules	GTE	VCR + Cyclo A/W	9 Gy/8#, 6 MeV	Progressive disease, brain mets	3 months, 11 days (died)
3	Naidu MR, Indian J Pediatr 1989 [6]	ES	Frontonasal region	8 cm	None	GTE	None	Postop RT	CR	1 year (NED)
4	Hachitanda Y, Arch Pathol Lab Med 1990 [7]	pPNET	Rt temporal region	4.5 cm	Cervical LNs	Excision	1 Cycle VCR + Cyclo F/B CDDP	Focal RT 22.5 Gy	Progressive ds, local recurrence and CSF mets at 4 months post-op	11 months
5	Lim TC, Head Neck 1994 [8]	pPNET	Face	Small eyelid tumor, grew to 20 cm	None	Debulking				
	Cyclo + VCR + Epi + Mtx + CDDP	None	Progressive ds	10 months (died)						
6	Paley C, J Pediatr Hematol Oncol 1996 [9]	pPNET	Multiple cutaneous nodules	Few mm to 3–4 cm	None	None	None	None	Self-resolving, absent at 3 months	16 months (NED)
7	Erdmann D, J Hand Surg 1996 [10]	pPNET	hand	4 cm	None	Resection	VAC/IE × 12 cycles	None	CR	4 years (NED)
8	Kaneko, Genes Chromosomes Cancer 1996 [11]	pPNET	Cheek	9 cm	None	Partial resection				
	Carbo + cyclo + Pirarubicin + CDDP + Eto	None	CR– > Progressive ds (bone marrow, pelvis, liver mets)	2 years (died)						
9	Daw JL, J Hand Surg 1997 [12]	pPNET	Hand	4 cm	Yes (thigh and scalp mets)	Below elbow amputation, WLE thigh lesion	VAC	None	Progressive ds (periorbital and brain mets)	15 months (died)
10	Hsieh HY, Br J Radiol 1998 [13]	ES	Right humeral diaphysis	16 cm	None	Shoulder disarticulation	None	none	Soft tissue mets right thigh, left inguinal region	2 years (on FU)
11	Smith LM, Med Pediatr Oncol 1998 [14]	pPNET	Paraspinal (L2)	6 cm	Lung mets	Resection	Induction chemo, PSCT	Focal RT	CR– > recurrence at 8 years	8 years (died)
12	Wang JW, Acta Orthop Scand 1999 [15]	ES	Right humerus, ST extn+	10 cm	None	Refused initially, shoulder disarticulation for palliation	None	None	↑ Size, lung and liver mets	1.5 years (died)
13	Lee, Med Pediatr Oncol 2000 [16]	pPNET	Sacrococcygeal region	> 5 cm	None	Debulking	No	None	Progressive ds (brain mets)	3 months (died)
14	Sebire NJ, Pediatr Dev Pathol 2002 [16]	pPNET	S/C masses, upper back	NA	NA	Yes (details NA)	IVAD	None	CR	Alive
15	Sebire NJ, Pediatr Dev Pathol 2002 [17]	pPNET	Forearm	NA	NA	none	none	Palliative RT	Progressive ds	1 week (died)
16	Sebire NJ, Pediatr Dev Pathol 2002 [17]	pPNET	Neck	NA	NA	none	IVAD	none	Progressive ds	6 months (died)
17	Sebire NJ, Pediatr Dev Pathol 2002 [17]	pPNET	Sacrum	NA	NA	Yes (details NA)	VCR + AMD	none	Progressive ds	3 months (died)
18	Sebire NJ, Pediatr Dev Pathol 2002 [17]	pPNET	S/C masses, upper back	NA	NA	Yes (details NA)	IVAD	None	CR	Alive
19	Sebire NJ, Pediatr Dev Pathol 2002 [17]	PNET	Knee	NA	NA	None	None	None	Progressive ds	1 month (died)
20	Sebire NJ, Pediatr Dev Pathol 2002 [17]	pPNET	Neck	NA	NA	Yes (details NA)	IVAD	No	CR	Alive
21	Sebire NJ, Pediatr Dev Pathol 2002 [17]	pPNET	Axilla	NA		No	IVAD	No	Progressive ds	1.5 years (died)
22	El Hayek M, J Pediatr Hematol Oncol 2004 [18]	pPNET	Left hand	3.8 cm	No	None	VAC/IE × 4→ Cyclo + Topo × 2	None	Progressive ds, skeleton, lungs, liver, and brain mets	2.5 years (died)
23	Carvalho, Int J Pediatr Otorhinolaryngol 2006 [19]	PNET	Maxilla	4 cm	No	Partial resection	VCR + AMD (MMT95 protocol); Cyclo + Adria; Carbo + Eto	No	Progressive ds (local)	2 months (died)
24	Meazza C, J Pediatr Hematol Oncol 2008 [20]	pPNET	Abdomen	NA	Abdominal wall, liver	None	VCR + AMD 2 cycles	None	Progressive ds, peritoneal, lung, neck nodes	25 days (died)
25	Saito, Pediatr Blood Cancer 2008 [21]	ES	Retroperitoneum	6 cm	Brain, eye, spinal canal	None	VCR + Cyclo weekly followed by			
	VCR + Cyclo + Eto + Adria: 7 cycles	70.5 Gy to brain lesion, 33 Gy to	retroperitoneum	Progressive ds	2 years 10 months (died)					
26	Rosa, Pediatr Blood Cancer 2009 [22]	pPNET	Neck	13 cm	None	None	None	None	Perinatal death	Died at 14 h after birth
27	Ban, J Clin Neurosci 2010 [23]	pPNET	Paraspinal soft tissue	8 cm	None	T11-L1 laminectomy				
	VCR + Adria + Eto + CDDP High dose – 9 cycles followed by stem cell transplant	None	CR	17 months (NED)						
28	Atla, Indian J Pathol Microbiol 2011 [24]	ES	Chest wall	16 cm	None	None	None	None	Perinatal death	Died within 2 min of birth
29	Krenova, Am J Dermatopathol 2011 [25]	pPNET	Retroperitoneum	6 cm	Liver, lungs, mediastinum, bones, brain, cerebrospinal meninges	None	Cyclo–Topotecan (COG protocol for high risk neuroblastoma)	None	Progressive ds	4 months (died)
30	Kella, J Coll Physicians Surg Pak 2011 [26]	ES	Scapular region	7 cm	None	Gross excision	VCR-Adria	None	Progressive ds with neck nodes	1 month (died)
31	Crocoli, J Pediatr Surg 2012 [27]	pPNET	Chest wall	15 cm	Bone	Gross excision	VAC-ICE	None	CR	54 months (NED)

