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Targeted Therapy in a Rare Spindle Cell Tumor with *ETV6-NTRK3* Gene Fusion Rearrangement: A Case Report

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Abstract

Introduction Advances in genomic tools have significantly improved the classification of soft tissue tumors (STTs), enabling the identification of specific subsets characterized by recurrent fusions and genetic alterations involving the *Raf-1 proto-oncogene, serine/threonine kinase* (*RAF1*), *B-Raf proto-oncogene, serine/threonine kinase* (*BRAF*), and *neurotrophic tyrosine receptor kinase* (*NTRK*) genes. The present study aims to address the clinical challenge of diagnosing and managing a rare case of spindle cell tumor by examining the utility of molecular characterization, particularly focusing on *NTRK* rearrangements and their relationship with clinical outcomes. These tumors are defined by the coexpression of S100 and CD34 markers, lacking SOX-10 expression. Genetic changes can also be observed in STTs exhibiting spindle cell morphology, with fibroblastic or neural characteristics.

Case Description The current report presents a rare case of a spindle cell tumor in a 15-year-old male patient. Comprehensive histopathological and molecular analyses revealed the tumor's distinct entity through the coexpression of S100 and CD34 markers and an unusual *ETV6-NTRK3* gene rearrangement. The identification of the *ETS variant transcription factor 6-neurotrophic receptor tyrosine kinase 3* (*ETV6-NTRK3*) gene fusion was critical for tailoring a personalized therapeutic approach using larotrectinib. Periodic imaging assessments during treatment demonstrated a significant tumor response, culminating in a complete metabolic response by fluorodeoxyglucose (FDG) positron-emission tomography-computed tomography (PET-CT).

Keywords
- sarcomas
- rare diseases
- S100 proteins
- tyrosine kinase inhibitors

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Conclusion This rare case underscores the importance of precise diagnostic criteria and advanced molecular testing in effectively managing rare STTs. The identification of the *ETV6-NTRK3* rearrangement facilitated a successful personalized treatment strategy, highlighting the need for interdisciplinary collaboration in patient care. Integrating genomic insights into clinical practice is essential for managing complex spindle cell tumors and improving patient outcomes.

Introduction

The 2020 classification of soft tissue tumors (STTs) delineated by the World Health Organization (WHO) represents a pivotal advancement in the standardization of sarcoma diagnostics.[1] This classification seeks to enhance diagnostic accuracy and optimize therapeutic strategies by fostering the integration of clinical insights with collaborative efforts among pathologists, geneticists, and healthcare practitioners.[2] Despite these advancements, the inherent complexity of mesenchymal tumors poses substantial challenges, often leading to diagnostic inaccuracies. Additionally, the nuanced contributions of molecular biomarkers in the characterization of novel tumor entities further complicate the diagnostic landscape.[3]

As this classification continues to evolve, sustained education and interdisciplinary collaboration will be essential to address these challenges and improve the overall understanding and management of soft tissue sarcomas within clinical practice.[4]

Recent developments in genomic technologies have profoundly transformed the classification of STTs, facilitating the identification of distinct tumor subsets defined by specific genetic alterations.[5] The latest WHO classification introduces a novel category of spindle cell tumors that coexpress S100 and CD34 markers while notably lacking SOX-10 expression. These tumors are characterized by recurrent genetic alterations involving the *Raf-1 proto-oncogene, serine/threonine kinase* (*RAF1*), *B-Raf proto-oncogene, serine/threonine kinase* (*BRAF*),, and *neurotrophic tyrosine receptor kinase* (*NTRK*) genes, which are integral to tumorigenesis and may influence therapeutic interventions.[6]

Among these genetic alterations, the *ETV6-NTRK3* fusion has emerged as a critical focus due to its implications for both diagnosis and treatment. This particular gene rearrangement is associated with a distinctive clinical presentation, and has demonstrated favorable responses to targeted therapies, such as larotrectinib, which selectively inhibit *NTRK* signaling pathways.[7] The rarity of such cases, combined with their potential for personalized therapeutic approaches, underscores the clinical importance of identifying molecular alterations in STTs.[8]

This report aims to present a rare case of a spindle cell tumor characterized by the co-expression of S100 and CD34, as well as an *ETS variant transcription factor 6-neurotrophic receptor tyrosine kinase 3* (*ETV6-NTRK3*) gene fusion rearrangement. It follows the Vase Report (CARE) guidelines to ensure thorough documentation and transparency.[9] Ethical approval was granted by the Ethics in Human Research Committee of Hospital da Força Aérea do Galeão, under registration number CAAE 58431022.7.0000.5250. The study was conducted following Good Clinical Practice Guidelines. Written informed consent was obtained from the patient prior to the commencement of the study.

