STRN-NTRK3-rearranged Mesenchymal Tumor of the Uterus

Expanding the Morphologic Spectrum of Tumors With NTRK Fusions

To the Editor:

We have followed with great interest several recent reports published mainly in this journal on *NTRK*-rearranged mesenchymal tumors. The largest series by Davis and colleagues focused on *NTRK*-rearranged pediatric mesenchymal tumors. Although the studied tumors showed certain variation in histologic appearances, all lesions manifested patterns previously reported in infantile fibrosarcoma.[1] Tumors with lipofibromatosis-like morphology and S100-protein and CD34 co-expression harboring *NTRK1* fusions were reported by Agaram et al,[2] and potentially related tumors with *NTRK1/2* fusions by Suurmeijer et al.[3]

In 2 other publications, very similar tumors with fibrosarcoma-like morphology were presented. In the first one, a soft tissue tumor with *STRN3* (exon 3)-*NTRK3* (exon 14) fusion along with a bone tumor harboring *STRN* (exon 3)-*NTRK3* (exon 14) rearrangement was described. Both cases showed diffuse pan-TRK and CD34 immunostaining, whereas S100 protein was negative.[4] In the second article, 4 additional cases with *RBPMS-NTRK3* and various *NTRK1* fusions were reported. Apart from diffuse pan-TRK positivity, the neoplasms showed focal S100 protein expression but were negative for CD34 staining. Of note, the tumors involved the uterine cervix (n = 3) and corpus (n = 1) and were thus the first *NTRK*-rearranged tumors ever reported in this location.[5] One additional intermediate to high-grade uterine sarcoma with myxoid stroma and no specific line of differentiation harboring *SPECC1L-NTRK3* fusion was mentioned in another publication, but detailed information including photomicrographs was lacking.[6]

In our files, we have found another case of a uterine neoplasm with *NTRK* fusion that showed a very unusual and distinctive morphologic pattern which, to our best knowledge, has not been described in *NTRK*-rearranged mesenchymal tumor so far.

The patient was a 26-year-old woman with the clinical diagnosis of degenerated uterine fibroid. It measured 23×18×4 cm and weighed ~700 g. Grossly, it was yellow pink in color and focally showed cystic degeneration and calcifications. It was microscopically composed of individual cells or small clusters of relatively bland, epithelioid to plasmacytoid cells that were surrounded by a rich network of arborizing capillaries with focal perivascular hyalinization (Fig. 1C) and mostly moderately myxoid stoma (Figs. 1A, B). More prominent myxoid change was present in some parts (Fig. 1C). The cells focally showed ischemic-type necrosis, but overt pleomorphism, mitotic activity, or coagulative necrosis were not found.

Immunohistochemically, the neoplasm was diffusely and strongly positive with S100 protein (Fig. 1D) and CD34 (Fig. 1E), and exhibited both strong cytoplasmic and nuclear expression of pan-TRK immunostain (A7H6R, Cell signaling; Fig. 1F). All other immunostains, including several myogenic, neural, perineurial, melanotic, neuroendocrine, and vascular markers, as well as various keratins and CD10, were negative. The proliferation index (Ki-67) was <5%. Ultrastructurally, the cells were closely apposed by straight membranes and had multifocal pseudopodia. No cell junctions or basal lamina were found, and only a few pinocytotic vesicles were present. There was a prominent Golgi apparatus, stacks of nondilated rough endoplasmic reticulum, scattered mitochondria, a few lysosomes, and lipid droplets. Dense core granules were not detected.

Although the tumor had a vague neural-like appearance, we originally interpreted it as a benign or low-grade unclassifiable uterine stromal tumor. The patient was alive, with no evidence of disease for 3 years and then was lost for further follow-up.

