Mezenchymální tumory s onkogenními kinázovými fúzemi (*NTRK*, *RET*, *RAF*, *BRAF*, *ALK*, *MET*)

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Šiklův ústav patologie, FN Plzeň

NTRK fúze v mezenchymálních tumorech

- Vzácné: **0.2-1%** všech sarkomů
- Tumory s *NTRK*-rearanžemi jsou častější v pediatrické populaci, ale identicky vypadající tumory se vyskytují i u dospělých
- **1998 – *ETV6-NTRK3*** fúze byla detekována v **infantilním fibrosarkomu a** celulárním kongenitálním mezoblastickém nefromu (= identický tumor v ledvinách)
- **2014 – další *NTRK* genové fúze** jsou postupně detekovány **v mezenchymálních tumorech s rozličnou morfologií:**

  - Infantilní fibrosarkom/Celulární kongenitální mezoblastický nefrom
  - Inflamatorní myofibroblastický tumor
  - Adultní fibrosarkom NOS

jednotky zahrnuté ve WHO 2013

  - LG vřetenobuněčný sarkom
  - Myopericytom/hemangiopericytoma-like
  - Lipofibromatosis-like
  - Schwannom/low-grade MPNST-like

OXFORD

JNCI J Natl Cancer Inst (2016) 108(1): djv307

doi: 10.1093/jnci/djv307
First published online November 12, 2015
Correspondence

CORRESPONDENCE

Evaluation of a Congenital Infantile Fibrosarcoma by Comprehensive Genomic Profiling Reveals an *LMNA-NTRK1* Gene Fusion Responsive to Crizotinib

Victor Wong, Dean Pavlick, Tim Brennan, Roman Yelensky, John Crawford, Jeffrey S. Ross, Vincent A. Miller, Denise Malicki, Philip J. Stephens, Siraj M. Ali*, Hyunah Ahn

Modern Pathology (2017), 1–11

Recurrent *EML4–NTRK3* fusions in infantile fibrosarcoma and congenital mesoblastic nephroma suggest a revised testing strategy

Alanna J Church[1], Monica L Calicchio[2], Valentina Nardi[3], Alena Skalova[4], Andre Pinto[5], Deborah A Dillon[6], Carmen R Gomez-Fernandez[5], Namitha Manoj[7], Josh D Haimes[7], Joshua A Stahl[7], Filemon S Dela Cruz[8], Sarah Tannenbaum-Dvir[9], Julia L Glade-Bender[9], Andrew L Kung[7], Steven G DuBois[10], Harry P Kozakewich[1], Katherine A Janeway[10], Antonio R Perez-Atayde[1] and Marian H Harris[1]

Journal of Pathology
J Pathol 2016; **238:** 700–710
Published online in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.4701

ORIGINAL PAPER

Paediatric and adult soft tissue sarcomas with *NTRK1* gene fusions: a subset of spindle cell sarcomas unified by a prominent myopericytic/haemangiopericytic pattern

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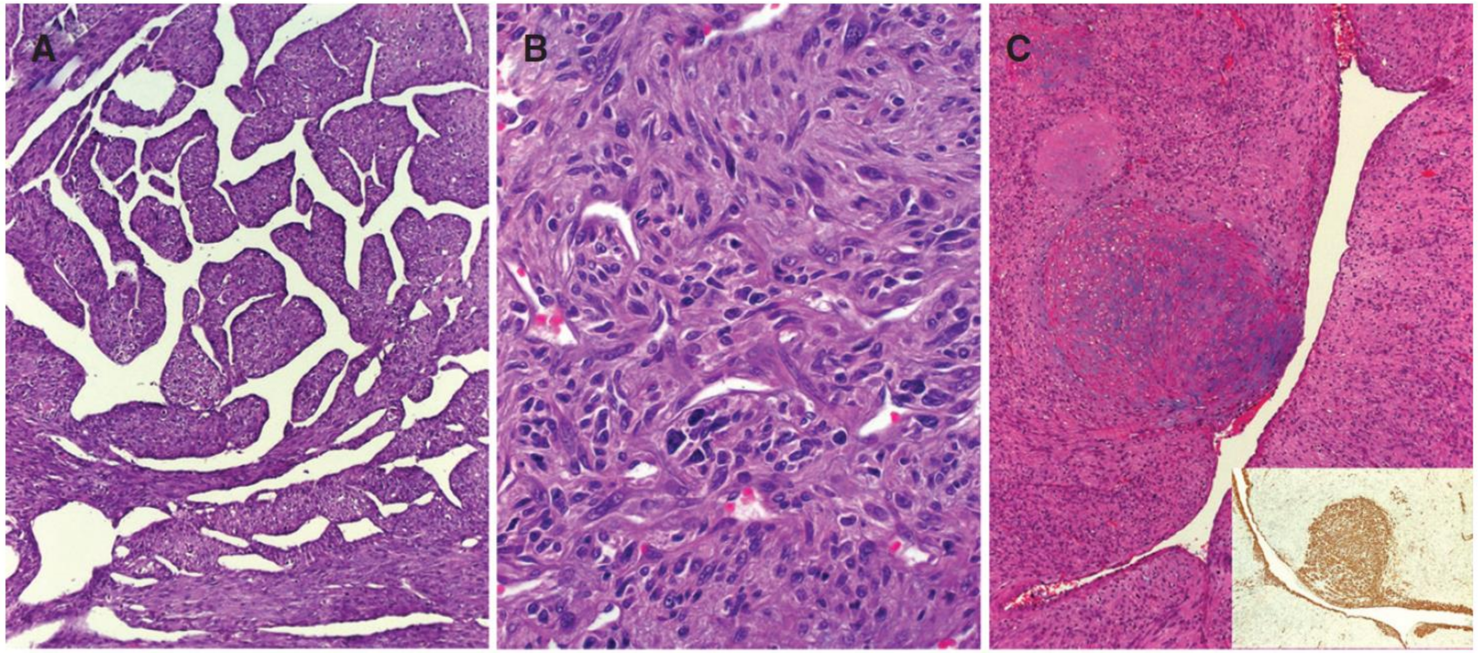


RT–PCR gene fusion
LMNA–NTRK1
TPM3–NTRK1
NA
TPM3–NTRK1

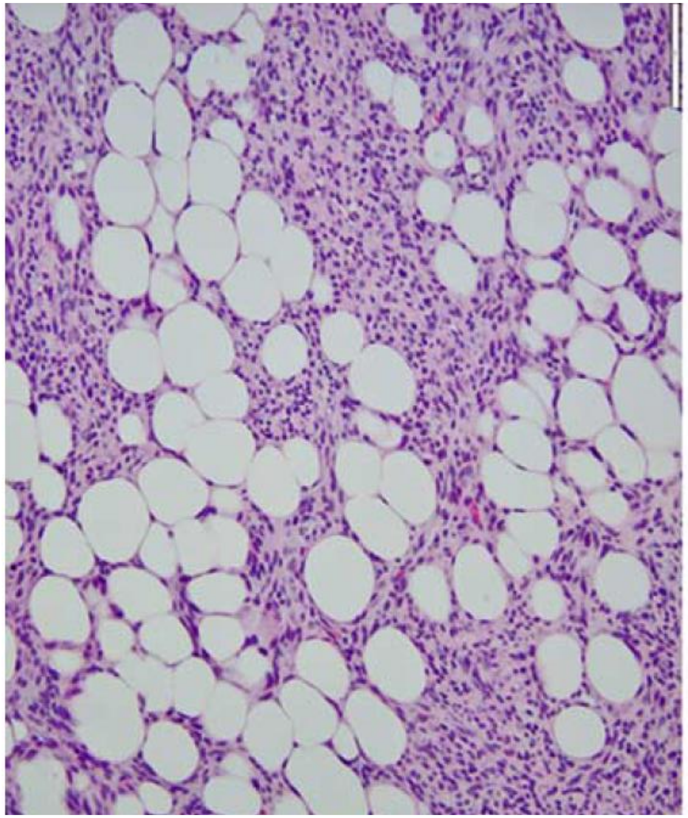
IHC +

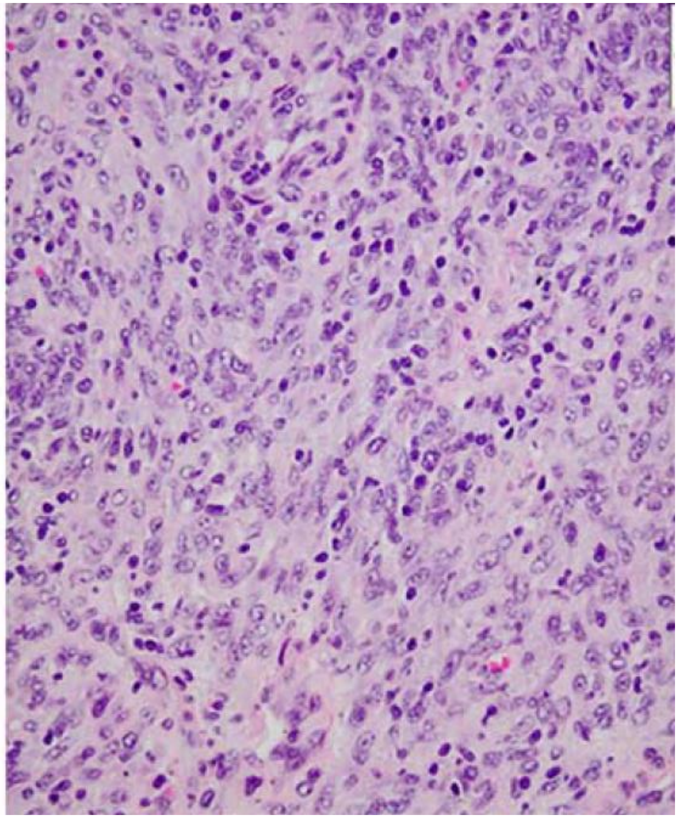
- CD34
- SMA

(*Am J Surg Pathol* 2016;40:1407–1416)

Recurrent *NTRK1* Gene Fusions Define a Novel Subset of Locally Aggressive Lipofibromatosis-like Neural Tumors

Narasimhan P. Agaram, MBBS, Lei Zhang, MD,* Yun-Shao Sung, MS,* Chun-Liang Chen, MS,* Catherine T. Chung, MD,† Cristina R. Antonescu, MD,* and Christopher DM Fletcher, MD, FRCPath‡*





Genetic Abnormality
TPR-NTRK1
TPM3 - NTRK1
LMNA-NTRK1
LMNA-NTRK1
LMNA-NTRK1
LMNA-NTRK1
NTRK1
NTRK1
NTRK1
NTRK1
ROS1
ALK

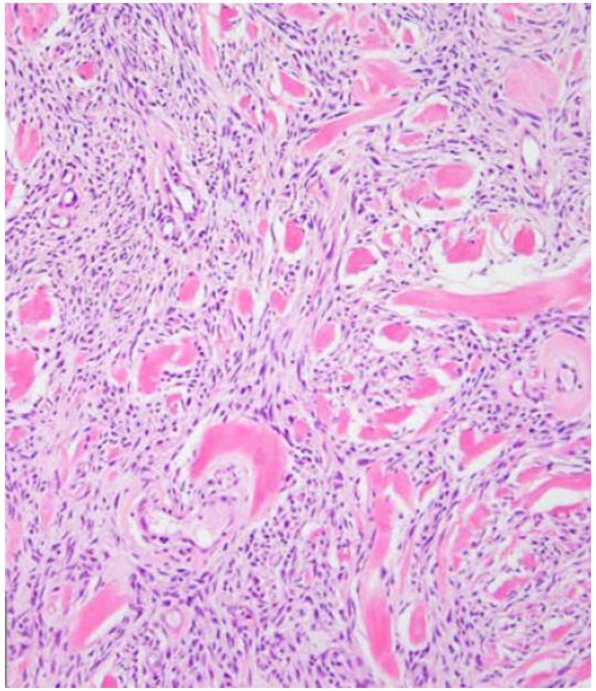
IHC +

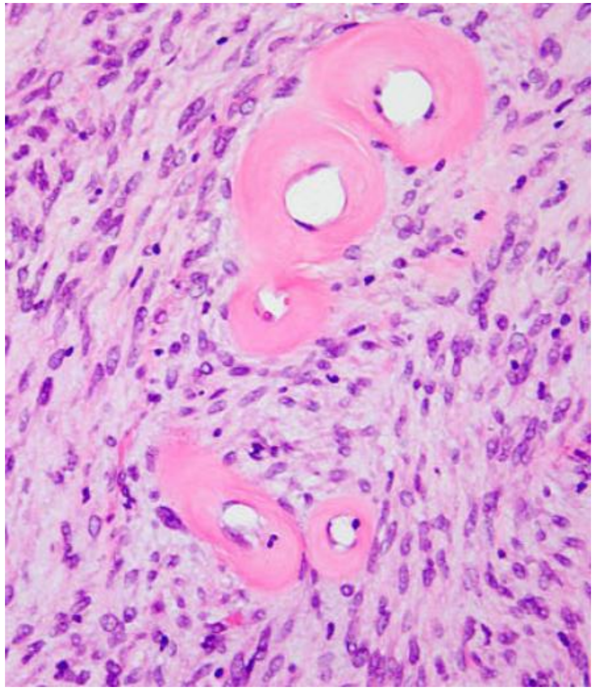
- CD34
- S100

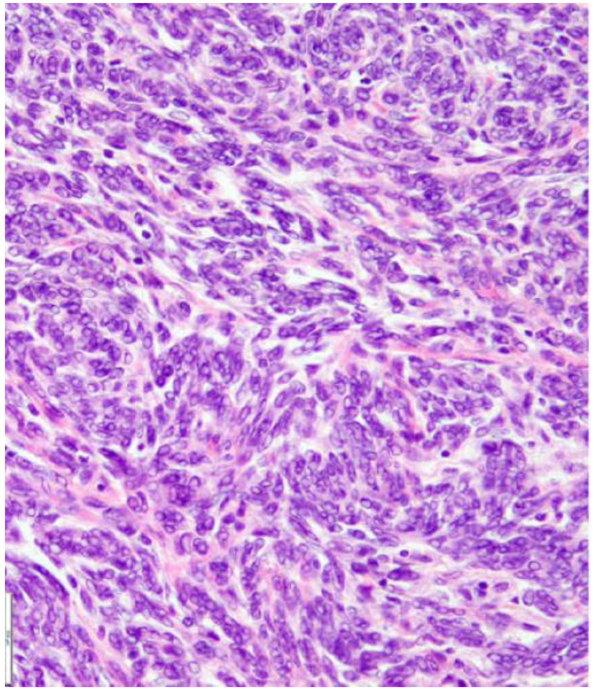
A novel group of spindle cell tumors defined by S100 and CD34 co-expression shows recurrent fusions involving RAF1, BRAF, and NTRK1/2 genes

Albert J. H. Suurmeijer[1] | Brendan C. Dickson[2] | David Swanson[2] | Lei Zhang[3] | Yun-Shao Sung[3] | Paolo Cotzia[3] | Christopher D. M. Fletcher[4] | Cristina R. Antonescu[3]

Genes Chromosomes Cancer. 2018;1–11.







LMNA–NTRK1
LMNA–NTRK1
LMNA–NTRK1
LMNA–NTRK1
LMNA–NTRK1
LMNA–NTRK1
LMNA–NTRK1
LMNA–NTRK1
TPM3–NTRK1[c]
TPM3–NTRK1
TPM3–NTRK1
TPR–NTRK1
NTRK1
NTRK1
SPECC1L–NTRK2[a]

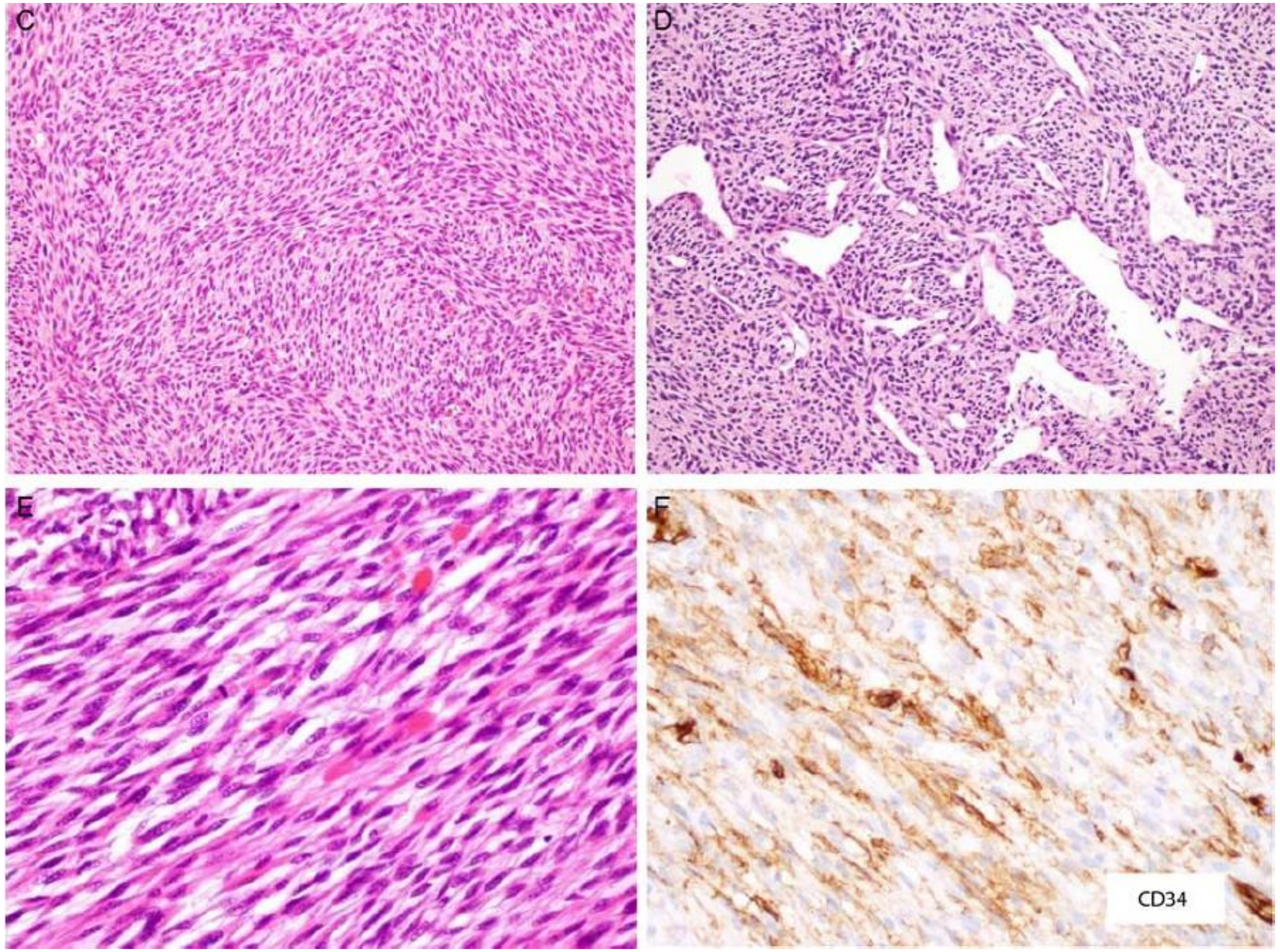
IHC +

- CD34
- S100

Novel *NTRK3* Fusions in Fibrosarcomas of Adults

Fumito Yamazaki, MD,† Fumihiko Nakatani, MD, PhD,‡§ Naofumi Asano, MD, PhD,§||¶ Susumu Wakai, CT,# Masaya Sekimizu, MD,* Sachiyo Mitani, BS,* Takashi Kubo, PhD,*** Akira Kawai, MD, PhD,‡§ Hitoshi Ichikawa, PhD,*** and Akihiko Yoshida, MD, PhD‡#*