Case Report

In 2018, a 15-year-old male patient presented with progressive edema in the right hallux, which had persisted for several months and was accompanied by mild pain and discomfort. Following a comprehensive evaluation by an oncological orthopedic team, the decision was made to perform a partial amputation of the right foot. The initial anatomopathological report revealed a low-grade fibrous tumor characterized by 3 mitoses per 10 high-power fields, mild nuclear atypia, absence of necrosis, nonevaluable margins, and infiltration into adjacent connective tissue, specifically the tendon. Differential diagnoses were considered during the initial evaluation, encompassing various mesenchymal neoplasms. However, imaging studies indicated no evidence of distant disease foci at that time.

In September 2020, a computed tomography (CT) scan of the chest revealed two new low-density nodular opacities with contrast enhancement and slightly irregular contours, one measuring 1.4×1.0 cm in the anterior segment of the upper lobe of the right lung and the other measuring 1.0×1.0 cm in the middle lobe. Subsequent fluorodeoxyglucose (FDG) positron emission tomography-CT (PET-CT) performed in November 2020 demonstrated similar nodular opacities, with the larger nodule measuring 2.2×0.8 cm, with a maximum standardized uptake value (SUVmax) of 9.6, in the right upper lobe and the smaller measuring approximately 9 mm (SUVmax: 2.6) in the middle lobe. The significance of the elevated values in the PET-CT findings suggested higher metabolic activity, thereby guiding clinical decision-making regarding further diagnostic and therapeutic interventions.

Following these imaging findings, the patient underwent optimal resection of suspicious lung nodules in February 2021. The pathological report included comprehensive immunohistochemical (IHC) evaluations, demonstrating diffuse immunopositivity for CD34, CD99, and protein S100, alongside weak multifocal positivity for transducin-like enhancer of split 1 (TLE1) and focal immunoreactivity for

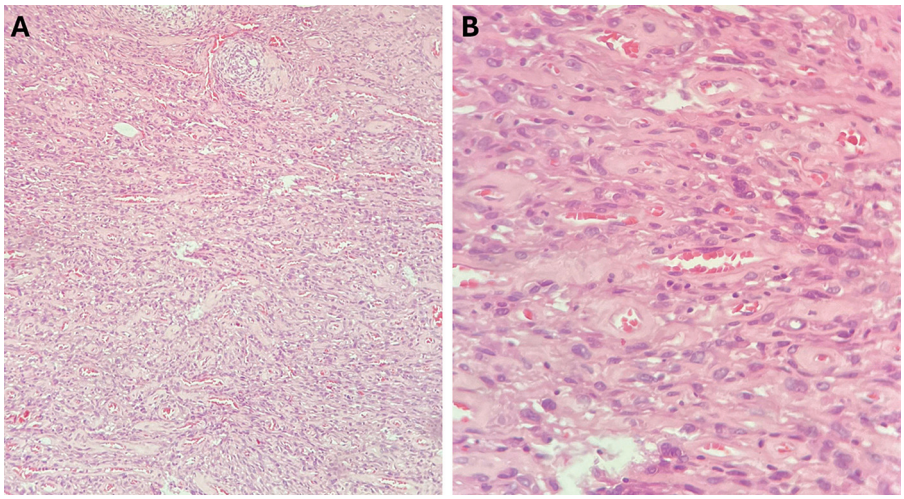

Fig. 1 Hematoxylin and eosin (H&E) stained tumor tissue. (**A**)100x magnification depicting overall cellular composition and structure. (**B**) 400x magnification highlighting detailed cellular features.

epithelial membrane antigen (EMA), as well as focal faint *NTRK/Pan-tyrosine receptor kinase (Pan-TRK*) staining. A low Ki-67 proliferative index (< 5%) further supported the diagnosis. Based on these results, it was concluded that the tumor was likely a spindle cell tumor coexpressing S100 and CD34 markers, possibly with a confirmed *NTRK* rearrangement, aligning with the emerging entities identified in the WHO 2020 classification. ►**Figs. 1** and **2** illustrate the hematoxylin and eosin (H&E) staining and IHC analysis, respectively.

