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Case Report

Targeted Therapy Using the Selective Tropomyosin Kinase Receptor Inhibitor Larotrectinib in an Infant with Infantile Fibrosarcoma with a *TPM3–NTRK1* Gene Fusion with Lung and Central Nervous System Metastases: Case Report

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ABSTRACT

This case report describes the outcomes of tropomyosin receptor kinase (TRK) inhibitor treatment in an infant with an infantile fibrosarcoma (IFS) with a *TPM3–NTRK1* gene fusion. The IFS on the left foot was refractory to chemotherapy and was partially resected. After 5 months, there was local recurrence and further surgery was performed. The patient developed pulmonary and central nervous system metastases. Pan-TRK antibody staining was positive and genomic profiling with next-generation sequencing confirmed a *TPM3–NTRK1* gene fusion. The patient started treatment with larotrectinib in February 2019, with a durable response, including a clear reduction in brain metastases. Research on novel gene fusions and molecular testing to direct the use of targeted therapy should be encouraged, especially in refractory solid tumors.

Introduction

Although rare, fibrosarcomas are the most common malignant mesenchymal tumor in the first year of life [1-3]. In children up to 2 years of age, the tumor is termed infantile fibrosarcoma (IFS) and in 80-90% of cases, it presents with the translocation t(12;15)(p13;q25). This translocation causes fusion of the neurotrophic tyrosine kinase receptor *NTRK* genes and the *ETV6* gene **(***ETV6–NTRK3*) resulting in chimeric transcripts with oncogenic potential [4]. The overall prognosis of IFS is good (3-year overall survival rate >90%) following initial surgery and chemotherapy, although progression or relapse are possible [5-7]. Conservative surgery is the treatment of choice for IFS because, although locally aggressive, distant metastases are rare. In unresectable tumors, the use of chemotherapy generally enables local tumor control [7]. Occasionally, some cases of IFS can regress spontaneously; in contrast, others can present with aggressive behaviour and are refractory to treatment [8-10]. Van Grotel *et al.* reported a case of IFS with the classic translocation in a 2-month old infant who presented with numerous lung metastases on diagnosis [9].

In another study, the authors presented an aggressive IFS with a rare *LMNA–NTRK1* translocation that was refractory to treatment [10]. With the recent technological advances in genomic sequencing, new information on oncogenic events has been reported for various cancers. The high frequency of *NTRK* gene fusions in IFS has driven the development of targeted therapy with a tyrosine kinase receptor inhibitor, and specifically, a tropomyosin receptor kinase (TRK) inhibitor [11, 12]. Here, the authors present the case of an infant with chemotherapy-refractory IFS who presented with pulmonary and central nervous system (CNS) metastases. Molecular analyses detected a *TPM3–NTRK1* gene fusion. The objectives of this case report are to

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discuss the molecular biology of IFS and describe the outcomes of this patient with TRK fusion IFS (*TPM3–NTRK1* gene fusion) treated with larotrectinib-a selective TRK inhibitor.

Case Report

A female infant aged 1 year and 2 months old presented with a hardened tumor in the plantar region of the left foot; the tumor had been present for 2 months. On examination, the posterior two-thirds of the plantar region were bulging, but painless, with ill-defined limits and marked vascularization. The histological diagnosis was fibrosarcoma. Optical microscopy revealed fusocellular sarcoma with long, intersecting fascicles (Figure 1).

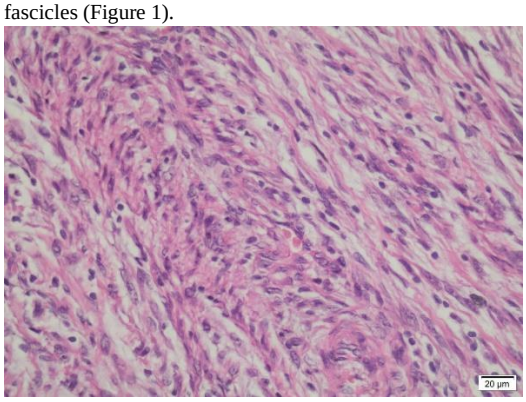

Figure 1: HE 400× magnification photomicrographs showing an infant fibrosarcoma; a neoplasm with a fusocellular pattern and long intersecting fascicles in a herringbone pattern.

