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NTRK3-rearranged spindle cell neoplasm of the skin: diagnostic pitfalls of an emerging entity, a case report

Andreia Coutada[1] ✉, Carla Di Loreto[2,3], Alenka Matjašič[4], Boštjan Luzar[4]

[1]Department of Pathology, Portuguese Oncology Institute of Porto (IPO Porto) / Porto Raquel Seruca Comprehensive Cancer Center (P.CCC), Porto, Portugal. [2]Institute of Pathology, Academic Hospital of Udine, Udine, Italy. [3]Department of Medicine, University of Udine, Udine, Italy. [4]Institute of Pathology, Medical Faculty, University of Ljubljana, Ljubljana, Slovenia.

Abstract

Neurotrophic tyrosine receptor kinase-rearranged spindle cell neoplasms (NTRK-RSCNs) are an emerging category of rare soft tissue tumors recently recognized by the World Health Organization Classification of Soft Tissue and Bone Tumours. NTRK-RSCNs mostly affect the superficial soft tissues of the extremities and trunk, and they can occur across a broad age range. These tumors exhibit a wide morphologic spectrum, often mimicking other mesenchymal tumors. Recognition of NTRK-RSCNs is crucial for targeted therapy in selected cases, given the recent approval of kinase inhibitors. We describe the case of a 55-year-old male with an NTRK-RSCN located on the arm, harboring the novel fusion partner *PPFIBP1::NTRK3*, while providing additional clinical and morphological characteristics of this rare entity.

Keywords: kinase fusion neoplasm, NTRK3, cutaneous spindle cell neoplasm, soft tissue tumor, case report

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Introduction

Neurotrophic tyrosine receptor kinase-rearranged spindle cell neoplasms (NTRK-RSCNs) are an emerging category of molecularly defined rare soft tissue tumors (STTs) recently recognized by the 2020 World Health Organization Classification of Soft Tissue and Bone Tumours as a provisional entity (1). In light of advancements in next-generation sequencing (NGS) and recent approval of targeted therapies for solid tumors with kinase fusions, NTRK-RSCNs have received increased interest. Histologically, this entity is characterized by a wide morphologic spectrum of spindle cell neoplasms that can mimic several other mesenchymal tumors, making their diagnosis quite challenging. Misdiagnosis can result in missed opportunities for targeted therapies, leading to inappropriate treatment and inaccurate prognosis estimations, all of which can significantly impact patient outcomes, especially in the context of metastases or locally advanced unresectable tumors. Herein we report a case of NTRK-RSCN in an adult harboring the novel fusion partner *PPFIBP1::NTRK3* while providing additional clinical and morphological characteristics of this rare entity.

Case report

A 55-year-old male patient presented with a nodular lesion in the upper distal extremity (Fig. 1A) that had been growing slowly over the past 10 years with multiple recurrences following incomplete excision. The tumor was considered a dermatofibrosarcoma protuberans (DFSP) over the years.

Histological examination of the latest recurrence revealed involvement of the entire dermis and subcutis by an infiltrative neoplasm with variable cellularity (Fig. 1A). The tumor cells showed a mostly spindle cell morphology with mild atypia and were arranged either haphazardly within an abundant myxoid matrix (Fig. 1B) or in fascicles (Fig. 1C). Vascular proliferation with focal mild perivascular lymphocytic infiltrate was present in the background of the tumor (Fig. 1D). Mitotic activity was low (one mitosis per 10 high-power fields). Necrosis was absent. Previous biopsies of the tumor exhibited a similar morphology.

By immunohistochemistry, the tumor cells were negative for cytokeratin MNF116 (Fig. 2A) and focally positive for EMA (Fig. 2B). S100 was mostly negative, with focal areas of nuclear positivity (Fig. 2C), and SOX10 was negative (Fig. 2D). CD34 exhibited patchy positivity (Fig. 2E). Pan-TRK showed weak to moderate diffuse cytoplasmatic and focal nuclear staining (Fig. 2F). Genetic analysis by NGS using the ArcherDx FusionPlex Expanded Sarcoma panel detected a *PPFIBP1::NTRK3* fusion, confirming the diagnosis of NTRK-RSCN. Complete excision of the tumor was performed, with 5 mm margins.

