Prediktivní testování solidních tumorů

Michal Michal
Plzeň

Mammary Analogue Secretory Carcinoma of Salivary Glands, Containing the *ETV6-NTRK3* Fusion Gene: A Hitherto Undescribed Salivary Gland Tumor Entity

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Abstract: We present a series of 16 salivary gland tumors with histomorphologic and immunohistochemical features reminiscent of secretory carcinoma of the breast. This is a hitherto undescribed and distinctive salivary gland neoplasm, with features resembling both salivary acinic cell carcinoma (AciCC) and low-grade cystadenocarcinoma, and displaying strong similarities to breast secretory carcinoma. Microscopically, the tumors have a lobulated growth pattern and are composed of microcystic and glandular spaces with abundant eosinophilic homogenous or bubbly secretory material positive for periodic acid-Schiff, mucicarmine, MUC1, MUC4, and mammaglobin. The neoplasms also show strong vimentin, S-100 protein, and STAT5a positivity. For this tumor, we propose a designation mammary analogue secretory carcinoma of salivary glands (MASC). The 16 patients comprised 9 men and 7 women, with a mean age of 46 years (range 21 to 75). Thirteen cases occurred in the parotid gland, and one each in the minor salivary glands of the buccal mucosa, upper lip, and palate. The mean size of the tumors was 2.1 cm (range 0.7 to 5.5 cm). The duration of symptoms was recorded in 11 cases and ranged from 2 months to 30 years. Clinical follow-up was available in 13 cases, and ranged from 3 months to 10 years. Four patients suffered local recurrences. Two patients died, 1 of them owing to multiple local recurrences with extension to the temporal bone, and another owing to metastatic dissemination to cervical lymph nodes, pleura, pericardium, and lungs. We have shown a t(12;15) (p13;q25) *ETV6-NTRK3* translocation in all but one case of MASC suitable for analysis. One case was not analyzable and another was not available for testing. This translocation was not found in any conventional salivary AciCC (12 cases), nor in other tumor types including pleomorphic adenoma (1 case) and low-grade cribriform cystadenocarcinoma (1 case), whereas *ETV6-NTRK3* gene rearrangements were proven in all 3 tested cases of mammary secretory carcinoma. Thus, our results strongly support the concept that MASC and AciCC are different entities.

Key Words: salivary gland, acinic cell carcinoma, secretory carcinoma, mammary type, molecular pathology, *ETV6-NTRK3* translocation

(*Am J Surg Pathol* 2010;34:599–608)

Mammary Analogue Secretory Carcinoma of Salivary Glands

Molecular Analysis of 25 ETV6 Gene Rearranged Tumors With Lack of Detection of Classical ETV6-NTRK3 Fusion Transcript by Standard RT-PCR: Report of 4 Cases Harboring ETV6-X Gene Fusion

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Abstract: *ETV6* gene abnormalities are well described in tumor pathology. Many fusion partners of *ETV6* have been reported in a variety of epithelial and hematological malignancies. In salivary gland tumor pathology, however, the *ETV6-NTRK3* translocation is specific for mammary analogue secretory carcinoma (MASC), and has not been documented in any other salivary tumor type. The present study comprised a clinical and molecular analysis of 25 cases morphologically and immunohistochemically typical of MASC. They all also displayed the *ETV6* rearrangement as visualized by fluorescent in situ hybridization but lacked the classical *ETV6-NTRK3* fusion transcript by standard reverse-transcriptase-polymerase chain reaction. In 4 cases, the classical fusion transcript was found by more sensitive, nested reverse-transcription-polymerase chain reaction. Five other cases harbored atypical fusion transcripts as detected by both standard and nested reverse-transcription-polymerase chain reaction. In addition, fluorescent in situ hybridization with an *NTRK3* break-apart probe was also performed; rearrangement of *NTRK3* gene was detected in 16 of 25 cases. In 3 other cases, the tissue was not analyzable, and in 2 further cases analysis could not be performed because of a lack of appropriate tissue material. Finally, in the 4 remaining cases whose profile was *NTRK3* split-negative and *ETV6* split-positive, unknown (non-*NTRK*) genes appeared to fuse with *ETV6* (*ETV6-X* fusion). In looking for possible fusion partners, analysis of rearrangement of other kinase genes known to fuse with *ETV6* was also performed, but without positive results. Although numbers were small, correlating the clinico-pathologic features of the 4 *ETV6-X* fusion tumors and 5 MASC cases with atypical fusion transcripts raises the possibility of that they may behave more aggressively.

Key Words: mammary analogue secretory carcinoma, MASC, *ETV6-NTRK3*, *ETV6-X* fusion transcript, clinicopathologic analysis

(*Am J Surg Pathol* 2016;40:3–13)

Mammary analogue secretory carcinoma (MASC) of salivary gland origin is a recently described tumor that harbors a characteristic balanced chromosomal translocation, t(12;15) (p13;q25) resulting in an *ETV6-NTRK3* fusion[1] identical to that in secretory carcinoma of the breast.[2] Histologically, MASC is composed of uniform cells with bland-looking vesicular nuclei and eosinophilic vacuolated cytoplasm, arranged in tubular, microcystic and solid growth patterns with abundant periodic acid-Schiff –positive secretions. MASC may histologically resemble zymogen granule-poor acinic cell carcinoma, low-grade cribriform cystadenocarcinoma, and adenocarcinoma not otherwise specified.[1] However, the diagnosis of MASC in most cases is not difficult based on histologic, immunohistochemical, and molecular features. Detection of *ETV6* by fluorescent in situ hybridization (FISH) is technically feasible and more than 150 cases of MASC have been published in the last 4 years since its original description in 2010.[1]

There have been several studies extending the description of the clinical, histologic, and immunohistochemical features of MASC[3–12] and the number of

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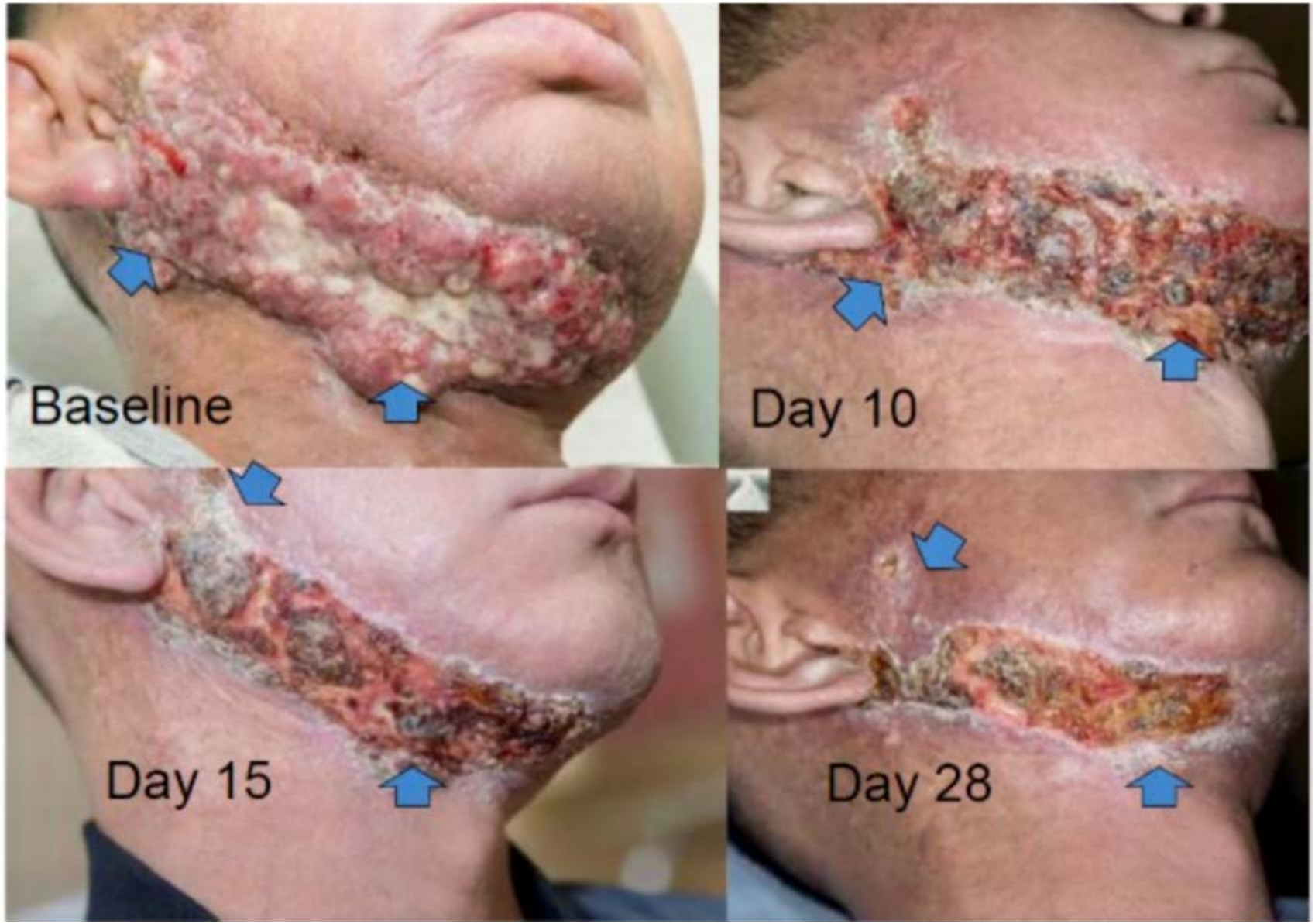
Americká farmaceutická firma uvede na trh lék, který vypíná spouštěč rakoviny v některých nádorech. Češi budou hledat vhodné pacienty