Immunohistochemistry (IHC) analysis indicated fibroblast/myofibroblast differentiation, with a proliferative index measured by Ki67 expression of around 5%. Magnetic resonance imaging (MRI) of the left foot showed a 3.8 × 5.8 × 4.3 cm lesion, without compromised regional lymph nodes. Other staging examinations, including chest computed tomography (CT), were normal. The final diagnosis was non-metastatic, unresectable IFS.

The family reported a maternal family history of a grandmother with cervical cancer at 44-year-old, and a great-uncle and great-grandmother with leukemia (over 60-year-old). On the paternal side, the family history included a great-aunt with breast cancer, three cousins with breast cancer (one was under 50-year-old), a cousin with head and neck cancer when under 10 years of age and another cousin with retinoblastoma. Given the family history, a commercial multigene panel was performed to search for germline point variants, deletions, and duplications in 83 genes associated with hereditary predisposition to cancer, using Illumina technology, with ≥50x depth. Only one intronic variant of uncertain significance was identified in the *PMS2* gene, c.537 + 6G>A.

Upon diagnosis, three cycles of vincristine, actinomycin-D, and cyclophosphamide (VAC) chemotherapy were started, after which the tumor was stable at the reassessment examinations (Figure 2). The patient received two more cycles of ifosfamide and etoposide; however, upon imaging, the tumor had progressed. The chemotherapy regimen was then altered to vinblastine and methotrexate, resulting in a partial response. The patient then underwent conservative surgical resection with positive surgical margins. Five months after surgery, the patient relapsed with local recurrence and another resection of the tumor was performed, with coincident margins. Treatment with vinblastine and methotrexate was maintained.

