Published in final edited form as:

J Pediatr Hematol Oncol. 2008 January ; 30(1): 4–7. doi:10.1097/MPH.0b013e31815cf71f.

Dilemmas Associated With Congenital Ewing Sarcoma Family Tumors

Su Young Kim, MD, PhD,^{*}, Maria Tsokos, MD[†], and Lee J. Helman, MD^{*}

^{*}Pediatric Oncology Branch, National Institutes of Health, Bethesda, MD

[†]Department of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD

Abstract

The case report by Meazza et al describes the rapidly fatal outcome of a child born with a congenital peripheral primitive neuroectodermal tumor (pPNET). The case report prompted us to ask several questions. (1) Is there such an entity as congenital pPNET? (2) Do translocation-negative Ewing sarcoma family tumors (ESFT) exist? (3) What is the outcome for newborns with congenital ESFT and how does this affect treatment options?

IS THERE SUCH AN ENTITY AS CONGENITAL pPNET, OR ARE THESE MISDIAGNOSES?

Three cases demonstrate that congenital pPNET is a very rare disease entity. The first report describes a female newborn with a tumor in the cheek infiltrating the temporal fossa.¹ The tumor was partially resected and diagnosed as an undifferentiated sarcoma. Cytogenetics later revealed a t(17;22)(q12;q12) translocation. Molecular studies identified fusion of Ewing sarcoma (EWS) with E1AF, the first report of this specific binding partner. The baby underwent chemotherapy with carboplatin, cyclophosphamide, pirarubicin (adriamycin analog), etoposide, and cisplatin. Restaging at 1 year of age revealed no signs of tumor. However, metastatic disease to the bone marrow, pelvis, and liver was detected 9 months later and the baby died of progressive disease after several months.

The second report describes a newborn with a blue nodule on his hip.² The nodule increased in size and more nodules appeared over a period of several months. A biopsy suggested a diagnosis of an immature peripheral nerve sheath tumor, but efforts to locate the primary lesion were negative. The patient returned at 2 years of age with an enlarging mass in the paraspinal region. At this point, biopsy revealed a small round cell tumor and cytogenetics revealed t(7;22)(p21;q11.2), consistent with a EWS-ETV1 translocation. The child was treated with chemotherapy, autologous stem cell transplant, and consolidative radiation and did very well. However, at the age of 8, the patient presented again with widespread metastatic disease and passed away shortly thereafter (Dr Lynn Smith, personal communication).

The third report describes a female baby, born with a mass localized in the mouth and nasal cavity.³ Biopsy suggested a histologic diagnosis of alveolar rhabdomyosarcoma. The lesion progressed despite chemotherapy consisting of vincristine and actinomycin. At 1 month of age, reverse transcription polymerase chain reaction (RT-PCR) demonstrated the EWS-FLI1

fusion product, and the diagnosis was changed to a pPNET. The tumor progressed rapidly despite treatment with adriamycin and cyclophosphamide, followed by etoposide and carboplatin. The baby died of respiratory complications at 2 months of age. Autopsy was not performed.

These 3 cases demonstrate that congenital pPNET is a disease entity. In all of these cases, the initial diagnoses were incorrect. This is understandable, considering that small round cell tumors bear their name because of their similar histologic appearance. These include alveolar rhabdomyosarcoma, desmoplastic small round cell tumor, lymphoma, neuroblastoma, poorly differentiated synovial sarcoma, and the more recently described midline carcinoma with t(15;19) translocation.⁴ Another small round blue cell tumor is EWS, which is now considered to be the poorly differentiated counterpart of pPNET. EWS and pPNET, as well as the so-called Askin tumor (pPNET of the chest wall) belong to the same group of tumors and are collectively termed ESFT. These tumors are characterized by the same molecular translocations and immunophenotyping. Immunohistochemistry is very effective in distinguishing ESFT from other small round cell tumors. However, many times, poor quality of the sample or lack of definitive staining of the sample makes diagnosis very difficult. Because the majority of pediatric solid tumors are defined by specific translocations, molecular studies have been instrumental in confirming, or in some cases, in defining the diagnosis.

DO TRANSLOCATION-NEGATIVE ESFT EXIST?

This question has been answered in 2 recent publications and summarized in a commentary that accompanies these articles.⁵⁻⁷ Theoretically, the answer is No, but practically the answer is Yes.

Ng et al⁵ report the case of a balanced t(2;16) (q35;p11) translocation that brings together FUS and FEV. FUS has considerable homology with EWS. Both are members of the TET (TLS/FUS—EWS—TAFII68) family of RNA-binding proteins. Translocations involving FUS would not be detected if only EWS is tested. Wang et al⁶ report the case of an EWS-SP3 fusion. SP3 contains a zinc finger DNA-binding domain. Both of these findings increase the number of different binding partners in ESFT to a total of 12. Wang et al⁶ describe these translocations in detail and we summarize their tables below for convenience.