(*continued on next page*)

Table 1 (continued)

S.No.	Author	Diagnosis	Site	Size	Mets	Surgery	Chemotherapy	Radiotherapy	Follow up	Overall survival
32	Hawkes, Indian J Med Paediatr Oncol 2012 [28]	pPNET	Coccyx	2.5 cm	None	Gross excision	VAC 8 cycles	None	CR	16 months (NED)
33	Okpokowuruk, Pan Afr Med J 2013 [29]	ES	Ulna	12 cm	None	Above elbow amputation	None	None	Died of sepsis	2 months (systemic sepsis)
34	Jinkala, J Pediatr Hematol Oncol 2014 [30]	ES	Scapula	10 cm	Bone, bone marrow	Debulking	None	None	Progressive ds	NA
35	Jin, Pediatr Neonatol 2014 [31]	pPNET	Arm	5 cm	None	Gross excision	CDDP + Cyclo: 4 cycles	None	Progressive ds with lung and liver metastases	3 months (died)

Adria: adriamycin; AMD: actinomycin D; Carbo: carboplatin; CDDP: cisplatin; CR: complete response; Cyclo: cyclophosphamide; ds: disease; ES: Ewing's sarcoma; Eto: etoposide; GTE: gross total excision; IE: ifosfamide/epirubicin; IVAD: ifosfamide/vincristine/adriamycin; mets: metastases; NA: not available; pPNET: peripheral primitive neuroectodermal tumor; S/C: subcutaneous; Topo: topotecan; VAC: vincristine/actinomycin D/cyclophosphamide; VCR: vincristine.

Histopathology revealed a well-encapsulated, globular mass ($5.5 \times 4 \times 3$ cm), closest margin being one centimeter. Immunohistochemistry showed MIC-2 positivity, and synaptophysin and leukocyte common antigen negativity. Overall features suggested pPNET of the right arm (Fig. 2a–d). Staging workup ruled out systemic metastases. Postoperative MRI did not show any tumor residuum or axillary nodes.