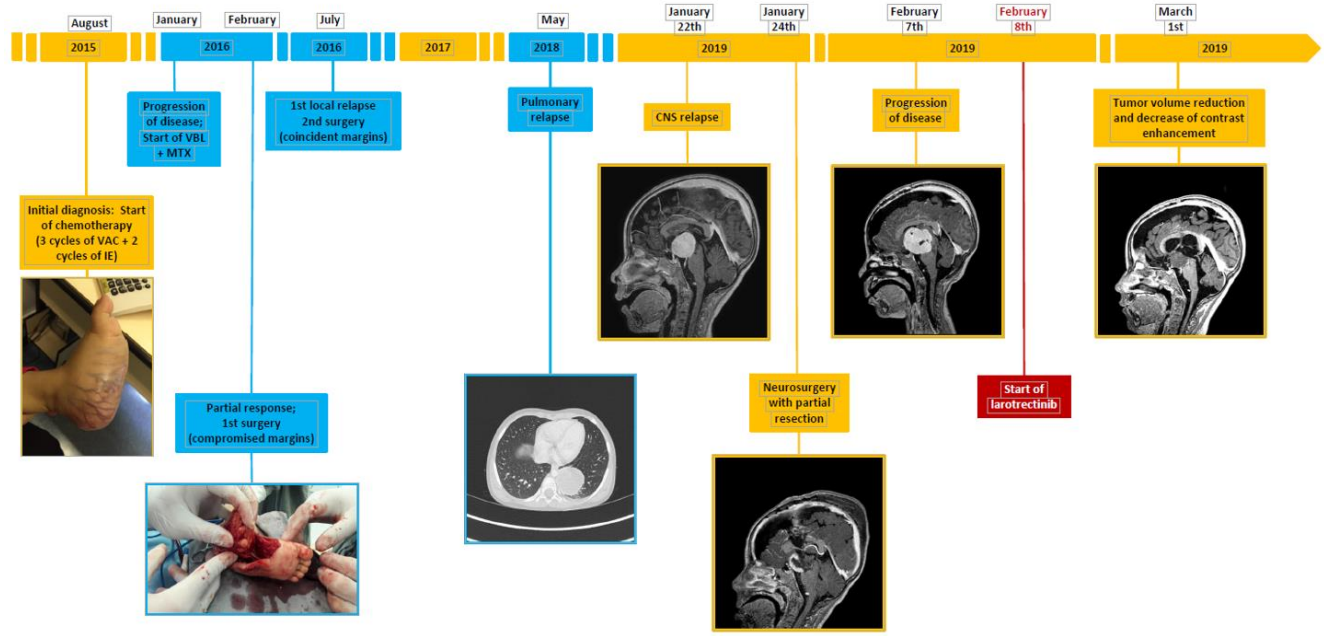

Figure 2: Timeline of treatment in the episode of care.

The patient presented no evidence of disease for 21 months after the second local surgery, however, she presented with symptoms of a respiratory infection. A CT scan of the thorax showed an expansive, solid cystic formation with peripheral enhancement centered on the lower left lobe of the lung (Figure 2). The patient underwent a biopsy of the lung lesion and metastasis of the fibrosarcoma was confirmed. She

underwent a left inferior lobectomy with total resection of the tumor and negative surgical margins, and a lymphadenectomy with neoplasia-free lymph nodes. The tumor fragment obtained from the lobectomy was sent for molecular analysis. Four months after the surgery for the lung metastasis, the patient presented with signs of intracranial hypertension. A brain MRI showed a large, expansive formation in the suprasellar, hypothalamic-chiasmatic region projecting into the third ventricle. On physical examination, the plantar region of the left foot had also bulged, with local disease recurrence confirmed by MRI. The patient received ventriculoperitoneal shunt surgery and partial resection of the brain tumor. Pathological examination confirmed fibrosarcoma metastasis and there was bleeding of the tumor during surgery. Postoperatively, there was lack of spontaneous eye opening, signs of decorticate posturing, anisocoria, and limb spasticity. Three weeks after neurosurgery, imaging (MRI) examination showed an increase in the size of the brain tumor (Figure 3). Corticosteroids and anticonvulsants were prescribed.

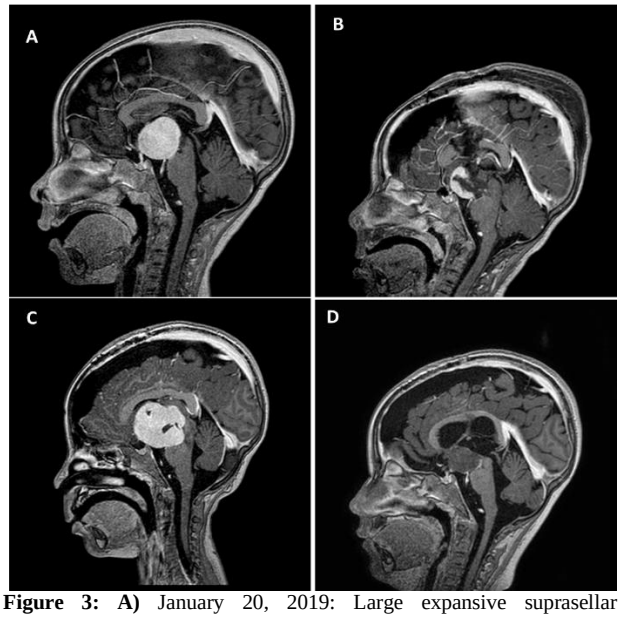

Figure 3: A) January 20, 2019: Large expansive suprasellar hypothalamic-chiasmatic formation with intense gadolinium enhancement projecting into the third ventricle. This formation results in deviation of the pituitary stalk to the left. **B)** January 24, 2019: Partial resection of the solid expansive formation with reduction of the paramedian component on the left and inside the third ventricle. **C)** February 7, 2019: Significant growth of the suprasellar lesion. Estimated volume on immediate postoperative examination, 7 cm^3; current estimated volume, 31.4 cm^3. **D)** March 1, 2019: Decrease in tumor size with significant reduction in contrast and diffusion restriction, indicating a good therapeutic response.