(*Am J Surg Pathol* 2019;43:523–530)



- Tumor **radia** 38 leté ženy:

***STRN-NTRK3* fúze**

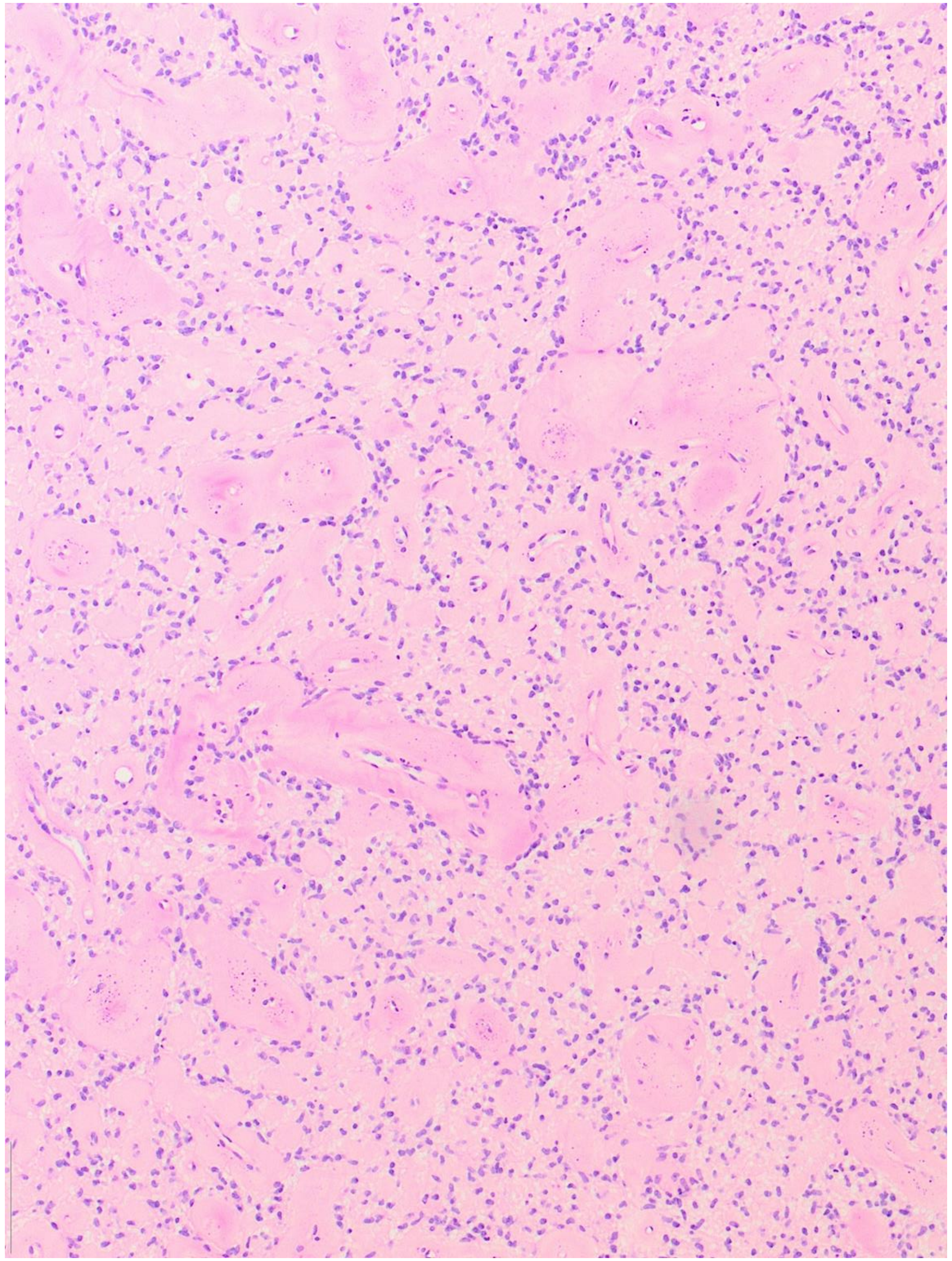
- Tumor stehna 26 letého muže:

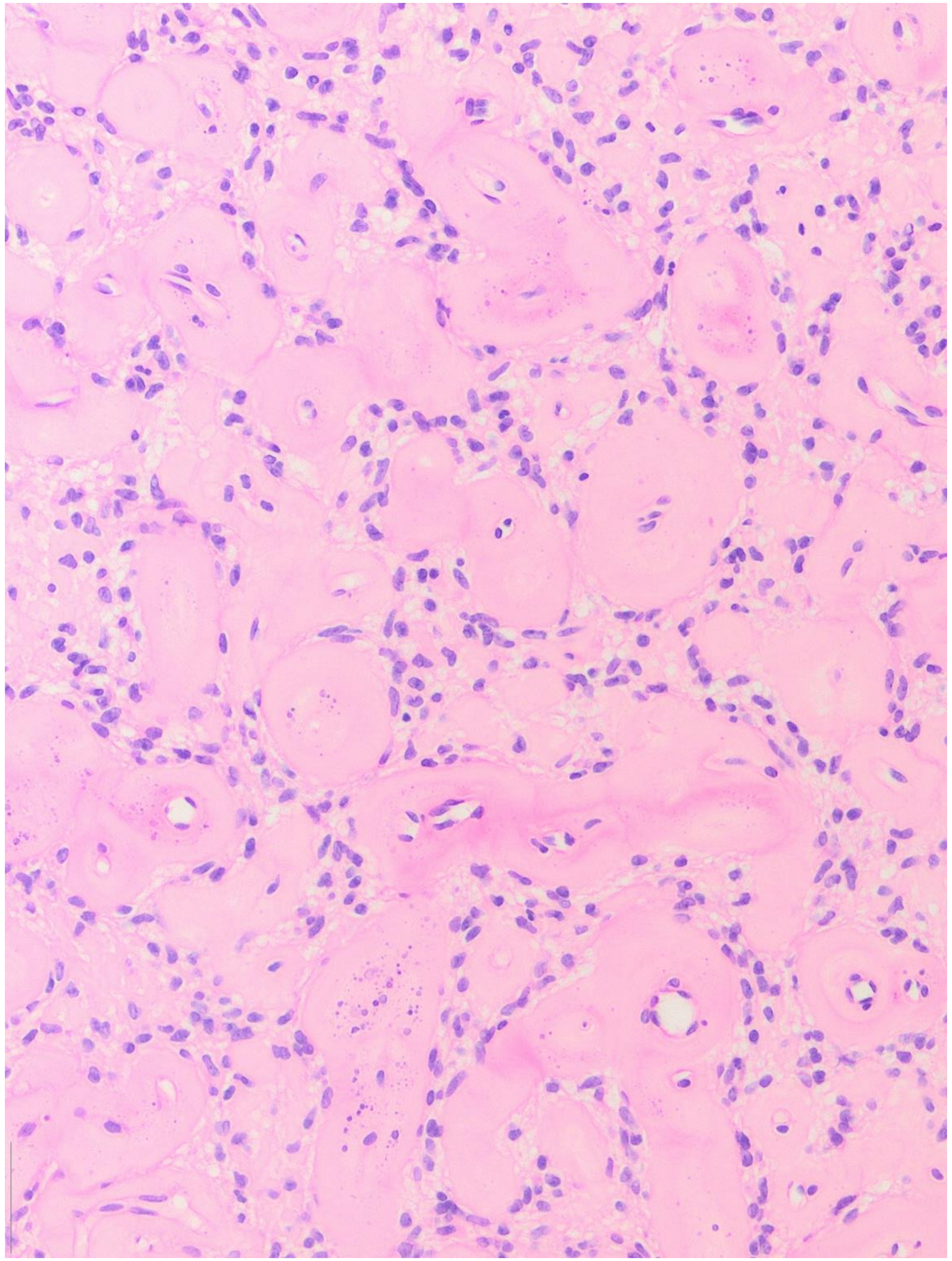
***STRN3-NTRK3* fusion**

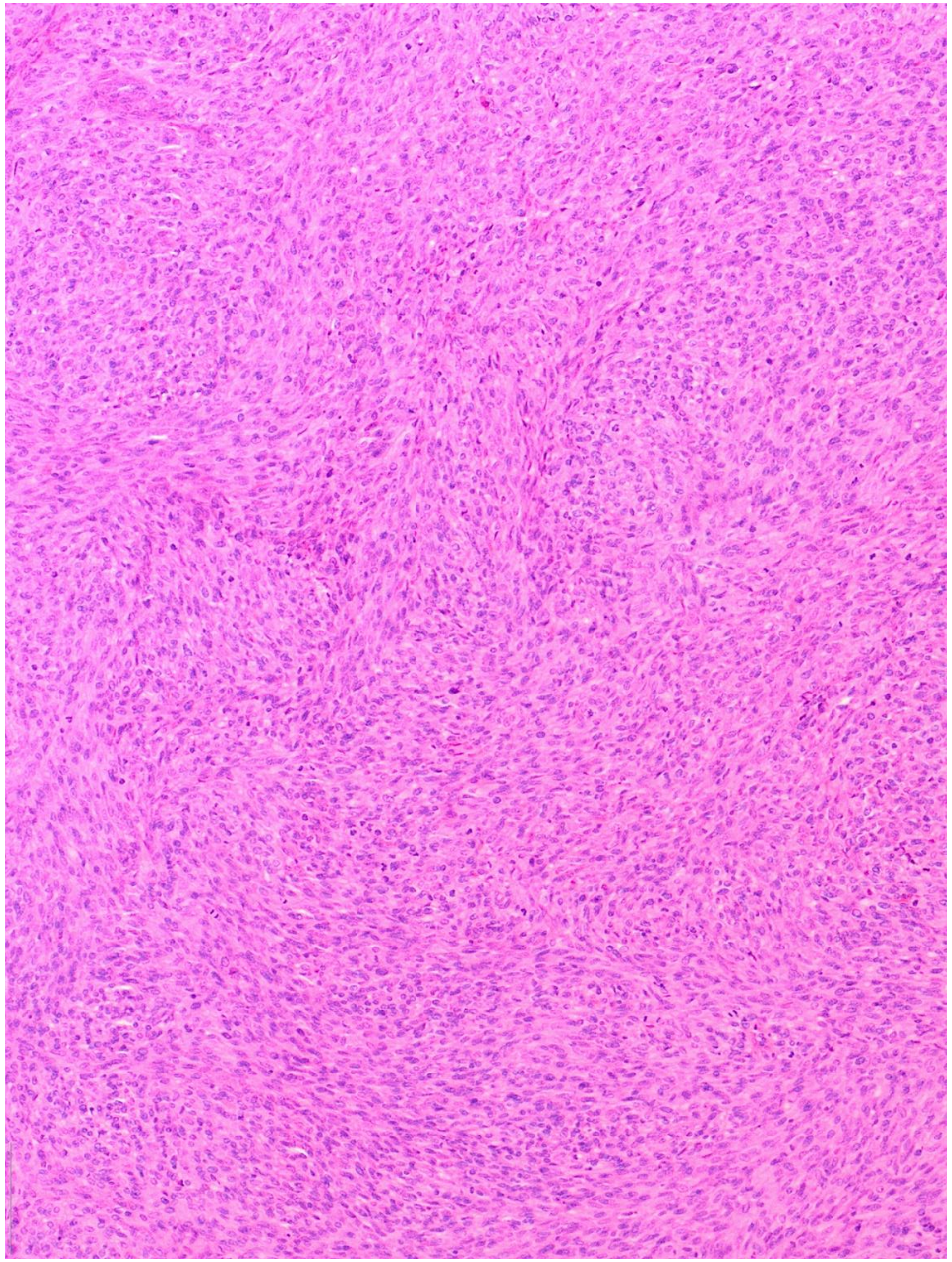
IHC +

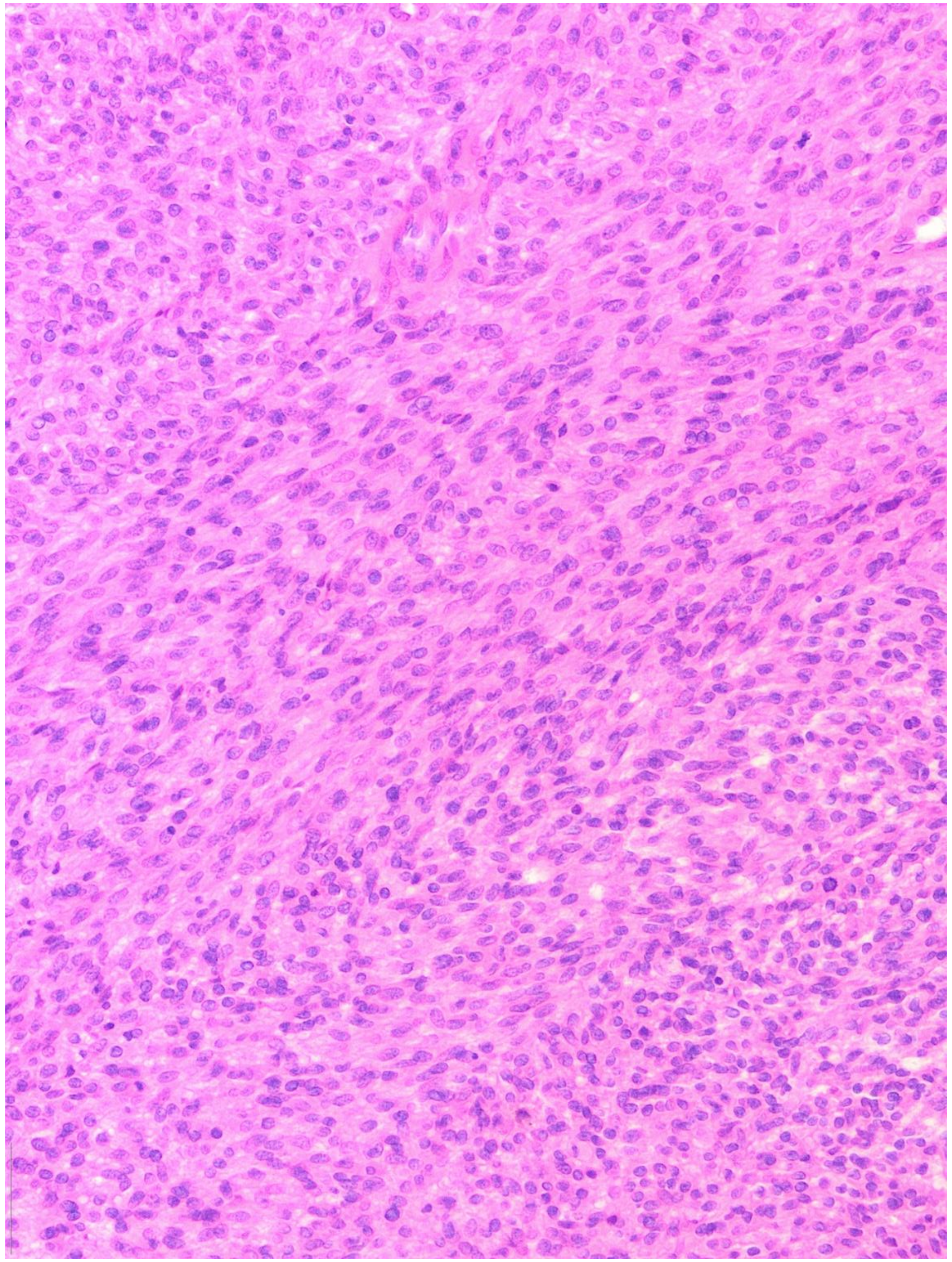
- CD34
- S100

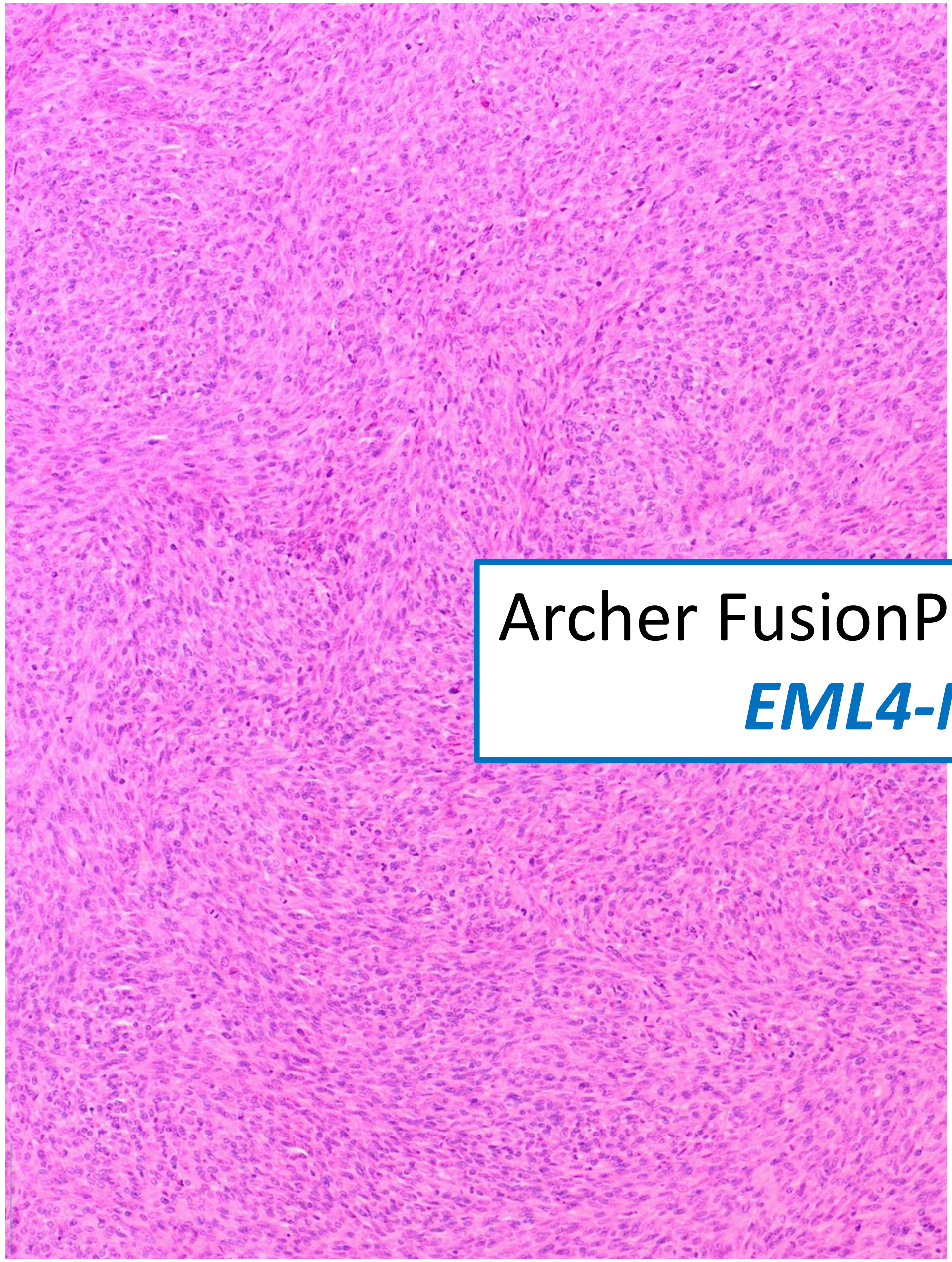
3 letý chlapec s tumorem horního rtu, který prorůstal do orbity, S100 a CD34 +

