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On TRacK With Larotrectinib in a Neonate With a Giant Congenital *ETV6::NTRK3* Fusion-Positive Infantile Fibrosarcoma of the Head and Neck

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ABSTRACT

Background: Infantile fibrosarcoma (IFS) is a rare pediatric tumor of intermediate malignancy with high local aggressiveness that typically presents in young infants. Its occurrence in the head and neck region is rare. Complete non-mutilating surgical resection is often not possible, requiring multimodal treatment. IFS frequently harbors neurotrophic receptor tyrosine kinase (*NTRK*) fusions. Targeted therapy with NTRK inhibitors is modifying treatment paradigms of IFS.

Methods: Herein, we report the case of a neonate with a giant unresectable congenital *ETV6::NTRK3* (+) IFS of the head and neck region without rapid response to chemotherapy who was treated with larotrectinib oral suspension.

Results: Larotrectinib was well tolerated and induced an impressive clinical and radiologic response.

Conclusions: This case illustrates an example of pediatric precision oncology in a neonate with an *ETV6::NTRK3* (+) congenital IFS of the head and neck region and provides further reference for the use of larotrectinib in the neonatal period.

1 | Introduction

Infantile fibrosarcoma (IFS) is a rare tumor of intermediate malignancy, with an estimated annual incidence rate of 4.3 per million children [1]. It is the most common soft tissue sarcoma in the first year of life, with a median age at diagnosis of 1.4 months [2]. Clinically, IFS almost always presents as a localized tumor [2, 3], most often arising from the extremities or the trunk as a rapidly growing mass lesion [4]. IFS of the head and neck region is rare and accounts for 6%–14% of cases [5]. Metastatic spread

Abbreviations: AFP, alpha fetoprotein; b-HCG, beta human chorionic gonadotropins; CSF, cerebrospinal fluid; DIC, disseminated intravascular coagulation; EMA, European Medicines Agency; FDA, Food and Drug Administration; H&E, hematoxylin and eosin; IFS, infantile fibrosarcoma; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NGS, next-generation sequencing; NSE, neuron-specific enolase; NTRK, neurotrophic receptor tyrosine kinase; PT, prothrombin time; PTH, parathyroid hormone; PTHrP, parathyroid hormone related protein; PTT, partial thromboplastin time; RNA, ribonucleic acid; TRK, tyrosine receptor kinase; VAC, vincristine, adriamycin, cyclophosphamide.

is uncommon (< 10%), although rare cases with metastases have been described [6–8]. Children with IFS generally have a good prognosis, with overall survival rates reported between 80% and 100% [2, 3]. Malignant hypercalcemia [9, 10] and coagulopathy have been described as clinical features of IFS [11, 12]. IFS often presents with rapid initial growth causing life-threatening complications. However, very rarely, patients with IFS show spontaneous regression [13–15]. Validated molecular markers predicting spontaneous regression have not yet been described so far [15, 16].

IFS harbor a *ETV6::NTRK3* fusion in 85% of cases [17]. The *ETV6::NTRK3* fusion arises from the translocation t(12;15)(p13;q25), which fuses the amino-terminal helix–loop–helix oligomerization domain of the *ETV6* transcription factor with the carboxyl-terminal tyrosine kinase domain of the neurotrophic tyrosine kinase receptor, type 3 (*NTRK3*). The neurotrophic receptor tyrosine kinase (*NTRK*) genes are involved in the growth, differentiation, and survival of neurons [18, 19]. NTRK fusions are key oncogenic drivers of IFS [20, 21]. The highly selective tropomyosin receptor kinase (TRK) inhibitor larotrectinib, which was approved by the FDA in 2018 and by the EMA in 2019 after showing a high level of activity in Phase 1 and 2 clinical trials in children and adults with relapsed and refractory TRK fusion cancers, regardless of histology [22, 23], is modifying treatment paradigms of IFS [24]. Herein, we report the case of a neonate with a life-threatening giant unresectable congenital IFS of the head and neck region without rapid response to chemotherapy and with impressive response to treatment with larotrectinib.