Throughout the patient's follow-up period, a CT scan performed in March 2021 revealed an opacity with irregular contours and pleural extensions, measuring 1.5 × 0.7 cm in the middle lobe. An FDG PET-CT scan conducted in April 2021 further identified the emergence of a new subpleural opacity, which measured approximately 1.8 × 1.4 cm (SUVmax: 5.9) and was accompanied by adjacent pleural thickening (SUVmax: 6.5) and atelectatic bands. Given these concerning findings, the patient underwent a second resection of the lung lesion in May 2021, resulting in confirmation of the diagnosis of a spindle cell tumor with the same IHC profile, reinforcing the presence of the *NTRK* rearrangement.

To investigate potential genetic alterations and confirm the presence of a known driver genes, samples from both lung metastasectomy procedures were analyzed using next-generation sequencing (NGS) using the Oncomine Focus Assay kit on the Ion S5 System (ThermoFisher Scientific Inc.). The generated sequences were aligned against the GRCh37/hg19 reference genome and processed through the Ion Torrent bioinformatics pipeline, version 5.10, and the Ion Reporter software (ThermoFisher Scientific Inc.), version 5.10. This analysis confirmed the *ETV6-NTRK3* gene fusion at locus chr12:12,006,495 to chr15:88,576,276 (variant ID ETV6-NTRK3.E4N14). ►**Figs. 3** and **4** delineate the specific breakpoints involved in the *NTRK3-ETV6* gene fusion,

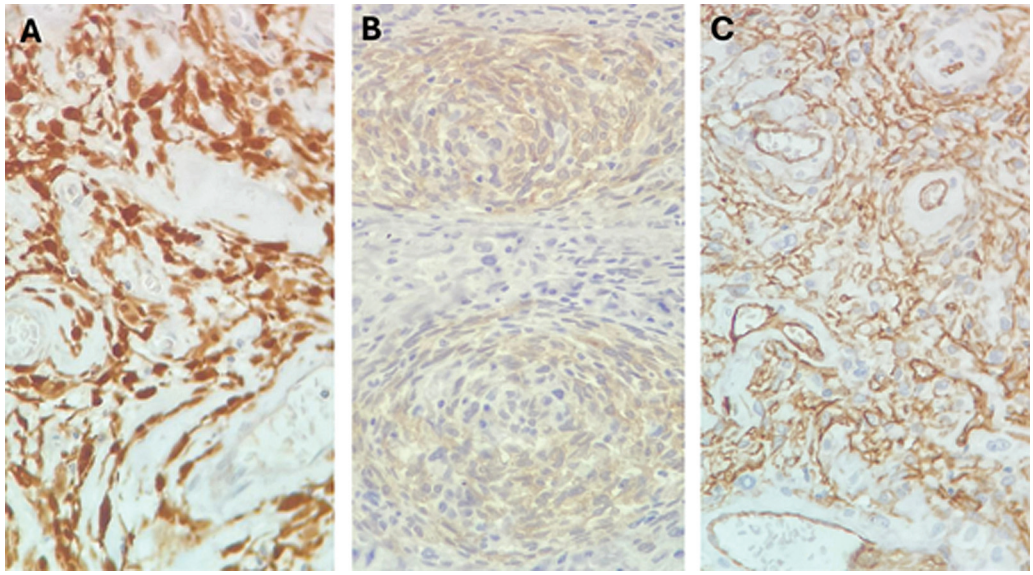

Fig. 2 Immunohistochemical staining of tumor tissue. (**A**) S100 (polyclonal; 400x). (**B**) CD34 (clone QBEnd/10; 400x). (**C**) NTRK/Pan-NTRK (clone EPR17341; 400x).