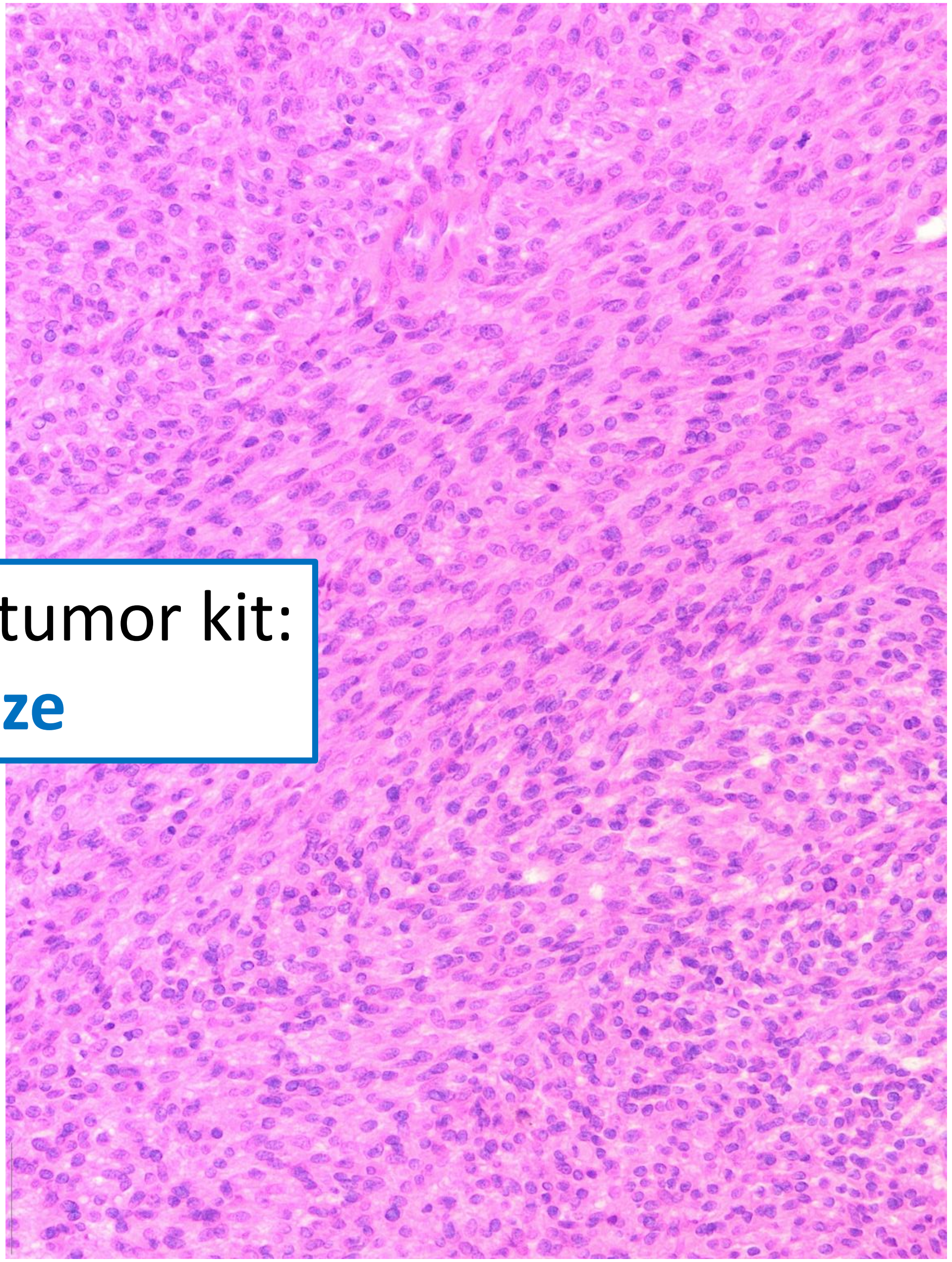












Archer FusionPlex Solid tumor kit:

EML4-NTRK3 **fúze**

(*Am J Surg Pathol* 2016;40:1051–1061)

ETV6-NTRK3 Is Expressed in a Subset of ALK-Negative Inflammatory Myofibroblastic Tumors

Ali H. Alassiri, MD,† Rola H. Ali, MD,‡ Yaoqing Shen, PhD,§ Amy Lum, BSc,‖ Caron Strahlendorf, MD,¶ Rebecca Deyell, MD,¶ Rod Rassekh, MD,¶ Poul H. Sorensen, MD, PhD,# Janessa Laskin, MD,‖ Marco Marra, PhD,§ Stephen Yip, MD, PhD,# Cheng-Han Lee, MD, PhD,** and Tony L. Ng, MD, PhD*#*

Demonstration of ETV6-NTRK3 in IMTs lends support to the notion that there is biological overlap between IMT and CIFS due to the commonality in their pathogenesis driven by oncogenic fusion tyrosine kinases. This is supported by the clinical behavior of both

ROS1, *PDGFRβ*, or *NTRK1* fusion oncogenes.[27,28] We propose that assigning specific clinicopathologic classifiers such as IMT and CIFS among tyrosine kinase–driven myofibroblastic/fibroblastic tumors may be of lesser importance than the identification of the fusion event itself, particularly with the availability of ther-

Original Article

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Jiný úhel pohledu

Expanding the Spectrum of Pediatric *NTRK*-rearranged Mesenchymal Tumors

Jessica L. Davis, MD,† Christina M. Lockwood, PhD,‡ Bradley Stohr, MD, PhD,†
Carolin Boecking, MD,† Alyaa Al-Ibraheemi, MD,§ Steven G. DuBois, MD,∥
Sara O. Vargas, MD,§ Jennifer O. Black, MD,¶ Michael C. Cox, PharmD,#
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Catherine M. Albert, MD,∥∥ David M. Parham, MD,¶¶ Douglas S. Hawkins, MD,∥∥
and Erin R. Rudzinski, MD##*

(*Am J Surg Pathol* 2019;43:435–445)

Case	Fusion
1	*TPM3-NTRK1*
2	*TPM3-NTRK1*
3	*TPM3-NTRK1*
4	*TPM3-NTRK1*
5	*TPM3-NTRK1*
6	*TPM3-NTRK1*
7	*TPM3-NTRK1*
8	*TPM3-NTRK1*
9	*TPM3-NTRK1*
10	*LMNA-NTRK1*
11	*LMNA-NTRK1*
12	*LMNA-NTRK1*
13	*MIR584F1-NTRK1*
14	*SQSTM1-NTRK1*
15	*TPR-NTRK1*
16	*NTRK1*
17	*STRN-NTRK2*
18	*EML4-NTRK3*
19	*ETV6-NTRK3**
20	*ETV6-NTRK3**
21	*ETV6-NTRK3**
22	*ETV6-NTRK3**
23	*ETV6-NTRK3*
24	*ETV6-NTRK3*
25	*ETV6-NTRK3*
26	*ETV6+*
27	*ETV6+*
28	*ETV6+*
29	*ETV6+*
30	*ETV6+*

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6	*TPM3-NTRK1*
7	*TPM3-NTRK1*
8	*TPM3-NTRK1*
9	*TPM3-NTRK1*
10	*LMNA-NTRK1*
11	*LMNA-NTRK1*
12	*LMNA-NTRK1*
13	*MIR584F1-NTRK1*
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16	*NTRK1*
17	*STRN-NTRK2*
18	*EML4-NTRK3*
19	*ETV6-NTRK3**
20	*ETV6-NTRK3**
21	*ETV6-NTRK3**
22	*ETV6-NTRK3**
23	*ETV6-NTRK3*
24	*ETV6-NTRK3*
25	*ETV6-NTRK3*
26	*ETV6+*
27	*ETV6+*
28	*ETV6+*
29	*ETV6+*
30	*ETV6+*

Group 1

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(*Am J Surg Pathol* 2019;43:435–445)

Group 2

Group 1

Case	Fusion
1	*TPM3-NTRK1*
2	*TPM3-NTRK1*
3	*TPM3-NTRK1*
4	*TPM3-NTRK1*
5	*TPM3-NTRK1*
6	*TPM3-NTRK1*
7	*TPM3-NTRK1*
8	*TPM3-NTRK1*
9	*TPM3-NTRK1*
10	*LMNA-NTRK1*
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18	*EML4-NTRK3*
19	*ETV6-NTRK3**
20	*ETV6-NTRK3**
21	*ETV6-NTRK3**
22	*ETV6-NTRK3**
23	*ETV6-NTRK3*
24	*ETV6-NTRK3*
25	*ETV6-NTRK3*
26	*ETV6+*
27	*ETV6+*
28	*ETV6+*
29	*ETV6+*
30	*ETV6+*

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(*Am J Surg Pathol* 2019;43:435–445)

ETV6) *NTRK* fusions. The clinical features, morphology, immunophenotype, and genetics of 12 classic *ETV6-NTRK3* fused infantile fibrosarcoma and 18 variant *NTRK*-rearranged mesenchymal tumors were evaluated. For both classic and variant groups, the age at diagnosis ranged from birth to 15 years (median, 4 mo) with no sex predilection; the most common sites involved were the extremities and trunk. The rate of local recurrence and metastasis were not significantly different (recurrence rate: 11% classic, 40% variant; metastatic rate: 18% classic, 25% variant). Classic and variant *NTRK* tumors had an overlapping spectrum of histologic features, containing haphazardly arranged primitive cells in a myxoid background and/or spindle cells in long fascicles. Both groups showed diffuse pan-TRK expression by immunohistochemistry. Otherwise, the immunoprofile was nonspecific, but similar between both groups. No statistical difference was seen in any clinicopathologic feature between the classic *ETV6-NTRK3* and variant fusion cohorts.

Group 2

Case	Fusion
1	*TPM3-NTRK1*
2	*TPM3-NTRK1*
3	*TPM3-NTRK1*
4	*TPM3-NTRK1*
5	*TPM3-NTRK1*
6	*TPM3-NTRK1*
7	*TPM3-NTRK1*
8	*TPM3-NTRK1*
9	*TPM3-NTRK1*
10	*LMNA-NTRK1*
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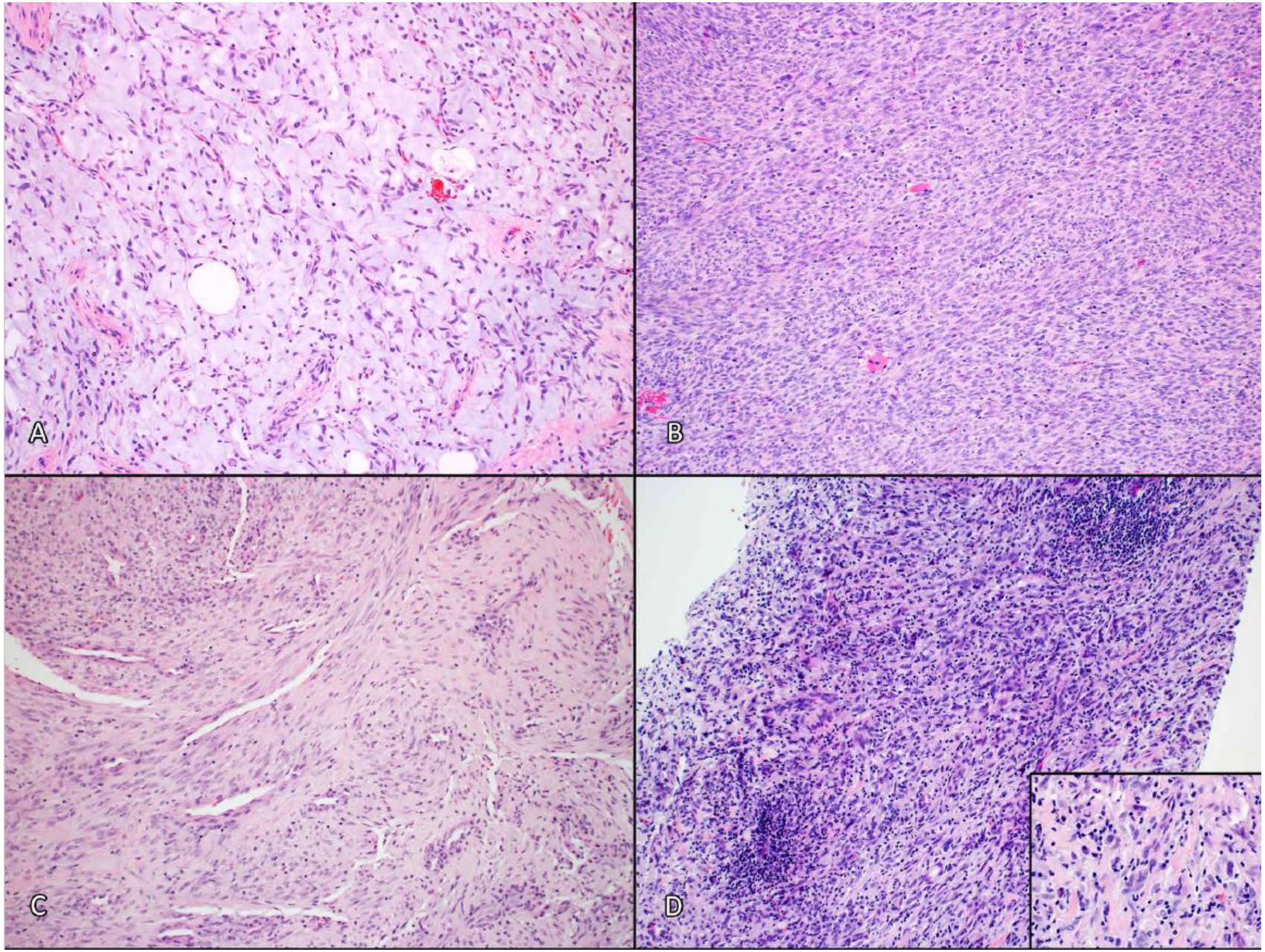
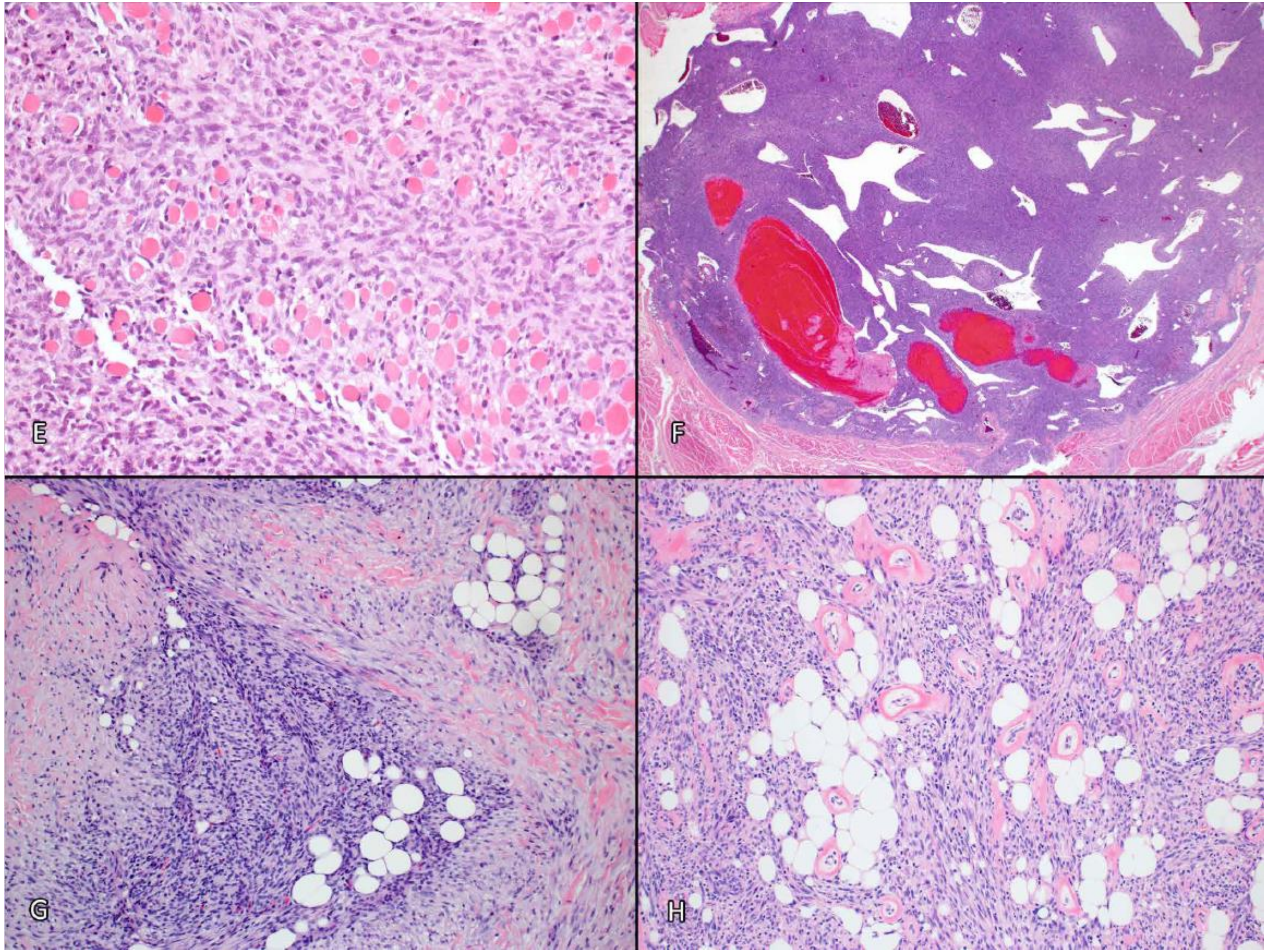
22	*ETV6-NTRK3**
23	*ETV6-NTRK3*
24	*ETV6-NTRK3*
25	*ETV6-NTRK3*
26	*ETV6+*
27	*ETV6+*
28	*ETV6+*
29	*ETV6+*
30	*ETV6+*

Group 1



A. Primitive cells in myxoid background B. Spindle cells in intersecting fascicles = fibrosarcoma C. Myoid areas D. IMT-like morphology with marked chronic inflammation and focal nuclear atypia



E. Infiltrative/fibromatosis-like growth pattern F. HPC-like vasculature G. Biphasic pattern with alternating areas of hypercelluar primitive cells and less cellular collagenized zones H. Prominent hyalinized vessels (i.e. perivascular hyalinosis)

Expanding the Spectrum of Pediatric *NTRK*-rearranged Mesenchymal Tumors

Jessica L. Davis, MD,† Christina M. Lockwood, PhD,‡ Bradley Stohr, MD, PhD,† Carolin Boecking, MD,† Alyaa Al-Ibraheemi, MD,§ Steven G. DuBois, MD,|| Sara O. Vargas, MD,§ Jennifer O. Black, MD,¶ Michael C. Cox, PharmD,# Mark Luquette, MD,** Brian Turpin, DO,†† Sara Szabo, MD,‡‡ Theodore W. Laetsch, MD,§§ Catherine M. Albert, MD,|||| David M. Parham, MD,¶¶ Douglas S. Hawkins, MD,|||| and Erin R. Rudzinski, MD##*

(*Am J Surg Pathol* 2019;43:435–445)

Tumory v obou skupinách byly obvykle složeny z 2 a více morfologických patternů

„Pediatrické *NTRK*-rearranžované mezenchymální tumory jak s klasickými *ETV6-NTRK3* fúzemi, tak s alternativními *NTRK* fúzemi pravděpodobně představují spektrum jedné léze s rozpoznatelnými klinickopatologickými vlastnostmi“

Pouze *NTRK*?