After several years, we reevaluated this case due to its resemblance to the recently reported epithelioid tumors with *GLI1* gene rearrangements.[7] To verify this possibility, FusionPlex Sarcoma kit (ArcherDx Inc., Boulder, CO) was performed on the NextSeq instrument (Illumina, San Diego, CA), as described previously.[8] This assay revealed an *STRN-NTRK3* fusion, with breakpoints involving exon 3 of the *STRN* gene and exon 14 of the *NTRK3* gene (Supplementary Fig. 1, Supplemental Digital Content 1, http://links.lww.com/PAS/A797). Subsequent FISH analysis with a 12q13.3 GLI1 break-apart probe (SureFISH/Agilent) carried out to completely exclude the possibility of GLI1 rearrangement was negative. We also performed FISH using a 15q25.3 NTRK3 break-apart probe (SureFISH/Agilent), as well as RT-PCR, to confirm the presence of the detected fusion, but both assays failed to detect this rearrangement. However, in our experience with >3000 cases tested at our institution using the ArcherDx technology, it is not an uncommon situation, given the higher sensitivity of NGS-based assays. This discrepancy was also described in the report by Davis et al[1] who noted this in 4/11 (36%) of *ETV6-NTRK3*-rearranged cases. Moreover, the identical *STRN* (exon 3)-*NTRK3* (exon 14) fusion was also detected in the abovementioned bone tumor,[4] *STRN* (exon 3)-*ALK* was reported in numerous cancer types,[9–13] and *STRN* (exon unknown)-*NTRK2* fusion was found in infantile fibrosarcoma.[1] On the basis of these facts, there is little doubt the detected fusion was indeed oncogenic.

In summary, we presented a case of a uterine neoplasm with an *STRN-NTRK3* fusion exhibiting a novel and

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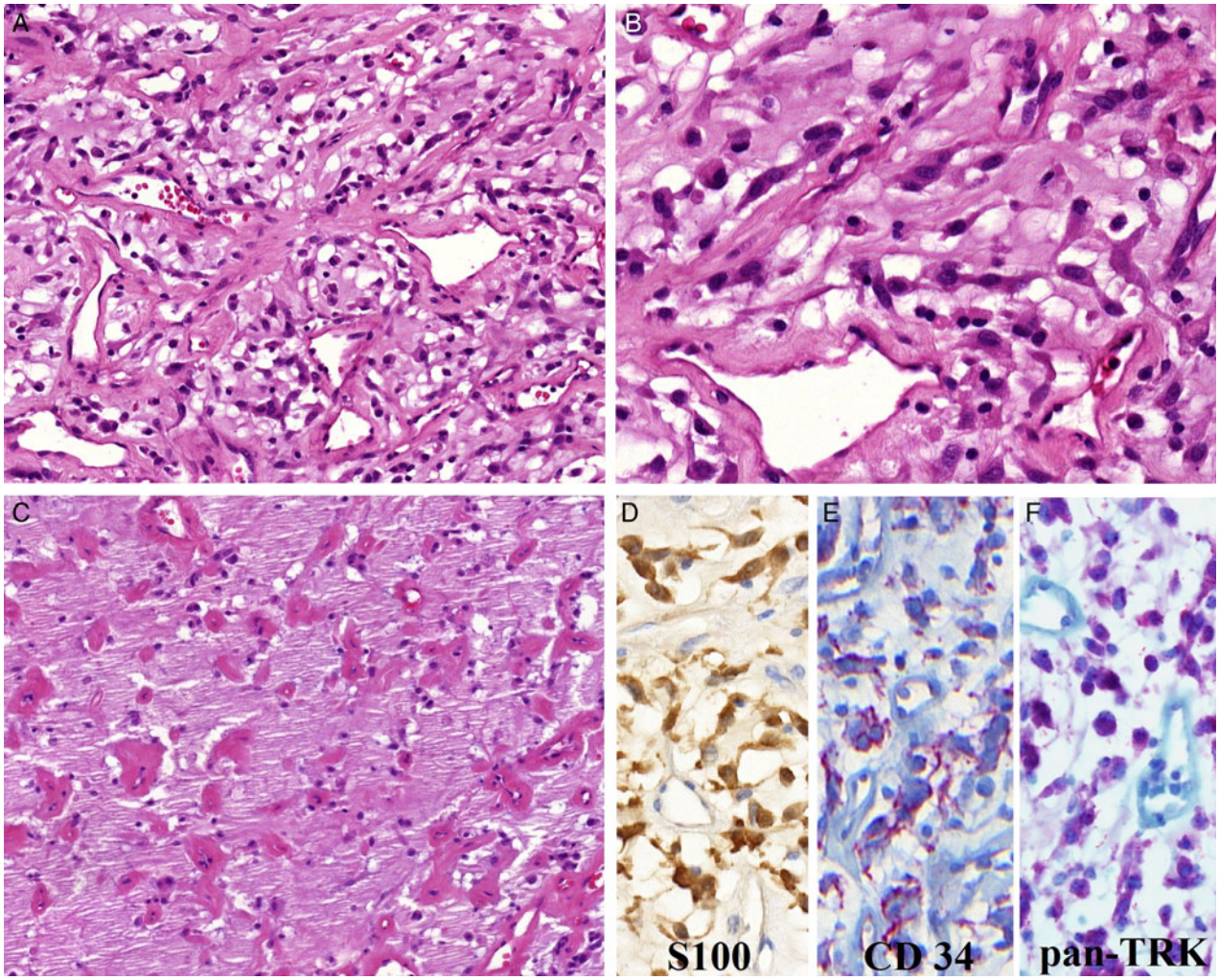