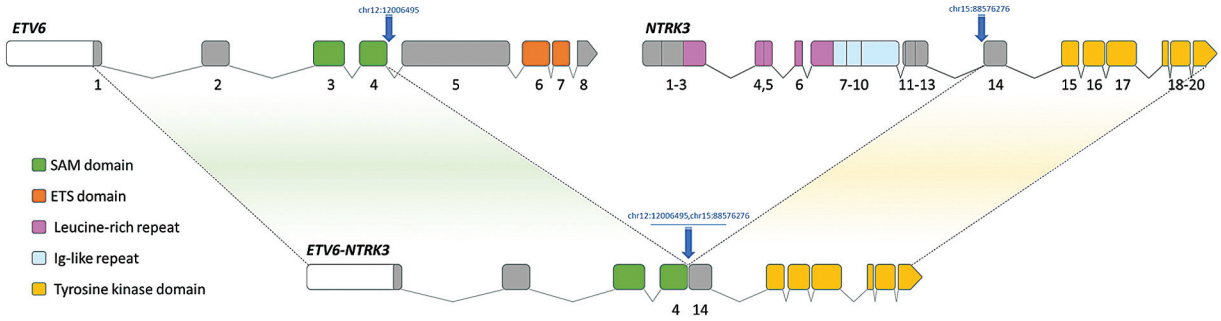

Fig. 3 Schematic representation of the exon composition of the *ETV6-NTRK3* fusion. The predicted fusion product contains 11 exons, 4 from the 5′ partner *ETV6* (NM_001987.5), which includes the sterile alpha motif (SAM) domain responsible for dimerization, and 7 from the 3′ partner *NTRK3* (NM_001012338.2), preserving the tyrosine kinase domain. The *ETV6* breakpoint is located on chromosome 12, position 12,006,495, exon 4, whereas the *NTRK3* breakpoint is situated on chromosome 15, position 88,576,276, exon 14 (chr12:12,006,495; chr15:88,576,276).

located at chr12:12,006,495 and chr15:88,576,276, respectively, providing essential insight into the molecular mechanisms underpinning this tumor.

In light of the patient's progressive disease, a new FDG PET-CT conducted in August 2021 revealed notable lymph node enlargement in the right upper tracheal region, characterized by central necrosis and suspected secondary implantation. The lesion in the right talus remained unchanged. Consequently, a decision was made to initiate treatment with larotrectinib at the standard dose of 100 mg twice a day. Thereafter, the initial assessment of treatment response was conducted in January 2022 through FDG PET-CT imaging, which revealed a marked reduction in the dimensions and metabolic activity of the right upper tracheal lymph node—now measuring approximately 1.6×1.5 cm (previously 3.3×3.0) with a current SUVmax of 2.1 (previously 3.1).

Subsequent imaging in April 2022 demonstrated continued reduction in the size of the right upper paratracheal