(*Am J Surg Pathol* 2018;42:28–38)

Recurrent *BRAF* Gene Fusions in a Subset of Pediatric Spindle Cell Sarcomas

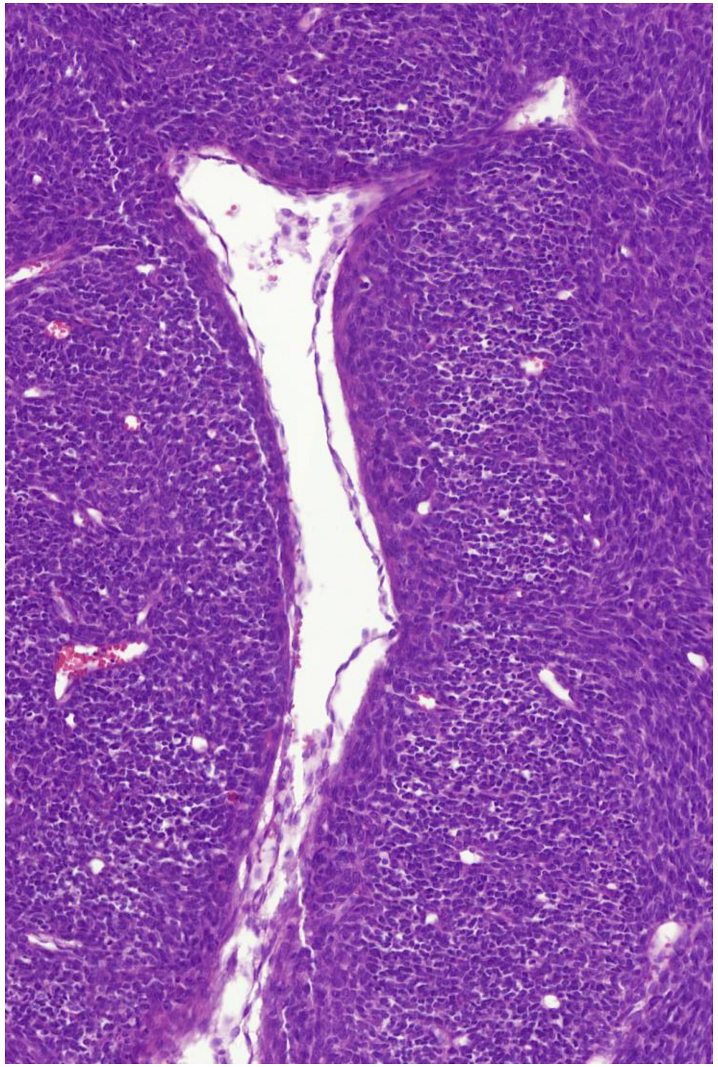
Expanding the Genetic Spectrum of Tumors With Overlapping Features With Infantile Fibrosarcoma

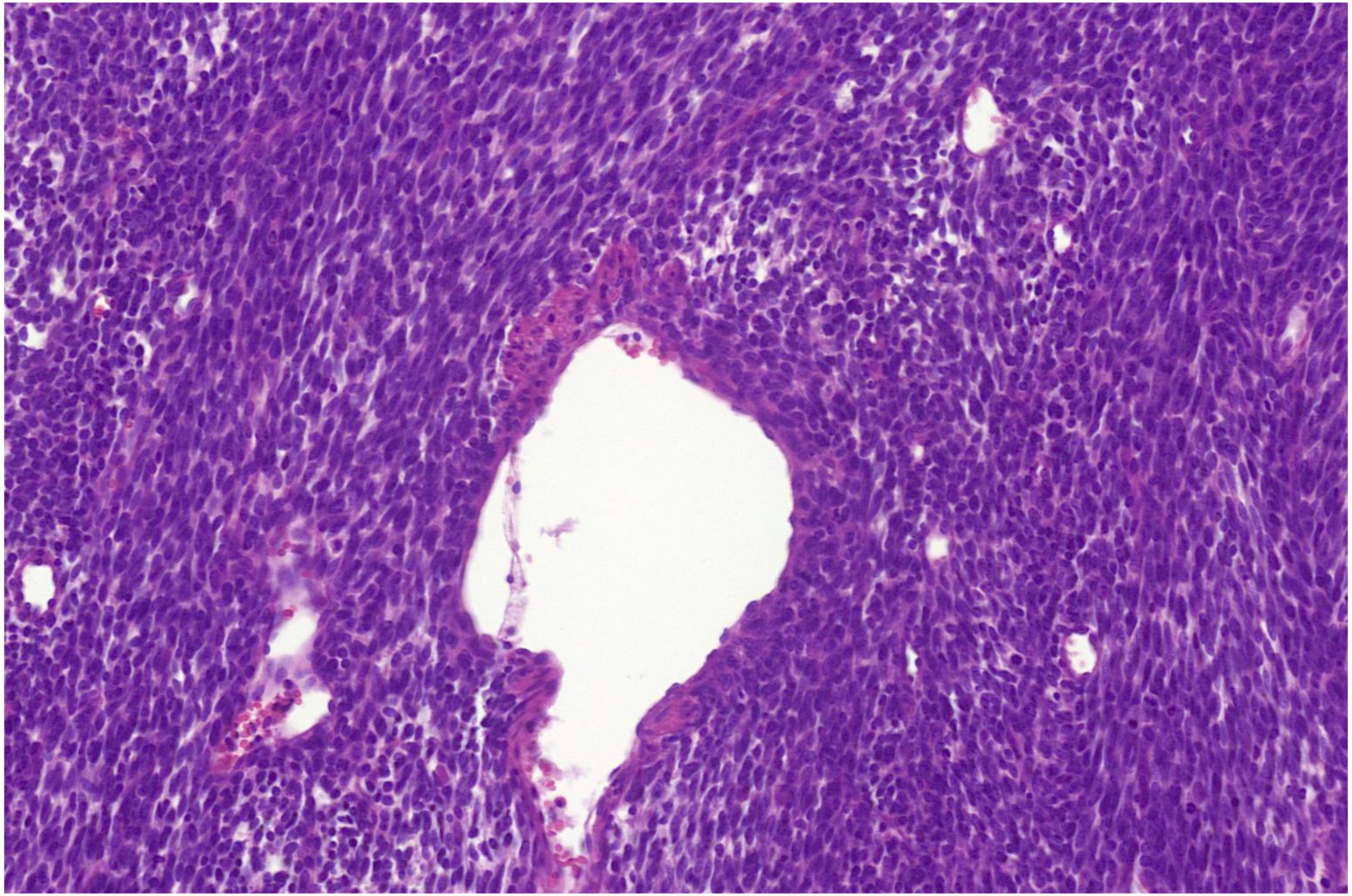
Yu-Chien Kao, MD,† Christopher D.M. Fletcher, MD, FRCPath,‡ Rita Alaggio, MD,§ Leonard Wexler, MD,‖ Lei Zhang, MD,* Yun-Shao Sung, MSc,* Dicle Orhan, MD,¶ Wei-Chin Chang, MD,#**†† David Swanson, BSc,‡‡ Brendan C. Dickson, MD,‡‡ and Cristina R. Antonescu, MD**

No.	Age	Sex	Site	SMA	CD34	S100	Desmin	Gene Fusions
1	16 y	F	RP	Patchy +	NA	–	–	*SEPT7-BRAF**,†
2	3 y	F	Pelvis	NA	NA	NA	NA	*BRAF* rearrangement†
3	6 mo	F	Pelvis	Focal+	–	–	–	*BRAF* rearrangement†
4	1.5 y	M	T6-12 spine (extradural)	NA	NA	–	–	*CUX1-BRAF*†,‡
5	2 d	M	Thigh	Focal+	–	–	Rare cells	*BRAF* rearrangement†
6	1 y	M	Foot	–	+	–	–	*EML4-NTRK3**,†
7	7 wk	M	RP	+	+	–	–	*TPM3-NTRK1*†,§
8	12 y	F	Forearm	NA	NA	NA	NA	Unknown
9	5 mo	F	Lumbar	+	–	–	–	Unknown
10	3 y	F	RP	–	NA	–	–	Unknown

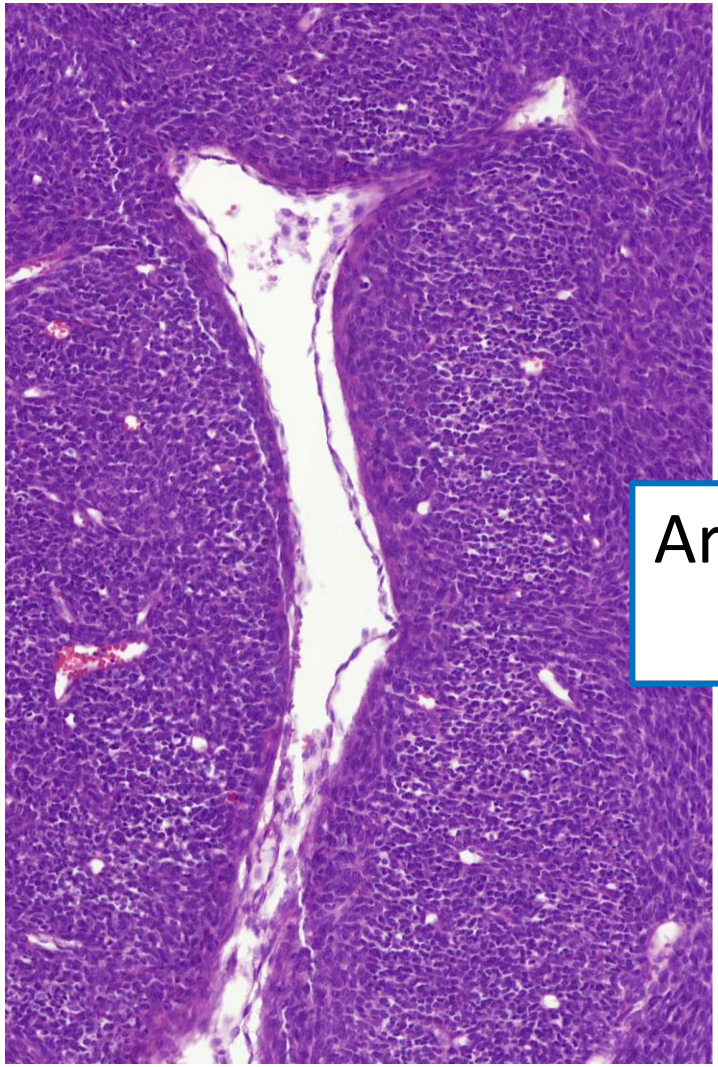
infant with a retroperitoneal lesion. Our findings of recurrent *BRAF* gene rearrangements in tumors showing morphologic overlap with IFS expand the genetic spectrum of fusion-positive spindle cell sarcomas, to include unusual presentations, such as older children and adolescents and predilection for axial location, thereby opening new opportunities for kinase-targeted therapeutic intervention.

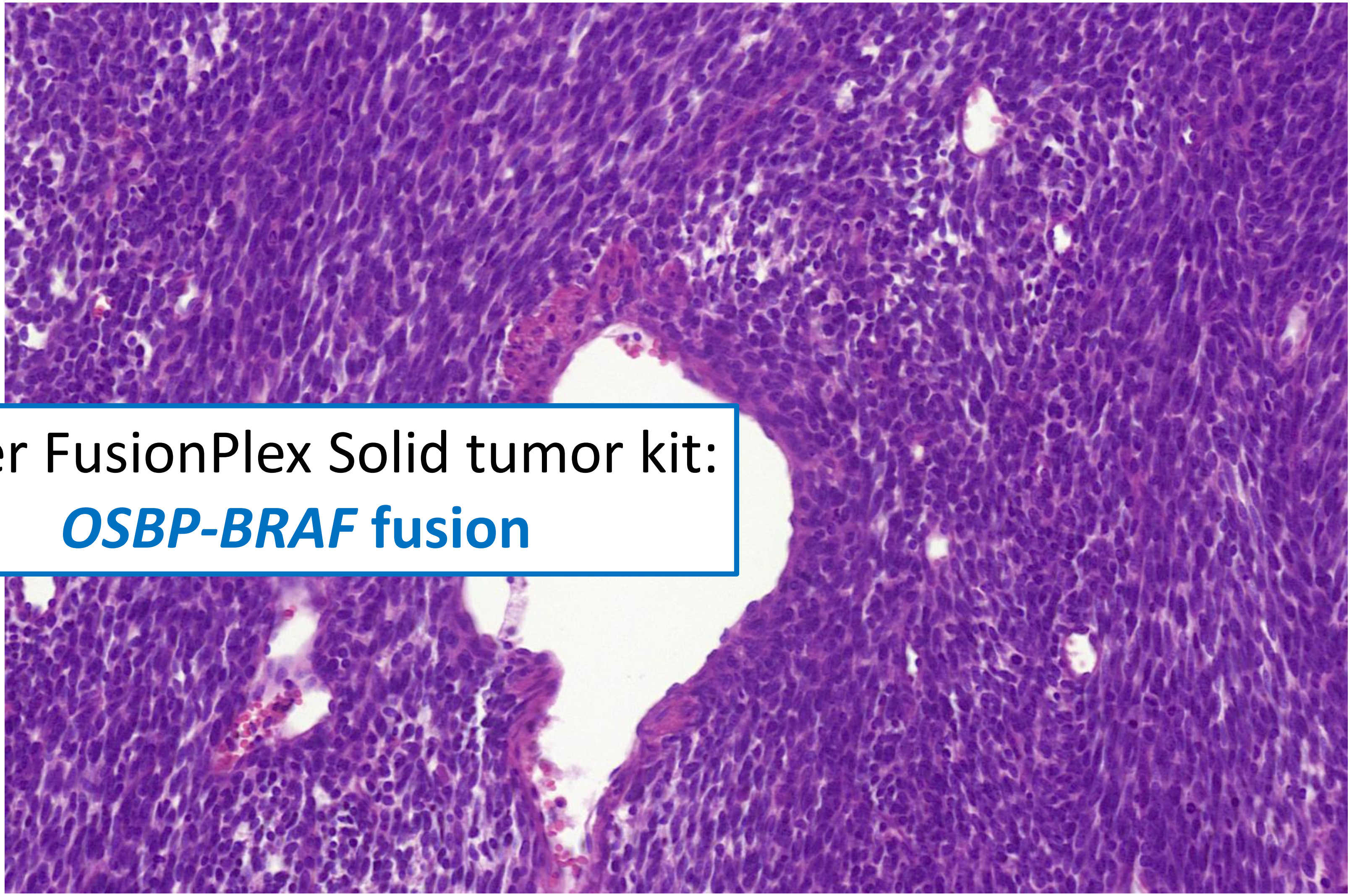
1-roční chlapec s retroperitoneálním tumorem, který prorůstal do paravertebrální svaloviny – morfologicky **odpovídal infantilnímu fibrosarkomu**, ale **ETV6 FISH byla negativní**





1-roční chlapec s retroperitoneálním tumorem, který prorůstal do paravertebrální svaloviny – morfologicky **odpovídal infantilnímu fibrosarkomu**, ale **ETV6 FISH byla negativní**



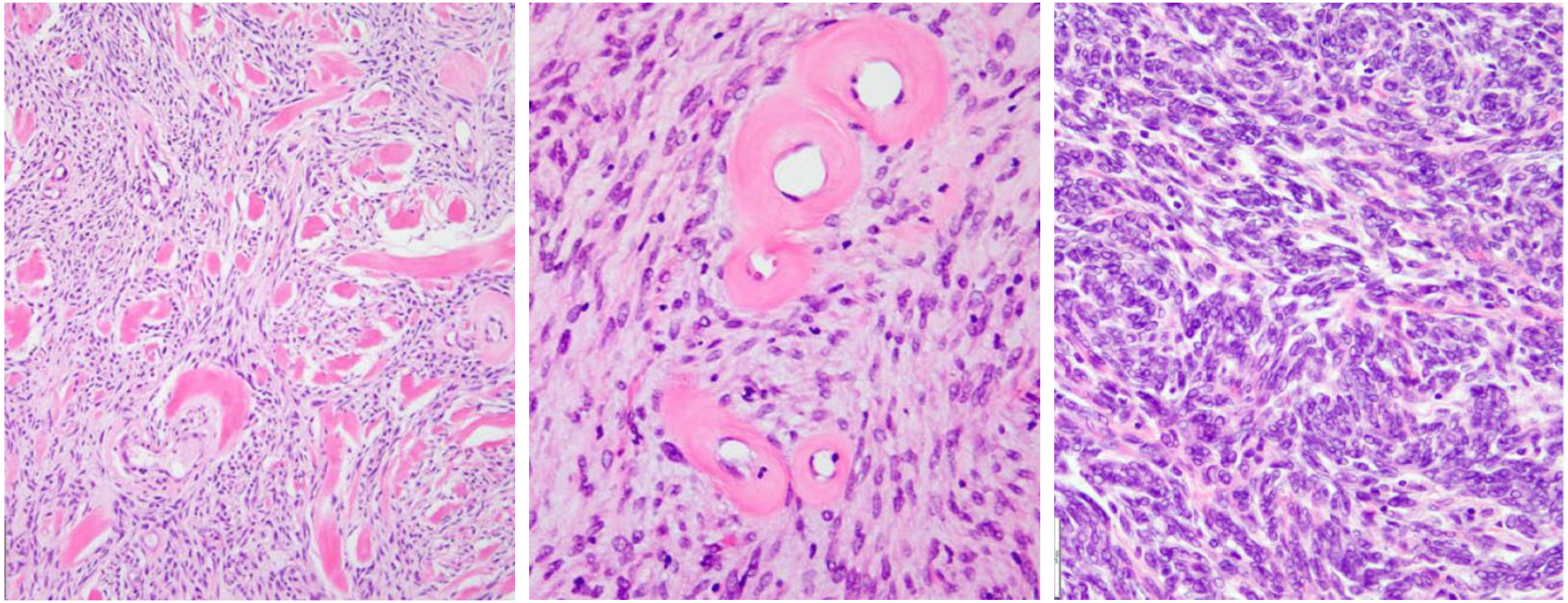


Archer FusionPlex Solid tumor kit:
***OSBP-BRAF* fusion**

A novel group of spindle cell tumors defined by S100 and CD34 co-expression shows recurrent fusions involving RAF1, BRAF, and NTRK1/2 genes

Albert J. H. Suurmeijer[1] | Brendan C. Dickson[2] | David Swanson[2] | Lei Zhang[3] | Yun-Shao Sung[3] | Paolo Cotzia[3] | Christopher D. M. Fletcher[4] | Cristina R. Antonescu[3]

Genes Chromosomes Cancer. 2018;1–11.



