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Case Report

SMARCB1-Inactivated Congenital Rhabdoid Tumor Harboring NTRK Fusion: Case Report

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Abstract

A three-day-old child presented with an inborn lump in the zygomatic region. The surgical resection was performed, and microscopic examination showed a tumor consisting of cells of medium size, with eccentric nucleolated nuclei and high mitotic and apoptotic activity. The tumor cells were positive for Vimentin, EMA, Pancytokeratin, SMA, MSA, and PanTRK, the loss of nuclear INI1 expression was detected as well. An extrarenal extracranial rhabdoid tumor was diagnosed, and PanTRK positivity led to further molecular tests, which revealed both *SMARCB1* deletion and *ETV6::NTRK3* fusion. This report is, to our knowledge, one of the first cases of *NTRK*-rearranged rhabdoid tumor and the first such case of an extrarenal extracranial rhabdoid tumor. In addition, we present a review of the literature.

Keywords: Rhabdoid Tumor; *SMARCB1*; NTRK; Immunohistochemistry; MLPA; RNA-sequencing

Introduction

Rhabdoid tumors (RT) are rare pediatric solid cancers with characteristic morphology and specific driver mutations affecting *SMARCB1*, less typically *SMARCA4*. Depending on localization, RT are classified into atypical teratoid RT of the central nervous system, RT of the kidney, and extracranial extrarenal RT of soft tissues. *NTRK* genes rearrangements as drivers in RT are highly improbable. Here we describe a *SMARCB1*-inactivated congenital soft tissue RT with an extremely aggressive clinical course, harboring a chimeric *NTRK3* transcript, in a male infant.

Case Presentation

A three-day-old male patient born with a visible lump in the right zygomatic region was hospitalized in a multi-profile facility for diagnosis and treatment planning. The lump, bluish-purple in color, 1.5 cm in diameter, wide and indistinctly outlined at the base, protruding under stretched, glossy skin, adherent to the dermis and painless on palpation. The child was examined by a maxillofacial surgeon who suspected a hemangioma. Subsequent ultrasound scan of facial soft tissues and MRI of the brain with contrast enhancement revealed a mass in soft tissues of the right zygomatic region, of heterogeneous consistency, with a relatively sharp and even outline, spreading to the right eyelid and infiltrating the right temporal muscle, accumulating the contrasting agent at

margins. By the age of 14 days, the tumor increased in volume to 3.0×2.5×2.0 cm.

At the age of 15 days, the patient underwent surgical resection of the mass. Cytology assay revealed medium-to-large non-hematopoietic malignant tumor elements with wide cytoplasm and eccentrically located nucleolated round nuclei, occasional binucleated and single multinucleated cells, suggestive of rhabdomyosarcoma. A vincristine-doxorubicin-cyclophosphamide scheme was commenced immediately, authorized by a tumor board on the basis of a life-threatening emergency in advance of histological diagnosis.

Histopathological examination revealed polymorphic neoplastic cells of medium size, with eccentric nucleolated nuclei and high mitotic and apoptotic indexes, infiltrating the parotid gland and dermal tissues (Figure 1). The antibody panel for immunohistochemistry was expanded considering the neonatal age of the patient and the superficial localization of the tumor. The tumor was positive for Vimentin, focally positive for EMA, Pancytokeratin, SMA, MSA, PanTRK, with solitary cells positive for Desmin and Calponin. Staining for s100, CK5/6, Synaptophysin, Chromogranin, p63, and SOX-10 proteins revealed no expression. The loss of nuclear expression of INI1 was evident. The antibodies, clones, dilutions, antigen retrieval methods, and vendors are listed in (Table 1). Appropriate positive and negative controls for each antibody were run concurrently. The findings confirmed the diagnosis of extrarenal extracranial rhabdoid tumor (Figure 1).

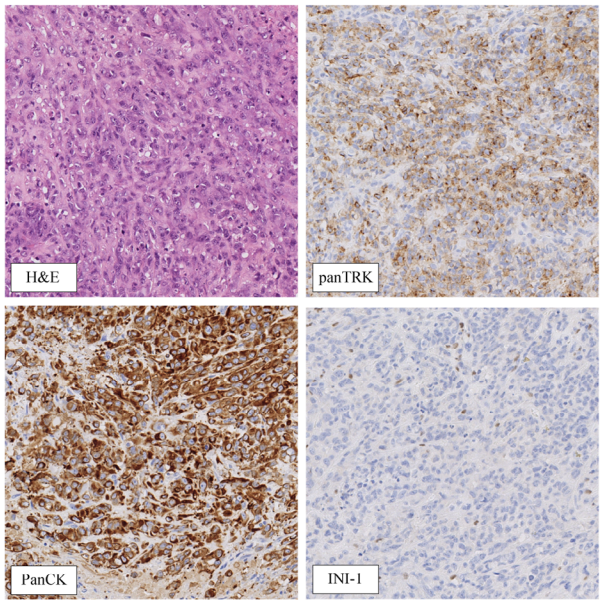

Figure 1: Proliferation of polymorphic medium-sized cells with eccentric nucleolated nuclei and abundant cytoplasm and high mitotic and apoptotic indexes in hyalinized stroma. H&E, x200. Positive reaction with anti-PanTRK antibody, diffuse strong positivity for Pancytokeratin and the loss of nuclear expression of INI1.