Simona Janíková - redaktorka 31. 10. 2017 00:00 (aktualizováno 08:19) Události

- **Vědci z plzeňské Bioptické laboratoře našli v jednom typu nádoru slinných žláz zmutovaný gen, který spouští rakovinu.**
- **Díky tomu se spojili s americkou společností Ignyta, která vyrábí léky pro cílenou onkologickou léčbu.**
- **Její medikament, který bude na trhu za dva roky, by měl léčit všechny nádory se stejným zmutovaným genem.**
- **Plzeňští vědci pro něj budou hledat pacienty v celé Evropě.**


Baseline
Day 10
Day 15
Day 28

Molecular Profiling of Mammary Analog Secretory Carcinoma Revealed a Subset of Tumors Harboring a Novel *ETV6-RET* Translocation

Report of 10 Cases

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Abstract: *ETV6* gene abnormalities are well described in tumor pathology. Many fusion partners of *ETV6* have been reported in a variety of epithelial, mesenchymal, and hematological malignancies. In salivary gland tumor pathology, however, the *ETV6-NTRK3* translocation is specific for (mammary analog) secretory carcinoma, and has not been documented in any other salivary tumor type. The present study comprised a clinical, histologic, and molecular analysis of 10 cases of secretory carcinoma, with typical morphology and immunoprofile harboring a novel *ETV6-RET* translocation.

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Key Words: salivary, mammary analog secretory carcinoma, MASC, *ETV6-NTRK3*, *ETV6-RET* fusion transcript

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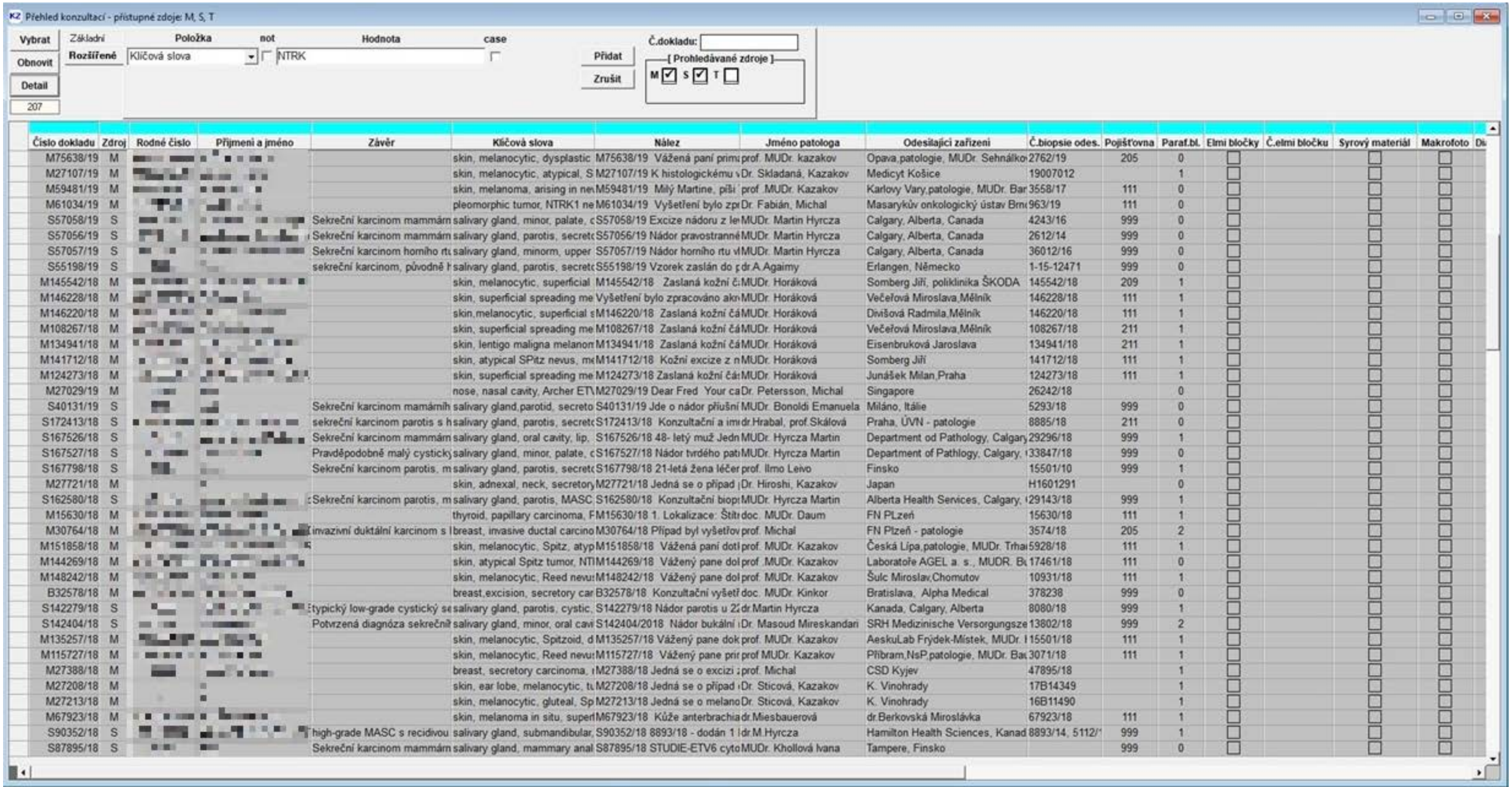
(Mammary analog) secretory carcinoma of salivary gland origin is a recently described tumor that harbors a characteristic balanced t(12;15)(p13;q25) chromosomal translocation resulting in an *ETV6-NTRK3* fusion[1] identical to that commonly found in secretory carcinoma (SC) of the breast.[2] The *ETV6-NTRK3* fusion gene encodes a chimeric tyrosine kinase with transforming activity in epithelial and myoepithelial cells in the mouse mammary gland.[3]

Over many years, Skalova et al[1] began to identify a distinctive, hitherto unrecognized neoplasm arising in the salivary glands characterized by morphologic and immunohistochemical features strongly reminiscent of those of SC of the breast. These salivary carcinomas are