It is expected that all ESFT samples will be translocation positive. Currently, there are 18 cases of non-EWS-FLI1 and non-EWS-ERG translocations.⁶ This demonstrates that these translocations are so rare, that confirmative molecular analysis may not be warranted, especially if the diagnosis is clear. It is also likely that other rare translocations will be identified in the years to come.

Our belief is that molecular studies are more accurate than immunohistochemistry for diagnosis. The policy at our institution is similar to that used by Meazza et al. Samples are tested for EWS-FLI1 and EWS-ERG by RT-PCR. In cases where the histology suggests a paucity of viable sample, nested RT-PCR is performed. In cases that are negative, break-apart FISH analysis of the EWS gene is performed. In translocation-negative samples, and when a diagnosis of ESFT is not clear, we attempt to definitively rule out other etiologies.

A retrospective study performed at our institution evaluated 76 tumor samples with a histopathologic diagnosis of ESFT.⁸ Eighteen samples were translocation-negative. Of these, 7 were inadequate for RT-PCR testing as a result of inappropriate tissue handling or tissue necrosis and lack of viable tumor cells. Six samples in which adequate tissue was obtained had no evidence of any characteristic translocation. Five patients (7%) were found to have a different diagnosis after histopathologic and molecular characterization. The

revised diagnoses were as follows: neuroblastoma, Wilms' tumor, malignant peripheral nerve sheath tumor, and undifferentiated sarcoma in 2 cases.

The effort by Meazza et al to rule out other possible tumors was substantial. Most clinicians would have suspected neuroblastoma in a newborn with an abdominal mass and a blueberry skin nodule. The fact that CD99 was expressed in a membranous pattern and that EMA was also expressed suggested that the nodule was not a neuroblastoma. The lack of detection of the more common translocation transcripts EWS-FLI1 and EWS-ERG suggested the possibility of an uncommon rearrangement (EWS-ETV1, EWS-E1AF, EWS-FEV). However, the lack of rearrangement by break-apart EWS FISH analysis suggested that EWS was not involved in this tumor. The presence of a FUS, or another uncommon variant, translocation remains a possibility.

WHAT IS THE OUTCOME OF A CHILD BORN WITH A CONGENITAL ESFT, AND HOW DOES THIS AFFECT TREATMENT OPTIONS?

The rarity of this tumor type, in combination with the paucity of patients who present in the neonatal period, makes it very difficult to provide an authoritative answer to this question. The clinical courses of the 3 patients who had molecular confirmation of congenital ESFT differed greatly. One infant had significant progression of the tumor despite intensive chemotherapy.³ One child was disease free after adjuvant therapy but developed recurrent disease after 21 months.¹ The third patient had prolonged survival after adjuvant therapy, however, succumbed to metastatic disease at 8 years of age.² The latter 2 cases involved uncommon translocations (non-EWS-FLI1 and non-EWS-ERG). However, the presence of an uncommon translocation does not seem to predict the course of disease. Wang et al⁶ have shown that clinical outcomes are quite variable for patients with uncommon translocations, with some patients presenting with metastatic disease and progressing rapidly, whereas others have long periods of disease-free survival.

Meazza et al have referenced almost all of the reports of congenital ESFT in their paper. We have added 2 additional cases.^{1,3} The table below is a summary of course and outcome in cases that we could evaluate.

The most optimistic interpretation of these cases suggests that 6 of 21 (29%) patients are alive. This excludes 1 of the patients, who recurred with metastatic disease at 2 years of age and whose family refused further therapy (Ref. 10). However, the only documented long-term survival is at 4 years (Ref. 13). Long-term follow-up of the 3 patients described in Ref. 17 was not possible (Dr Neil Sebire, personal communication). Therefore, the most pessimistic interpretation of the above data would suggest only a 5% (1/22) chance of long-term survival. One of the patients had multiple cutaneous nodules at birth, covering the scalp, face, chest, back, and the extremities (Ref. 9). By 3 months of age, all of the lesions had disappeared without any treatment. The baby had no signs of recurrence at 16 months of age.

The other 5 children who are alive had the common feature of undergoing surgery followed by therapy with either radiation or chemotherapy (Refs. 11,13,17). This is not surprising, because it is consistent with current treatment protocols for ESFT. Local control, either by surgery or radiation therapy, must be accompanied by intensive chemotherapy to eliminate micrometastatic disease. The standard protocol for metastatic ESFT calls for 5-drug therapy, consisting of VAdriaC/IE (vincristine, adriamycin, cyclophosphamide, ifosfamide, etoposide). Meazza et al based their chemotherapy regimen on a presumptive diagnosis of rhabdomyosarcoma. The current COG protocol for metastatic rhabdomyosarcoma also calls for a backbone of VAdriaC/IE with irinotecan and dactinomycin (COG ARST0431).