LMNA–NTRK1
LMNA–NTRK1
LMNA–NTRK1
LMNA–NTRK1
LMNA–NTRK1
LMNA–NTRK1
LMNA–NTRK1
LMNA–NTRK1
TPM3–NTRK1[c]
TPM3–NTRK1
TPM3–NTRK1
TPR–NTRK1
NTRK1
NTRK1
SPECC1L–NTRK2[a]

A novel group of spindle cell tumors defined by S100 and CD34 co-expression shows recurrent fusions involving RAF1, BRAF, and NTRK1/2 genes

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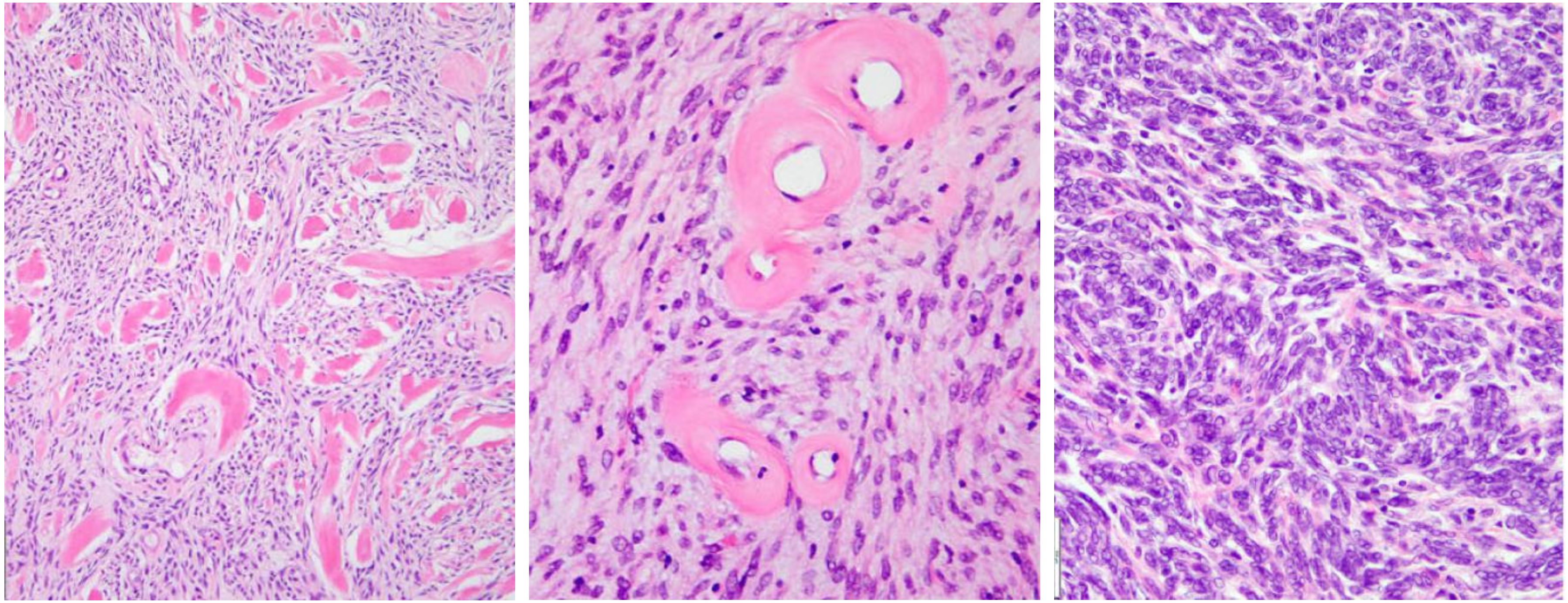
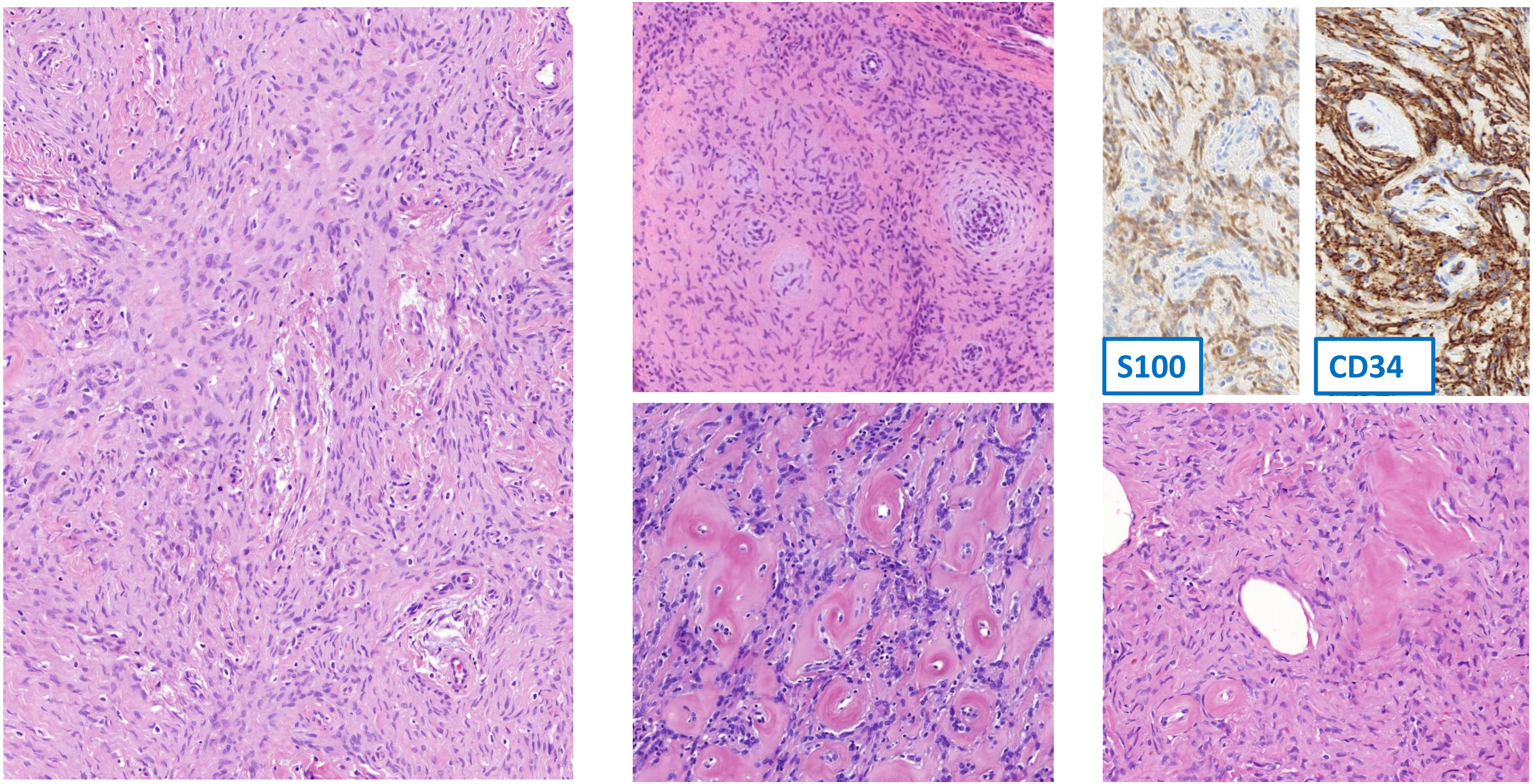
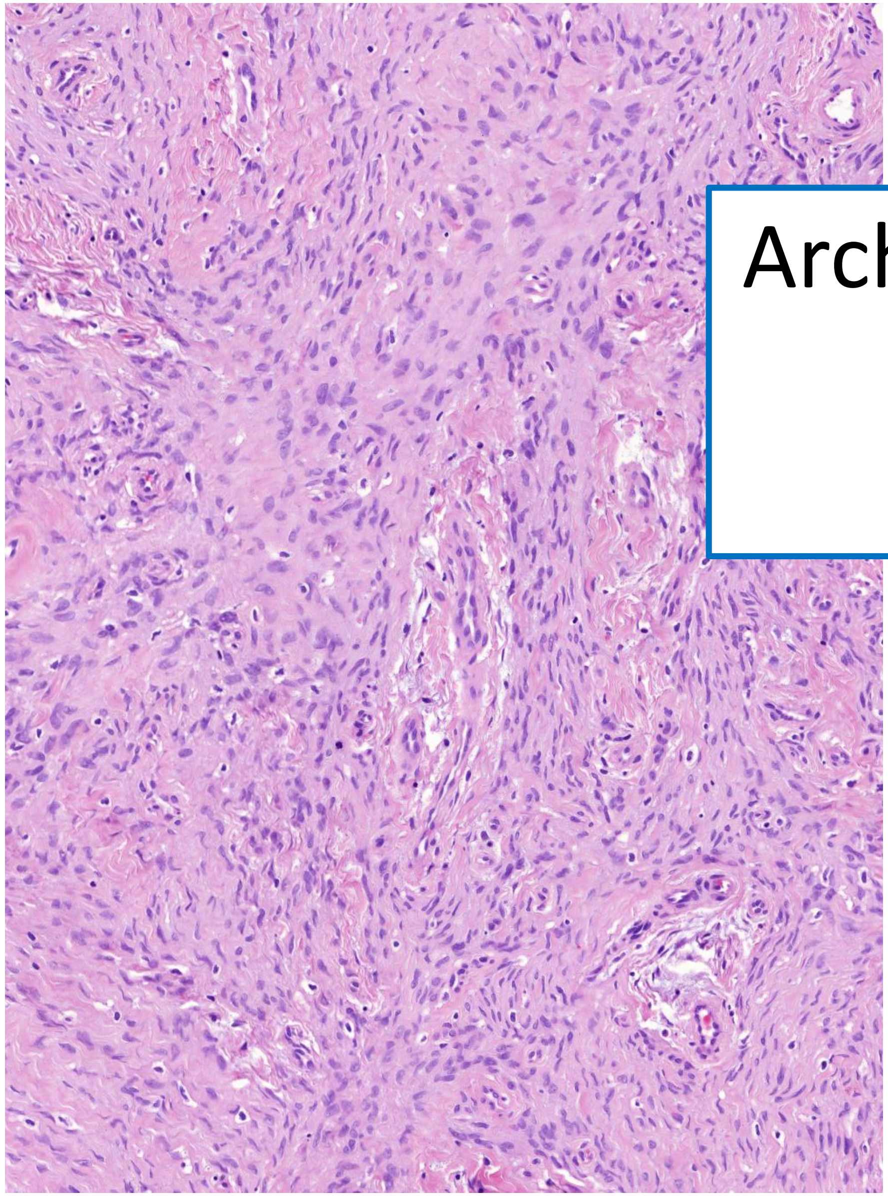


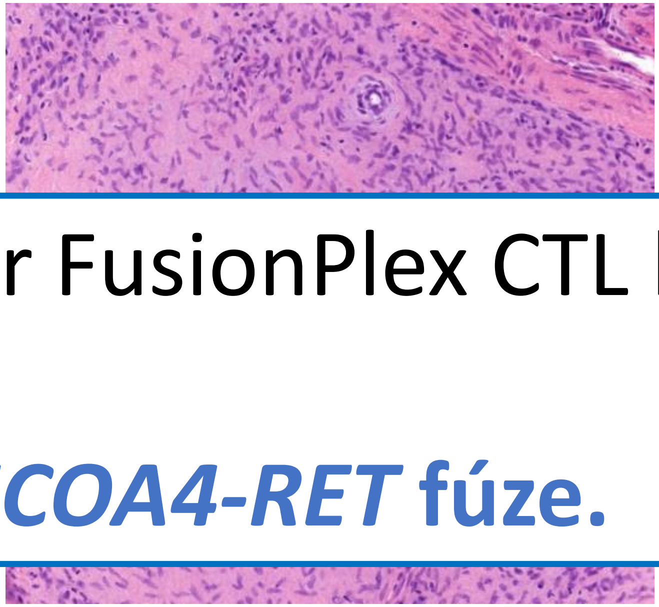
LMNA–NTRK1	*PDZRN3–RAF1*[a]
LMNA–NTRK1	*SLMAP–RAF1*[a]
LMNA–NTRK1	*TMF1–RAF1*[b]
LMNA–NTRK1	*RAF1*
LMNA–NTRK1	*RAF1*
LMNA–NTRK1	*RAF1*
LMNA–NTRK1	*RAF1*
LMNA–NTRK1	*RAF1*
TPM3–NTRK1[c]	*BRAF*
TPM3–NTRK1	*BRAF*
TPM3–NTRK1	
TPR–NTRK1	
NTRK1	
NTRK1	
SPECC1L–NTRK2[a]	

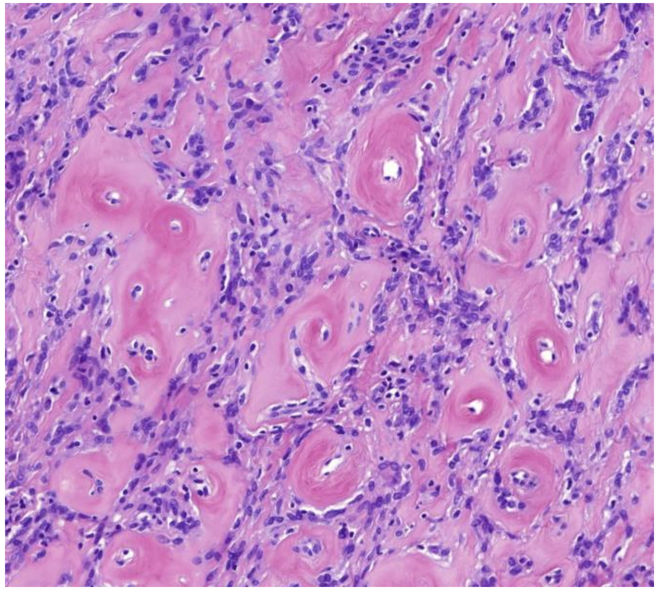
Muž, 29 let, recidivující tumor paže

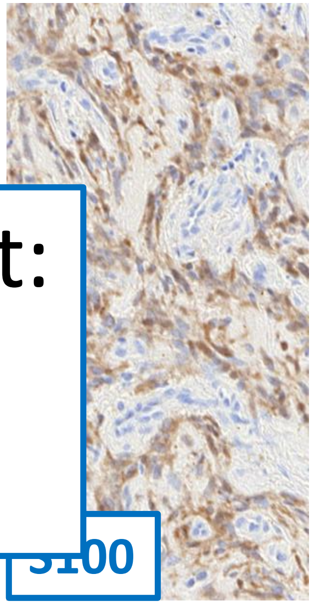


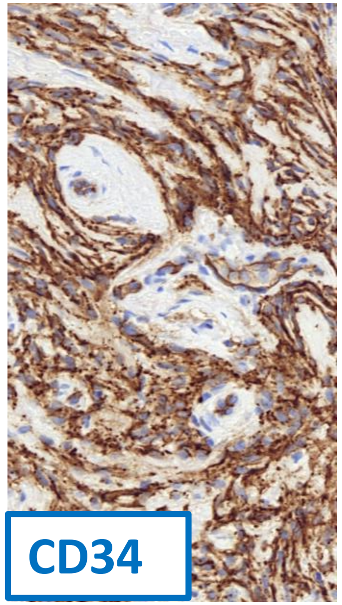
Muž, 29 let, recidivující tumor paže

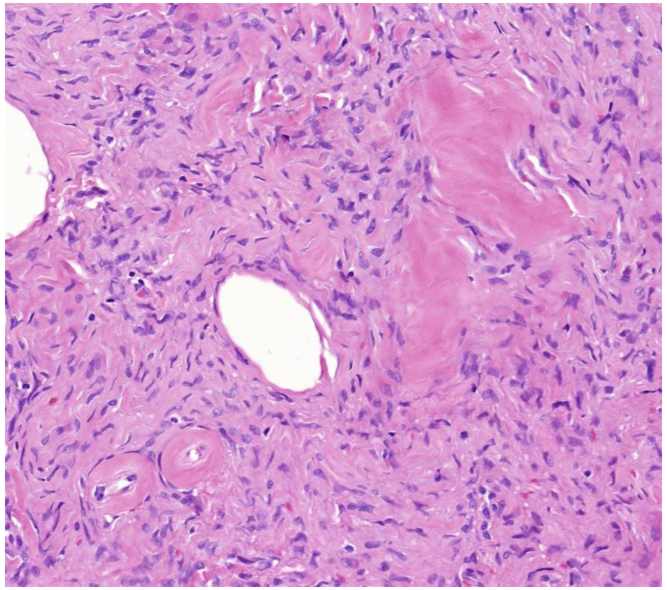








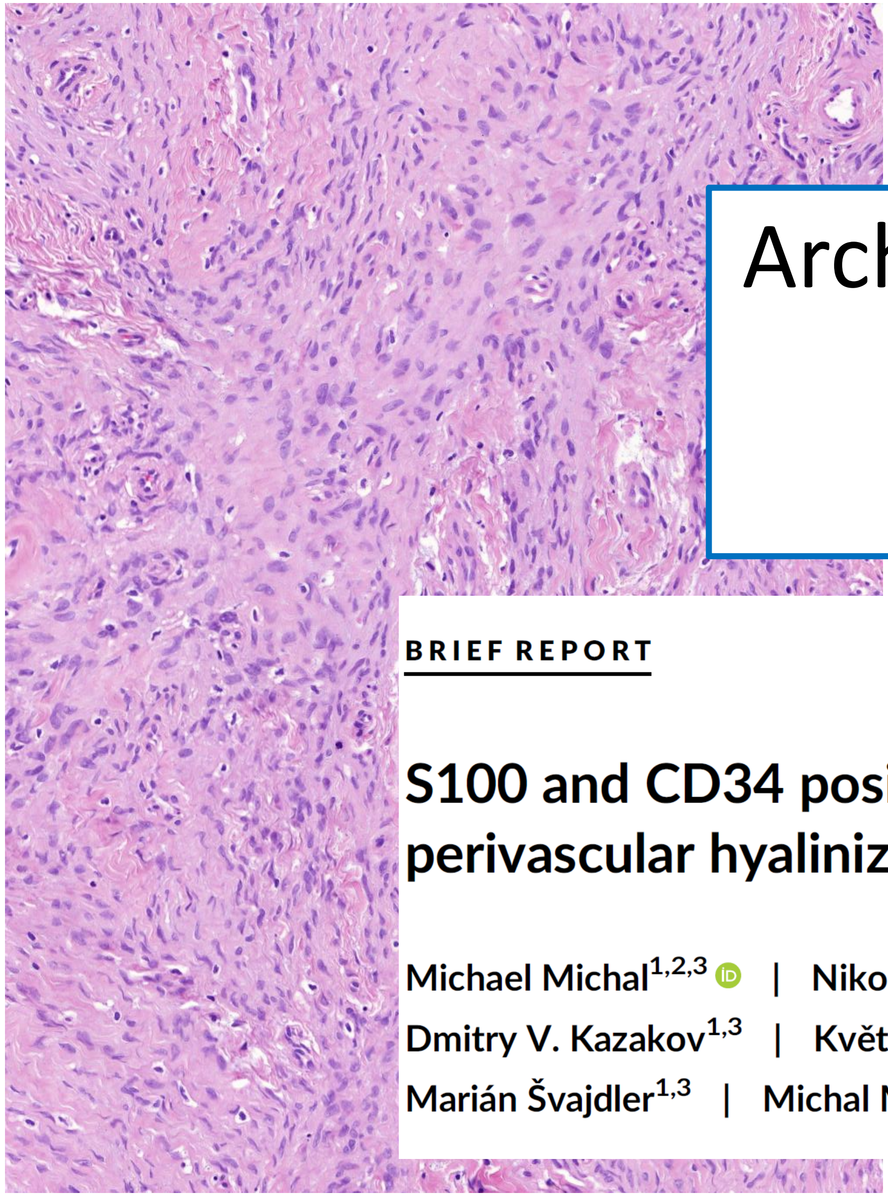


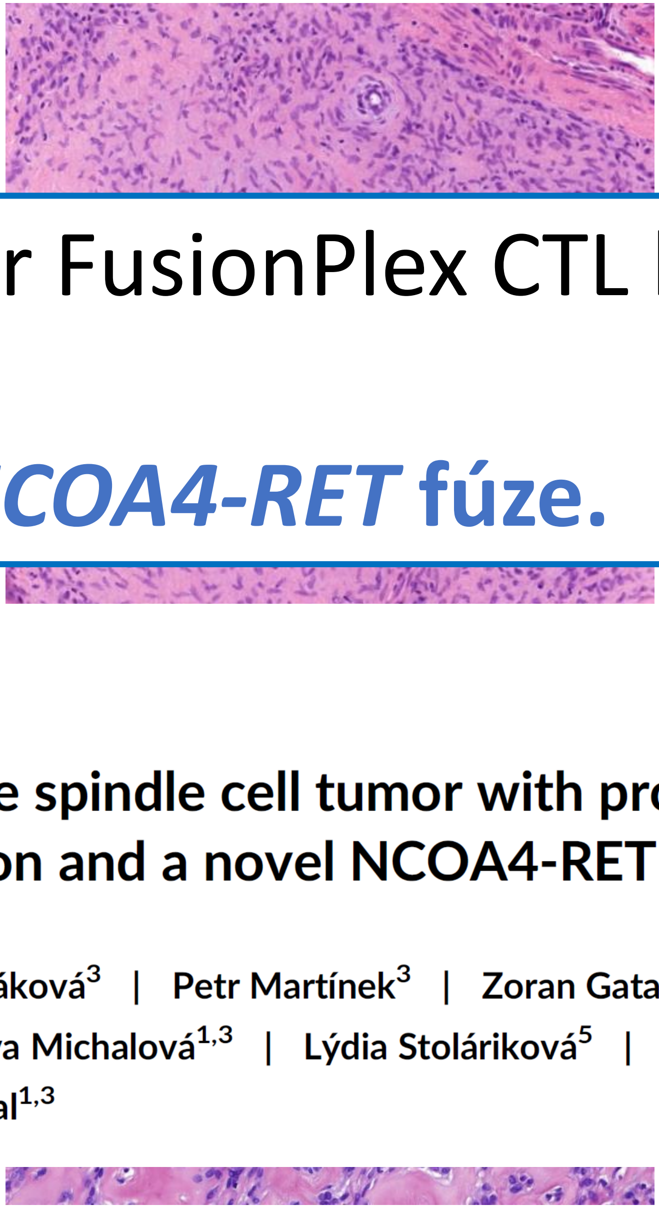


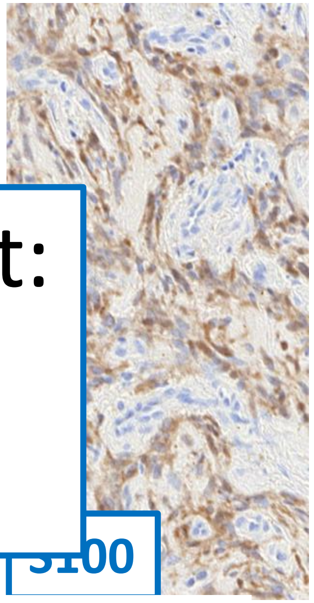
Archer FusionPlex CTL kit:

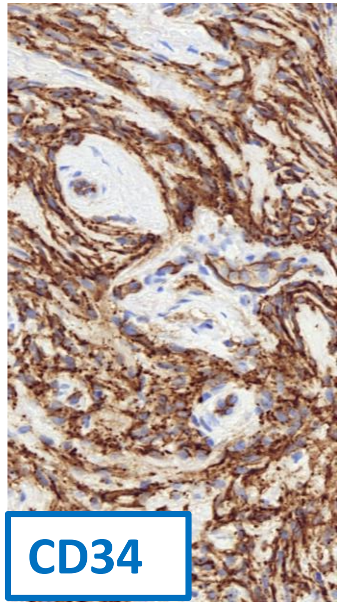
***NCOA4-RET* fúze.**

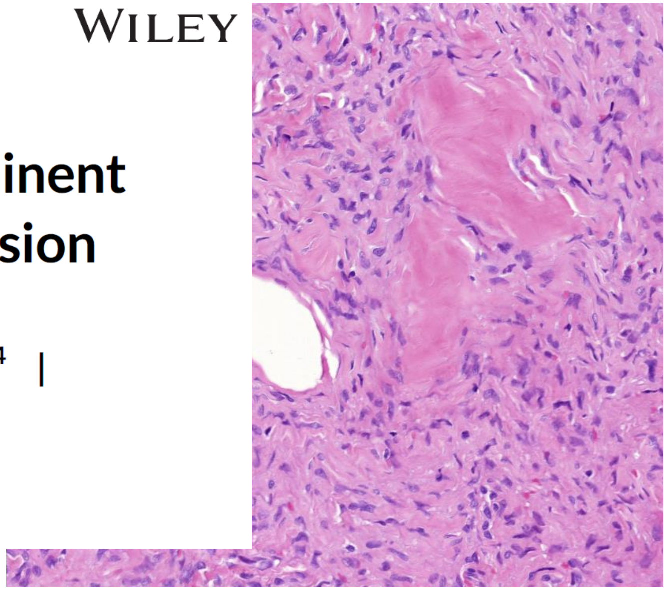
Muž, 29 let, recidivující tumor paže











Archer FusionPlex CTL kit:

***NCOA4-RET* fúze.**

BRIEF REPORT

WILEY

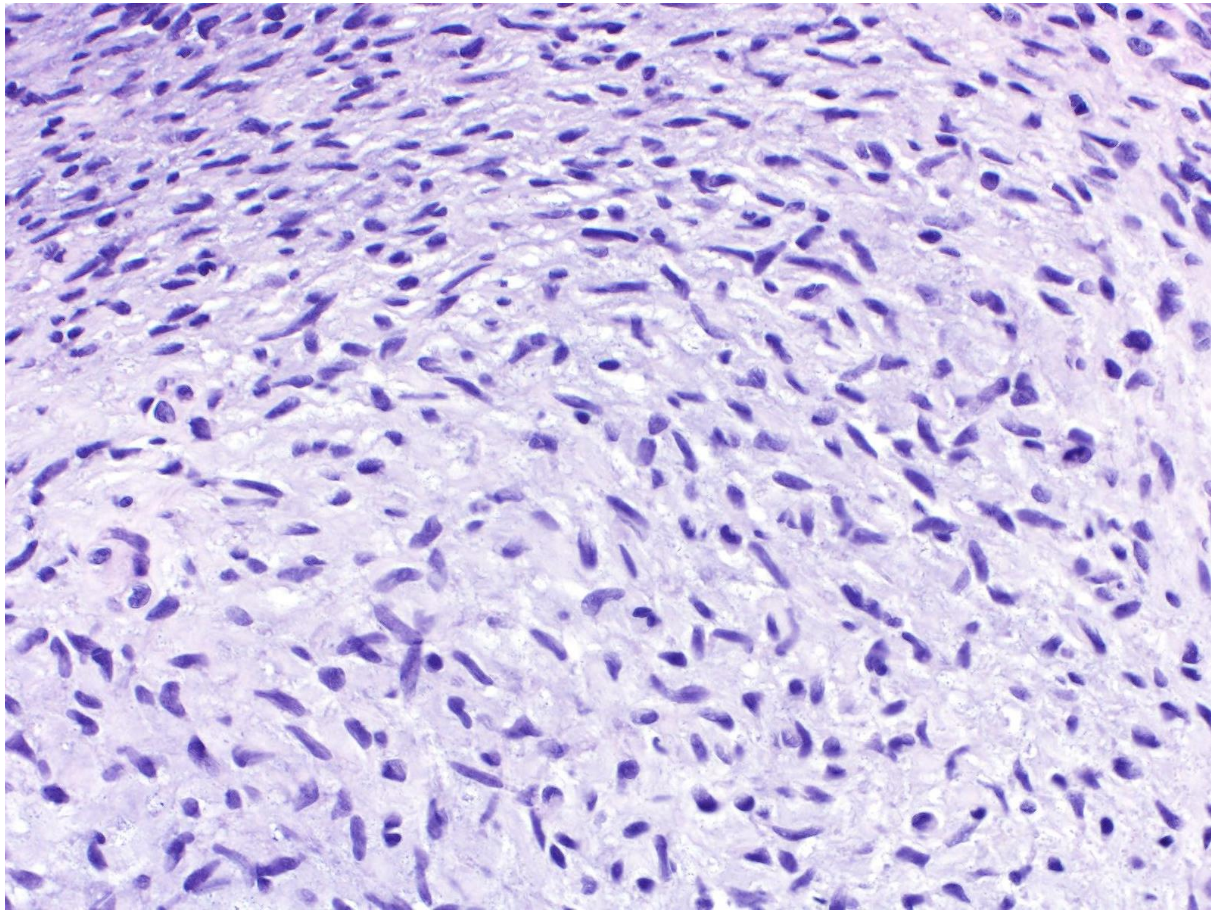
S100 and CD34 positive spindle cell tumor with prominent perivascular hyalinization and a novel NCOA4-RET fusion

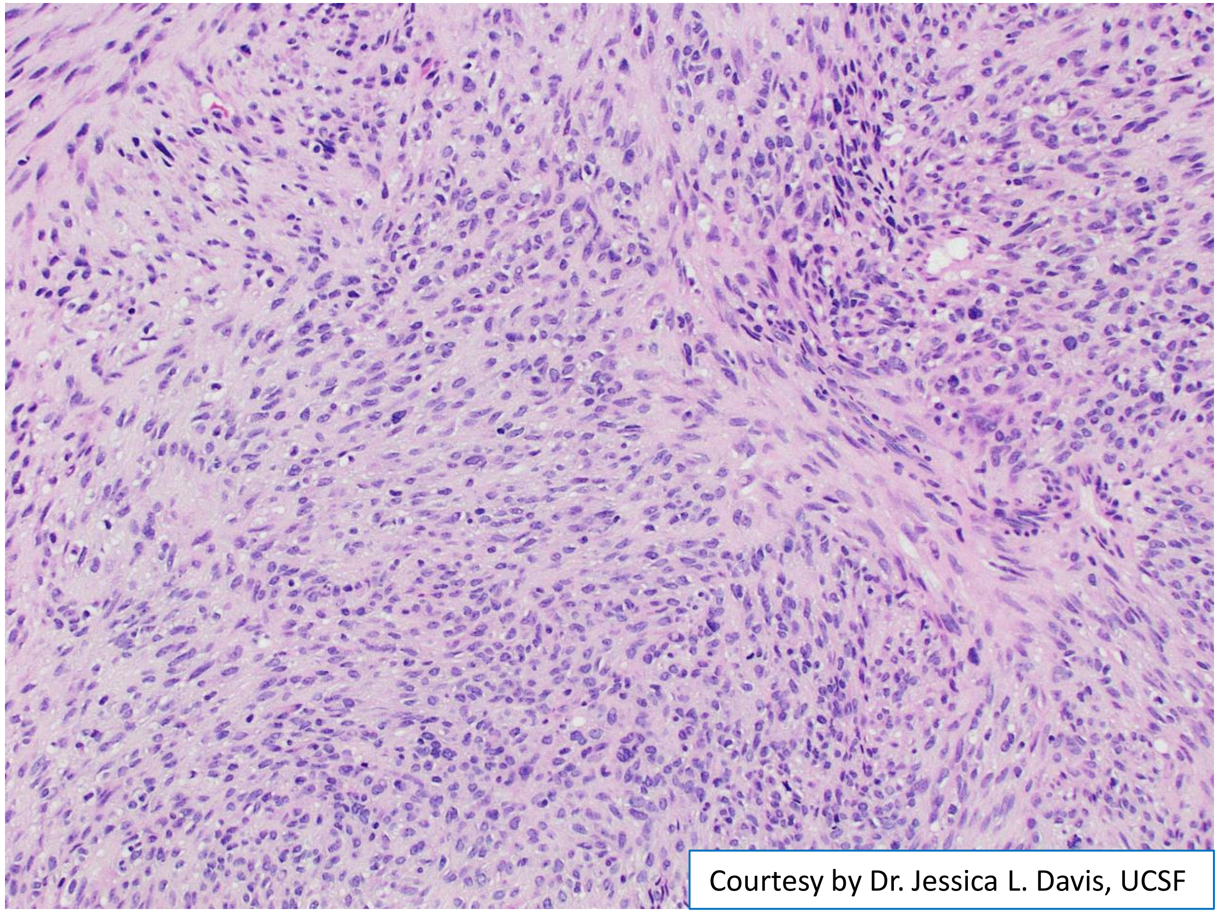
Michael Michal[1,2,3] | Nikola Ptáková[3] | Petr Martínek[3] | Zoran Gatalica[4] | Dmitry V. Kazakov[1,3] | Květoslava Michalová[1,3] | Lýdia Stoláriková[5] | Marián Švajdler[1,3] | Michal Michal[1,3]

13. Recurrent *RET* Gene Fusions in Pediatric Spindle Mesenchymal Neoplasms

J Davis[1], *S Vargas*[2], *T Boyd*[2], *S Forrest*[3], *K Janeway*[3], *K Winsnes*[4], *S Yang*[5], *M VanSandt*[5], *C Corless*[5], *A Church*[2], ***A Al-Ibraheemi***[2]; [1]Oregon Health & Science University, Portland, Oregon; [2]Boston Childrens Hospital, Boston, Massachusetts; [3]Dana Farber Cancer Institute, Boston, Massachusetts; [4]Oregon Health & Science University/ Doernbecher Children's Hospital, Portland, Oregon; [5]Oregon Health & Science University, Portland, Oregon

Society of Pediatric Pathology Meeting, March 15th - 17th, 2019





13. Recurrent *RET* Gene Fusions in Pediatric Spindle Mesenchymal Neoplasms

J Davis[1], *S Vargas*[2], *T Boyd*[2], *S Forrest*[3], *K Janeway*[3], *K Winsnes*[4], *S Yang*[5], *M VanSandt*[5], *C Corless*[5], *A Church*[2], ***A Al-Ibraheemi***[2]; [1]Oregon Health & Science University, Portland, Oregon; [2]Boston Childrens Hospital, Boston, Massachusetts; [3]Dana Farber Cancer Institute, Boston, Massachusetts; [4]Oregon Health & Science University/ Doernbecher Children's Hospital, Portland, Oregon; [5]Oregon Health & Science University, Portland, Oregon

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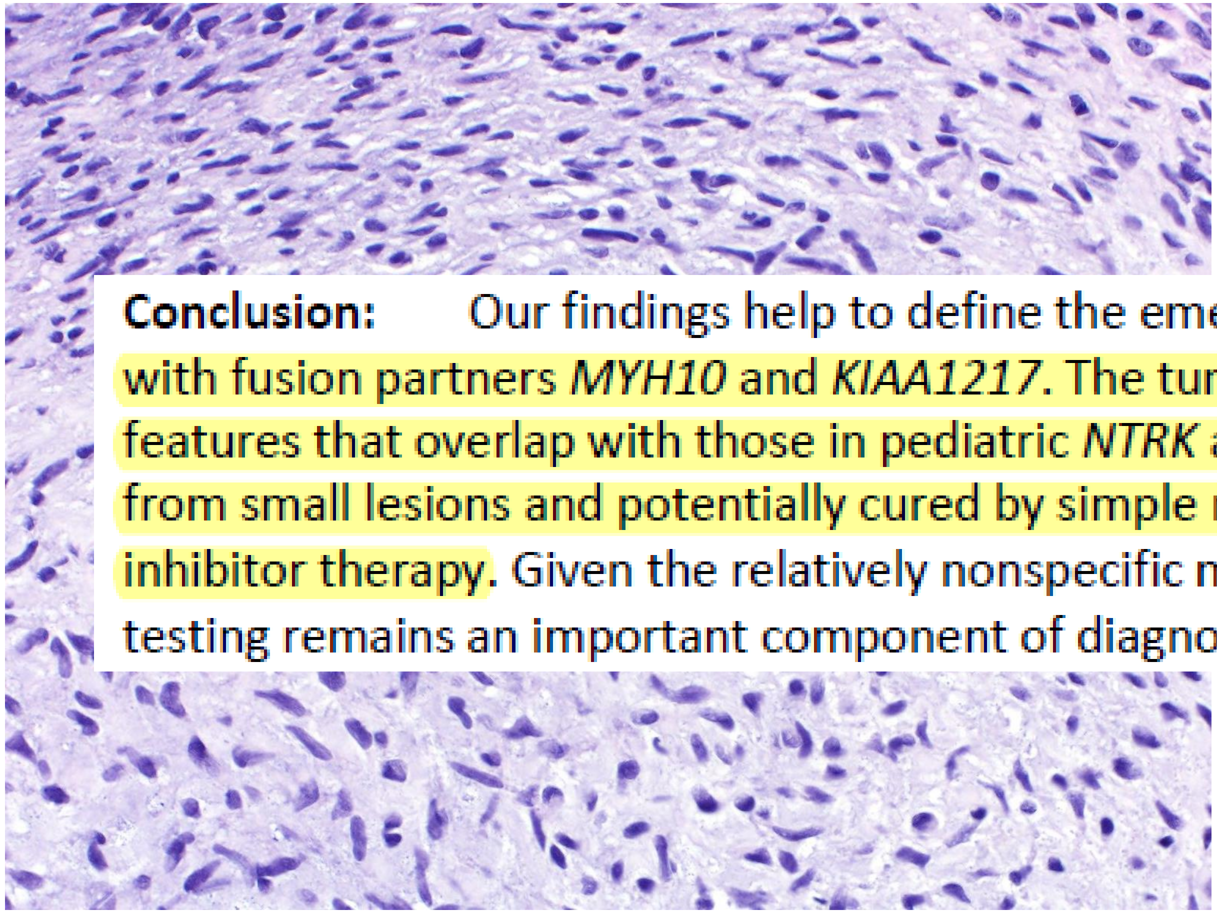
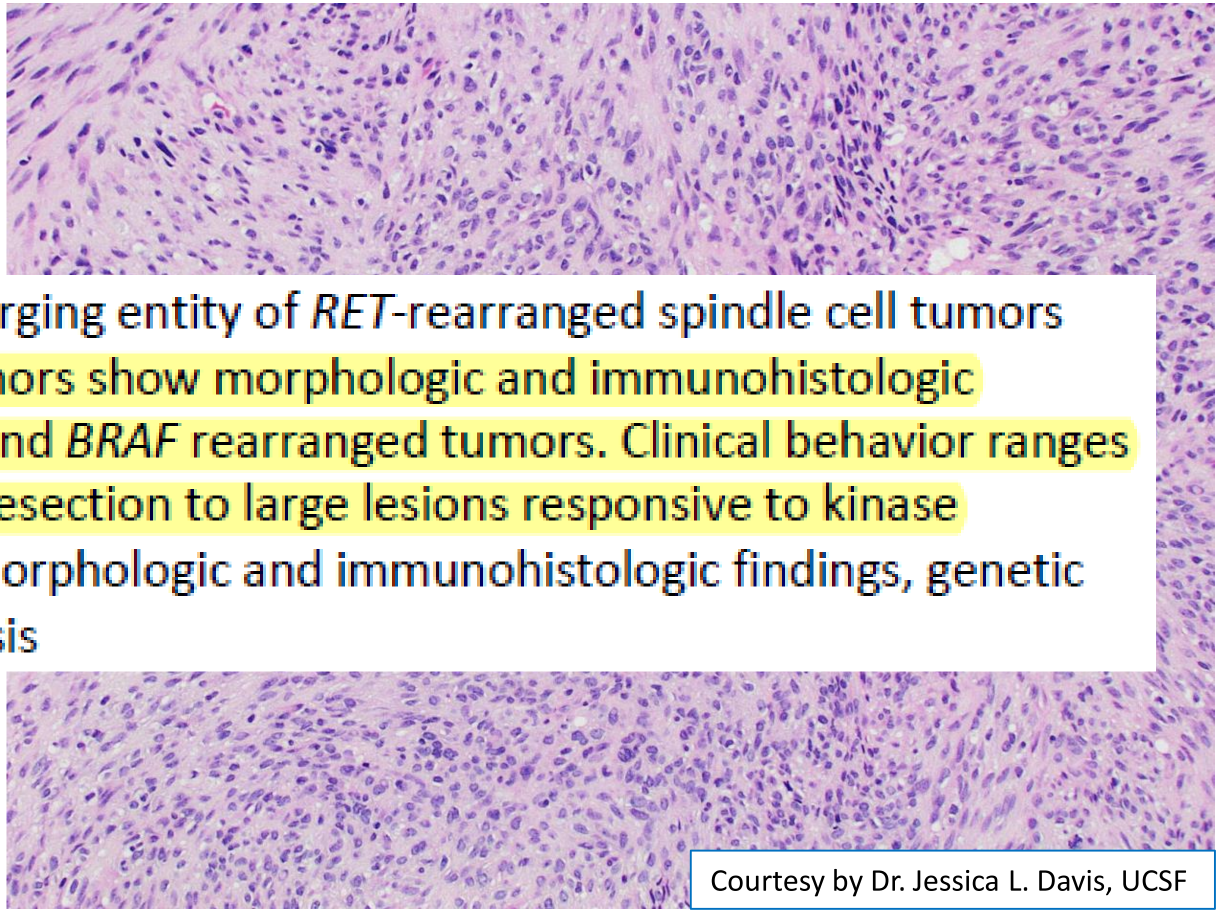