2 | Case Presentation

At 37.2 weeks of gestation, an emergency cesarean section was performed in a 37-year gravida 2 para 1 showing signs of fetal distress. She had presented to the emergency department after concerning decrease in fetal movements during the past 72 h. Obstetricians faced difficulty extracting the fetus through the Pfannenstiel incision. An unexpected huge prenatally undetected right cervicofacial mass lesion was observed extending from the right cervical area to the orbit, protruding into the mouth, displacing the tongue and uvula, impeding oral closure, and displacing the right eye cranially (Figure 1A). Rapid postnatal growth of the mass lesion was observed. Subsequently, stridor and progressive respiratory distress developed during the first day of life due to further compression on the airway both from the oral and the cervical component of the tumor. Nasotracheal intubation became mandatory to secure the airway.

Magnetic resonance imaging (MRI) of the head and neck showed a 9.8 × 8.3 × 9.4 cm highly vascularized mass lesion with cystic and hemorrhagic changes as well as solid stroma-rich components, extending from the supraclavicular level cranially to the fossa temporalis and the floor of the right orbit, with displacement and destruction of the surrounding soft tissues and bones, with involvement of the hard and soft palate, nasopharynx, larynx, encasement of the right external carotid artery, and displacement of the trachea (Figure 2A). An X-ray of the cranium confirmed divergence of the osseous structures of the mandibular bone, the maxillary, and the lower orbital wall by the tumor. Laboratory results showed signs of disseminated intravascular coagulation (DIC) with thrombocytopenia, prolonged PT, PTT, hypofibrinogenemia, and elevated D-dimers. Fresh frozen plasma, fibrinogen concentrates, platelet transfusions, as well as low-dose heparin-infusions were required for management of DIC. Hypercalcemia and hypophosphatemia were noted with elevated PTHrP and decreased PTH levels. LDH, uric acid, NSE, ferritin, b-HCG, and AFP were within normal age range limits. Homovanillic and vanillylmandelic acid in urine were normal. Clinical, radiologic, and laboratory features were highly suspicious for a congenital IFS.

The clinical status of the patient worsened further due to rapid growth of the lesion. Impending airway compression despite endotracheal intubation, with requirement of vasopressors due to

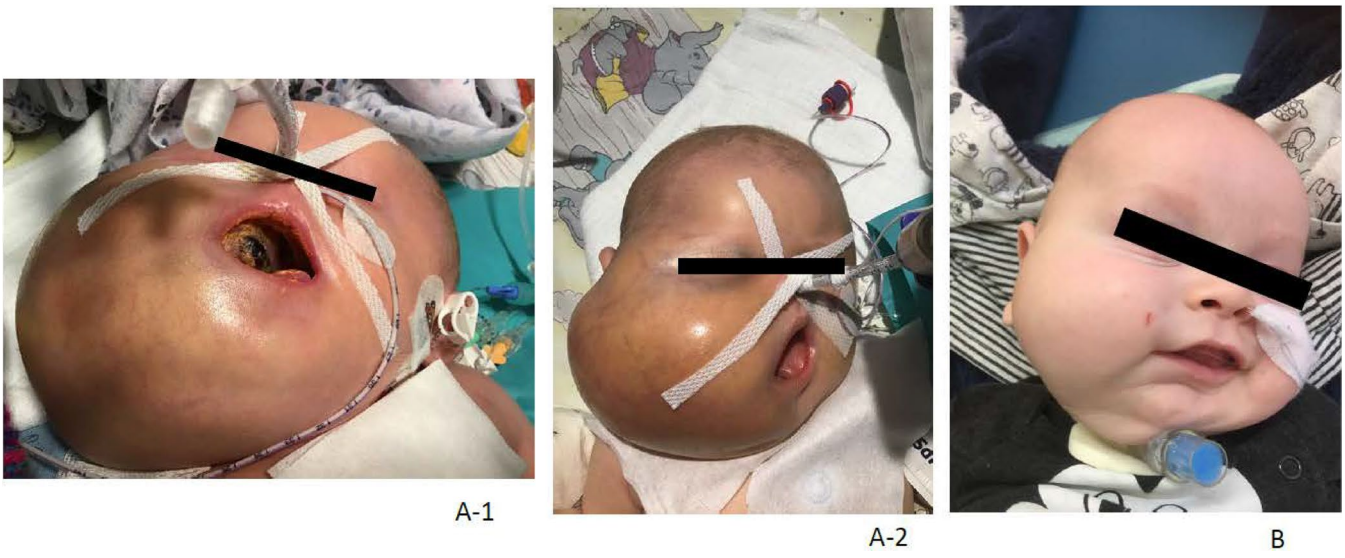

FIGURE 1 | Clinical changes due to large congenital IFS (A1, A2) before treatment; (B) after 4 months of therapy with larotrectinib.