Přehled konzultací - přístupné zdoje: M, S, T
Vybrat
Obnovit
Detail
207
Základní
Rozšířené
Položka
Klíčová slova
not
Hodnota
NTRK
case
Přidat
Zrušit
Č.dokladu:
[Prohledávané zdroje]
M S T
Číslo dokladu
Zdroj
Rodné číslo
Příjmení a jméno
Závěr
Klíčová slova
Nález
Jméno patologa
Odesílající zařízení
Č.biopsie odes.
Pojišťovna
Paraf.bl.
Elmi bločky
Č.elmi bločku
Syrový materiál
Makrofoto
M75638/19 M skin, melanocytic, dysplastic M75638/19 Vážená paní prim prof. MUDr. kazakov Opava,patologie, MUDr. Sehnálko 2762/19 205 0
M27107/19 M skin, melanocytic, atypical, S M27107/19 K histologickému v Dr. Skladaná, Kazakov Medicyt Košice 19007012 1
M59481/19 M skin, melanoma, arising in ne M59481/19 Milý Martine, píši prof .MUDr. Kazakov Karlovy Vary,patologie, MUDr. Bar 3558/17 111 0
M61034/19 M pleomorphic tumor, NTRK1 ne M61034/19 Vyšetření bylo zpr Dr. Fabián, Michal Masarykův onkologický ústav Brn 963/19 111 0
S57058/19 S Sekreční karcinom mammárn salivary gland, minor, palate, c S57058/19 Excize nádoru z le MUDr. Martin Hyrcza Calgary, Alberta, Canada 4243/16 999 0
S57056/19 S Sekreční karcinom mammárn salivary gland, parotis, secret S57056/19 Nádor pravostranné MUDr. Martin Hyrcza Calgary, Alberta, Canada 2612/14 999 0
S57057/19 S Sekreční karcinom horního rt salivary gland, minorm, upper S57057/19 Nádor horního rtu v MUDr. Martin Hyrcza Calgary, Alberta, Canada 36012/16 999 0
S55198/19 S sekreční karcinom, původně h salivary gland, parotis, secret S55198/19 Vzorek zaslán do p dr.A.Agaimy Erlangen, Německo 1-15-12471 999 0
M145542/18 M skin, melanocytic, superficial M145542/18 Zaslaná kožní č MUDr. Horáková Somberg Jiří, poliklinika ŠKODA 145542/18 209 1
M146228/18 M skin, superficial spreading me Vyšetření bylo zpracováno akn MUDr. Horáková Večeřová Miroslava,Mělník 146228/18 111 1
M146220/18 M skin,melanocytic, superficial s M146220/18 Zaslaná kožní čá MUDr. Horáková Divišová Radmila,Mělník 146220/18 111 1
M108267/18 M skin, superficial spreading me M108267/18 Zaslaná kožní čá MUDr. Horáková Večeřová Miroslava,Mělník 108267/18 211 1
M134941/18 M skin, lentigo maligna melanon M134941/18 Zaslaná kožní čá MUDr. Horáková Eisenbruková Jaroslava 134941/18 211 1
M141712/18 M skin, atypical SPitz nevus, m M141712/18 Kožní excize z n MUDr. Horáková Somberg Jiří 141712/18 111 1
M124273/18 M skin, superficial spreading me M124273/18 Zaslaná kožní čá MUDr. Horáková Junášek Milan,Praha 124273/18 111 1
M27029/19 M nose, nasal cavity, Archer ET M27029/19 Dear Fred Your ca Dr. Petersson, Michal Singapore 26242/18 0
S40131/19 S Sekreční karcinom mamárních salivary gland,parotid, secreto S40131/19 Jde o nádor příušní MUDr. Bonoldi Emanuela Miláno, Itálie 5293/18 999 0
S172413/18 S sekreční karcinom parotis s h salivary gland, parotis, secret S172413/18 Konzultační a im dr.Hrabal, prof.Skálová Praha, ÚVN - patologie 8885/18 211 0
S167526/18 S Sekreční karcinom mammárn salivary gland, oral cavity, lip, S167526/18 48- letý muž Jedn MUDr. Hyrcza Martin Department od Pathology, Calgary 29296/18 999 1
S167527/18 S Pravděpodobně malý cystický salivary gland, minor, palate, c S167527/18 Nádor tvrdého pat MUDr. Hyrcza Martin Department of Pathlogy, Calgary, 33847/18 999 0
S167798/18 S Sekreční karcinom parotis, m salivary gland, parotis, secret S167798/18 21-letá žena léčer prof. Ilmo Leivo Finsko 15501/10 999 1
M27721/18 M skin, adnexal, neck, secretory M27721/18 Jedná se o případ Dr. Hiroshi, Kazakov Japan H1601291 0
S162580/18 S Sekreční karcinom parotis, m salivary gland, parotis, MASC S162580/18 Konzultační biop MUDr. Hyrcza Martin Alberta Health Services, Calgary, 29143/18 999 1
M15630/18 M thyroid, papillary carcinoma, F M15630/18 1. Lokalizace: Štít doc. MUDr. Daum FN PLzeň 15630/18 111 1
M30764/18 M Invazivní duktální karcinom s I breast, invasive ductal carcino M30764/18 Případ byl vyšetřov prof. Michal FN Plzeň - patologie 3574/18 205 2
M151858/18 M skin, melanocytic, Spitz, atyp M151858/18 Vážená paní dot prof. MUDr. Kazakov Česká Lípa,patologie, MUDr. Trhal 5928/18 111 1
M144269/18 M skin, atypical Spitz tumor, NTI M144269/18 Vážený pane dol prof. MUDr. Kazakov Laboratoře AGEL a. s., MUDR. B 17461/18 111 0
M148242/18 M skin, melanocytic, Reed nevu M148242/18 Vážený pane dol prof. MUDr. Kazakov Šulc Miroslav,Chomutov 10931/18 111 1
B32578/18 M breast,excision, secretory car B32578/18 Konzultační vyšetř doc. MUDr. Kinkor Bratislava, Alpha Medical 378238 999 0
S142279/18 S Atypický low-grade cystický se salivary gland, parotis, cystic, S142279/18 Nádor parotis u 2 dr.Martin Hyrcza Kanada, Calgary, Alberta 8080/18 999 1
S142404/18 S Potvrzená diagnóza sekreční salivary gland, minor, oral cavi S142404/2018 Nádor bukální Dr. Masoud Mireskandari SRH Medizinische Versorgungsze 13802/18 999 2
M135257/18 M skin, melanocytic, Spitzoid, d M135257/18 Vážený pane dok prof. MUDr. Kazakov AeskuLab Frýdek-Místek, MUDr. I 15501/18 111 1
M115727/18 M skin, melanocytic, Reed nevu M115727/18 Vážený pane prir prof MUDr. Kazakov Příbram,NsP,patologie, MUDr. Ba 3071/18 111 1
M27388/18 M breast, secretory carcinoma, M27388/18 Jedná se o excizi prof. Michal CSD Kyjev 47895/18 1
M27208/18 M skin, ear lobe, melanocytic, t M27208/18 Jedná se o případ Dr. Sticová, Kazakov K. Vinohrady 17B14349 1
M27213/18 M skin, melanocytic, gluteal, Sp M27213/18 Jedná se o melano Dr. Sticová, Kazakov K. Vinohrady 16B11490 1
M67923/18 M skin, melanoma in situ, superf M67923/18 Kůže anterbrachia dr.Miesbauerová dr.Berkovská Miroslávka 67923/18 111 1
S90352/18 S high-grade MASC s recidivou salivary gland, submandibular, S90352/18 8893/18 - dodán 1 dr.M.Hyrcza Hamilton Health Sciences, Kanad 8893/14, 5112/ 999 1
S87895/18 S Sekreční karcinom mammárn salivary gland, mammary anal S87895/18 STUDIE-ETV6 cyto MUDr. Khollová Ivana Tampere, Finsko 999 0

- Nyní provádíme sekvenace až 60 nádorů týdně, tzn. 1-2 NGS „runy“ týdně

- *NTRK* translokace jsme diagnostikovali již celkem u 212 nádorů

TruSight170 a TruSight Oncology 500 - Illumina

ArcherDX platformy

ArcherDX platformy
FusionPlex® Sarcoma
FusionPlex® Solid Tumor
VariantPlex® Solid Tumor
FusionPlex® CTL
FusionPlex ® Myeloid
FusionPlex ® Lympoma