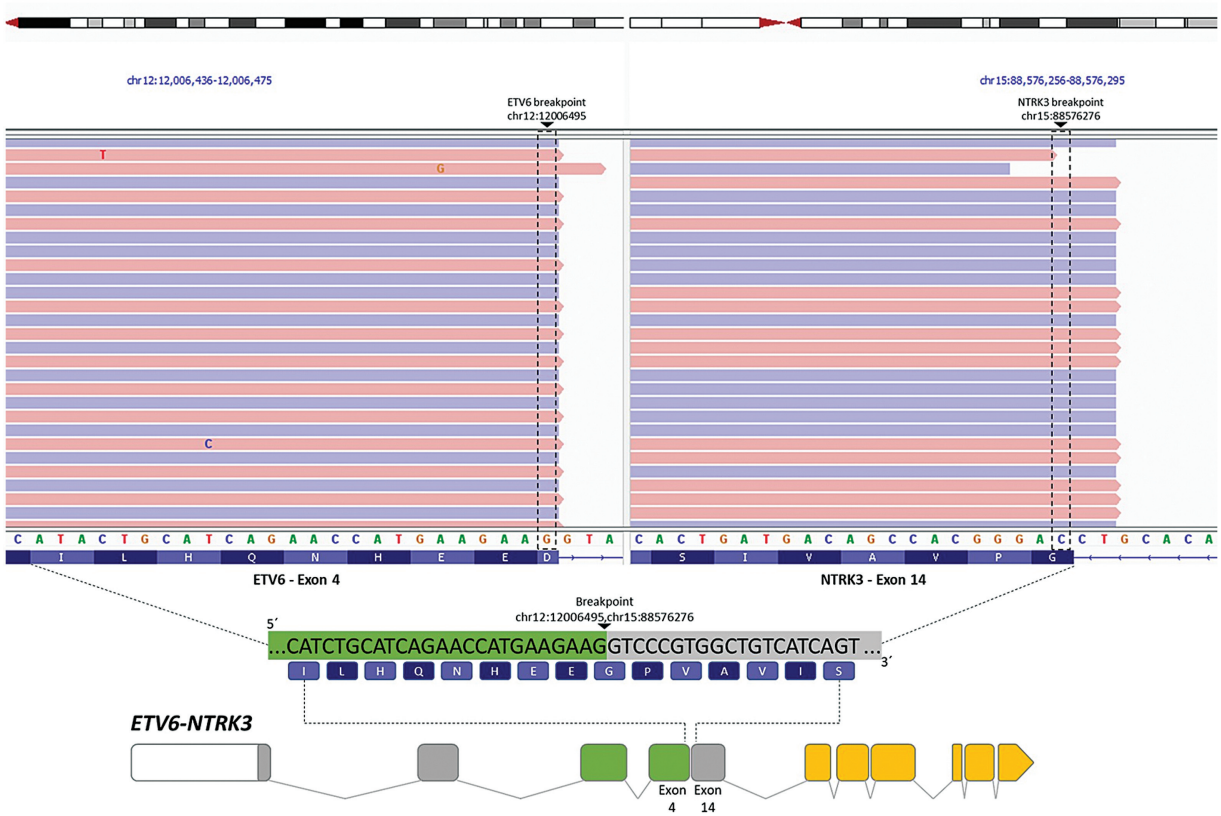

Fig. 4 An integrative genomics viewer (IGV) split-screen view of read alignments displaying the identified *ETV6-NTRK3* fusion, highlighting the breakpoints in the *ETV6* locus (left) (chr12:12006495) and the *NTRK3* locus (right) (chr15:88576276). On the left panel, the aligned reads correspond to exon 4 of *ETV6*, while on the right panel, the reads are aligned with exon 14 of *NTRK3*. Pink bars indicate reverse strand reads, and light blue bars indicate forward strand reads. Below, the nucleotide sequence spanning the breakpoint region is shown, along with the predicted protein sequence. The green segment represents the *ETV6* sequence, while the gray segment represents the *NTRK3* sequence. At the bottom, a schematic diagram illustrates the predicted fusion protein and the exons involved, specifically exons 1–4 of *ETV6* and 14–20 of *NTRK3*.