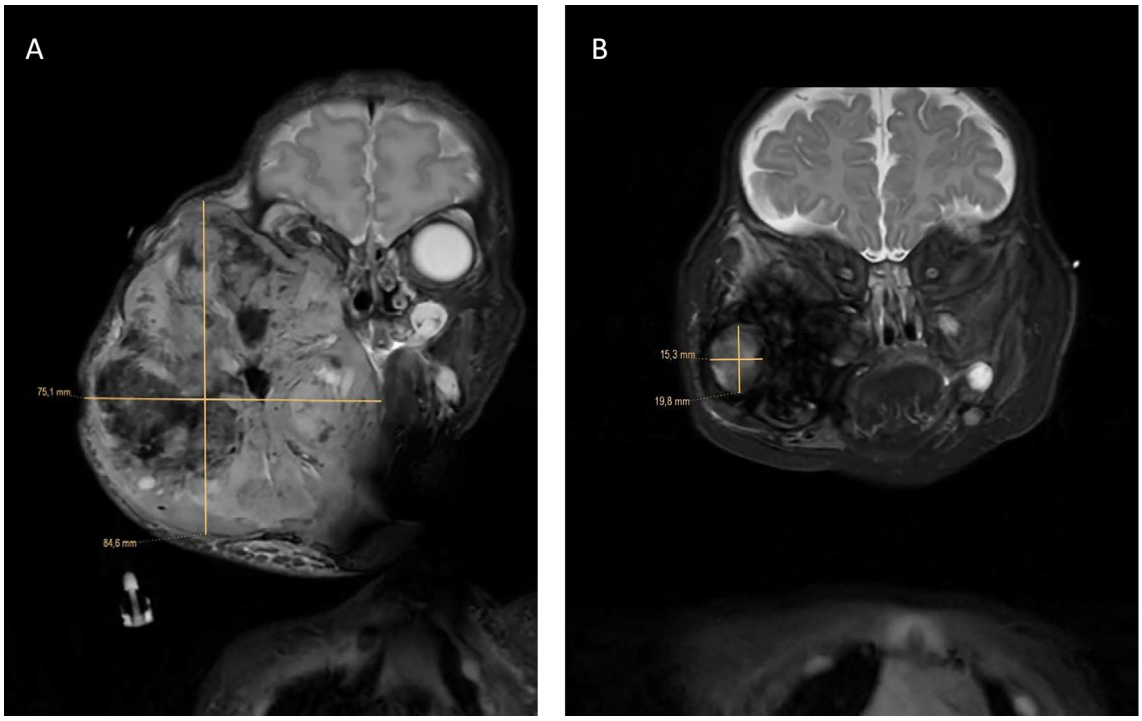

FIGURE 2 | (A) MRI of the head and neck (A) on Day 1 of life, showing a highly vascularized mass lesion with cystic as well as solid stroma-rich components, extending from the supraclavicular level cranially to the floor of the right orbit, with displacement and destruction of the surrounding soft tissues and bones (maximal diameters of the contrast enhancing lesion on Day 1 taken at a right angle to each other for volumetric analysis were $8.6 \times 8.2 \times 8.8$ cm ($0.52 \times a \times b \times c = 322.7\,cm^3$). (B) Revealing an 85.4% mass reduction after 3.5 months of therapy with larotrectinib (maximal diameters taken at a right angle to each other for volumetric analysis were $4.2 \times 4.4 \times 4.9$ cm ($0.52 \times a \times b \times c = 47.1\,cm^3$)). The contrast enhancing residual tumor mass after 3.5 months of treatment with larotrectinib had maximal diameters of $2.8 \times 1.8 \times 2.2$ cm ($0.52 \times a \times b \times c = 5.8\,cm^3$).