Table 1: Gene Content in the TruSight Tumor 170 Assay

SNVs and Indels (from DNA)									
AKT1	*BRIP1*	*CREBBP*	*FANCI*	*FGFR2*	*JAK3*	*MSH3*	*PALB2*	*RAD51D*	*TSC1*
AKT2	*BTK*	*CSF1R*	*FANCL*	*FGFR3*	*KDR*	*MSH6*	*PDGFRA*	*RAD54L*	*TSC2*
AKT3	*CARD11*	*CTNNB1*	*FBXW7*	*FGFR4*	*KIT*	*MTOR*	*PDGFRB*	*RB1*	*VHL*
ALK	*CCND1*	*DDR2*	*FGF1*	*FLT1*	*KMT2A (MLL)*	*MUTYH*	*PIK3CA*	*RET*	*XRCC2*
APC	*CCND2*	*DNMT3A*	*FGF2*	*FLT3*	*KRAS*	*MYC*	*PIK3CB*	*RICTOR*	
AR	*CCNE1*	*EGFR*	*FGF3*	*FOXL2*	*MAP2K1*	*MYCL1*	*PIK3CD*	*ROS1*	
ARID1A	*CD79A*	*EP300*	*FGF4*	*GEN1*	*MAP2K2*	*MYCN*	*PIK3CG*	*RPS6KB1*	
ATM	*CD79B*	*ERBB2*	*FGF5*	*GNA11*	*MCL1*	*MYD88*	*PIK3R1*	*SLX4*	
ATR	*CDH1*	*ERBB3*	*FGF6*	*GNAQ*	*MDM2*	*NBN*	*PMS2*	*SMAD4*	
BAP1	*CDK12*	*ERBB4*	*FGF7*	*GNAS*	*MDM4*	*NF1*	*PPP2R2A*	*SMARCB1*	
BARD1	*CDK4*	*ERCC1*	*FGF8*	*HNF1A*	*MET*	*NOTCH1*	*PTCH1*	*SMO*	
BCL2	*CDK6*	*ERCC2*	*FGF9*	*HRAS*	*MLH1*	*NOTCH2*	*PTEN*	*SRC*	
BCL6	*CDKN2A*	*ERG*	*FGF10*	*IDH1*	*MLLT3*	*NOTCH3*	*PTPN11*	*STK11*	
BRAF	*CEBPA*	*ESR1*	*FGF14*	*IDH2*	*MPL*	*NPM1*	*RAD51*	*TERT*	
BRCA1	*CHEK1*	*EZH2*	*FGF23*	*INPP4B*	*MRE11A*	*NRAS*	*RAD51B*	*TET2*	
BRCA2	*CHEK2*	*FAM175A*	*FGFR1*	*JAK2*	*MSH2*	*NRG1*	*RAD51C*	*TP53*	
Amplifications (from DNA)									
AKT2	*BRCA2*	*CHEK1*	*ERCC2*	*FGF5*	*FGF14*	*FGFR4*	*MDM4*	*NRG1*	*RAF1*
ALK	*CCND1*	*CHEK2*	*ESR1*	*FGF6*	*FGF19*	*JAK2*	*MET*	*PDGFRA*	*RET*
AR	*CCND3*	*EGFR*	*FGF1*	*FGF7*	*FGF23*	*KIT*	*MYC*	*PDGFRB*	*RICTOR*
ATM	*CCNE1*	*ERBB2*	*FGF2*	*FGF8*	*FGFR1*	*KRAS*	*MYCL1*	*PIK3CA*	*RPS6KB1*
BRAF	*CDK4*	*ERBB3*	*FGF3*	*FGF9*	*FGFR2*	*LAMP1*	*MYCN*	*PIK3CB*	*TFRC*
BRCA1	*CDK6*	*ERCC1*	*FGF4*	*FGF10*	*FGFR3*	*MDM2*	*NRAS*	*PTEN*	
Fusions and Splice Variants (from RNA)									
ABL1	*BRAF*	*EML4*	*ETV4*	*FGFR4*	*KIF5B*	*MYC*	*NTRK2*	*PIK3CA*	*TMPRSS2*
AKT3	*BRCA1*	*ERBB2*	*ETV5*	*FLI1*	*KIT*	*NOTCH1*	*NTRK3*	*PPARG*	
ALK	*BRCA2*	*ERG*	*EWSR1*	*FLT1*	*KMT2A (MLL)*	*NOTCH2*	*PAX3*	*RAF1*	
AR	*CDK4*	*ESR1*	*FGFR1*	*FLT3*	*MET*	*NOTCH3*	*PAX7*	*RET*	
AXL	*CSF1R*	*ETS1*	*FGFR2*	*JAK2*	*MLLT3*	*NRG1*	*PDGFRA*	*ROS1*	
BCL2	*EGFR*	*ETV1*	*FGFR3*	*KDR*	*MSH2*	*NTRK1*	*PDGFRB*	*RPS6KB1*	

