A Novel Finding in Pediatric Leiomyosarcoma: Expanding Spectrum of FGFR rearrangements in Childhood Cancers

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Abstract

Non Rhabdomyosarcoma Soft Tissue Sarcomas (NRSTS) are rare in the pediatric age group, accounting for 1-7% of all pediatric tumors. Leiomyosarcoma, a subtype of NRSTS, is exceedingly rare in pediatric population. Due to the rarity of this condition, management is extrapolated from other common NRSTS which involves surgery, chemotherapy and radiation. Chemotherapy is not very effective in management of pediatric leiomyosarcoma and molecular information may help guide targeted therapies. We describe a patient with a FGFR1-TACC1 gene rearrangement which, based on other models, predicts for sensitivity to FGFR inhibitors.

Introduction:

Leiomyosarcoma is a type of Non-Rhabdomyosarcoma Soft Tissue Sarcoma (NRSTS) derived from smooth muscle stem cells. Among pediatric patients, NRSTS are exceedingly rare cancers, comprising approximately 1-7% of all pediatric cancer cases [1-4]. Among NRSTS, the incidence of pediatric leiomyosarcomas is estimated to be approximately <1%, with most cases among adolescent patients [1,4]. They can present in the trunk, head and neck region, and upper or lower limbs [1]. Pediatric leiomyosarcoma treatment is extrapolated from the treatment of NRSTS and includes a combination of surgery, radiation and chemotherapy depending on the tumor grade, tumor size, extent of resection and presence of metastases [5]. Spunt et al recently described 3 risk-based groups approach of NRSTS including low risk, intermediate risk and high-risk disease. Low risk group had event free survival (EFS) of 89% and overall survival (OS) of 96%; intermediate risk group had EFS of 65% and OS of 79% and high-risk group had EFS of 21% and OS of 35%. They noted that most of the low risk group patients did well with surgery alone while the survival was poor for the intermediate and high-risk groups despite chemotherapy and radiation therapy. The lack of response to the conventional chemotherapy and radiation has generated interest in molecular targeted therapy for NRSTS. Pazopanib, a tyrosine kinase inhibitor has shown some activity in NRSTS including leiomyosarcoma [12]. A recent COG study, ARST1321, is evaluating the effect of adding tyrosine kinase inhibitor to chemotherapy and radiation back bone for NRSTS.

The genomic landscape of pediatric leiomyosarcoma is poorly understood. Here we describe molecular findings in a child with leiomyosarcoma including a novel gene rearrangement.

Case Report:

An 11-year-old Caucasian female presented with a <5cm firm, left sided, non-tender neck mass for a month, with no constitutional symptoms. She was initially treated with a course of antibiotics for suspected lymphadenitis with no response. Following surgical resection, histopathology revealed that the tumor is composed of admixture of spindle and ovoid cells (Fig. A1&2). Rare mitosis was seen (Fig. A3). A panel of

immunostains was performed and showed a strongly positive caldesmon and weakly positive smooth muscle actin; supporting the diagnosis of low grade leiomyosarcoma with positive microscopic margins. Her CT chest was negative for metastatic disease and PET scan showed mild FDG avidity in left side of the neck – level IIb node - with no other areas of PET avidity. Concerned with the microscopic margins, a second surgery was performed, but continued to show microscopic margins. She was finally staged as Stage I (G1, T1b, N0, M0 disease) by the AJCC guidelines. We opted for no further treatment as a third surgery seeking negative microscopic margins will be disfiguring with unclear benefit. Furthermore, radiation has been associated with long-term consequences with unclear benefit to a patient with low risk disease. She is closely monitored with serial imaging. MRI and PET CT performed at 3 and 6 month interval has not shown evidence of local disease.

