CORRESPONDENCE

Evaluation of a Congenital Infantile Fibrosarcoma by Comprehensive Genomic Profiling Reveals an LMNA-NTRK1 Gene Fusion Responsive to Crizotinib


Affiliations of authors: Rady Childrens Hospital, San Diego, CA (VW, JC, DM, HA); Foundation Medicine, Inc., Cambridge, MA (DP, TB, RY, JSR, VAM, PJ, SMA); Albany Medical College, Albany, NY (JSR).

Correspondence to: Siraj M. Ali, MD, PhD, Clinical Development, Foundation Medicine, Inc., 150 Second St., Cambridge, MA 02141 (e-mail: siraj@foundationmedicine.com).

We present a case of a reverse transcription polymerase chain reaction (RT-PCR) ETV6-NTRK3 negative congenital infantile fibrosarcoma (CIFS) harboring an LMNA-NTRK1 gene fusion with an eight-month ongoing, near-complete response to crizotinib. CIFS is a rare, typically low-grade sarcoma of children younger than age two years and is associated with a good to excellent prognosis, with an 80% median five-year survival. The majority of CIFS cases remain localized, although a minority of CIFS cases metastasize and then require systemic chemotherapy (1). To date, the only recognized diagnostic marker for CIFS is the presence of the ETV6-NTRK3 gene fusion (2), which is also the hallmark of the presumed related cellular congenital mesoblastic nephroma (3). Much of our understanding of CIFS comes from the study of mesoblastic nephroma, but metastatic disease in either setting still presents a great management challenge.

An infant age one month presented to his primary physician with a purplish lesion on his right buttock, marked by progression in size and associated bleeding. At age seven months, an excisional biopsy was performed on a 4.5x4 cm lesion and histology showed a "dense proliferation of spindle cells in a herringbone pattern, with a mitotic rate of up to 10 mitotic figures in a single high power field." Immunohistochemical staining for CD34 and vimentin were positive, broadly consistent with a diagnosis of sarcoma (4). Testing by both RT-PCR and break-apart fluorescence in situ hybridization (FISH) for the canonical ETV6-NTRK3 gene fusion was negative (4). A second surgery was performed to achieve gross total resection of the primary lesion. At age 14 months, a local relapse occurred at the site of the primary lesion, accompanied by bilateral pulmonary metastases and a suspected S5 vertebral body metastasis. The patient underwent wide local excision of the recurrent buttock lesion with resulting clear margins. Subsequently, the patient received two cycles of vincristine, actinomycin-D, and cyclophosphamide chemotherapy, but had documented disease progression in his lungs and S5 lesion. While receiving two cycles of ifosfamide and doxorubicin, he developed progressive disease: enhancement in the S5 vertebral body, increased prominence of nodules in the lung, and a new posterior right acetabulum lesion. Given the metastatic behavior of this lesion and the lack of the canonical fusion associated with CIFS, spindle cell sarcoma and ex-dermatofibrosarcoma protubers (DFSP) were considered as diagnoses. However, FISH for the pathognomonic DFSP-PDGRF fusion was also negative.

As chemotherapeutic options were exhausted, the primary formalin-fixed paraffin-embedded lesion was submitted for comprehensive genomic profiling (CGP) using a combined DNA and RNA sequencing hybrid capture-based assay (Foundation Medicine, Inc). DNA-based hybridization capture was performed on the entire coding sequence of 405 cancer-related genes and introns from 31 genes involved in rearrangements. RNA-based hybridization capture was performed on 265 genes known to be rearranged in hematologic malignancies, sarcomas, and pediatric cancers. Captured libraries were sequenced by DNA- and RNA-seq, with 100% of related genomic regions sequenced to be greater than 100X coverage and 477X median coverage (5).

Consistent with prior FISH and RT-PCR testing, neither the canonical ETV6-NTRK3 gene fusion nor the PDGRF rearrangement was present in the genomic profile. With NTRK1 serving as the baited gene, paired-end sequencing underlying CGP led to the identification of an LMNA-NTRK1 fusion similar to the fusion recently found in spitzoid melanomas, but with a distinct exonic structure (6). A 737 kbp deletion yielded the 5' end of LMNA (localized to 1q22), including exons 1-10 fused to the 3' end of NTRK1 (also localized to 1q22), including exons 12-17 (Figure 1A). NTRK1 encodes a receptor tyrosine kinase responsible for signal transduction of neuroepithelial and neuron survival, whereas LMNA encodes a key component of the nuclear lamina involved in nuclear assembly and chromatin organization. The
tumor also harbored homozygous losses of both CDKN2A and CDKN2B (both localized on 9p21), but no additional clinically relevant genomic alterations.

Based on the report of minor response to crizotinib of a non–small cell lung cancer case harboring an NTRK1 fusion as well as preclinical data (7), the patient was started on crizotinib (80mg b.i.d.) in a liquid formulation administered orally. After six weeks of treatment, imaging demonstrated regression of pulmonary metastases (Figure 1C) and stabilization of the skeletal lesions. Imaging again was repeated at 12 weeks of treatment and showed a continuation of response to crizotinib therapy. Currently, the patient is experiencing no adverse effects from treatment and continues crizotinib monotherapy with no evidence of disease beyond two stable skeletal lesions. Radiation oncology has advised against intervention on the skeletal lesions at this time.

The findings in this case, initially considered as CIFS on the basis of morphology and found to have a paralogous fusion to ETV6-NTRK3, suggest this could be ad hoc labeled a ‘variant’ CIFS case. Taken to an extreme, this could suggest that the 30% of cases dubbed CIFS on a histologic basis but without canonical ETV6-NTRK3 fusions (4) may instead harbor paralogous fusions such as LMNA-NTRK1. After progressing on two lines of cytotoxic therapy, this patient has an ongoing response to crizotinib. Crizotinib was assessed as having a similar IC50 against NTRK1, ALK, and ROS1 fusion proteins in vitro (Figure 1B), but this example, and the prior report above (7), is, to our knowledge, the only published instance of crizotinib being rationally utilized for treatment of an advanced malignant neoplasm harboring an NTRK1 fusion; crizotinib has been shown to inhibit proliferation of ETV6-NTRK3–dependent tumor cells in xenograft models (8). A recent report suggests the promise of NTRK inhibitors in development, but until the approval of such agents, the findings here do suggest a possible therapeutic option for CIFS cases today. These trials are not currently accepting pediatric patients, and to do so may entail pediatric-specific formulations of therapies as exemplified in this correspondence. The benefit this patient is experiencing conversely suggests that currently available multitargeted inhibitors with NTRK activity could be considered in situations where options have otherwise been exhausted (9). This case further illustrates how comprehensive genomic profiling can identify clinically relevant alterations that predict effective targeted therapy options for CIFS patients found to be ETV6-NTRK3 negative and needing systemic therapy, while also improving our understanding of the genomic basis of this class of pediatric sarcoma.

References