Table 3: Genes included in the TruSight Oncology 500 panel

DNA content										
ABL1	*BRD4*	*CUX1*	*FAM175A*	*GATA6*	*IGF1*	*MAP3K13*	*NOTCH4*	*POLE*	*RPTOR*	*TAF1*
ABL2	*BRIP1*	*CXCR4*	*FAM46C*	*GEN1*	*IGF1R*	*MAP3K14*	*NPM1*	*PPARG*	*RUNX1*	*TBX3*
ACVR1	*BTG1*	*CYLD*	*FANCA*	*GID4*	*IGF2*	*MAP3K4*	*NRAS*	*PPM1D*	*RUNX1T1*	*TCEB1*
ACVR1B	*BTK*	*DAXX*	*FANCC*	*GLI1*	*IKBKE*	*MAPK1*	*NRG1*	*PPP2R1A*	*RYBP*	*TCF3*
AKT1	*C11orf30*	*DCUN1D1*	*FANCD2*	*GNA11*	*IKZF1*	*MAPK3*	*NSD1*	*PPP2R2A*	*SDHA*	*TCF7L2*
AKT2	*CALR*	*DDR2*	*FANCE*	*GNA13*	*IL10*	*MAX*	*NTRK1*	*PPP6C*	*SDHAF2*	*TERC*
AKT3	*CARD11*	*DDX41*	*FANCF*	*GNAQ*	*IL7R*	*MCL1*	*NTRK2*	*PRDM1*	*SDHB*	*TERT*
ALK	*CASP8*	*DHX15*	*FANCG*	*GNAS*	*INHA*	*MDC1*	*NTRK3*	*PREX2*	*SDHC*	*TET1*
ALOX12B	*CBFB*	*DICER1*	*FANCI*	*GPR124*	*INHBA*	*MDM2*	*NUP93*	*PRKAR1A*	*SDHD*	*TET2*
ANKRD11	*CBL*	*DIS3*	*FANCL*	*GPS2*	*INPP4A*	*MDM4*	*NUTM1*	*PRKCI*	*SETBP1*	*TFE3*
ANKRD26	*CCND1*	*DNAJB1*	*FAS*	*GREM1*	*INPP4B*	*MED12*	*PAK1*	*PRKDC*	*SETD2*	*TFRC*
APC	*CCND2*	*DNMT1*	*FAT1*	*GRIN2A*	*INSR*	*MEF2B*	*PAK3*	*PRSS8*	*SF3B1*	*TGFBR1*
AR	*CCND3*	*DNMT3A*	*FBXW7*	*GRM3*	*IRF2*	*MEN1*	*PAK7*	*PTCH1*	*SH2B3*	*TGFBR2*
ARAF	*CCNE1*	*DNMT3B*	*FGF1*	*GSK3B*	*IRF4*	*MET*	*PALB2*	*PTEN*	*SH2D1A*	*TMEM127*
ARFRP1	*CD274*	*DOT1L*	*FGF10*	*H3F3A*	*IRS1*	*MGA*	*PARK2*	*PTPN11*	*SHQ1*	*TMPRSS2*
ARID1A	*CD276*	*E2F3*	*FGF14*	*H3F3B*	*IRS2*	*MITF*	*PARP1*	*PTPRD*	*SLIT2*	*TNFAIP3*
ARID1B	*CD74*	*EED*	*FGF19*	*H3F3C*	*JAK1*	*MLH1*	*PAX3*	*PTPRS*	*SLX4*	*TNFRSF14*
ARID2	*CD79A*	*EGFL7*	*FGF2*	*HGF*	*JAK2*	*MLL*	*PAX5*	*PTPRT*	*SMAD2*	*TOP1*
ARID5B	*CD79B*	*EGFR*	*FGF23*	*HIST1H1C*	*JAK3*	*MLLT3*	*PAX7*	*QKI*	*SMAD3*	*TOP2A*
ASXL1	*CDC73*	*EIF1AX*	*FGF3*	*HIST1H2BD*	*JUN*	*MPL*	*PAX8*	*RAB35*	*SMAD4*	*TP53*
ASXL2	*CDH1*	*EIF4A2*	*FGF4*	*HIST1H3A*	*KAT6A*	*MRE11A*	*PBRM1*	*RAC1*	*SMARCA4*	*TP63*
ATM	*CDK12*	*EIF4E*	*FGF5*	*HIST1H3B*	*KDM5A*	*MSH2*	*PDCD1*	*RAD21*	*SMARCB1*	*TRAF2*
ATR	*CDK4*	*EML4*	*FGF6*	*HIST1H3C*	*KDM5C*	*MSH3*	*PDCD1LG2*	*RAD50*	*SMARCD1*	*TRAF7*
ATRX	*CDK6*	*EP300*	*FGF7*	*HIST1H3D*	*KDM6A*	*MSH6*	*PDGFRA*	*RAD51*	*SMC1A*	*TSC1*
AURKA	*CDK8*	*EPCAM*	*FGF8*	*HIST1H3E*	*KDR*	*MST1*	*PDGFRB*	*RAD51B*	*SMC3*	*TSC2*
AURKB	*CDKN1A*	*EPHA3*	*FGF9*	*HIST1H3F*	*KEAP1*	*MST1R*	*PDK1*	*RAD51C*	*SMO*	*TSHR*
AXIN1	*CDKN1B*	*EPHA5*	*FGFR1*	*HIST1H3G*	*KEL*	*MTOR*	*PDPK1*	*RAD51D*	*SNCAIP*	*U2AF1*
AXIN2	*CDKN2A*	*EPHA7*	*FGFR2*	*HIST1H3H*	*KIF5B*	*MUTYH*	*PGR*	*RAD52*	*SOCS1*	*VEGFA*
AXL	*CDKN2B*	*EPHB1*	*FGFR3*	*HIST1H3I*	*KIT*	*MYB*	*PHF6*	*RAD54L*	*SOX10*	*VHL*
B2M	*CDKN2C*	*ERBB2*	*FGFR4*	*HIST1H3J*	*KLF4*	*MYC*	*PHOX2B*	*RAF1*	*SOX17*	*VTCN1*
BAP1	*CEBPA*	*ERBB3*	*FH*	*HIST2H3A*	*KLHL6*	*MYCL1*	*PIK3C2B*	*RANBP2*	*SOX2*	*WISP3*
BARD1	*CENPA*	*ERBB4*	*FLCN*	*HIST2H3C*	*KMT2B*	*MYCN*	*PIK3C2G*	*RARA*	*SOX9*	*WT1*
BBC3	*CHD2*	*ERCC1*	*FLI1*	*HIST2H3D*	*KMT2C*	*MYD88*	*PIK3C3*	*RASA1*	*SPEN*	*XIAP*
BCL10	*CHD4*	*ERCC2*	*FLT1*	*HIST3H3*	*KMT2D*	*MYOD1*	*PIK3CA*	*RB1*	*SPOP*	*XPO1*
BCL2	*CHEK1*	*ERCC3*	*FLT3*	*HLA-A*	*KRAS*	*NAB2*	*PIK3CB*	*RBM10*	*SPTA1*	*XRCC2*
BCL2L1	*CHEK2*	*ERCC4*	*FLT4*	*HLA-B*	*LAMP1*	*NBN*	*PIK3CD*	*RECQL4*	*SRC*	*YAP1*
BCL2L11	*CIC*	*ERCC5*	*FOXA1*	*HLA-C*	*LATS1*	*NCOA3*	*PIK3CG*	*REL*	*SRSF2*	*YES1*
BCL2L2	*CREBBP*	*ERG*	*FOXL2*	*HNF1A*	*LATS2*	*NCOR1*	*PIK3R1*	*RET*	*STAG1*	*ZBTB2*
BCL6	*CRKL*	*ERRFI1*	*FOXO1*	*HNRNPK*	*LMO1*	*NEGR1*	*PIK3R2*	*RFWD2*	*STAG2*	*ZBTB7A*
BCOR	*CRLF2*	*ESR1*	*FOXP1*	*HOXB13*	*LRP1B*	*NF1*	*PIK3R3*	*RHEB*	*STAT3*	*ZFHX3*
BCORL1	*CSF1R*	*ETS1*	*FRS2*	*HRAS*	*LYN*	*NF2*	*PIM1*	*RHOA*	*STAT4*	*ZNF217*
BCR	*CSF3R*	*ETV1*	*FUBP1*	*HSD3B1*	*LZTR1*	*NFE2L2*	*PLCG2*	*RICTOR*	*STAT5A*	*ZNF703*
BIRC3	*CSNK1A1*	*ETV4*	*FYN*	*HSP90AA1*	*MAGI2*	*NFKBIA*	*PLK2*	*RIT1*	*STAT5B*	*ZRSR2*
BLM	*CTCF*	*ETV5*	*GABRA6*	*ICOSLG*	*MALT1*	*NKX2-1*	*PMAIP1*	*RNF43*	*STK11*	
BMPR1A	*CTLA4*	*ETV6*	*GATA1*	*ID3*	*MAP2K1*	*NKX3-1*	*PMS1*	*ROS1*	*STK40*	
BRAF	*CTNNA1*	*EWSR1*	*GATA2*	*IDH1*	*MAP2K2*	*NOTCH1*	*PMS2*	*RPS6KA4*	*SUFU*	
BRCA1	*CTNNB1*	*EZH2*	*GATA3*	*IDH2*	*MAP2K4*	*NOTCH2*	*PNRC1*	*RPS6KB1*	*SUZ12*	
BRCA2	*CUL3*	*FAM123B*	*GATA4*	*IFNGR1*	*MAP3K1*	*NOTCH3*	*POLD1*	*RPS6KB2*	*SYK*	
RNA content*										
ABL1	*BCL2*	*CSF1R*	*ESR1*	*EWSR1*	*FLI1*	*KIF5B*	*MSH2*	*NRG1*	*PAX7*	*RAF1*
AKT3	*BRAF*	*EGFR*	*ETS1*	*FGFR1*	*FLT1*	*KIT*	*MYC*	*NTRK1*	*PDGFRA*	*RET*
ALK	*BRCA1*	*EML4*	*ETV1*	*FGFR2*	*FLT3*	*MET*	*NOTCH1*	*NTRK2*	*PDGFRB*	*ROS1*
AR	*BRCA2*	*ERBB2*	*ETV4*	*FGFR3*	*JAK2*	*MLL*	*NOTCH2*	*NTRK3*	*PIK3CA*	*RPS6KB1*
AXL	*CDK4*	*ERG*	*ETV5*	*FGFR4*	*KDR*	*MLLT3*	*NOTCH3*	*PAX3*	*PPARG*	*TMPRSS2*

* The products to evaluate DNA and RNA variants consist of the TruSight Oncology 500 DNA panel and the TruSight Tumor 170 RNA panel.

Od konce roku 2015 jsme provedli NGS sekvenaci cca 10.000 nádorů pro tyto účely:

- Diagnostická NGS sekvenace
- Celerity Biosciences
- Ignyta
- Bayer
- Tkáňová banka
- Soukromé laboratoře v západní Evropě
- Naše publikační projekty

Odpovědět Odpovědět všem Předat dál

pá 16. 8. 2019 23:12

prof. Michal Michal

FW: Entretinib approved -- Biopticka played a huge role

Komu

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Zpráva byla předána dál dne 16. 8. 2019 23:14.

From: Steve Potts [mailto:spotts@celeritybio.com]
Sent: Friday, August 16, 2019 5:06 AM
To: prof. Michal Michal <Michal@medima.cz>
Subject: Entretinib approved -- Biopticka played a huge role

Hi Michal,
Entrectinib got approved -- for both TRK and ROS1 and for adult and pediatric! First time in history for a pan tumor approval for two biomarkers at once, and one hitting both adult and pediatric is even better. We could never have done it without you. This is particularly good for patients, as with two drug choices it will drive prices down.

Please tell Alena and the whole team at Biopticka that Ignyta could never have done this without Biopticka pathology. Roche probably won't tell you this, but we all appreciate you guys!

Ignyta and Biopticka wrote some history together!

Steve

Entrectinib byl schválen…na ROS1 i na NTRK. Poprvé v historii pan tumor inhibitor…..
…….prosím řekni Aleně a celému Vašemu týmu, že bez Vás by to Ignyta nikdy nedokázala. Roche Vám to asi nikdy neřekne ale my jsme si Vás velice cenili.