FIGURE 1. The tumor was composed of individual cells or small clusters of relatively bland, epithelioid to plasmacytoid cells that were surrounded by a rich network of arborizing capillaries and mostly moderately myxoid stoma. Overt pleomorphism, mitotic activity, or coagulative necrosis were not found (A, B). Perivascular hyalinization and more prominent myxoid change were present in some parts (C). Immunohistochemically, the neoplasm was diffusely and strongly positive with S100 protein (D), CD34 (E) and exhibited both cytoplasmic and nuclear expression of pan-TRK stain (F).

yet undescribed morphologic pattern. Further cases with longer follow-up are needed to ascertain the real biological potential of this neoplasm.

Michael Michal, MD, PhD*†
Veronika Hájková, MSc‡
Alena Skálová, MD, PhD*
Michal Michal, MD*
*Department of Pathology
†Biomedical Center, Faculty of Medicine in Pilsen, Charles University
‡Bioptical Laboratory Ltd, Pilsen
Czech Republic

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SMARCA4 Loss Is Very Rare in Thoracic Mesothelioma

To the Editor:

We read with great interest the recent study by Perret et al published in the journal entitled "SMARCA4-deficient Thoracic Sarcomas; Clinicopathologic Study of 30 cases with an Emphasis on Their Nosology and Differential Diagnoses."[1]

Although we find the distinction from pulmonary adenocarcinoma with SMARCA4 loss gray, we commend the authors for their proposed strict definition for SMARCA4-deficient thoracic sarcoma (SMARCA4-DTS) which requires a rhabdoid and/or poorly differentiated phenotype (no specific line of differentiation); complete loss of expression of SMARCA4 and SMARCA2 and focal or diffuse expression of at least 2 of 3 of the following markers: SOX2, CD34 or SALL4; indicating that cases with morphologic evidence of glandular or squamous differentiation should not be considered SMARCA4-DTS but rather carcinomas with SMARCA4 loss. We note in their study that SMARCA4-deficient thoracic sarcomas were shown to occur more frequently in males (M:F = 9:1) with median age of 48 years and history of smoking. We were particularly interested that 5 of 30 (17%) of cases in their series were pleurally based masses and a further 4 cases (13%) had significant pleural involvement. That is,