The patient remains in good health with no evidence of local recurrence and/or distant metastases (follow-up: 12 months).

Discussion

NTRK-RSCNs, distinct from infantile fibrosarcoma (IFS), were first introduced in 2016 by Agaram et al. (2) as lipofibromatosis-like neural tumors (LPF-NTs). The authors encountered a group of superficial STTs resembling LPFs, featuring variable cytologic atypia and a distinct immunoprofile of S100 protein and CD34 positivity, together with recurrent *NTRK1* gene fusions. Since then, the literature has been expanding rapidly with the recognition of distinct morphologic patterns and the identification of an increasing number of other recurrent kinase alterations beyond *NTRK1/2/3* and implicated in the receptor tyrosine kinase pathway activation, such as *RAF1*, *BRAF*, *RET*, *MET*, *ALK*, *EGFR*, *ROS1*, and *ABL1* (2–5).

The wide morphologic spectrum of STTs with kinase fusions encompasses LPF-NTs; spindle cell tumors with co-expression of S100 and CD34, resembling a malignant peripheral nerve sheath tumor (MPNST); IFS with canonical *ETV6::NTRK3* fusion; IFS-like tumors with other kinase fusions; and adult type fibrosarcomas or

✉ Corresponding author: ascoutada@gmail.com

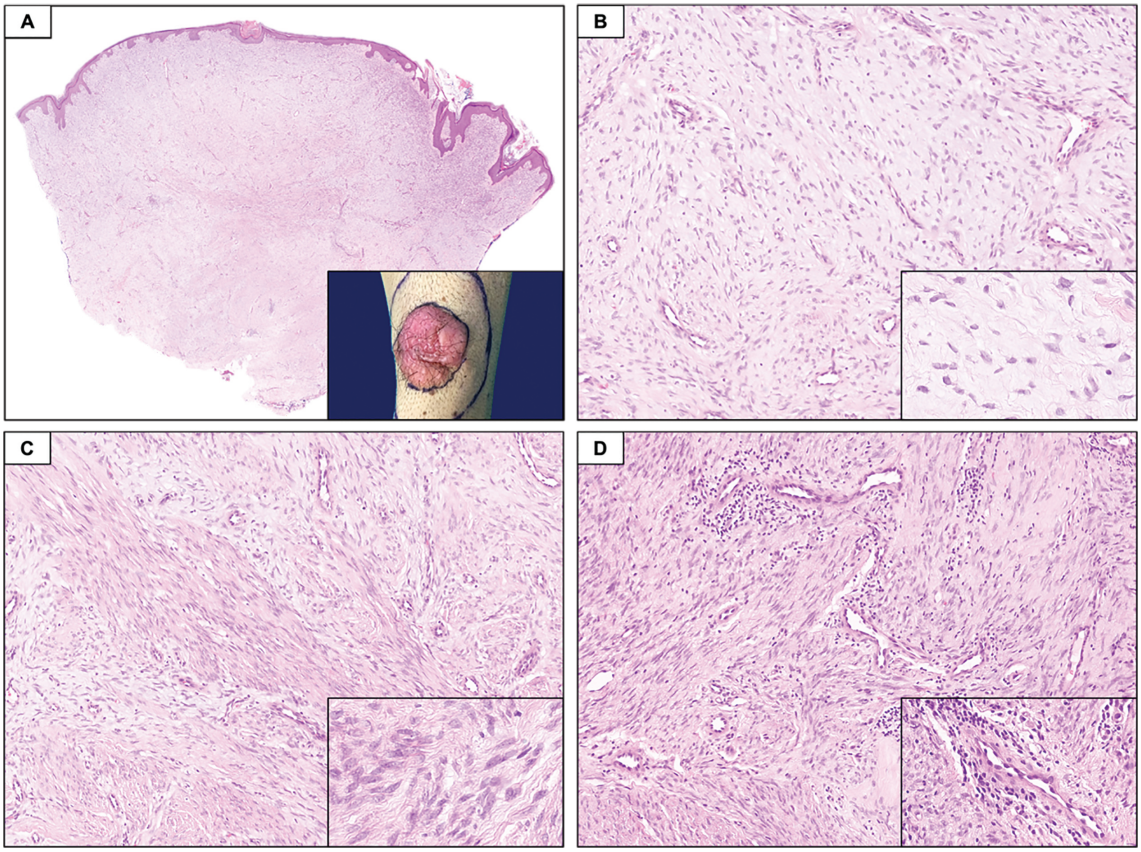