Ignyta a Bioptická laboratoř psali historii společně.
Steve

Nové genové fúze v nádorech slinných žláz (NGS)

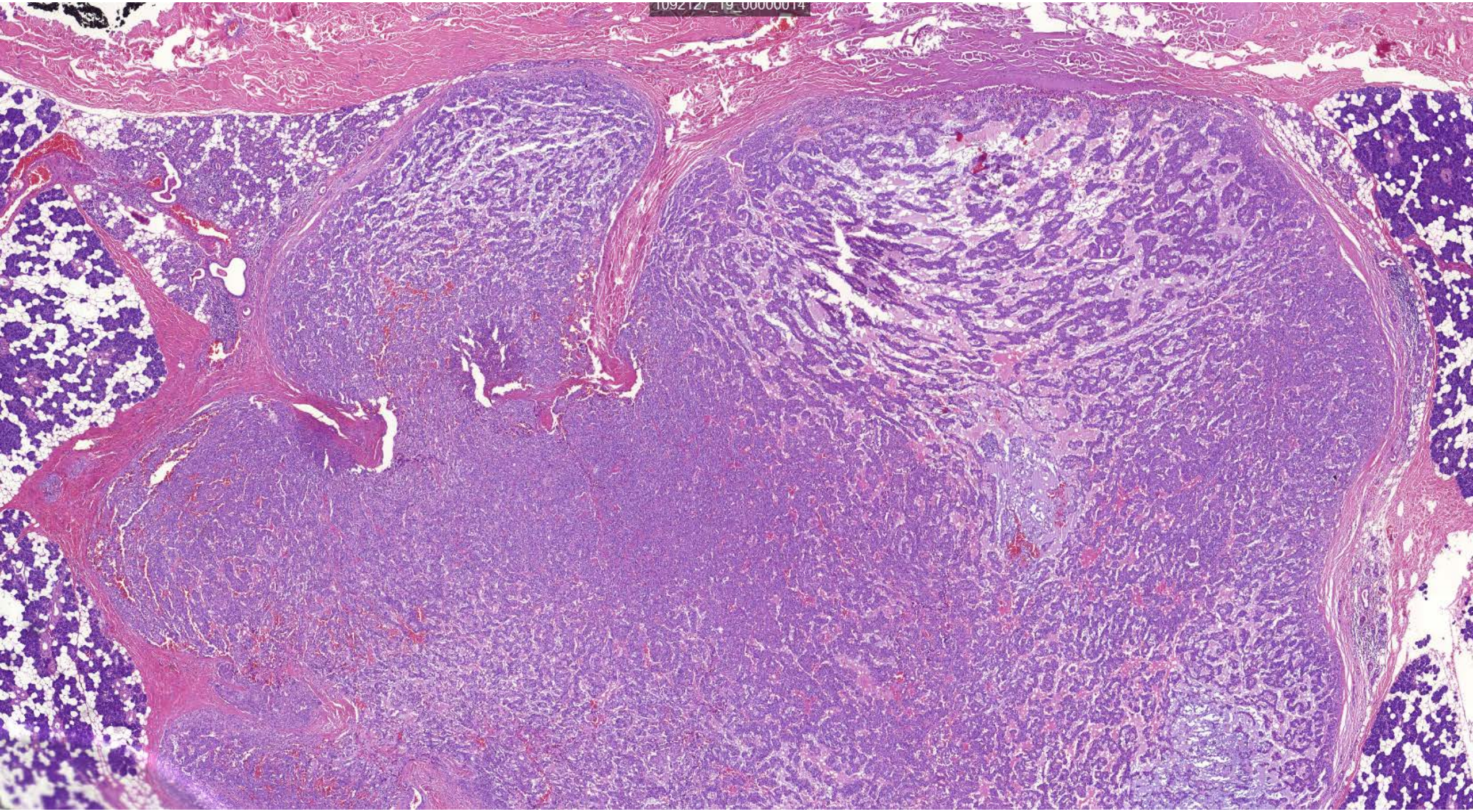
Age/sex	Diagnosis	Site	Gene fusion by NGS	FISH or RT-PCR
67/F	MyoCC	PA	*FUS-GIPR*	FISH
56/F	MASC	PA	*VIM-RET*	RT-PCR
57/F	OnkocytárníME	PA	*NTF3-PLAG1*	RT-PCR
57/F	Apokrinní Epi-MyoCC	PA	*HMGA2-FLJ41278*	FISH

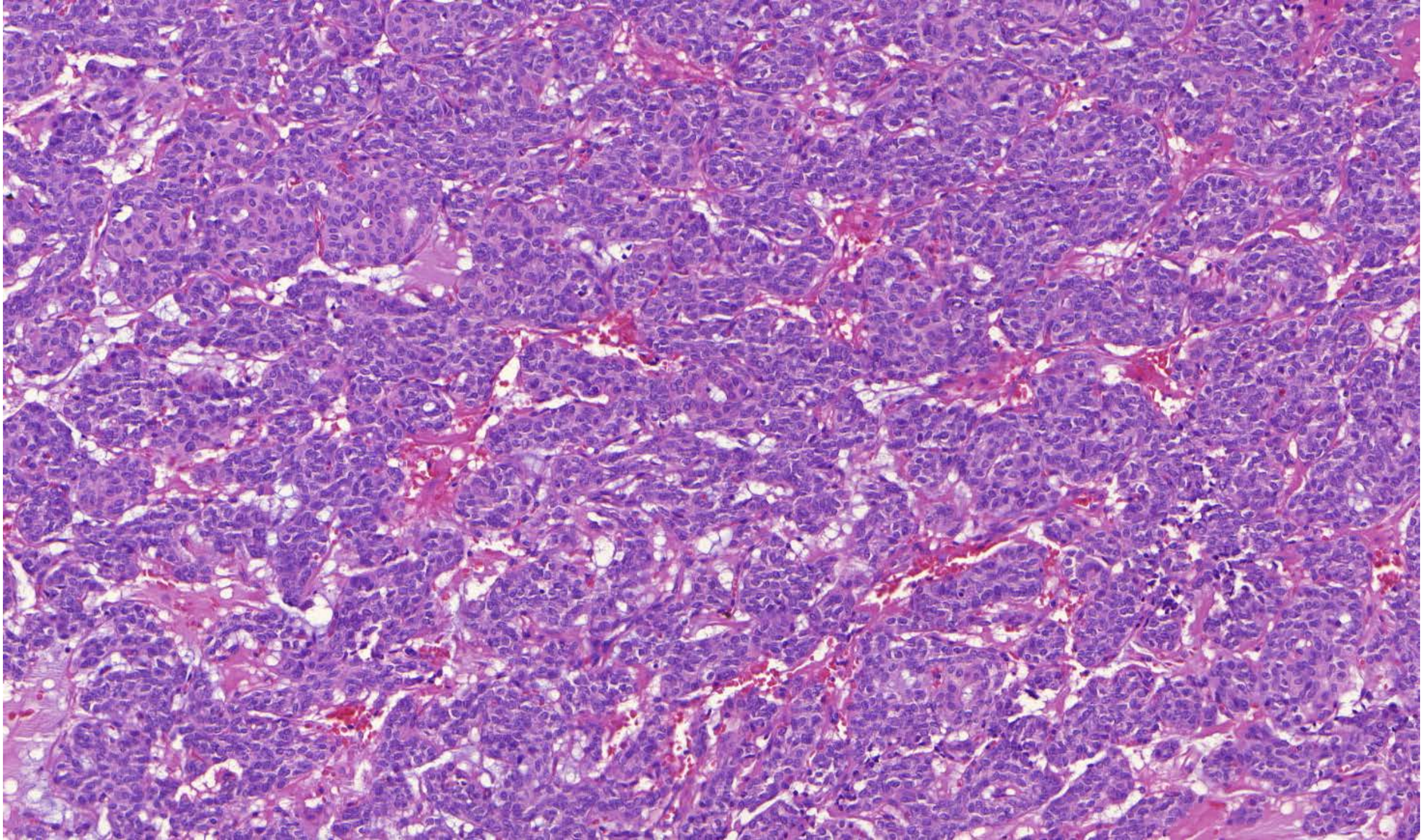
MyoCC- myoepiteliální karcinom
EMyoCC- epi-myoepiteliální karcinom
ME- myoepiteliom