The unusual presentation of leiomyosarcoma in our patient led to molecular analysis of her tumor with next generation sequencing (NGS) showed chromosomal re-arrangement involving FGFR1-TACC1 and copy number loss of MTAP, CDKN2A, and CDKN2B on array CGH

Discussion:

As leiomyosarcoma is exceedingly rare in pediatric age group, treatment is extrapolated from experience with other non-rhabdomyosarcoma soft tissue sarcomas. Since, our patient had low grade disease measuring< 5cm in diameter with no metastatic disease, we decided to closely observe her with serial imaging rather than radiation therapy to avoid the long-term consequences of radiation. The presence of residual disease placed our patient at risk for local recurrence. The risk of recurrence in low risk tumors with positive margins was 18%, with 80% EFS. Out of the patients who recurred, all were local recurrence only and salvaged with surgery, with or without radiation. Only one patient died of metastatic disease following salvage therapy with radiation. Furthermore, delaying the administration of radiotherapy in young children until the time of local recurrence (which may years after tumor resection) may diminish the late toxicity of this treatment modality [5-7].

With the recent success of targeted therapies such as BRAF, EGFR and TKI in the management of cancers, many groups have taken advantage of the availability of genomic sequencing to understand the biology of these tumors and develop a personalized therapeutic option. NGS, showed a chromosomal re-arrangement involving FGFR1-TACC1 as well as copy number loss of MTAP, CDKN2A, and CDKN2B on array cGH.

FGFR fusion genes were first discovered in Glioblastoma Multiforme (GBM) and have since been found in many other solid tumors like breast, prostate, gastric, NSCLC, adenocarcinoma and colorectal carcinomas [8-10], however, to date, none has been described in pediatric leiomyosarcoma.

In our patient, the genomic breakpoints map to exon 18 of FGFR1 at the 5' end and intron 1 of TACC1 at the 3' end, both located on chromosome 8. Figure 1C shows the chromosomal rearrangement seen in the patient as well as the breakpoint locations. The fusion was observed at the DNA level, where part of FGFR1 gene, 5' of the exon 18 breakpoint is duplicated and inverted at the 3' breakpoint position within TACC1.

Fusion genes generally result in constitutive activation of the 3' partner gene. It is possible the duplicated and reinserted FGFR1 may be transcribed resulting in increased activity of FGFR1 tyrosine kinase. Preclinical studies show that FGFR–TACC fusion proteins allow FGFR to dimerize, leading to autophosphorylation and constitutive FGFR tyrosine kinase activation. The distinctive feature of TACC proteins is a coiled-coil domain at the C terminus, known as the TACC domain, which mediates localization to the mitotic spindle. Together, aberrant FGFR and TACC signaling results in increased cell proliferation and cancer progression [9,10]. Perhaps the most convincing data on the importance of this gene fusion comes from in vitro studies showing the FGFR-TACC fusion predicts for sensitivity to FGFR inhibitors [10-12]. As such it is logical that the use of these inhibitors may benefit this subset of patients. In lieu of the newly FDA approved FGFR inhibitor, Erdafitinib, in the event of recurrence the use of this TKI in combination with chemotherapy and radiation remains a therapeutic option for this patient. Among other copy number losses reported in this patient, only loss of CDKN2A has been reported previously in leiomyosarcomas.

The paucity of pediatric leiomyosarcomas and differences in the biology compared to adult tumors, justifies molecular analysis of such tumors. For our patient, oncological transformation may be explained partially by chromosomal arrangements. It also provides a therapeutic option in case of disease progression.

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References:

1. De Saint Aubain Somerhausen N, Fletcher CDM. Leiomyosarcoma of soft tissue in children: Clinicopathologic analysis of 20 cases. Am J Surg Pathol. 1999;23(7):755-763. doi:10.1097/00000478-199907000-00002
2. Steppan D, Pratilas C, Loeb D. Targeted therapy for soft tissue sarcomas in adolescents and young adults. Adolesc Health Med Ther. 2017;Volume 8:41-55. doi:10.2147/ahmt.s70377
3. Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds). Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995, National Cancer Institute, SEER Program. NIH Pub. No. 99-4649. Bethesda, MD, 1999.4.
4. Loeb DM, Thornton K, Shokek O. Pediatric Soft Tissue Sarcomas. Surg Clin North Am. 2008;88(3):615-627. doi:10.1016/j.suc.2008.03.008
5. Spunt SL, Million L, Chi YY, et al. A risk-based treatment strategy for non-rhabdomyosarcoma soft-tissue sarcomas in patients younger than 30 years (ARST0332): a Children's Oncology Group prospective study. Lancet Oncol. 2020;21(1):145-161. doi:10.1016/S1470-2045(19)30672-2
6. Brennan MF. The enigma of local recurrence. Ann Surg Oncol. 1997;4(1):1-12. doi:10.1007/BF02316804
7. Spunt SL, Hill DA, Motosue AM, et al. Clinical features and outcome of initially unresected nonmetastatic pediatric nonrhabdomyosarcoma soft tissue sarcoma. J Clin Oncol. 2002;20(15):3225-3235. doi:10.1200/JCO.2002.06.066
8. Costa R, Carneiro BA, Taxter T, et al. FGFR3-TACC3 fusion in solid tumors: Mini review. Oncotarget. 2016;7(34):55924-55938. doi:10.18632/oncotarget.10482
9. Lasorella A, Sanson M, Iavarone A. FGFR-TACC gene fusions in human glioma. Neuro Oncol. 2017;19(4):475-483. doi:10.1093/neuonc/now240
10. Dupain C, Harttrampf AC, Urbinati G, Geoerger B, Massaad-Massade L. Relevance of Fusion Genes in Pediatric Cancers: Toward Precision Medicine. Mol Ther - Nucleic Acids. 2017;6:315-326. doi:10.1016/j.omtn.2017.01.005
11. Singh D, Chan JM, Zoppoli P, et al. Transforming fusions of FGFR and TACC genes in human glioblastoma. Science (80-). 2012;337(6099):1231-1235. doi:10.1126/science.1220834
12. Stransky N, Cerami E, Schalm S, Kim JL, Lengauer C. The landscape of kinase fusions in cancer. Nat Commun. 2014;5. doi:10.1038/ncomms5846
13. Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: A phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC Study 62043). J Clin Oncol. 2009;27(19):3126-3132. doi:10.1200/JCO.2008.21.3223

A.

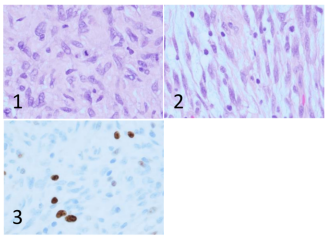

Fig. 1A: Immunohistochemical stains of surgical sections.
Panel 1. (400x): Section of the neoplasm show ovoid appearing cells with occasional mitosis.
Panel 2 (400x): Sections show areas of spindle cell appearance of the neoplasm.
Panel 3 (400x): KI-67 immunostaining shows a proliferative index of approximately 15%.

B.

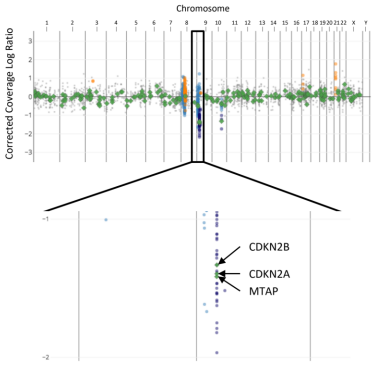

Fig. 1B: Array CGH showing copy number loss of CDKN2B, CDKN2A and MTAP

C.

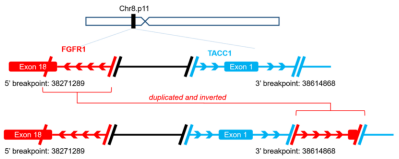

Figure 1C: Chromosomal rearrangement seen in patient's tumor sample. The 5' breakpoint: 38271289 and 3' breakpoint: 38614868 map to genes FGFR1 and TACC1 on chromosome 8 respectively (hg 19). Part of FGFR1 gene up to the 5' breakpoint in exon 18, shown in red, is duplicated and inverted into the 3' breakpoint mapping to intron 1 of TACC1 gene, shown in blue.