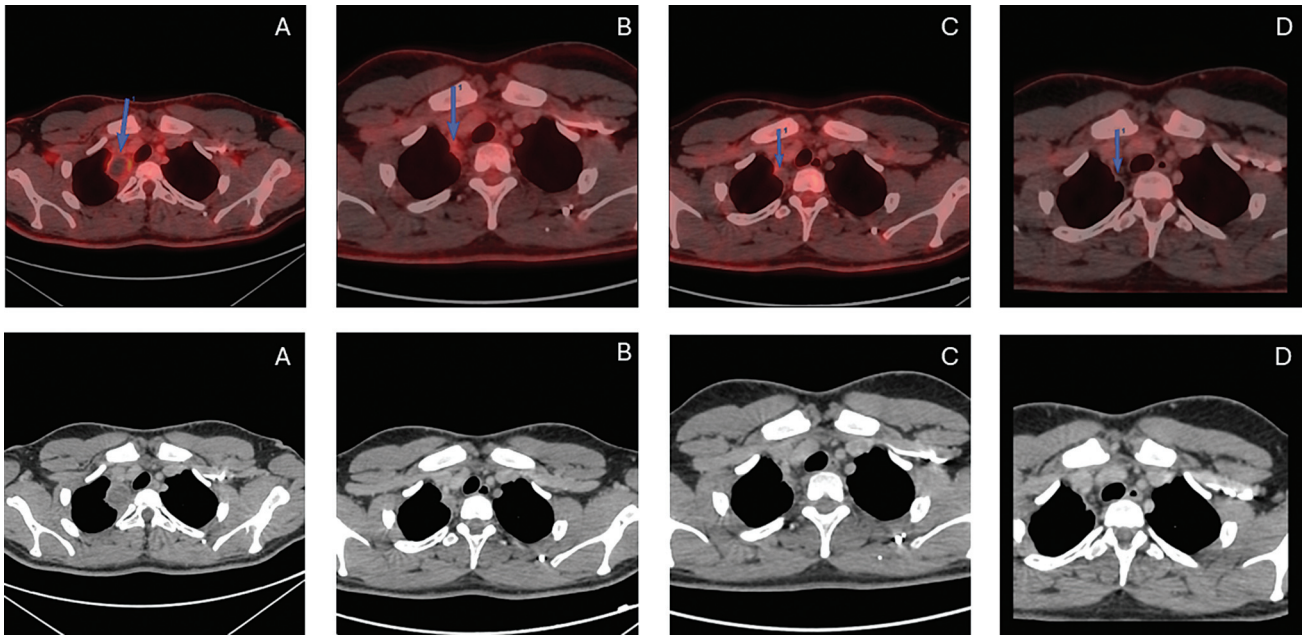

Fig. 5 Sequential fluorodeoxyglucose (FDG) positron-emission tomography-computed tomography (PET-CT) images tracking treatment progress. (**A**) August 2021, enlarged lymph node in the right upper tracheal region. (**B**) January 2022, reduction in node size and radiopharmaceutical uptake. (**C**) August 2022, continued decrease in node size. (**D**) November 2022, complete metabolic response with no signs of active malignancy.

lymph node. A follow-up FDG PET-CT performed in August 2022 showed findings consistent with previous assessments, indicating a persistent favorable response to therapy in the thoracic nodal region. Subsequently, an FDG PET-CT scan conducted in November 2023 revealed a complete metabolic response in the nodal lesion, with no metabolic findings suggesting active malignancy. ►**Fig. 5** displays sequential images from the FDG PET-CT scans throughout the treatment course, illustrating the patient's positive trajectory.

Upon the initiation of larotrectinib, the patient reported mild and transient gastrointestinal side effects during the initial weeks of therapy, including grade 2 anorexia and grade 1 diarrhea and nausea. These adverse effects were managed effectively, permitting the patient to maintain the prescribed dosage without reduction. Currently, the patient exhibits excellent general health and demonstrates good tolerance to larotrectinib, reporting a significant improvement in quality of life. The treatment strategy is to continue until the emergence of progressive disease or the onset of intolerable toxicity.

Discussion

This report presents a rare case of a spindle cell tumor in a 15-year-old male patient, characterized by a unique *ETV6-NTRK3* gene rearrangement. The identification of this rearrangement contributes to the growing understanding of the molecular landscape of spindle cell tumors, particularly those exhibiting coexpression of S100 and CD34. These genetic findings highlight the importance of advanced genetic testing in informing treatment decisions. The presence of the *ETV6-NTRK3* fusion aligns with emerging literature recognizing the clinical significance of *NTRK* fusions in STTs, indicating a distinct biological behavior that necessitates further investigation.[10,11]

In the differential diagnosis, we considered tumors commonly associated with CD34 and S100 expression, including dermatofibrosarcoma protuberans, neurofibroma, and solitary fibrous tumors. These entities were systematically evaluated and excluded based on specific histopathological features identified in the tumor. The tumor exhibited uniform cytomorphology and a 'patternless' architecture, characteristic of spindle cell tumors, while lacking the distinctive features of the other differential diagnoses. The coexpression of CD34 and S100 was instrumental in the diagnostic process, reinforcing its classification a distinct entity within the spindle cell tumor spectrum. Additionally, the absence of SOX-10 expression, typically associated with neurogenic tumors, further supported this classification.[6]

The *ETV6-NTRK3* rearrangement identified in the patient was particularly noteworthy compared to previously reported cases.[12,13] While other *NTRK* fusions in spindle cell tumors have been documented in previous studies, the specific *ETV6-NTRK3* fusion has been less frequently reported.[14] This case adds to the increasing body of evidence regarding the clinical and pathological significance of *NTRK* fusions, suggesting an association between these alterations and aggressive tumor behavior. Moreover, these fusions present potential targets for therapeutic interventions. Notably, favorable responses to targeted therapies have been documented, underscoring their critical relevance in the management of these clinical entities.[6,15,16]