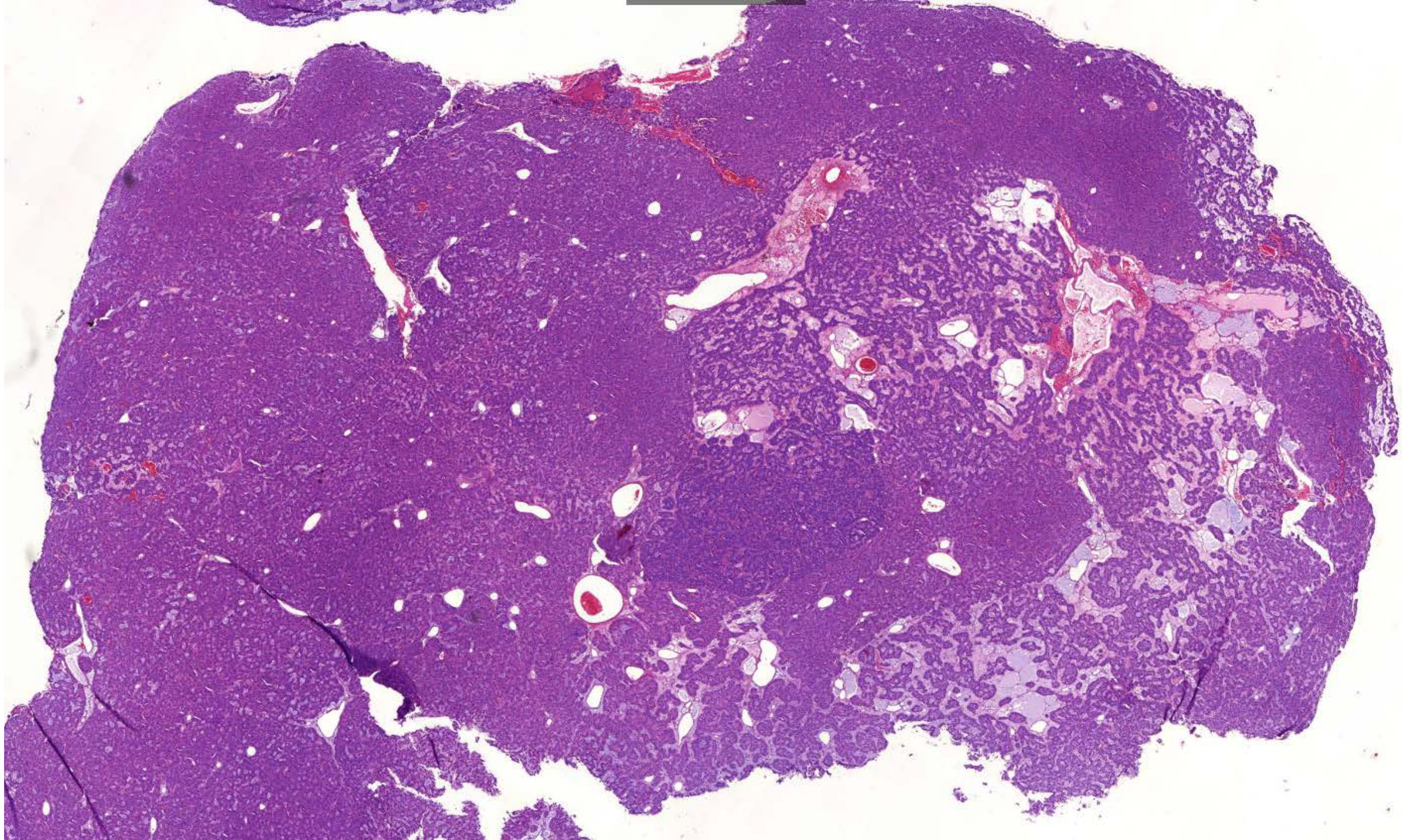
Nové fúze v nádorech slinných žláz

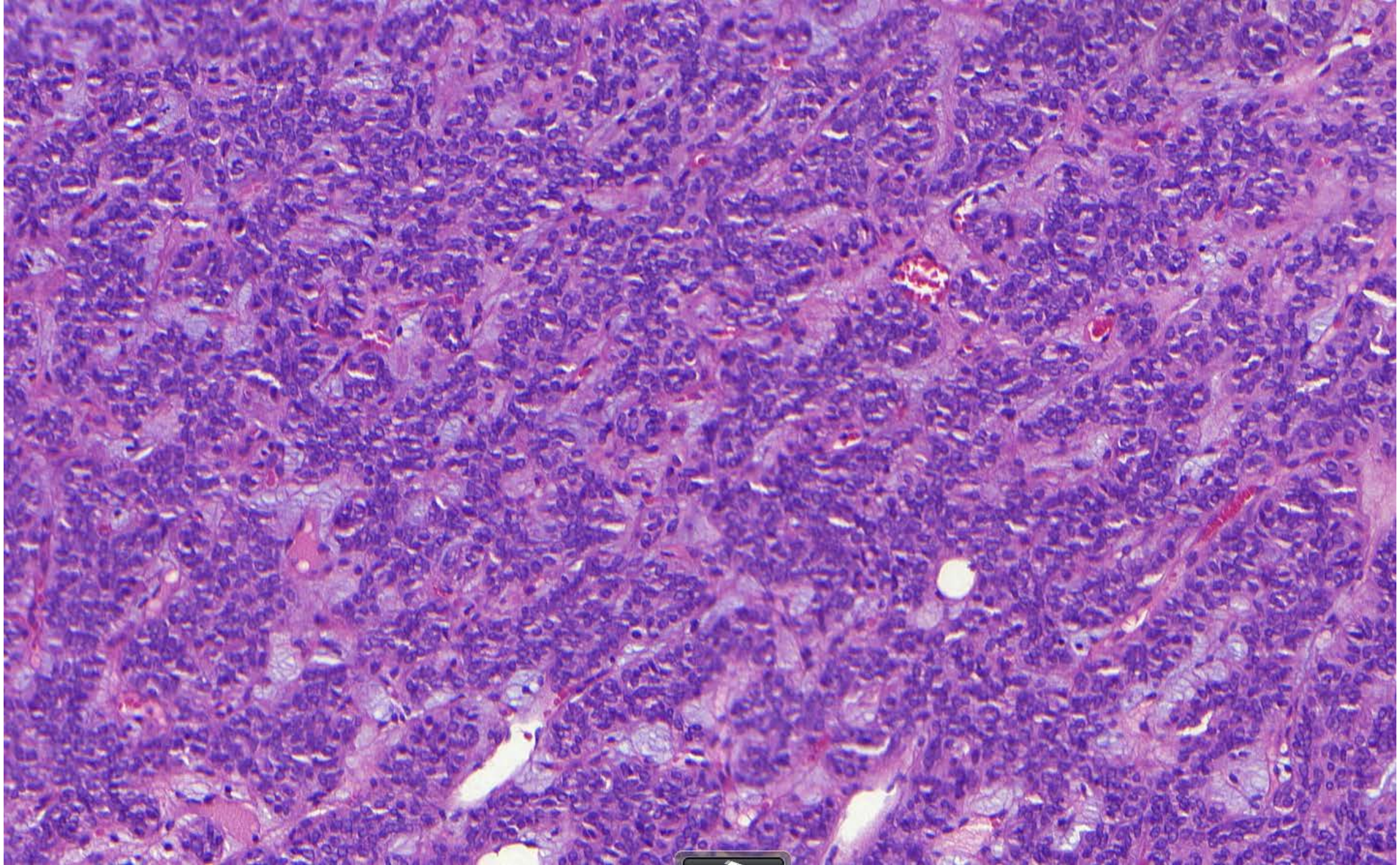
- Nové, dosud nepopsané fúze byly zjištěny v 4 salivárních nádorech
  - *FUS-GIPR* –low grade MyoCC
  - *VIM-RET* –MASC
  - *NTF3-PLAG1* - benigní onkocytický adenom myoepiteliom/LG myopiteliální karcinom
  - *HMGA2-FLJ41278* - apokrinní varianta EMyoCC

Low-grade karcinom slinných žláz s lobulární úpravou a s CDK4-NTRK1 translokací









STRN-NTRK3-rearranged mesenchymal tumor of the uterus expanding the morphologic spectrum of tumors with NTRK fusions

Michal M, Hájková V, Skálová A, Michal M

American Journal of Surgical Pathology 2019; Aug;43(8):1152-1154

5. vydání WHO klasifikace nádorů měkkých tkání

Vliv genetických metod (masivně paralelní sekvenování-next generation sequencing, NGS) na diagnostiku a léčení nádorů měkkých tkání

EWSR1-SMAD3–rearranged Fibroblastic Tumor

An Emerging Entity in an Increasingly More Complex Group of Fibroblastic/Myofibroblastic Neoplasms