The decision by Meazza et al to give only vincristine and actinomycin was predicated on the baby's young age, poor performance status, and renal function impairment, demonstrating the difficulty in treating these cases. In addition, guidelines from the European Pediatric Soft Tissue Sarcoma Group are to avoid the administration of ifosfamide in infants <1 month of age and anthracyclines in infants <3 months of age. Therapy in neonates is always complicated because of the immaturity of organs, leading to slower clearance of chemotherapy drugs. However, it seems that some neonates can tolerate ESFT-based therapy. Hayek et al report that 1 newborn girl began therapy with VAdriaC/IE at half the standard doses (Ref. 18). The baby tolerated this well and subsequent doses were escalated until all of the drugs were administered at standard doses. Unfortunately, the regimen was stopped because of disease progression.

The question of what constitutes optimal therapy for neonates in this scenario is problematic. The first step is to establish curative intent. This decision in itself is problematic, because the possibility of cure is very low, whereas the morbidity of treatment will be very high.

Meazza et al conclude their report with the following sentence. "A possible recommendation emerging from our experience is that front-line intensive chemotherapy should be attempted regardless of the patient's age." Based on our reading of the literature, we agree with this assessment. Once ESFT is diagnosed and curative intent is established, therapy should be directed at complete surgical resection and targeting of micrometastatic disease using standard ESFT-based chemotherapy. This must be mitigated with the knowledge that very few neonates will be able to tolerate such intensive therapy. One thing is certain. Clinicians cannot be dogmatic about formulating a treatment regimen when there are so little data. As always, the best interests of the baby and the family must dictate the treatment plan.

Acknowledgments

The authors thank the following people for very informative and interesting conversations: Dr Lynn Smith, Huntsman Cancer Institute; Dr Marc Ladanyi, Memorial Sloan-Kettering Cancer Center; and Dr Neil Sebire, Great Ormond Street Hospital.

REFERENCES

1. Kaneko Y, Yoshida K, Handa M, et al. Fusion of an ETS-family gene, E1AF, to EWS by t(17;22) (q12;q12) chromosome translocation in an undifferentiated sarcoma of infancy. *Genes Chromosomes Cancer*. 1996; 15:115–121. [PubMed: 8834175]
2. Smith LM, Adams RH, Brothman AR, et al. Peripheral primitive neuroectodermal tumor presenting with diffuse cutaneous involvement and 7;22 translocation. *Med Pediatr Oncol*. 1998; 30:357–363. [PubMed: 9589085]
3. Carvalho CM, Valette G, Nicolas G, et al. Maxillar localization of a congenital peripheral primitive neuroectodermal tumor: a case report. *Int J Pediatr Otorhinolaryngol*. 2006; 1:27–32.
4. French CA, Kutok JL, Faquin WC, et al. Midline carcinoma of children and young adults with NUT rearrangement. *J Clin Oncol*. 2004; 22:4135–4139. [PubMed: 15483023]
5. Ng TL, O'Sullivan MJ, Pallen CJ, et al. Ewing sarcoma with novel translocation t(2;16) producing an in-frame fusion of FUS and FEV. *J Mol Diagn*. 2007; 9:459–463. [PubMed: 17620387]
6. Wang L, Bhargava R, Zheng T, et al. Undifferentiated small round cell sarcomas with rare EWS gene fusions: identification of a novel EWS-SP3 fusion and of additional cases with the EWS-ETV1 and EWS-FEV fusions. *J Mol Diagn*. 2007; 9:498–509. [PubMed: 17690209]
7. Barr FG, Womer RB. Molecular diagnosis of Ewing family tumors: too many fusions? *J Mol Diagn*. 2007; 9:437–440. [PubMed: 17652636]
8. Dagher R, Pham TA, Sorbara L, et al. Molecular confirmation of Ewing sarcoma. *J Pediatr Hematol Oncol*. 2001; 23:221–224. [PubMed: 11846300]