Paraffin-embedded tissue from the metastatic lung tumor was sent for reverse transcription-polymerase chain reaction (RT-PCR) screening for the *ETV6–NTRK3* transcript from the translocation t(12;15)(p13;q25), but transcript was not detected. Subsequently, an IHC assay using the anti-pan-TRK monoclonal antibody (TRKA, B, C) EPR17341 was positive, indicating hyperexpression of the TRK proteins and the possible presence of a fusion in the *NTRK* gene family. Subsequently, the biopsy specimen was sent for comprehensive genomic profiling (FoundationOne, Cambridge, MA, USA) with next-generation sequencing (NGS), which detected a *TPM3–NTRK1* fusion. Additional molecular findings included low tumor mutational burden, microsatellite stability, an alteration in the *CD36 N53fs*24* gene, and loss of *CDNK2A* and *CDKN2B.* The identification of the *TPM3–NTRK1* fusion prompted for the initiation of treatment with the highly specific TRK (TRKA, B, and C) inhibitor, larotrectinib.

Therapy with larotrectinib (oral solution, 100 mg/m^2) was started and, after 14 days, the patient showed clinical improvement with a reduction of tumor volume in the plantar region of the foot. Three weeks after starting the targeted therapy, a cranial MRI showed a partial reduction in tumor size (RECIST -0.39) and an accentuated decrease in contrast uptake. The lesion on the foot had completely regressed 5 months after starting larotrectinib (RECIST -1). A chest CT showed no signs of pulmonary recurrence. The patient, now 6 years and 7 months old, has received larotrectinib for 24 months without signs of active disease, and with progressive improvement in motor and cognitive functions. Fatigue and weight gain (grade 2) have been noted in the past 22 months.

Discussion

IFS is defined by its clinical and histological characteristics, as well as the presence of the recurrent translocation t(12;15)(p13;q25) resulting in *ETV6–NTRK3* gene fusion in 80-90% of cases [4]. However, this gene fusion is not specific to IFS and has been described in several adult and pediatric tumors [11-14]. Other *NTRK* gene fusions have also been described in IFS, with fusion partners other than *ETV6* including *LMNA–NTRK1*, *SQSTM1–NTRK1*, *TPM3–NTRK1*, and *EML4–NTRK3* [10, 15-19]. Pavlick *et al*. investigated the presence of *NTRK* gene fusions in 2031 different tumors in patients under 21 years of age. Nine of the 2031 tumors (0.44%) had *NTRK* gene fusions. Of these, four were patients with IFS: two with an *ETV6–NTRK3* gene fusion, one with an *LMNA–NTRK1* gene fusion, and the other with an *SQSTM1–NTRK1* gene fusion [15]. All these gene fusions lead to constitutive expression in the chimeric proteins, driving oncogenesis and malignant transformation [13].

The infant with IFS presented in this case report developed refractoriness to chemotherapy and distant metastases. An initial analysis for an *NTRK* gene fusion was performed using RT-PCR to direct targeted treatment with a TRK inhibitor. Despite the high frequency of the translocation t(12;15) in IFS, the *ETV6–NTRK3* transcript was not detected in initial RT-PCR screening. However, IHC analysis showed positive hyperexpression of TRK protein, suggesting the presence of an *NTRK* gene fusion [20]. These results highlight the importance of using IHC in the initial screening for *NTRK* gene fusions in patients with IFS, considering that, although translocation t(12;15) with *ETV6–NTRK3* gene fusion is the most common mutation, we should also consider that other gene fusions may occur. IHC using a pan-TRK antibody has high sensitivity (95%) for the diagnosis of IFS and should be the first analysis used for screening. However, IHC can show TRK hyperexpression without necessarily indicating the presence of an *NTRK* gene fusion; therefore, more specific analyses are required to confirm this gene fusion [14, 21].