hemodynamic instability and the need for intensive transfusion support due to severe coagulopathy motivated the decision to start an empiric emergency cytoreductive chemotherapy with vincristine, adriamycin, and cyclophosphamide (VAC) on Day 2 of life. A biopsy of the lesion was performed on Day 3 of life. Pathology results were consistent with an IFS, with atypical spindle cells showing negativity for Desmin, S100, and CD34 as well as nuclear positivity for Pan Trk (Figure 3). Cerebrospinal fluid (CSF) cell-count and CSF cytology were normal. A bone marrow aspirate showed no evidence of cytomorphologic metastatic infiltration of the bone marrow. A whole-body MRI on Day 7 of life showed no evidence of metastatic disease. Regarding the primary tumor, further increase in size of the right cervical tumor was noted in comparison to prior studies. A tracheostomy was warranted. Grade 4 neutropenia, Grade 3 anemia, and Grade 4 thrombocytopenia occurred after chemotherapy. Erythrocyte and thrombocyte transfusions became necessary. Neutropenic fever with pneumonia complicated the course, requiring broad spectrum antibiotics.

RNA was isolated from the biopsy and NGS analysis was performed on the iSeq100 device (Illumina, San Diego, USA) using the Focus RNA Panel (Illumina, San Diego, USA). The *ETV6::NTRK3* fusion was detected with 244 432 reads.

On Day 11 of life, after diagnosis of *ETV6::NTRK3* fusion-positive IFS, therapy with larotrectinib 100 mg/m^2 was started twice daily through a nasogastric tube.

Clinically, a slow but steady decrease in size of the tumor could be observed over the following weeks and months. Radiologically, by Week 3 of treatment with larotrectinib, an MRI of the head and neck showed the first signs of response. Oral larotrectinib suspension was well tolerated, without hepatotoxicity, nor hematologic toxicity. No dose adjustments, nor treatment interruptions were required. Electrolyte derangements progressively resolved during the first 3 weeks. Isolated fresh frozen plasma, fibrinogen concentrate, and platelet transfusions were required during the first 2 weeks. The low-dose heparin-infusion could be discontinued by Week 3 of life.

Vasopressor support could be discontinued by Day 22 and after progressive weaning, extubation became possible after 3 weeks of mechanical ventilation. Discharge from hospital was enabled by the second month of life.

Radiologic response assessment 3.5 months after initiation of treatment with larotrectinib showed an 85.4% volume reduction, with no further compression of the trachea, the pharynx, nor the larynx (Figure 2B). In parallel with radiologic response, further functional improvement of the patient occurred. Initially, only nasogastric tube feeding was possible (Figure 1B). Progressive oral feeding could be initiated at the second month of life and by 6 months of age the nasogastric tube could be withdrawn. Through a transient tracheostomy speaking valve, phonation was successfully encouraged. A further MRI of the head and neck at 10 months of age only