Figure 1 | Histologic characteristics of *NTRK3*-rearranged spindle cell neoplasm: A) the tumor presented grossly as a large exophytic reddish well-demarcated nodule (bottom inset); histologically, the tumor displays variable cellular density and a highly infiltrative growth pattern that destroys the preexisting adnexal structures; the tumor extends to all the surgical margins; B) hypocellular areas are composed of spindle cells haphazardly arranged in an abundant myxoid stroma, with palely eosinophilic cytoplasm with indistinct cell borders, and inconspicuous nucleoli (bottom inset); C) hypercellular areas resemble a fibromatosis pattern of cells in sheets of fascicles or short bands, with spindle to ovoid morphology and mild atypia (bottom inset); D) mild to moderate lymphocytic infiltrate within the tumor and around blood vessels (bottom inset) can also be seen; blood vessels present some dilatation and branching.

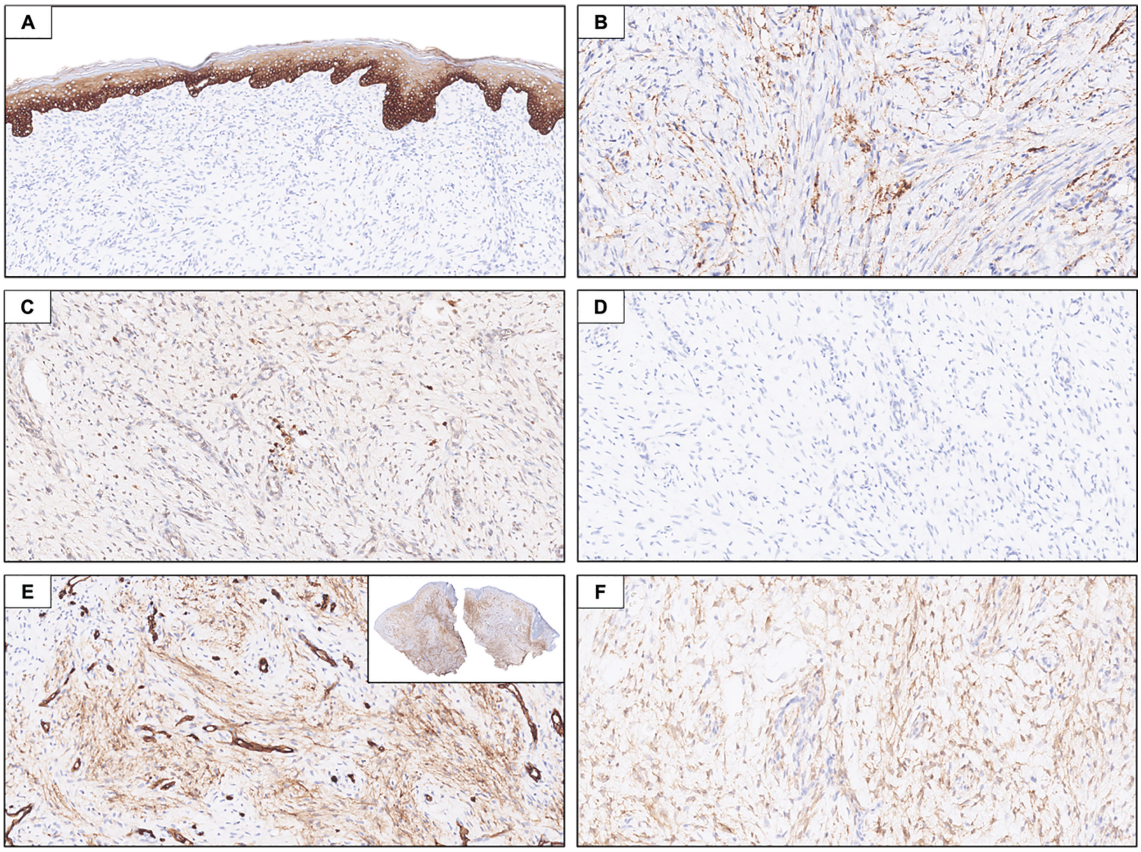


Figure 2 | Immunohistochemistry studies of *NTRK3*-rearranged spindle cell neoplasm: A) the tumor is negative for cytokeratin MNF116; B) EMA is focally positive; C) S100 is mostly negative, with focal nuclear positivity; D) SOX10 is negative; E) CD34 is unevenly positive, highlighting the vascular proliferation in the background; F) with pan-TRK, the tumor cells show weak to moderate diffuse cytoplasmatic and focal nuclear staining.