NGS analysis subsequently identified the rare *TPM3–NTRK1* gene fusion. NGS is a highly specific analysis that can sequence multiple genes and potentially identify new fusions. The decision to undertake

analyses to identify *NTRK* gene fusions should follow a diagnostic sequence that depends on the clinical and histological features of a tumor, as well as the variety of *NTRK* gene fusions with different partners and genomic breakdowns [21-23]. Actionable mutations are identified in many sequenced tumors, therefore the clinical utility of molecular testing for rare gene fusions and subsequent targeted therapy requires further study and long-term follow up of patient outcomes [22]. In Brazil, the cost and availability of genomic profiling is also a significant factor.

The unusual *TPM3–NTRK1* gene fusion found in this case is rare in IFS, but has been previously identified in pediatric and adult solid tumors [15, 16, 18]. The *TPM3* gene is located on chromosome 1q21.3 and the *NTRK1* gene on 1q23.1, about 2.7 Mb apart [24]. This fusion involves a complex mechanism of breakage and inversion, usually within exon 6 in the *TPM3* gene and exon 9 in the *NTRK1* gene [25]. It is a fusion that has also been described in lipofibromatosis-like neural tumors, papillary thyroid carcinomas, colorectal carcinomas, glioblastomas, uterine sarcomas, and spindle cell sarcomas [13, 25-27].

Davis *et al*. have reported six cases of infants with fibroblastic tumors without an *ETV6–NTRK3* gene fusion [18]. Of these, four presented with a *TPM3–NTRK1* gene fusion, one with *LMNA–NTRK1*, and another with *EML4–NTRK3*. Of the patients with fusions involving the *TPM3* gene, one had lung metastases. The patient described in this case report presented with an aggressive IFS tumor; metastases occurred in the midline region-a single extensive and expansive process centered on the lower lobe of the left lung—and subsequently, in the suprasellar, hypothalamic-chiasmatic region of the brain. Due to the rarity of IFS with a non-classical gene fusion such as *TPM3–NTRK1*, it is not possible to infer the importance of this fusion as a prognostic factor or as a new subgroup of sarcomas [10, 17]. In the Laetsch *et al.* study, of the 15 patients with *TRK* fusion cancer, eight cases were IFS, and of those, one had a *TPM3–NTRK1* gene fusion and a good response to larotrectinib therapy [16]. Haller *et al.* described four patients with a subgroup of spindle cell sarcomas, all with a prominent myopericytic/hemangiopericytic pattern, two of which had a *TPM3–NTRK1* gene fusion [27].

Loss (deletion) of *CDNK2A* and *CDKN2B* were identified by NGS. *CDKN2A* deletions associated with *NTRK1* fusions, as found in this patient, have previously been described [15, 27-29]. Pavlik *et al.* described a patient with soft tissue schwannoma with an *TPM3–NTRK1* gene fusion and homozygous loss of *CDKN2A/B*, and two other patients with homozygous loss of *CDKN2A/B* associated with other tumors and other fusions [15]. Haller *et al*. described four patients with *NTRK1* gene fusions, three of whom (one with *LMNA–NTRK1* and two with *TPM2–NTRK1* fusion) also had *CDKN2A* deletions, raising the question as to whether fusions associated with *NTRK1* may sometimes be associated with loss of *CDKN2A/B* in soft tissue sarcomas [27]. In a review by Doebele *et al.*, four out of eight patients with sarcomas and *NTRK1* gene fusions also presented with co-occurring *CDKN2A/B* deletion, although none had the *TPM3–NTRK1* fusion [28]. These gene losses are known to be common in multiple sarcoma types and, specifically, *CDKN2A* deletion and/or *p16INK4a* deletion have been associated with poor prognosis in peripheral nerve sheath sarcomas [30].