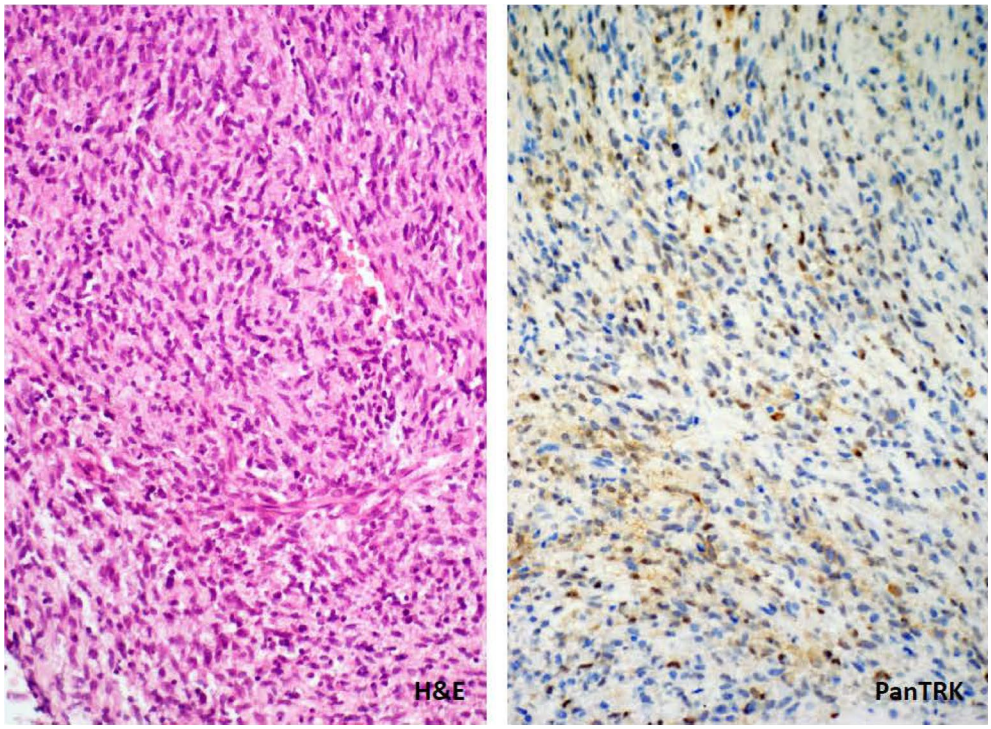

FIGURE 3 | H&E and immunohistochemistry with an antibody against PanTRK (original magnification ×200).

showed a small contrast enhancing lesion of 1 × 0.7 × 1.1 cm close the right collum mandibulae (Figure 4). Tracheal decannulation became possible by 10 months of age. Except for delayed phonation, achievement of all other developmental milestones was normal.

The surgical tracheostomy stoma closure was performed at 13 months of age. To our deepest sorrow, the patient deceased at 14 months of age due to complications after an unexpected cardiorespiratory arrest in the postoperative setting.

3 | Discussion

To the best of our knowledge, herein, we present the youngest neonate with congenital IFS reported to date in the literature successfully treated with larotrectinib at full dose (100 mg/m^2/d bid) starting on Day 11 of life. Patients enrolled to the initial pediatric Phase 1 study with larotrectinib were age 31 days to 18 years [22]. Later, the Loxo Oncology sponsored Phase 1/2 pediatric trial was amended to allow newborns to enroll. The Phase 1 follow-up and Phase 2 results of this trial have not been published yet. Although larotrectinib is now approved for advanced TRK fusion-positive solid tumors without age restrictions [23], few patients treated with larotrectinib below 1 month of age have been reported in the literature. Another reported case of neonatal IFS treated with larotrectinib started therapy at an initially reduced dose during the first cycle at Day 19 of life [25]. This is the second case of neonatal IFS reported in the literature treated with full dose larotrectinib upfront. The previously reported case was 20 days old when larotrectinib was started [26]. Reported toxicities of larotrectinib are Grade 1 and 2, including transaminitis, leukopenia, neutropenia, and vomiting [23]. In all three reported neonatal cases, larotrectinib was tolerated well. In this case, no toxicity was observed.

Very rapid complete responses to larotrectinib have been reported in infants [27], with median time to response of 1.8 months [5]. Review of the published cases of IFS below 1 month of age treated with larotrectinib showed that by 4 months of treatment, all cases had achieved partial responses [25, 26], no rapid complete responses have been reported so far. Although the number of published IFS cases treated with larotrectinib in the neonatal period is scarce, this might point toward possible biological differences of congenital IFS.

Chromosomal rearrangements involving *NTRK1*, *NTRK2*, and *NTRK3* have been reported in a broad range of other malignancies [28] including cellular congenital mesoblastic nephroma [29, 30], other mesenchymal neoplasms, and undifferentiated sarcomas [20], non-brain-stem high-grade gliomas [31], papillary thyroid cancer [32], secretory breast carcinoma [33], mammary analogue secretory carcinoma of salivary glands [34], "Phi-like" B-cell acute lymphoblastic leukemia [35], acute myeloid leukemia [36], and myeloproliferative disorders [37]. The highly selective TRK inhibitor larotrectinib has shown a high level of activity in children and adults with relapsed and refractory TRK fusion cancers in Phase 1 and 2 clinical trials in a tumor agnostic way [22–24]. Larotrectinib is approved as monotherapy in adults and children with solid tumors with proven NTRK gene fusions whose disease is locally advanced or metastatic, for whom surgical removal of the tumor is likely to result in severe sequelae and for whom no satisfactory therapeutic options are available. This is modifying treatment paradigms of IFS [24].