spindle cell sarcomas with a hemangiopericytic or myopericytoma-like pattern (4). Within this spectrum, tumors may show variable cellularity and a range of mitotic counts. Histologically, our case displayed a low-grade MPNST-like pattern with focal co-expression of S100 protein and CD34, and negativity for SOX10. Although not observed in our case, band-like stromal hyalinization or perivascular collagen rings are features frequently associated with the MPNST-like pattern, particularly in cases harboring a *NTRK1* fusion (3). Recognition of these features should prompt consideration of NTRK-RSCN (3).

Immunohistochemically, most tumors exhibit co-expression of S100 protein and CD34, with a range from focal to diffuse. SOX10 is consistently negative, whereas H3K27me expression is frequently retained (1–3, 6). Although not entirely specific, pan-TRK is a reliable diagnostic marker that can be used as a screening tool for identifying tumors that may show abnormalities involving the *NTRK* gene (2, 7). The pan-TRK staining pattern can be either cytoplasmatic or/and nuclear, and it can predict the fusion gene. Cytoplasmatic staining usually favors *NTRK1/2* rearrangements, whereas nuclear staining favors *NTRK3* rearrangements (2, 5, 7). Nevertheless, due to false-positive and false-negative cases for pan-TRK, molecular confirmation is recommended when NTRK-RSCN is suspected (5, 7). At present, RNA-based NGS testing is the most preferable method to detect *NTRK* fusions or other kinase alterations (7, 8).

NTRK1 gene fusion is the most common genetic abnormality among NTRK-RSCNs (1). Typically, it has a predilection for children and is commonly associated with a benign course and diverse morphology (2–4). Conversely, *NTRK3* gene fusion mostly affects adults and often displays intermediate- to high-grade morphology linked with more aggressive biological behavior, and it is characterized morphologically by fibrosarcoma- or MPNST-like patterns (4, 6). In contrast, our case presented a bland morphology and indolent clinical behavior. In addition to histologic grade, which seems to be related to prognosis in adults (1, 9), it has been suggested that the biological characteristics of the subset of low-grade NTRK3-RSCN may also be potentially linked to the type of fusion gene pair (10), but further studies are needed to confirm this. To date, some of the reported fusion partners of *NTRK3* in adult STTs include *RBPMS*, *EML4*, *SPECC1L*, *STRN*, *TFG*, *TMP4*, *EIF2S2*, and *SQSTM1* (10). To our knowledge, this is the first case report of a cutaneous spindle cell tumor harboring the fusion partner *PPFIBP1::NTRK3*.

NTRK-RSCNs typically affect the superficial soft tissues of the extremities and trunk, and they can occur across a broad age range, although they are more commonly observed in children and young adults (1). Due to their infiltrative growth pattern, they are characteristically locally aggressive, often leading to multiple recurrences, as seen in our case, but metastases are rare (1, 5).

Given the overlapping morphology and nonspecific IHC panel, the main differential diagnoses include DFSP, MPNST, and inflammatory myofibroblastic tumor. In most instances, the diagnosis can be determined through careful morphological and immunohistochemical evaluation with clinical correlation. However, in some cases this distinction is challenging, especially when dealing with limited biopsy samples. In such examples, additional molecular genetic testing is confirmatory of NTRK-RSCN.

Conclusions

Our rare case highlights the importance of recognizing the broad spectrum of morphologies of NTRK-RSCN, which should prompt pathologists to investigate further for kinase rearrangements. Co-expression of CD34 and S100 protein is probably the most reliable diagnostic pitfall characteristic for NTRK-RSCN. Given the spectrum of genetic alterations that these tumors may contain and the recent approval of kinase-inhibitors, their identification is essential because it creates opportunities for more effective treatment, particularly in the context of high-grade tumors with metastases or locally advanced unresectable tumors.

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