Antibody	Clone	Dilution	Source (city/state)
PanTRK	EPR17341	Prediluted	Ventana (Oro Valley, AZ, USA)
INI1	MRQ-27	1:50	Cell Marque (Rocklin, CA, USA)
Vimentin	V9	Prediluted	Ventana (Oro Valley, AZ, USA)
EMA	E29	Prediluted	Ventana (Oro Valley, AZ, USA)
Pancytokeratin	AE1/AE3/PCK26	Prediluted	Ventana (Oro Valley, AZ, USA)
SMA	1A4	Prediluted	Cell Marque (Rocklin, CA, USA)
MSA	HHF35	1:30	Cell Marque (Rocklin, CA, USA)
Desmin	D33	1:50	Cell Marque (Rocklin, CA, USA)
Calponin	EP798Y	Prediluted	Ventana (Oro Valley, AZ, USA)
s100	Polyclonal	Prediluted	Dako (Carpenteria, CA, USA)
CK 5/6	D5/16B4	Prediluted	Ventana (Oro Valley, AZ, USA)
Synaptophysin	SF11	Prediluted	Ventana (Oro Valley, AZ, USA)
Chromogranin	LK2H10	Prediluted	Ventana (Oro Valley, AZ, USA)
p63	4A4	Prediluted	Ventana (Oro Valley, AZ, USA)
SOX-10	EP268	1:100	Cell Marque (Rocklin, CA, USA)

Table 1: Antibody panel used in this case.

Fluorescent in situ hybridization (FISH) test was performed and no *NTRK* fusions were detected (NTRK1, NTRK2, NTRK3 Break Apart FISH Probes, CytoTest Inc., MD, USA). Considering this, further molecular tests were performed to comprehensively address the diagnosis. The purified tumor DNA was probed for multi-exon deletions in *SMARCB1* using the multiplex ligation-dependent probe amplification (MLPA) assay with SALSA® MLPA® Probemix P258 SMARCB1 (MRC Holland, the Netherlands). The analysis revealed a heterozygous deletion of *SMARCB1*

(NM_003073.5) exons 2-4 and homozygous deletion of *SMARCB1* exons 5-9. MLPA assay of the germline material revealed retained *SMARCB1* alleles, thus confirming the somatic origin of both deletions. Furthermore, targeted high-throughput sequencing of the tumor and normal DNA showed no additional genetic variants in *SMARCB1* gene.

Considering the positive signal with panTRK antibody, the material was further tested for NTRK family gene rearrangement using a multimodal OncoScope™ Non-Small Cell Lung Cancer Solution panel (Parseq Lab, Russia). The panel allows identification of chimeric transcripts containing an *NTRK1/2/3*, *ALK*, *ROS1,* or *RET* gene fragment. The high-throughput sequencing revealed an *ETV6* (NM_001987.5) exon 5 – *NTRK3* (NM_002530.4) exon 15 fusion. The finding was validated by reverse transcription polymerase chain reaction (PCR) assay with oligonucleotide primers published by Vokuhl et al. (2018) [1]. Verification by Sanger sequencing showed unambiguous alignment of the product to *ETV6* exon 5 and *NTRK3* exon 15 (Figure 2).