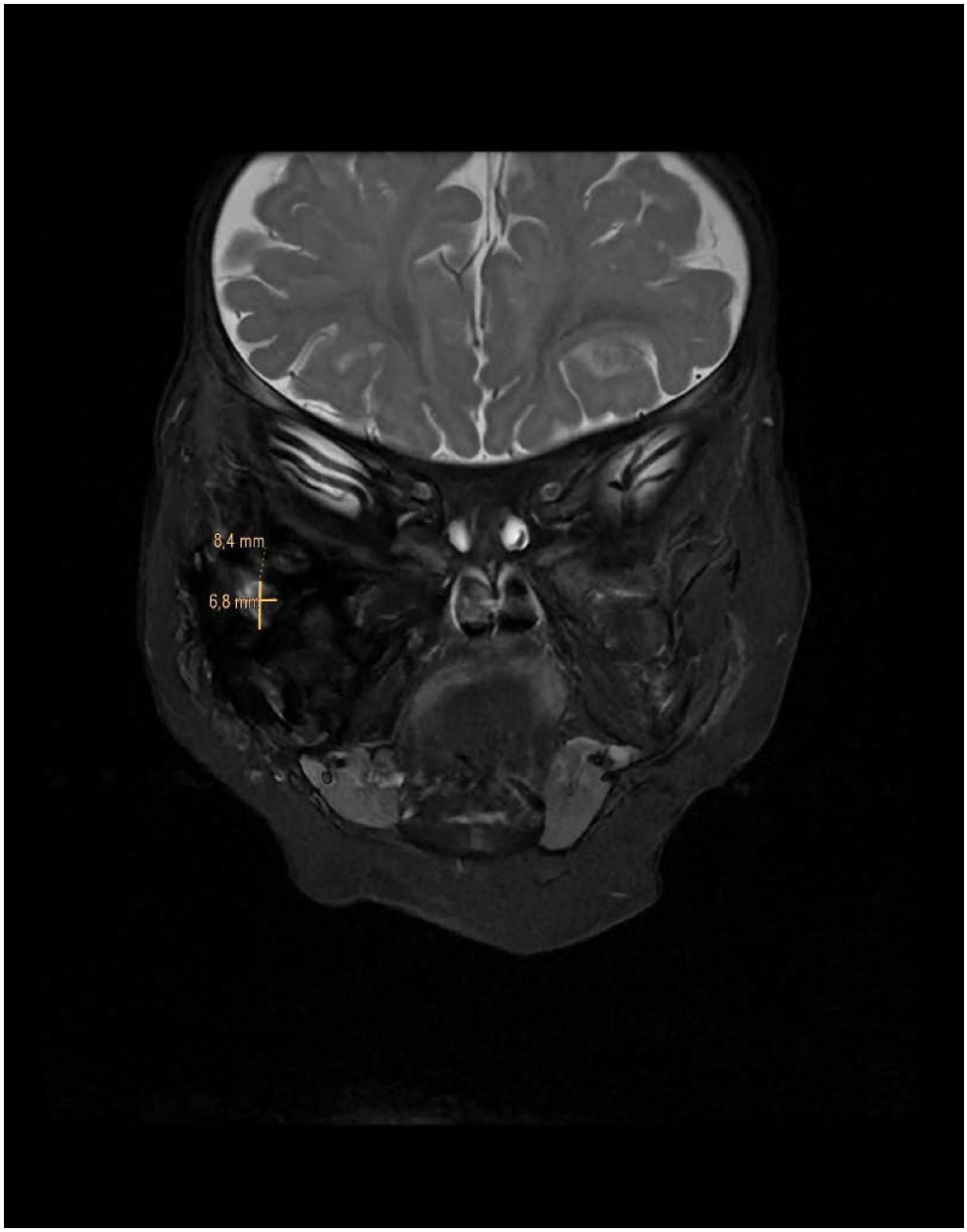

FIGURE 4 | MRI of the head and neck on Month 10 of life, showing a small contrast enhancing lesion of 1 × 0.7 × 1.1 cm close the right collum mandibulae.