He received 36 weeks of chemotherapy according to Pediatric Oncology Group/Children's Cancer Group (POG/CCG) protocol (VAC/IE), followed by adjuvant 3-D conformal tumor bed irradiation (6 MV photons, 45 Gray in 25 fractions), with no grade 3 or 4 morbidity. At seven years, he is disease-free, but has a comparative longitudinal limb shortening of two centimeters.

Discussion

Neonatal tumors comprise less than two percent of childhood malignancies, commonest histologies being teratoma and neuroblastoma. A high degree of genetic or syndromic association exists, although infections, maternal drug use and intrauterine ionizing radiation exposure may be responsible [3].

ESFTs are characterized by uniform, densely packed, small round cells with round nucleoli-free nuclei and indistinct cytoplasm. They express immunohistochemical (MIC-2 gene) and genetic markers ($t(11;22)$ and $t(21;22)$ translocations), as well as a novel fusion protein EWS-FLI1, suggesting neural crest origin [1]. Congenital ESFT is a rare entity. Angervall and Enzinger described 39 soft tissue tumors indistinguishable from ES of bone including one case of a 20-month boy with a congenital paravertebral mass [4]. The child did not receive any treatment and was lost to follow up. Treatment details in a congenital chest wall PNET were first described by Das et al. in 1982. Despite surgery, chemotherapy and radiotherapy, the child died of progressive disease after three months [5]. Other similar cases including ES or pPNET are mentioned in Table 1 [4–31]. Eleven of these patients achieved complete remission, seven following multimodality treatment, and one had spontaneous regression of cutaneous nodules [6,9–12,17,23,27,28].

Maygarden described 19 patients under three years with ES of bone, constituting 2.6% of all evaluable patients (19/734) registered in the five Intergroup ES Study protocols [32]. The most prominent differential in this age group is neuroblastoma, which can be distinguished by its neuron-specific enolase, Leu-7 and synaptophysin positivity, as well as *N*-myc amplification. There was a preponderance of females ($p < 0.001$) and a trend toward more proximal long bone, rib and pelvic tumors. All nineteen patients received chemotherapy and eighteen received radiotherapy. Overall survival (56%) matched with that in older children. Longest survival duration was 9.9 years. All disease-related deaths occurred within four years from diagnosis. Most prominent late morbidities in long-term survivors included post-radiation limb shortening in four children and adriamycin-related cardiotoxicity leading to cerebrovascular accident in one child.

In a recent NIH review, authors discuss various pertinent issues regarding congenital ESFT, namely, the truth to existence of such an entity, translocation-negative tumors, treatment options and outcome [33]. They quote three patients with round cell tumors initially misdiagnosed as other entities but later confirmed to have ESFT on molecular and immuno-

histochemical studies. They also mention, on the basis of a retrospective evaluation of 76 tumor samples, that characteristic translocations may occasionally be absent, either due to inadequate tissue, inadequate processing or, sometimes, existence of rare translocations that may be demonstrable only with nested RT-PCR or break-apart FISH analysis of EWS gene. They suggest that confirmatory analysis may not be warranted in diagnosis that is clear on histology and IHC. The clinical course in the retrospective evaluation of 21 cases described by the authors, however, was variable and did not appear to depend on the kind of translocations. The authors describe eight cases reported by Sebire et al., which have been assimilated in the current report as well; however three of these were diagnosed between three months and one year of age, and it is unclear if these were truly congenital.

European Soft Tissue Sarcoma Group recommends avoiding ifosfamide in children younger than a month and anthracyclines in those under three months. Immature organs, delayed chemotherapy clearance and possibility of long-term treatment effects are valid concerns, but reports show that these children tolerate VAC-based therapy well. In a retrospective evaluation of bone sarcomas treated on various POG/CCG protocols (1976–2005), only nine out of 1156 patients developed solid second malignancies at a median follow-up of 6.1 years. All nine patients had received cyclophosphamide, etoposide and radiation. Since one-third patients die from disease, relapse prevention still remains the major goal of therapy [34]. Treatment protocols incorporating novel chemotherapeutic and molecular agents, sophisticated surgical techniques and efforts to minimize radiation dose and volumes may help refine existing measures to enable these children attain a healthy and productive adulthood.

To our knowledge, this is the first case of an antenatally diagnosed congenital PNET treated successfully with current ESFT protocol, establishing its safety even in younger children. The long-term adverse effects need to be borne in mind while planning therapy, but not at the cost of compromised survival.

Conflict of interest

We have no conflict of interest to declare.

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