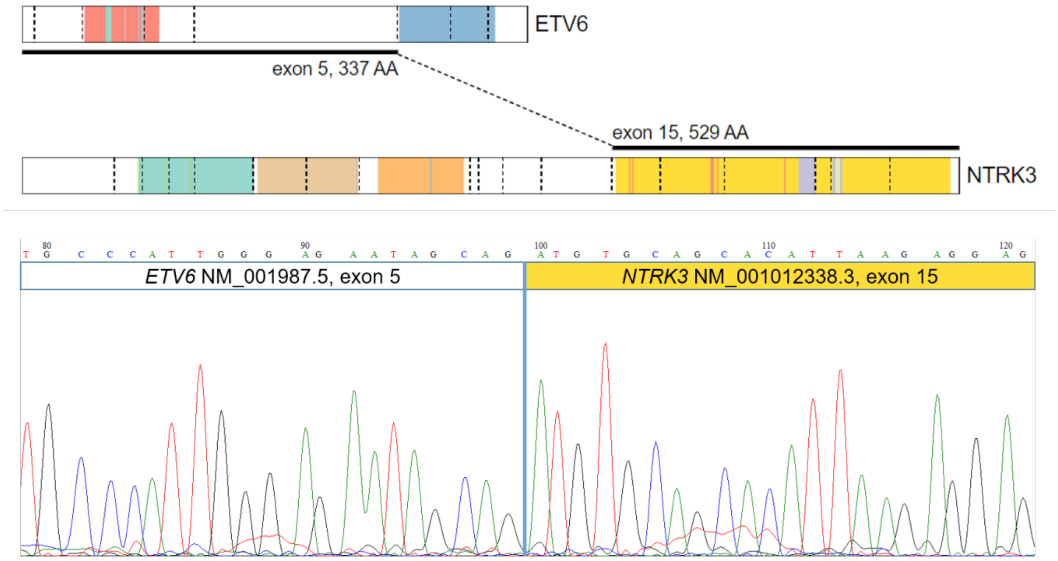

Figure 2: Top: schematic representation of *ETV6::NTRK3* fusion. The catalytic tyrosine-kinase domain of *NTRK3* is entirely preserved in the chimeric oncoprotein and highlighted in yellow. Bottom: Chromatogram obtained at fusion transcript validation by RT-PCR and Sanger sequencing. The reading frame is retained.

Chemotherapy was initiated according to EU-RHAB V2.2010 protocol with extra bevacizumab between the second and third cycles. Unfortunately, despite the intensive treatment, the negative clinical dynamics with continued growth of the tumor persisted ultimately turning into rapid progression of the disease with a fatal outcome at the age of 5 months and 21 days.

Discussion

RT are relatively rare pediatric cancers with unfavorable prognosis. The incidence rate per 1,000,000 children under 15 years is 0.89 for atypical teratoid RT, 0.19 for renal RT, and 0.32 for extrarenal extracranial RT [2,3].

The morphology of RT is characteristic: rhabdoid cells show clear boundaries; the nuclei are large, eccentrically located, vesicular, bean-shaped, or rounded, with prominent nucleoli, occasionally cells are binucleated; the cytoplasm is abundant, eosinophilic, may contain hyaline inclusions. Cell morphology can also be spindle-shaped, epithelioid, or neuroectodermal, and may vary within one tumor; the architecture may be layered, papillary, acinar, or trabecular. Other features include infiltrative growth patterns, high mitotic activity with abnormal mitotic figures, areas of necrosis, and hemorrhages [3].

Immunohistochemically, the tumors are positive for Pancytokeratin, EMA, CD99, Synaptophysin, SMA, Vimentin, GFAP, NFP, MSA, S100, Sall-4, Glypican-3. A characteristic, diagnostically decisive feature is the loss of signal for INI1 (less typically, BRG1) [3]. RT pathogenesis has been associated with inactivating mutations in SWI/SNF subunit-encoding genes. The highly conserved SWI/SNF chromatin remodeling complex is a crucial coactivator of gene expression in the nucleus. The core of the SWI/SNF complex binds chromatin to promote a release of energy sufficient for the dissociation of genomic DNA from nucleosome histones. The

loops of DNA expand by nucleosome repositioning and expelling of histone octamers, creating the free chromatin zones in promoter and coding regions of genes to enable the RNA-polymerase-II-mediated transcription [4]. RT pathogenesis is primarily driven by inactivating genetic events affecting this complex, most often *SMARCB1* gene encoding a SWI/SNF core subunit INI1. An immunohistochemically test for INI1 is mandatory for differential diagnosis in suspected RT.

The loss of INI1 causes widespread dysregulation of the gene expression program. The effects are profound enough to promote oncogenic transformation; accordingly, RT are minimally burdened by extra genetic events and genomically balanced. About 5% of RT are driven by inactivating mutations in *SMARCA4* encoding another SWI/SNF subunit, BRG-1 [3]. The impacts of *SMARCB1* and *SMARCA4* pathogenic variants are similar, as both genes encode core subunits in SWI/SNF and determine specific binding of the complex to chromatin.

The spectrum of tumors involving *SMARCB1* or *SMARCA4* inactivation is not limited to RT but also includes small-cell carcinoma of the ovary (hypercalcemic type), SMARCA4-deficient thoracic sarcoma and cribriform neuroepithelial tumor (CriNET). These tumors share rhabdoid morphology, unfavorable clinical course, and poor response to chemotherapy (except CriNET) [5-7].