Regarding surgery, the mainstay of treatment for patients with biopsy-proven IFS, when a complete, non-mutilating excision is believed to be possible, is primary surgery to obtain a complete resection [5]. The main burden of classic IFS therapy are sequelae of mutilating surgery, which should be avoided [2, 38]. When a complete, non-mutilating excision is not possible, an initial biopsy of the primary tumor is performed followed by systemic therapy [5].

Since spontaneous regression of IFS is exceptional, but has been described in 6% of patients [15], in the setting of an unresectable, nonthreatening IFS short-term close clinical and radiological observation could be considered before starting neoadjuvant therapy. In this case, upon presentation a life-threatening situation due to a large inoperable tumor in the head and neck region existed. While awaiting NTRK fusion results, chemotherapy was started due to urgent medical need. In this case, larotrectinib treatment induced a slow but continued response with literally no signs of toxicity. Therefore, no further surgical resection was deemed necessary. Larotrectinib treatment was planned for a total of 2 years. The unexpected respiratory arrest with secondary cardiac arrest which suddenly occurred in the postoperative setting of tracheostoma closure was deemed unrelated to the treatment with larotrectinib [39].

Although very good long-term data are available on the therapy of IFS with chemotherapy with or without resection, responses to chemotherapy in IFS tend to occur slowly over several months [5] with very few long-term sequelae [2, 3]. In this case, further growth of the lesion was observed after chemotherapy during

the following 9 days of life. Nevertheless, chemotherapy with VA(C) is the established regimen both for NTRK fusion negative IFS and as a "bridging treatment" in an advanced disease situation while awaiting molecular pathology results [3, 5, 38]. Although histologic similarities exist, it needs to be kept in mind that a notable subset of locally aggressive infantile soft tissue lesions are *ETV6::NTRK3* negative [40] and variant NTRK1/2/3, RET, MET, RAF1, BRAF, ALK, EGFR, and ABL1 fusions or alterations need to be ruled out [41–43].

Larotrectinib has demonstrated considerable efficacy in IFS with NTRK aberrations with sustained responses in chemotherapy-refractory, advanced IFS which even made a resection unnecessary [27]. The oral application, also available in form of a suspension, is very advantageous. No standard recommendation for the duration of therapy exists, but a treatment break is possible after 2 years in complete remission.

No data on long-term effects and late toxicities on NTRK inhibitors in infants are available so far. Furthermore, very few data on the risk of development of resistance and on second line NTRKI inhibitors have been reported until now. These aspects must be taken into consideration when parents are informed about treatment with larotrectinib [5, 44, 45].

These developments emphasize a new landscape of possible treatments for IFS. The classic multidisciplinary strategies [2, 3] including preoperative cytoreductive chemotherapy [46] and local therapy including conservative surgery are currently under reevaluation against the recent development of NTRK inhibitors such as larotrectinib, entrectinib and repotrectinib [5, 22]. In this very rare disease, where randomized controlled trials are considered not feasible, comparative data of larotrectinib versus selected historical controls treated with chemotherapy were evaluated in the EPI-VITRAKVI protocol [47], showing that treatment with larotrectinib had a reduced likelihood of encountering a medical treatment failure compared to standard of care with chemotherapy in pediatric patients with locally advanced or metastatic IFS, regardless of the line of treatment [48].

Currently, the decision for one or the other therapeutic option must be made in consideration of all known advantages and disadvantages, if possible, together with the parents.

4 | Conclusion

This case illustrates an example of pediatric precision oncology in a neonate with an unresectable, *ETV6::NTRK3* fusion-positive congenital IFS of the head and neck region without rapid response to chemotherapy. On-label use of targeted therapy with larotrectinib suspension showed an impressive response. This case provides a further reference for the use of larotrectinib in the neonatal period.

Acknowledgments

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Consent

Written consent was obtained from the patient's parents to publish this case and Supporting Information including photographs.

Conflicts of Interest

Monika Sparber-Sauer has acted as consultant and/or advisory board member for Roche, Bayer and Swedish Orphan Biovitrum (hemophilia). An independent research project on NTKR positive tumors Monika Sparber-Sauer was partially supported by Bayer (Investigation Supported research). The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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