9. Paley C, Valderrama E, Garcia M, et al. Congenital peripheral neuroectodermal tumor presenting as disseminated cutaneous disease. *J Pediatr Hematol Oncol.* 1996; 18:447.
10. Hsieh HY, Hsiao CC, Chen WS, et al. Congenital Ewing's sarcoma of the humerus. *Br J Radiol.* 1998; 71:1313–1316. [PubMed: 10319008]
11. Naidu MRC. Primary Ewing's tumor of the skull at birth. *Indian J Pediatr.* 1989; 56:541–543. [PubMed: 2633999]
12. Hachitanda Y, Tsuneyoshi M, Enjoji M. Congenital primitive neuroectodermal tumor with epithelial and glial differentiation. *Arch Pathol Lab Med.* 1990; 114:101–105. [PubMed: 2294862]
13. Erdmann D, Brown RE, Rumbolo PM. Congenital neuroepithelioma in an infant hand. *J Hand Surg [Br].* 1996; 21B:117–120.
14. Lim TC, Tan WTL, Lee YS. Congenital extraskeletal Ewing's sarcoma of the face: a case report. *Head Neck.* 1994; 16:75–78. [PubMed: 8125792]
15. Das L, Chang CH, Cushing B, et al. Congenital primitive neuroectodermal tumor (neuroepithelioma) of the chest wall. *Med Pediatr Oncol.* 1982; 10:349–358. [PubMed: 7110059]
16. Daw JL, Wiedrich TA, Bauer BS. Congenital primitive neuroectodermal tumor of the hand: a case report. *J Hand Surg.* 1997; 22A:743–746.
17. Sebire NJ, Ramsay AD, Levitt G, et al. Aberrant immunohisto-chemical expression in nonrhabdomyosarcoma soft tissue sarcomas of infancy: retrospective review of clinical material. *Pediatr Dev Pathol.* 2002; 5:579–586. [PubMed: 12370769]
18. El Hayek M, Trad O, Islam S. Congenital peripheral primitive neuroectodermal tumor refractory to treatment. *J Pediatr Hematol Oncol.* 2004; 26:770–772. [PubMed: 15543017]

<hr/>	
EWS-FLI1	
EWS-ERG	FUS-ERG
EWS-ETV1	
EWS-E1AF	
EWS-FEV	FUS-FEV
EWS-ZNF278	
EWS-POU5F1	
EWS-SP3	
	CIC-DUX4
	BRD4-NUT
<hr/>	

TET = family of RNA-binding proteins, thought to be implicated in protein-RNA binding (includes EWS, FUS)
ETS = family of transcription factors defined by the ETS domain, that interacts with DNA (includes FLI1, ERG, ETV1, E1AF, FEV)

Primary Location	Metastases	Original Diagnosis	Treatment Course	Outcome	References
Abdomen	Skin	ARMS	VA/VA	Dead 1 mo	Meazza
Cheekbone	None	US	PSR/chemotherapy	Dead 2y	[1]
Skin	None	MPNST	Various treatments	Dead 8 y	[2]
Maxillary bone	None	ARMS	VA/PSR/AdC/ECarbo	Dead 2 mo	[3]
Unknown	Skin	pPNET	None	Alive 18 mo	Ref. 9
Humerus	None	Ewing	CSR	Alive 2 y with mets	Ref. 10
Forehead	None	Ewing	CSR/RT	Alive 1 y	Ref. 11
Temporal bone	Lymph nodes	pPNET	CSR/VC/Cis/RT	Dead 1 y	Ref. 12
Hand	None	Neuroepithelioma	CSR/VAdC-IE × 12	Alive 4 y	Ref. 13
Eye lid	None	ERMS	VAdCMixCis	Dead 10 mo	Ref. 14
Chest wall	Skin, brain	pPNET	CSR/VC/RT/VC	Dead 3 mo	Ref. 15
Hand	Skin	pPNET	CSR/VAdC × 7	Dead 15 mo	Ref. 16
Back	Unknown	pPNET	Surgery/VAdI	Alive	Ref. 17
Forearm	Unknown	pPNET	RT	Dead 1 mo	Ref. 17
Neck	Unknown	pPNET	VAdI	Dead 6 mo	Ref. 17
Sacrum	Unknown	pPNET	Surgery/VA	Dead 4 mo	Ref. 17
Knee	Unknown	pPNET	Palliative therapy	Dead 4 mo	Ref. 17
Neck	Unknown	pPNET	Surgery/VAdI	Alive	Ref. 17
Axilla	Unknown	pPNET	VAdI	Dead 2 y	Ref. 17
Back	Unknown	pPNET	Surgery/VAdI	Alive	Ref. 17
Hand	None	pPNET	CSR/VAdC-IE × 4/CTopo × 2	Dead 2 y	Ref. 18

A indicates dactinomycin; Ad, adriamycin; ARMS, alveolar rhabdomyosarcoma; C, cyclophosphamide; Carbo, carboplatin; Cis, cisplatin; CSR, complete surgical resection; E, etoposide; ERMS, embryonal rhabdomyosarcoma; I, ifosfamide; MPNST, malignant peripheral nerve sheath tumor; Mix, methotrexate; PSR, partial surgical resection; RT, radiation therapy; Topo, topotecan; US, undifferentiated sarcoma; V, vincristine.