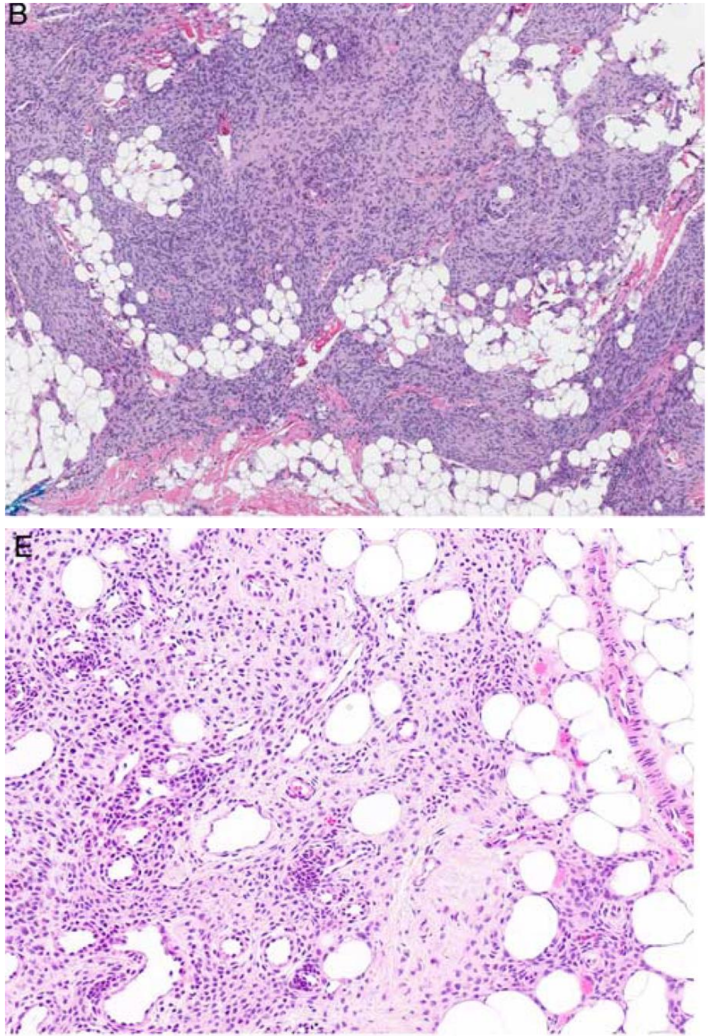
Conclusion: Our findings help to define the emerging entity of *RET*-rearranged spindle cell tumors with fusion partners *MYH10* and *KIAA1217*. The tumors show morphologic and immunohistologic features that overlap with those in pediatric *NTRK* and *BRAF* rearranged tumors. Clinical behavior ranges from small lesions and potentially cured by simple resection to large lesions responsive to kinase inhibitor therapy. Given the relatively nonspecific morphologic and immunohistologic findings, genetic testing remains an important component of diagnosis

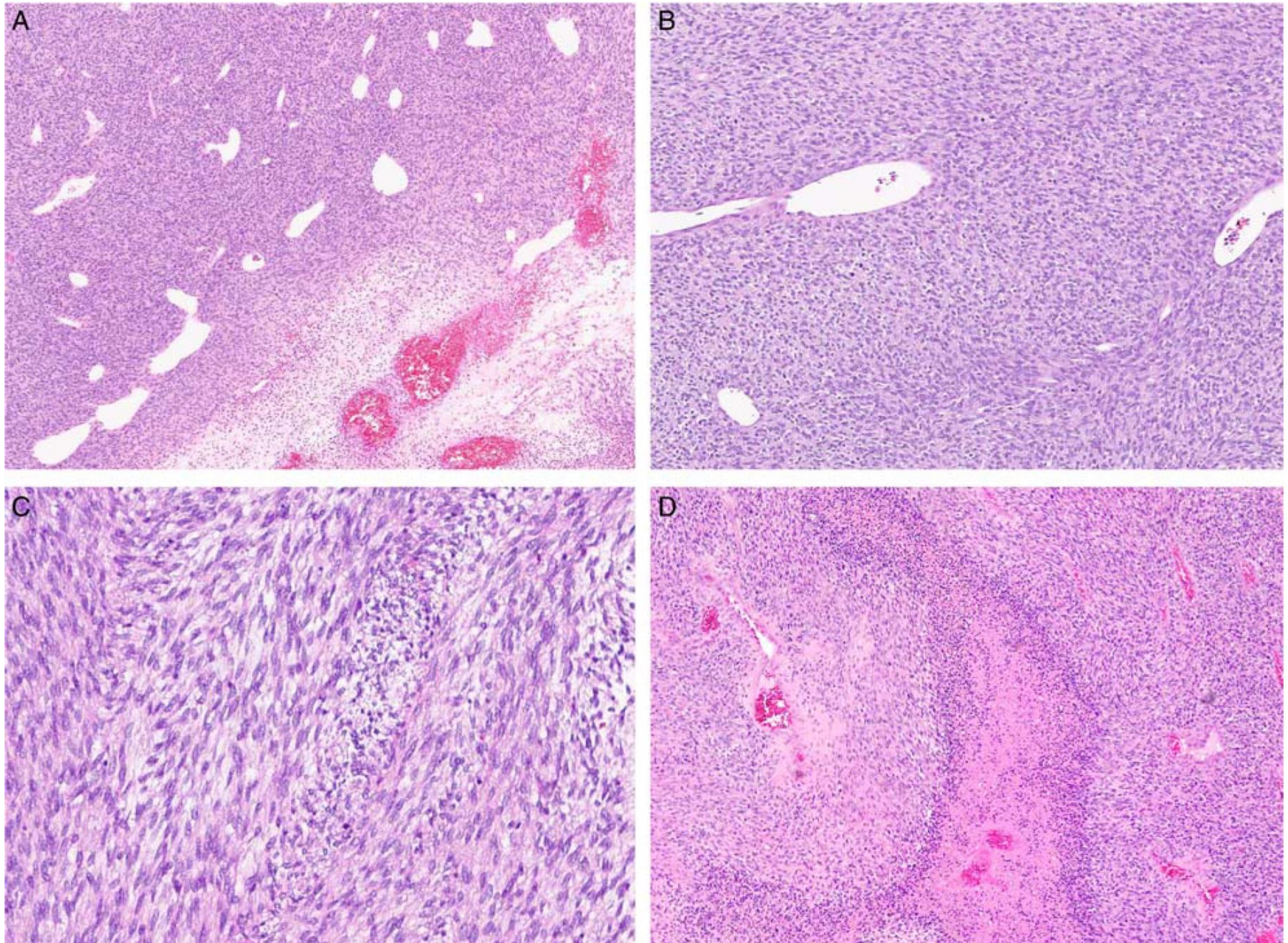
Courtesy by Dr. Jessica L. Davis, UCSF

Spindle Cell Tumors With RET Gene Fusions Exhibit a Morphologic Spectrum Akin to Tumors With NTRK Gene Fusions

Cristina R. Antonescu, MD, Brendan C. Dickson, MD,† David Swanson, BSc,† Lei Zhang, MD,**
Yun-Shao Sung, BSc, Yu-Chien Kao, MD,‡ Wei-Chin Chang, MD,§ Leili Ran, PhD,∥*
Alberto Pappo, MD,¶ Armita Bahrami, MD,# Ping Chi, MD, PhD,∥
*and Christopher D. Fletcher, MD***

(*Am J Surg Pathol* 2019;00:000–000)

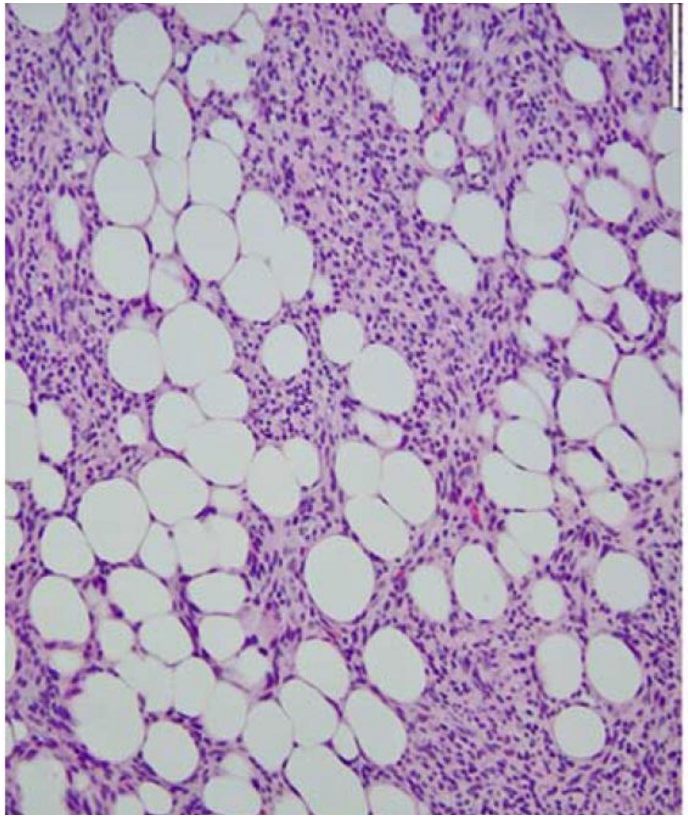


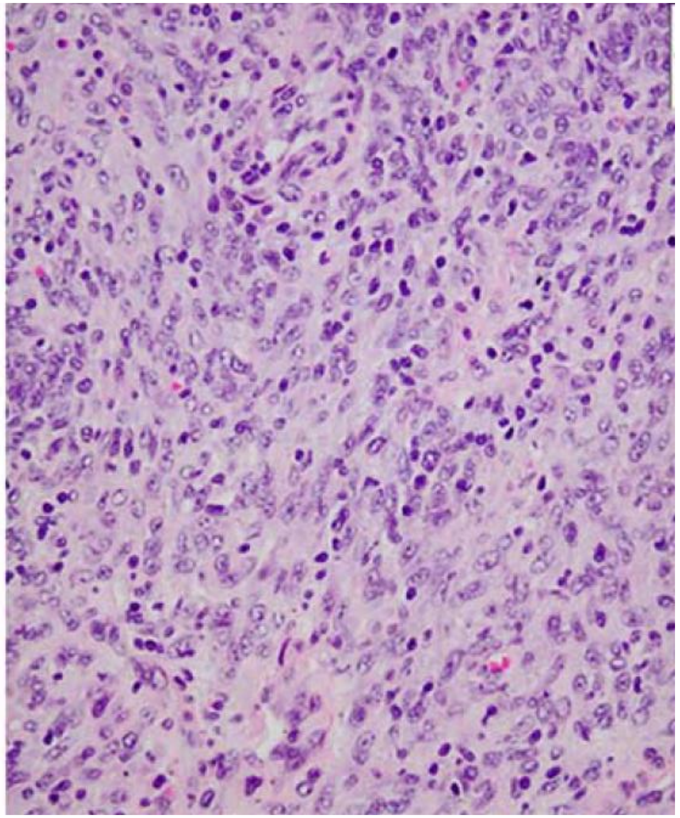


(*Am J Surg Pathol* 2016;40:1407–1416)

Recurrent *NTRK1* Gene Fusions Define a Novel Subset of Locally Aggressive Lipofibromatosis-like Neural Tumors

Narasimhan P. Agaram, MBBS, Lei Zhang, MD,* Yun-Shao Sung, MS,* Chun-Liang Chen, MS,* Catherine T. Chung, MD,† Cristina R. Antonescu, MD,* and Christopher DM Fletcher, MD, FRCPath‡*





Genetic Abnormality
TPR-NTRK1
TPM3 - NTRK1
LMNA-NTRK1
LMNA-NTRK1
LMNA-NTRK1
LMNA-NTRK1
NTRK1
NTRK1
NTRK1
NTRK1
ROS1
ALK

IHC +

- CD34
- S100

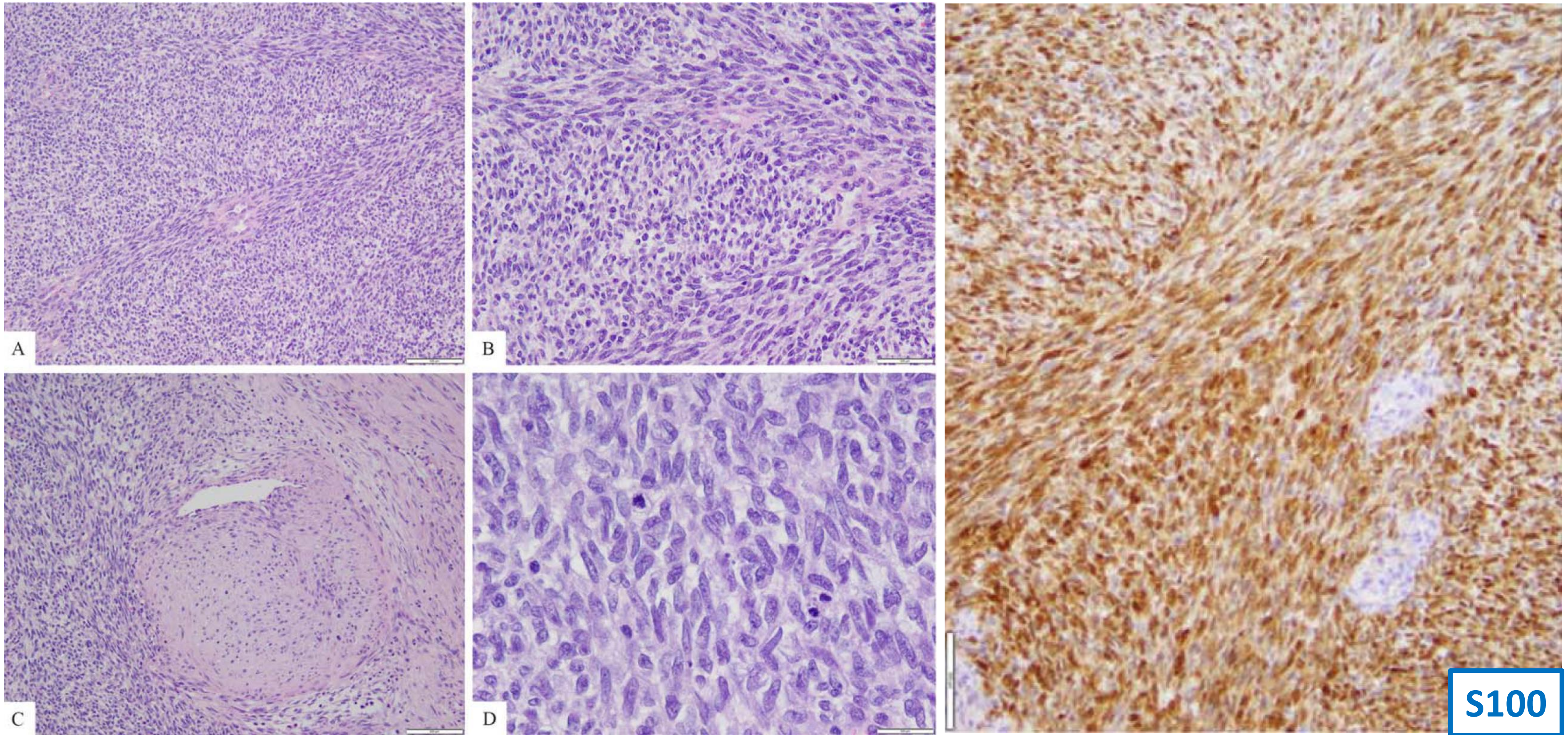
Inflamatorní myofibroblastický tumor

- **50-60%** případů má rearanži ***ALK*** genu
- **Alternativní** fúze zahrnují ***NTRK3, RET, ROS1, PDGFRB, IGF1R***
- Některé případy jsou morfologicky nerozlišitelné od infantilních fibrosarkomů

TFG-MET fusion in an infantile spindle cell sarcoma with neural features

Uta Flucke[1] | Max M. van Noesel[2] | Marc Wijnen[2] | Lei Zhang[3] | Chun-Liang Chen[3] | Yun-Shao Sung[3] | Cristina R. Antonescu[3]

Genes Chromosomes Cancer. 2017;56:663–667.



Sarkomy dělohy s *NTRK* fúzemi

NTRK Fusions Define a Novel Uterine Sarcoma Subtype With Features of Fibrosarcoma

Sarah Chiang, MD, Paolo Cotzia, MD,* David M. Hyman, MD,† Alexander Drilon, MD,‡ William D. Tap, MD,§ Lei Zhang, MD,* Jaclyn F. Hechtman, MD,* Denise Frosina, BS,* Achim A. Jungbluth, MD, PhD,* Rajmohan Murali, MBBS, MD, FRCPA,* Kay J. Park, MD,* Robert A. Soslow, MD,* Esther Oliva, MD,‖¶ A. John Iafrate, MD, PhD,‖¶ Ryma Benayed, PhD,* Marc Ladanyi, MD,* and Cristina R. Antonescu, MD**

(*Am J Surg Pathol* 2018;42:791–798)