Patients harboring *NTRK* gene fusions are typically recommended initial targeted therapy with either larotrectinib or

entrectinib, with a preference for larotrectinib due to its superior durability of responses and more favorable toxicity profile. The efficacy of larotrectinib was demonstrated in a pooled analysis of phase-I and -II trials involving 159 adult and pediatric patients affected by various *NTRK* fusion-positive cancers, including 69 individuals with STTs. Encouragingly, objective responses were observed in a high percentage of patients across different tumor types, such as 27 out of 28 patients with infantile fibrosarcoma (96%) and all four patients with gastrointestinal stromal tumors (100%), with notable responses in various other soft tissue sarcoma subtypes. Noteworthy was the extended response duration of 44 months seen in one sarcoma patient, underlining the treatment's potential for sustained benefits. However, a limitation of these studies was the absence of a centralized histology review. Larotrectinib became the first drug approved by the United States Food and Drug Administration (FDA) for a tissue-agnostic cancer indication, allowing its use regardless of tumor site upon detection of *NTRK* gene fusions.[17–21]

This case report emphasizes the essential role of interdisciplinary collaboration and molecular testing in the diagnosis and management of spindle cell tumors. The identification of the *ETV6-NTRK3* rearrangement has advanced the understanding of the genetic landscape of the tumor and enhanced the potential for personalized therapeutic strategies based on genetic profiling. Future research should investigate the implications of additional *NTRK* fusions in these tumors and evaluate the impact of targeted therapies on clinical outcomes.

By detailing the unique features of this case and its relevance to existing literature, the present report contributes to a comprehensive understanding of spindle cell tumors and their management, advocating for the integration of genomic insights into clinical practice to improve patient care.

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Conflict of Interests
The authors have no conflict of interests to declare.

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Ethical Approval
The present study, which was approved by the Human Research Ethics Committee at Hospital de Força Aérea do Galeão (HFAG) in Rio de Janeiro, Brazil (registration number CAAE 58431022.7.0000.5250), adhered strictly to Good Clinical Practice guidelines. Prior to any data collection, the participant provided written informed consent.

Data Availability
All data supporting the study findings are contained within the manuscript. Requests for additional data may be directed to the corresponding author.