Currently, precision medicine considers the molecular drivers of a tumor, as well as the histological tumor type, allowing individualized treatment through targeted therapies. In Brazil, larotrectinib was approved by the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária) in 2019. It is a potent and highly selective inhibitor of the TRKA, TRKB, and TRKC neurotrophin receptors. Administered orally, larotrectinib binds to the tyrosine kinase receptor domain of TRK and prevents its activation, resulting in cell growth inhibition and apoptosis. Regardless of the type of neurotrophin receptor and the fusion partner involved, larotrectinib has proved to be effective in the control and treatment of various types of solid tumors harboring an *NTRK* gene fusion in pediatric and adult patients (e.g. mesoblastic nephroma fibrosarcoma, soft tissue sarcoma, papillary thyroid cancer, secretory breast carcinoma, and lung cancer) [11, 23]. The objective response rate of larotrectinib was 93% in 15 pediatric patients with TRK fusion cancer and measurable tumors, including in one patient with IFS with a *TPM3–NTRK1* gene fusion [16].

In a recent article describing the results of three phase 1 and 2 studies, the use of larotrectinib in patients of different age groups and with different tumors with an *NTRK* gene fusion resulted in a response rate of 79%. These results confirm the effectiveness of larotrectinib as a targeted therapy in tumors with an *NTRK* gene fusion, regardless of the tumor location and histology, and the patient's age (i.e. it is a tumor-agnostic therapy) [31, 32]. Larotrectinib has been used as neoadjuvant therapy in five children with locally advanced TRK fusion sarcomas; partial tumor responses following treatment allowed curative surgery to be performed with low morbidity [12]. Although cases with lasting responses to TRK inhibitors have been described, including partial and complete responses to larotrectinib, some patients may develop resistance [16]. Fortunately, second generation TRK inhibitors are being developed clinically, which appear to supersede the acquired resistance to first-generation inhibitors [16, 32].

In the case reported here, larotrectinib produced a therapeutic response in a patient with tumor harboring the *TPM3–NTRK1* gene fusion, including an intracranial CNS response. The infant, who was in intensive care with brain metastasis and local disease progression, showed rapid clinical and radiological improvement 14 days after starting larotrectinib and remains without signs of local or pulmonary relapse after 24 months of treatment. In the CNS, the expansive metastatic disease decreased in size, with reduced contrast uptake demonstrating reduced disease activity. Larotrectinib has been well tolerated in pediatric patients in a phase 1 study, with elevated liver enzymes, cytopenias, and vomiting (grade 1) as the most frequent adverse events [16]. Pooled analysis of 159 patients, including 50 pediatric patients, from three phase 1/2 clinical trials confirm the tolerability of larotrectinib and indicate that long-term administration is feasible. The patient in this case report experienced weight gain (grade 2) and tiredness (grade 2) as adverse events on larotrectinib and follow up will be required. In locally advanced or metastatic solid tumors, identification of *NTRK* gene fusions may represent an important therapeutic opportunity. However, frequent and long-term monitoring is necessary until the resistance mechanisms to TRK inhibition have been well established.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability

Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing". This pertains to scope, time point, and process of data access. As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 01, 2014. Interested researchers can use the link to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the "Study sponsors section" of the portal. Data access will be granted to anonymized patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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Consent

Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Abbreviations

CDKN2A/B: Cyclin Dependent Kinase Inhibitor 2A/B
EML4: Echinoderm Microtubule Associated Protein-Like 4
ETV6: ETS Variant Transcription Factor 6
LMNA: Lamin A/C
NTRK1/3: Neurotrophic Receptor Tyrosine Kinase 1/3
SQSTM1: Sequestosome 1
TPM3: Tropomyosin 3

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