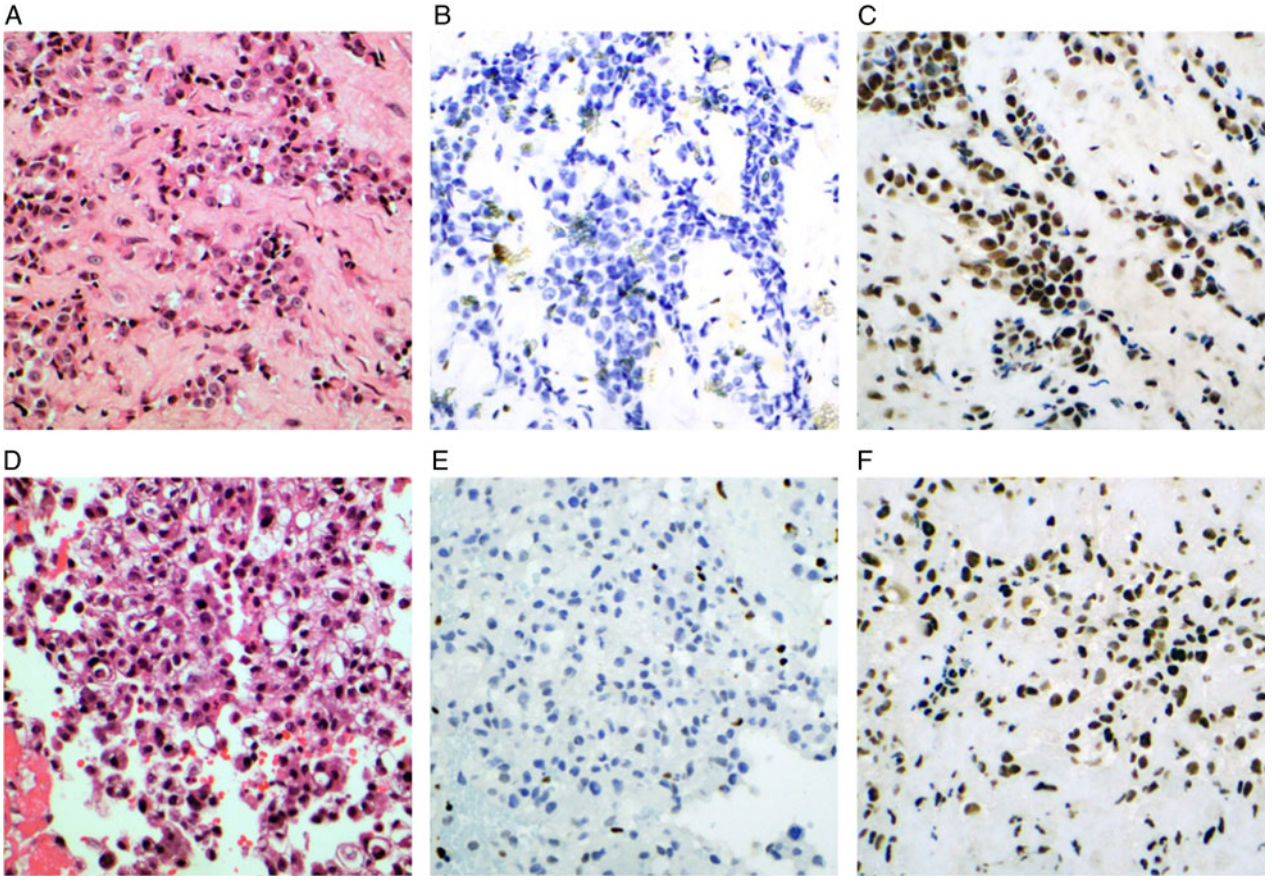

FIGURE 1. Histology and immunohistochemistry of SMARCA4 negative cases. Case 1 (A–C) and case 2 (D–F). H&E stain (A, D); Loss of SMARCA4 immunostaining in presence of positive internal control (B, E) and retained SMARCA2 immunostaining (C, F).