References
1 WHO Classification of Tumours Editorial Board. Soft tissue and bone tumours. In: WHO classification of tumours. 5th ed. Vol. 3. Lyon: International Agency for Research on Cancer; 2020
2 Choi JH, Ro JY. The 2020 WHO Classification of Tumors of Soft Tissue: Selected Changes and New Entities. Adv Anat Pathol 2021; 28(01):44–58. Doi: 10.1097/PAP.0000000000000284
3 Rothermundt C, Andreou D, Blay JY, Brodowicz T, Desar IME, Dileo P, et al; Writing committee on behalf of CSSS panellists. Controversies in the management of patients with soft tissue sarcoma: Recommendations of the Conference on State of Science in Sarcoma 2022. Eur J Cancer 2023;180:158–179. Doi: 10.1016/j.ejca.2022.11.008
4 Kallen ME, Hornick JL. The 2020 WHO Classification: What's New in Soft Tissue Tumor Pathology? Am J Surg Pathol 2021;45(01): e1–e23. Doi: 10.1097/PAS.0000000000001552
5 Suurmeijer AJH, Dickson BC, Antonescu CR. Complementary value of molecular analysis to expert review in refining classification of uncommon soft tissue tumors. Genes Chromosomes Cancer 2024; 63(01):e23196. Doi: 10.1002/gcc.23196
6 Suurmeijer AJH, Dickson BC, Swanson D, Zhang L, Sung YS, Cotzia P, et al. A novel group of spindle cell tumors defined by S100 and CD34 co-expression shows recurrent fusions involving RAF1, BRAF, and NTRK1/2 genes. Genes Chromosomes Cancer 2018; 57(12):611–621. Doi: 10.1002/gcc.22671
7 Suurmeijer AJ, Dickson BC, Swanson D, Zhang L, Sung YS, Huang HY, et al. The histologic spectrum of soft tissue spindle cell tumors with NTRK3 gene rearrangements. Genes Chromosomes Cancer 2019;58(11):739–746. Doi: 10.1002/gcc.22767
8 Choi JH, Ro JY. The Recent Advances in Molecular Diagnosis of Soft Tissue Tumors. Int J Mol Sci 2023;24(06):5934. Doi: 10.3390/ijms24065934
9 Riley DS, Barber MS, Kienle GS, Aronson JK, Von Schoen-Angerer T, Tugwell P, et al. CARE guidelines for case reports: explanation and elaboration document. J Clin Epidemiol 2017;89:218–235. Doi: 10.1016/j.jclinepi.2017.04.026
10 Yang H, Yu L. Cutaneous and Superficial Soft Tissue CD34^{+} Spindle Cell Proliferation. Arch Pathol Lab Med 2017;141(08):1092–1100. Doi: 10.5858/arpa.2016-0598-RA
11 Nagasubramanian R, Wei J, Gordon P, Rastatter JC, Cox MC, Pappo A. Infantile Fibrosarcoma with NTRK3-ETV6 Fusion Successfully Treated with the Tropomyosin-Related Kinase Inhibitor LOXO-101. Pediatr Blood Cancer 2016;63(08):1468–1470. Doi: 10.1002/pbc.26026
12 Chiang S, Cotzia P, Hyman DM, Drilon A, Tap WD, Zhang L, et al. NTRK Fusions Define a Novel Uterine Sarcoma Subtype with Features of Fibrosarcoma. Am J Surg Pathol 2018;42(06): 791–798. Doi: 10.1097/PAS.0000000000001055
13 Davis JL, Lockwood CM, Albert CM, Tsuchiya K, Hawkins DS, Rudzinski ER. Infantile NTRK-associated Mesenchymal Tumors. Pediatr Dev Pathol 2018;21(01):68–78. Doi: 10.1177/1093526617712639
14 Yamazaki F, Nakatani F, Asano N, Wakai S, Sekimizu M, Mitani S, et al. Novel NTRK3 Fusions in Fibrosarcomas of Adults. Am J Surg Pathol 2019;43(04):523–530. Doi: 10.1097/PAS.0000000000001194
15 Davis JL, Lockwood CM, Stohr B, Boecking C, Al-Ibraheemi A, DuBois SG, et al. Expanding the Spectrum of Pediatric NTRK-rearranged Mesenchymal Tumors. Am J Surg Pathol 2019;43(04): 435–445. Doi: 10.1097/PAS.0000000000001203

16 Kovalenko I, Roy P, Soni B, Sangha L, Toom S. Secretory Carcinoma of the Breast Mimicking Invasive Ductal Carcinoma: A Case Report. Am J Case Rep 2022;23:e936665. Doi: 10.12659/AJCR.936665
17 Gong LH, Liu WF, Niu XH, Ding Y. Two cases of spindle cell tumors with S100 and CD34 co-expression showing novel RAF1 fusions. Diagn Pathol 2022;17(01):80. Doi: 10.1186/s13000-022-01263-y
18 Hung YP, Fletcher CDM, Hornick JL. Evaluation of pan-TRK immunohistochemistry in infantile fibrosarcoma, lipofibromatosis-like neural tumour and histological mimics. Histopathology 2018;73 (04):634–644. Doi: 10.1111/his.13666
19 Abs D, Landman S, Osio A, Lepesant P, Schneider P, Obadia D, et al. Spindle cell tumor with CD34 and S100 co-expression and distinctive stromal and perivascular hyalinization showing EML4-ALK fusion. J Cutan Pathol 2021;48(07):896–901. Doi: 10.1111/cup.13926
20 Shreenivas A, Janku F, Gouda MA, Chen HZ, George B, Kato S, Kurzrock R. ALK fusions in the pan-cancer setting: another tumor-agnostic target? NPJ Precis Oncol 2023;7(01):101. Doi: 10.1038/s41698-023-00449-x
21 Michal M, Ptáková N, Martínek P, Gatalica Z, Kazakov DV, Michalová K, et al. S100 and CD34 positive spindle cell tumor with prominent perivascular hyalinization and a novel NCOA4-RET fusion. Genes Chromosomes Cancer 2019;58(09):680–685. Doi: 10.1002/gcc.22758