Chimeric oncoproteins produced by chromosome breakdown and abnormal fusion are central to many cancers. Exemplary in this regard are NTRK rearrangements that involve *NTRK1*, *NTRK2,* and *NTRK3* genes mapped to, respectively, 1q21-q22, 9q22.1, and 15q25 chromosomal regions. The corresponding proteins TRKA, TRKB, and TRKC are receptor tyrosine kinases (TRKs) with a conserved LRR1-3 motif. TRK ligands are secretory proteins called 'neurotrophins' including nerve growth factor NGF, brain-derived neurotrophic factor BDNF, and neurotrophins-3/4. The ligand-bound TRK phosphorylate their substrates to trigger RAS/RAF/MEK/ERK, PI3K/AKT/mTOR and PLCγ signaling cascades with multiple biological effects. Normal TRK-mediated signaling plays major roles in the embryonic development of the nervous system, synaptogenesis, axon and dendrite outgrowth, differentiation of sensory ganglia, nociception, proprioception, memory formation, as well as in cardiovascular, reproductive, and immune functionalities. Most significantly in the context of cancer, TRK-mediated signaling can support proliferation and suppress apoptosis.

The pathogenic aberrations comprise a 3′ kinase domain-encoding region of NTRK fused to a 5′ region of another gene, typically encoding a dimerization domain and controlled by a strong promoter. The unhinged, constitutive catalytic activity of TRK decoupled from the ligand binding represents a crucial driving force for oncogenesis [8].

NTRK fusion oncogenes are found in colorectal cancer, papillary thyroid carcinoma, non-small cell lung carcinoma, spitzoid tumors and melanomas, infantile fibrosarcoma, gastrointestinal stromal tumor, secretory breast carcinoma, mammary analog secretory carcinoma of the salivary glands, acute myeloid leukemia, high-grade glial tumors, congenital mesoblastic nephroma and other malignancies [9]. However, *NTRK* rearrangements in RT are highly improbable. To the best of our knowledge, the only published case of *NTRK*-rearranged RT (specifically, atypical teratoid RT) was identified by high-throughput RNA sequencing of tumor samples biobanked at the Institute Curie, France [10]. The simultaneous incidence of NTRK and *SMARCB1*/*A4* aberrations in other cancers is equally low. Boulanger et al. (2023) describe an aggressive, therapy-resistant case of squamous cell lung carcinoma harboring aberrations of both *NTRK1* and *SMARCA4* [11]. Thyroid carcinomas [12] and sinonasal tract melanomas can harbor NTRK rearrangements and SMARC genes variants, but not in the same tumor [13]. The combination of an alteration in the epigenetic modifier and a mutation leading to kinase activation is non-typical for tumors, however L. Auffret et al. described a new subtype of diffuse midline glioma, H3 K27 and *BRAF/FGFR1* co-altered. Authors stated that the mutation in epigenetic modifier (H3 K27M) occurs prior to the kinase activating genetic event (*BRAF* V600E) [14]. Consistently, in the described case we consider the *SMARCB1* as a primary oncogenic driver and the *ETV6::NTRK3* fusion as concurrent genetic alteration.

Regarding the negativity of the FISH probe for *NTRK* fusions in the discussed case, the information about sensitivity and false negative rates is limited and inconsistent to date. While some authors report a low false negative rate of 2,3% [15], other studies demonstrate limited sensitivity of 78% [16]. Considering this, one can assume that this case illustrates the probability of a false negative FISH result. However, major reasons for false negative FISH results are noncanonical breakpoints and *NTRK* partner genes [17,18], and the exact reasons for the inability to detect a canonical *ETV6::NTRK3* fusion using FISH in this case remain unclear and may lay in the area of technical imperfection.

Conclusion

The described case of extrarenal extracranial rhabdoid tumor in a newborn has a unique tumor genetic landscape combining characteristic inactivating deletion of *SMARCB1* to a gain-of-function *NTRK3* rearrangement. The emergence of *NTRK* and *SMARC* oncogenic variants within one tumor is highly improbable. This is the first reported case of extrarenal extracranial rhabdoid tumor harboring this combination.

A comprehensive search for accessory druggable targets is clinically justified, especially in tumors with invariably poor prognosis. The efficacy of TRK inhibitors in NTRK-rearranged soft-tissue tumors has been demonstrated in several studies and clinical observations [19,20]. In the present case, the opportunity for alternative therapy was excluded due to the rapid fatal progression of the disease.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from the next of kin of the subject described in this report.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Authors Contribution List

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Anna Fedorova – analyzed the literature, handled the clinical data, wrote and edited clinical and pathology sections.

Agnesa Panferova – performed diagnostics (molecular oncology).

Lyudmila Zemtsova – performed diagnostics (molecular oncology).

Nina Gegelia – performed diagnostics (molecular oncology).

Natalia Usman – performed diagnostics (molecular oncology).

Alexey Kislyakov – performed the diagnostics (morphology, immunohistochemistry).

Alexander Druy – analyzed the literature, drafted and wrote the molecular oncology sections.

Dmitry Konovalov – performed the diagnostics (morphology, immunohistochemistry), final edited the manuscript.

Authorship

Alexander Druy and Dmitry Konovalov share senior authorship of the article

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