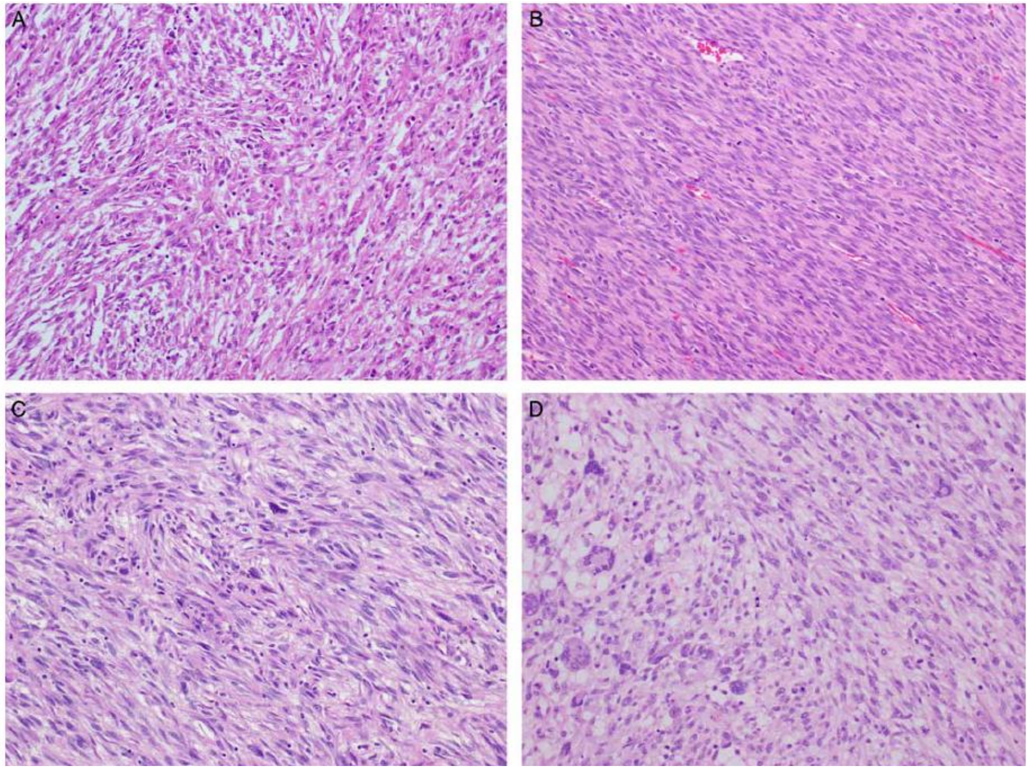
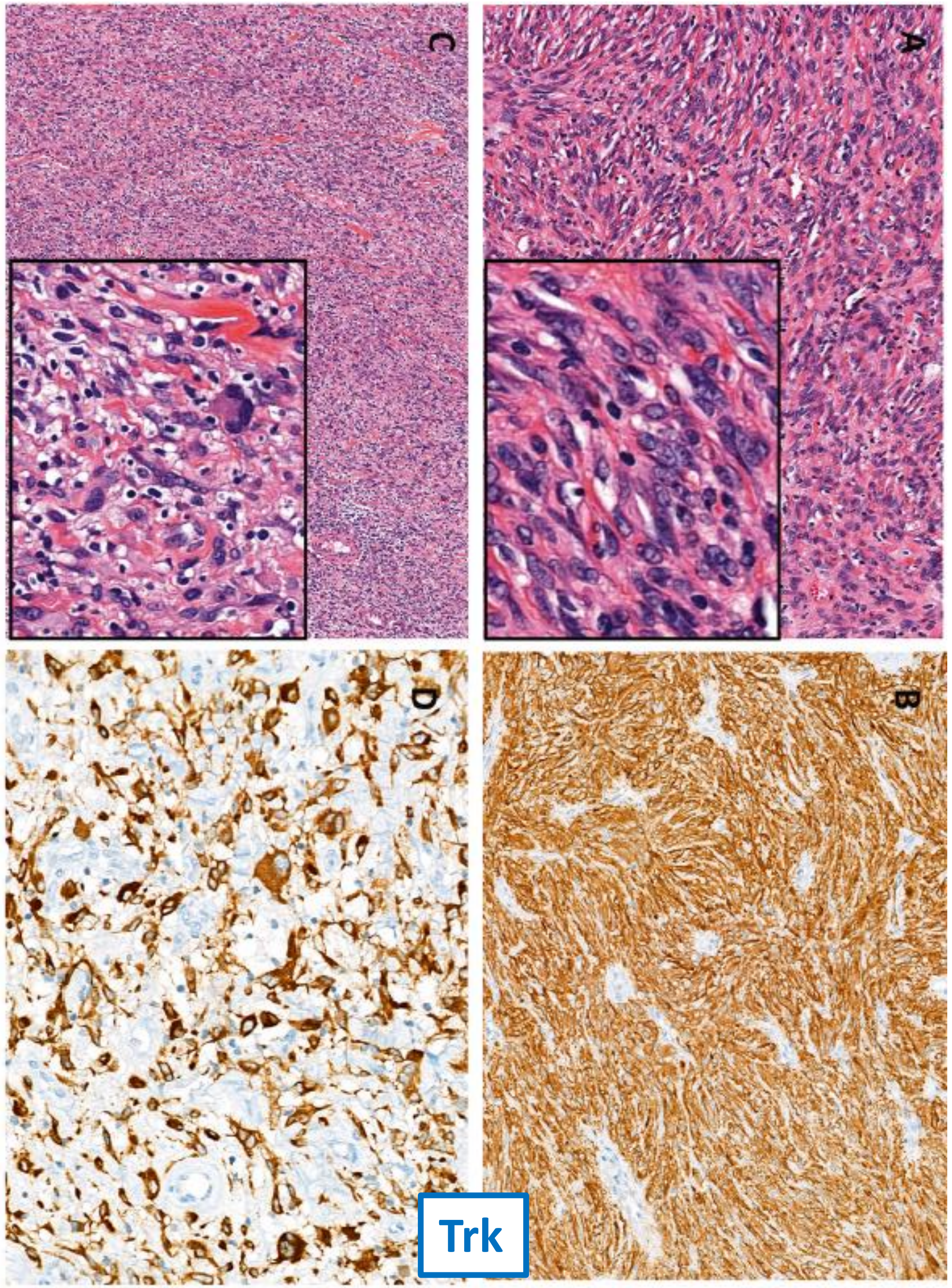


TABLE 1. Clinical Characteristics of the Cohort

Case	Age (y)	Signs and Symptoms	Disease Site	Stage	Treatment	Outcome (mo)
1	46	Vaginal bleeding	Cervix	1B	Surgery, chemotherapy	Alive with disease, 7
2	27	Fibroid uterus	Corpus	1B	Surgery	No evidence of disease, 11
3	47	Vaginal bleeding	Cervix	1B	Surgery, chemotherapy	Died of disease, 78
4	42	Vaginal bleeding	Cervix	1B	Surgery	No evidence of disease, 2



Modern Pathology
https://doi.org/10.1038/s41379-018-0184-6

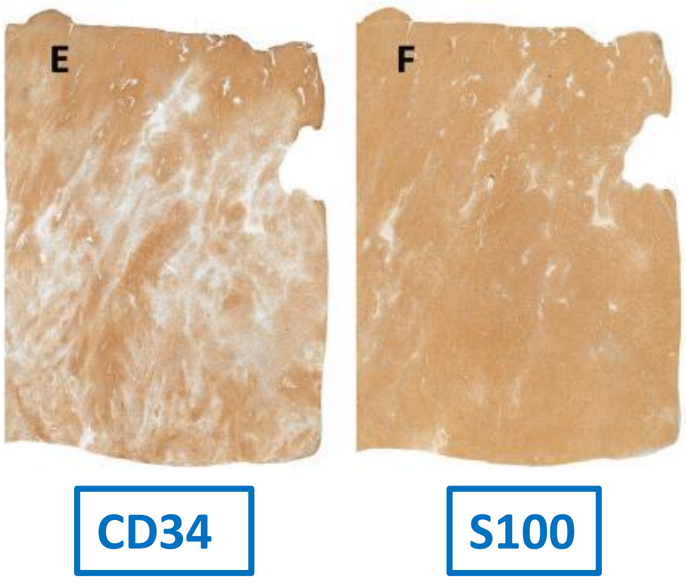
USCAP

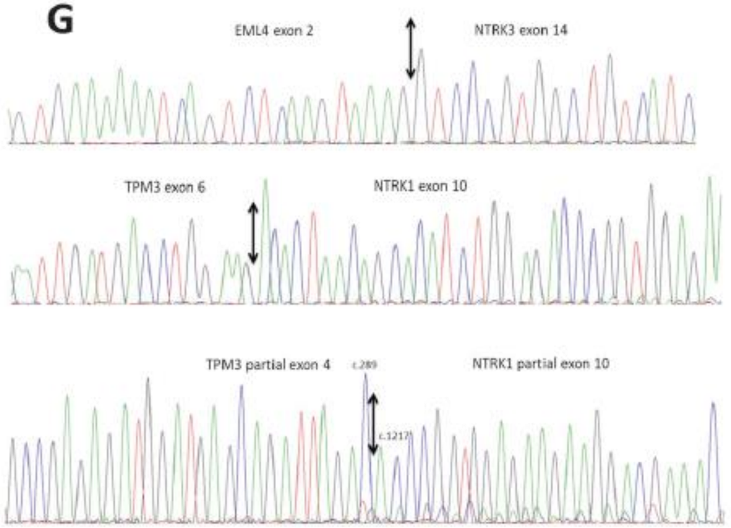
ARTICLE

Check for updates

Uterine and vaginal sarcomas resembling fibrosarcoma: a clinicopathological and molecular analysis of 13 cases showing common *NTRK*-rearrangements and the description of a *COL1A1-PDGFB* fusion novel to uterine neoplasms

Sabrina Croce[1,2] · Isabelle Hostein[1] · Teri A. Longacre[3] · Anne M. Mills[4] · Gaëlle Pérot[1] · Mojgan Devouassoux-Shisheboran[5] · Valérie Velasco[1] · Anne Floquet[6] · Frédéric Guyon[7] · Camille Chakiba[6] · Denis Querleu[7] · Emmanuel Khalifa[1] · Laetitia Mayeur[1] · Flora Rebier[1] · Sophie Leguellec[8] · Isabelle Soubeyran[1] · W. Glenn McCluggage[9]





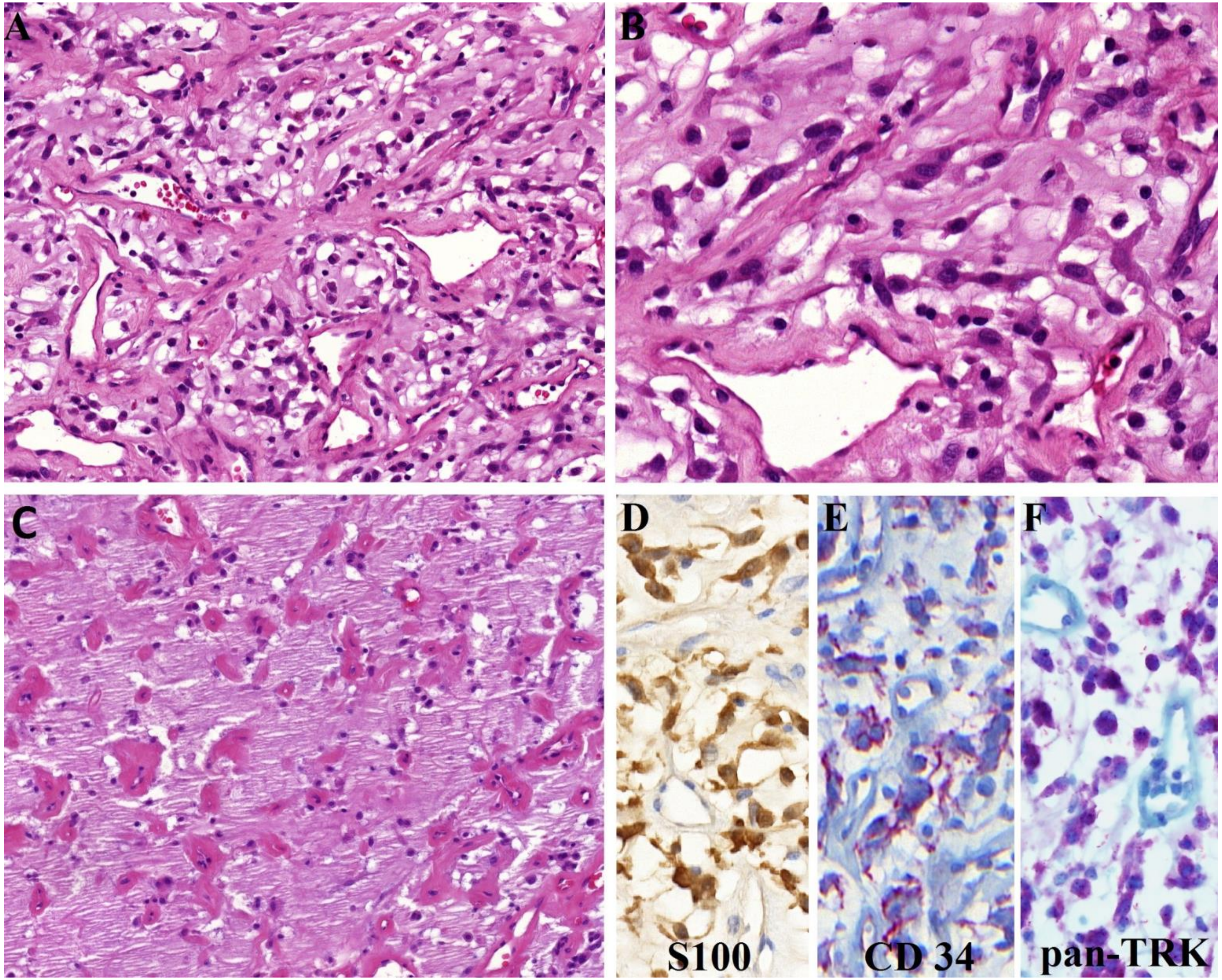
STRN-NTRK3-rearranged Mesenchymal Tumor of the Uterus

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

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



Léčba

Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study

Lancet Oncol 2018; 19: 705–14

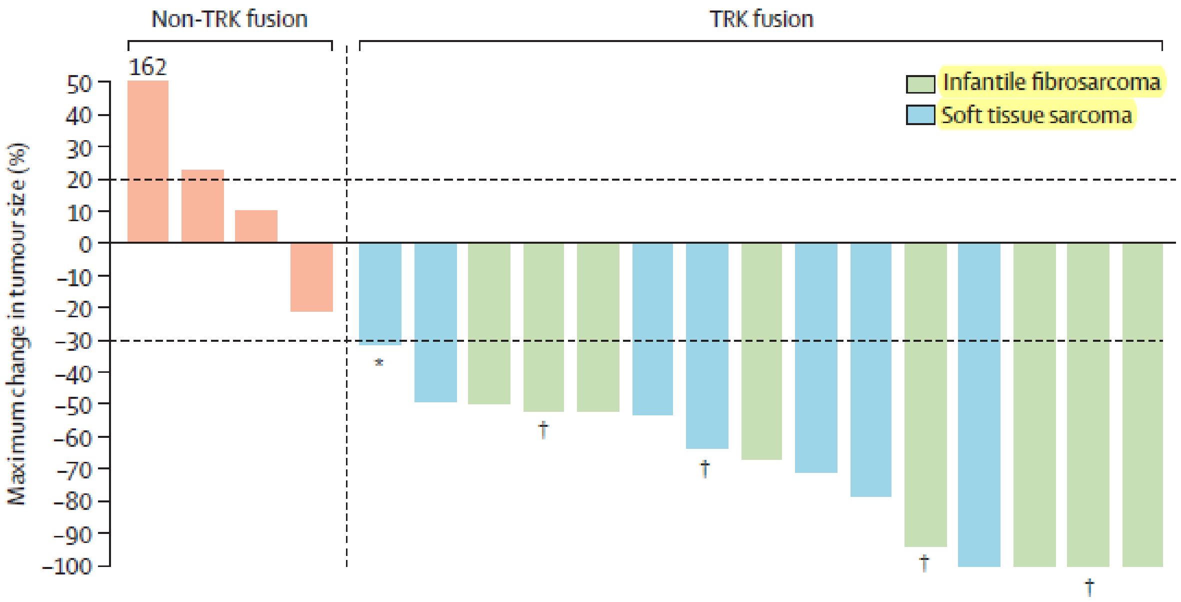
Theodore W Laetsch*, Steven G DuBois*, Leo Mascarenhas, Brian Turpin, Noah Federman, Catherine M Albert, Ramamoorthy Nagasubramanian, Jessica L Davis, Erin Rudzinski, Angela M Feraco, Brian B Tuch, Kevin T Ebata, Mark Reynolds, Steven Smith, Scott Cruickshank, Michael C Cox, Alberto S Pappo*, Douglas S Hawkins*

The Use of Neoadjuvant Larotrectinib in the Management of Children With Locally Advanced TRK Fusion Sarcomas

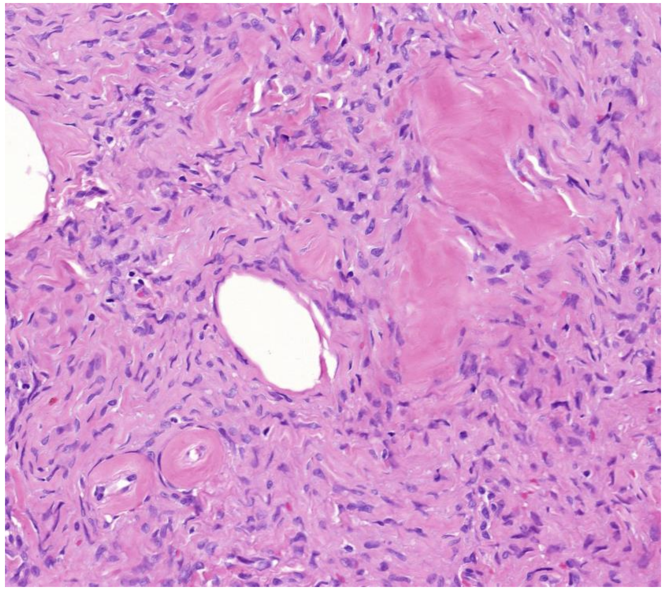
Steven G. DuBois, MD[1]; Theodore W. Laetsch, MD[2]; Noah Federman, MD[3]; Brian K. Turpin, DO[4]; Catherine M. Albert, MD[5]; Ramamoorthy Nagasubramanian, MD[6]; Megan E. Anderson, MD[7]; Jessica L. Davis, MD[8]; Hope E. Qamoos, MSN[9]; Mark E. Reynolds, PhD[9]; Scott Cruickshank, MA[9]; Michael C. Cox, PharmD[9]; Douglas S. Hawkins, MD[5]; Leo Mascarenhas, MD[10]; and Alberto S. Pappo, MD[11]

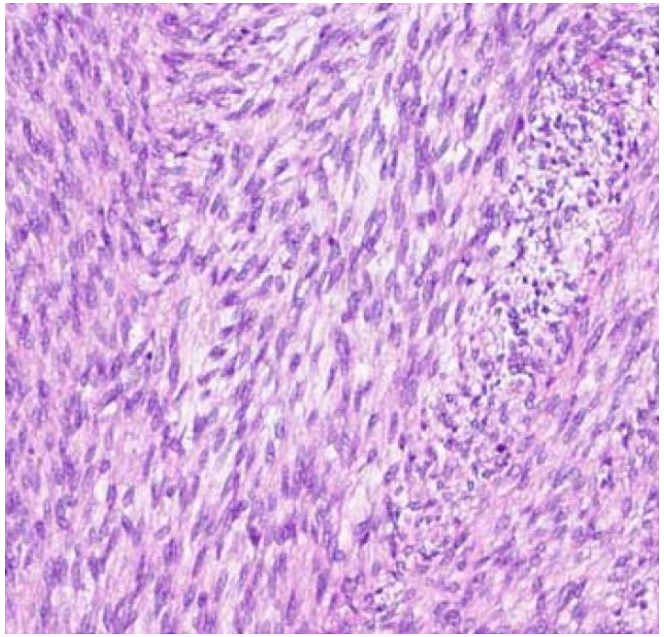
Cancer November 1, 2018

- Zhruba **90% pacientů** s NTRK rearanžovanými nádory reagovalo na terapii
- I pacienti s pokročilými metastatickými nádory dosáhli dlouhotrvající léčebné odpovědi
- **Terapie první volby** pro mnoho pediatrických pacientů s lokálně pokročilým onemocněním nyní zahrnuje **chemoterapii, radioterapii a v některých případech i „invalidizující“ chirurgický zákrok**
- **Preoperační použití Larotrectinibu** u takových pacientů vede k výraznému **zmenšení nádoru**, což napomáhá **omezit rozsah chirurgického zákroku**
- Daleko méně nežádoucích účinků ve srovnání s chemoterapií



Souhrn





- Mezenchymální tumory s kinázovými fúzemi jsou **částější mezi pediatrickými** pacienty, ale morfologicky identické tumory se mohou vyskytovat i u dospělých
- **Morfologické spektrum je široké**
  - low-grade vřetenobuněčné tumory, často s perivaskulární a stromální hyalinizací a CD34 a S100 koexpresí
  - high-grade vřetenobuněčné sarkomy/fibrosarkomy, CD34 a S100 méně často
- Biologické chování konkrétního tumoru lze, zdá se, částečně odhadnout na základě morfologie
- Poslední studie ukazují, že **mezi typem kinázové fúze** (*NTRK, BRAF, RET* atd) **a klinicko-patologickými vlastnostmi tumorů není nejspíš velký rozdíl**
- **Kinázové inhibitory (NTRK, RET) představují novou a efektivní možnost léčby** jak pro pacienty s lokálně pokročilým, tak metastatickým onemocněním

Děkuji za pozornost

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