Michael Michal, MD,†‡ Ryan S. Berry, MD,§ Brian P. Rubin, MD,§ Scott E. Kilpatrick, MD,§ Abbas Agaimy, MD,‖ Dmitry V. Kazakov, MD,*‡ Petr Steiner, MD,*‡ Nikola Ptakova, MSc,*‡ Petr Martinek, PhD,*‡ Ladislav Hadravsky, PhD,¶ Kvetoslava Michalova, PhD,*‡ Zoltan Szep, PhD,# and Michal Michal, MD*‡*

Abstract: Three cases of superficial acral fibroblastic spindle cell neoplasms with *EWSR1-SMAD3* fusion have been recently reported. Their differential diagnosis is broad, primarily comprising rare tumors from the fibroblastic/myofibroblastic category. The aim of this report is to present 4 new cases of this entity and to discuss the appropriate differential diagnosis. Also, as the ERG antibody seems to be a characteristic marker for these tumors, we analyzed ERG immunostaining characteristics in potential mimics of this entity. All cases in our cohort occurred in women aged 5 to 68 years (mean, 36.5 y). Two were located on the hand, 1 on foot, and the last case arose on the calf. The tumor size ranged from 1 to 1.5 cm in the greatest dimension, with a mean size of 1.2 cm. Except for one recent case, follow-up was available, ranging from 7 to 18 years (mean, 11.7 y), with a recurrence noted in 1 case after 10 years. All tumors were subcutaneous and showed 2 main components. One consisted of bland, spindled cells with elongated nuclei which were round when observed on the cross-section. These cells mostly grew in relatively hypercellular, well-organized, and intersecting fascicles. The second component was prominently hyalinized and paucicellular, but lacked calcifications. Both components showed either a distinct zonation pattern, or they were randomly intermingled with each other. In all 3 analyzable tumors, next-each case. By fluorescence in situ hybridization, one tested case also revealed unbalanced rearrangement of the *EWSR1* gene. All 4 cases showed strong, diffuse nuclear expression of ERG, whereas none of the mimics stained with this antibody except for weak to moderate staining in calcifying aponeurotic fibromas (9/10 cases). Two tumors showed focal weak to moderate expression of SAT-B2. The 4 herein presented cases further broaden the clinicopathologic spectrum of tumors with *EWSR1-SMAD3* gene fusion. They also confirm that they represent a novel entity for which we propose the name *EWSR1-SMAD3*–rearranged fibroblastic Tumor. Our study also proves that in the context of fibroblastic/myofibroblastic tumors, ERG immunohistochemistry is a relatively specific marker for these neoplasms.

Key Words: soft tissues, acral fibroblastic spindle cell neoplasm, *EWSR1-SMAD3*–rearranged fibroblastic tumor, ERG, lipofibromatosis, lipofibromatosis-like neural tumor, myofibroma, fibromatosis, calcifying aponeurotic fibroma

(*Am J Surg Pathol* 2018;42:1325–1333)

Although several new entities have been defined or redefined during the last few decades, still there are

EWSR1-SMAD3 translokovaný fibroblastický tumor

PRRX-NCOA1/2 fibroblastický tumor

Kulatobuněčné sarkomy s CIC-DUX4 translokací

Sarkom s

EWSR1-NFATc2

translokací

Sarkom s internal tandem duplikací BCOR genu

Sarkom s BCOR-MAML3 rearanží

Sarkom s ZC3H7B-BCOR rearanží

Cellular Myofibroma/Myopericytoma s SRF-RELA translokací

Original contribution

Fibro-osseous Pseudotumor of digits and myositis Ossificans show consistent *COL1A1-USP6* rearrangement: a Clinicopathological and genetic study of 27 cases ☆

Marián Švajdler MD PhD [a, b], Michael Michal MD PhD [a, b, c], Petr Martínek PhD [b], Nikola Ptáková [b], Zdeněk Kinkor MD PhD [a, b], Peter Szépe MD CSc [d], Peter Švajdler MD [e], Roman Mezencev PhD [f], Michal Michal MD [a, b]

Nová klasifikace rabdomyosarkomů

Rabdomyosarkomy s kulatobuněčným fenotypem
Embryonální RBMS
Alveolární RBMS
Rabdomyosarkomy s vřetenobuněčným fenotypem
RBMS s VGLL2/NCOA2/MEIS1/SRF/TEAD1 fúzemi
RBMS s MYOD1 mutací
RBMS s TFCP2 fúzemi
Pleomorfní RBMS
Sarkom s EWSR1-PATZ1 fúzí
Mezenchymální chondrosarkom s myoidními diff
Sarkom s RBMS-like morfologií-DICER1 mutant

PRDM10-rearranged Soft Tissue Tumor

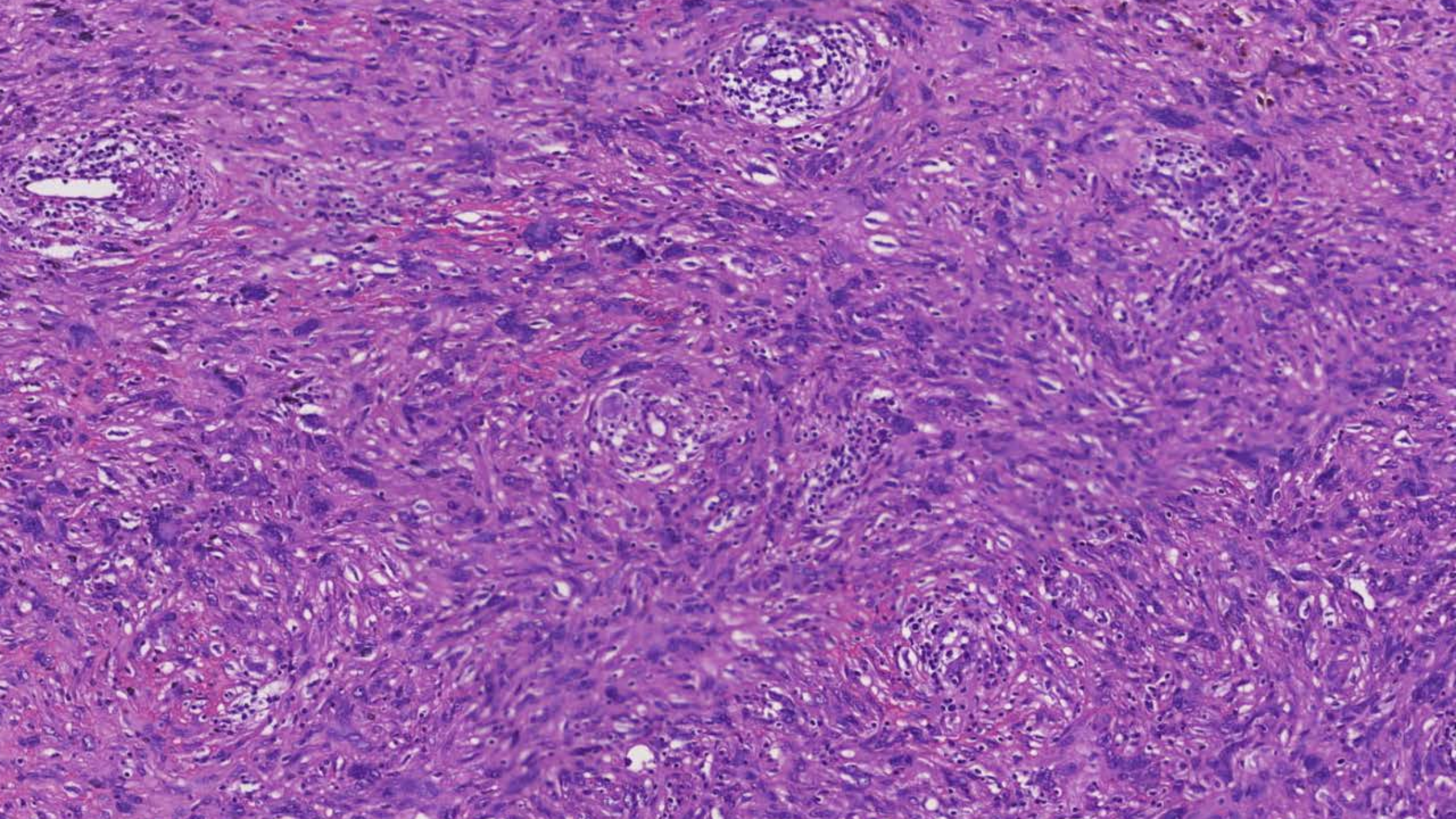
A Clinicopathologic Study of 9 Cases

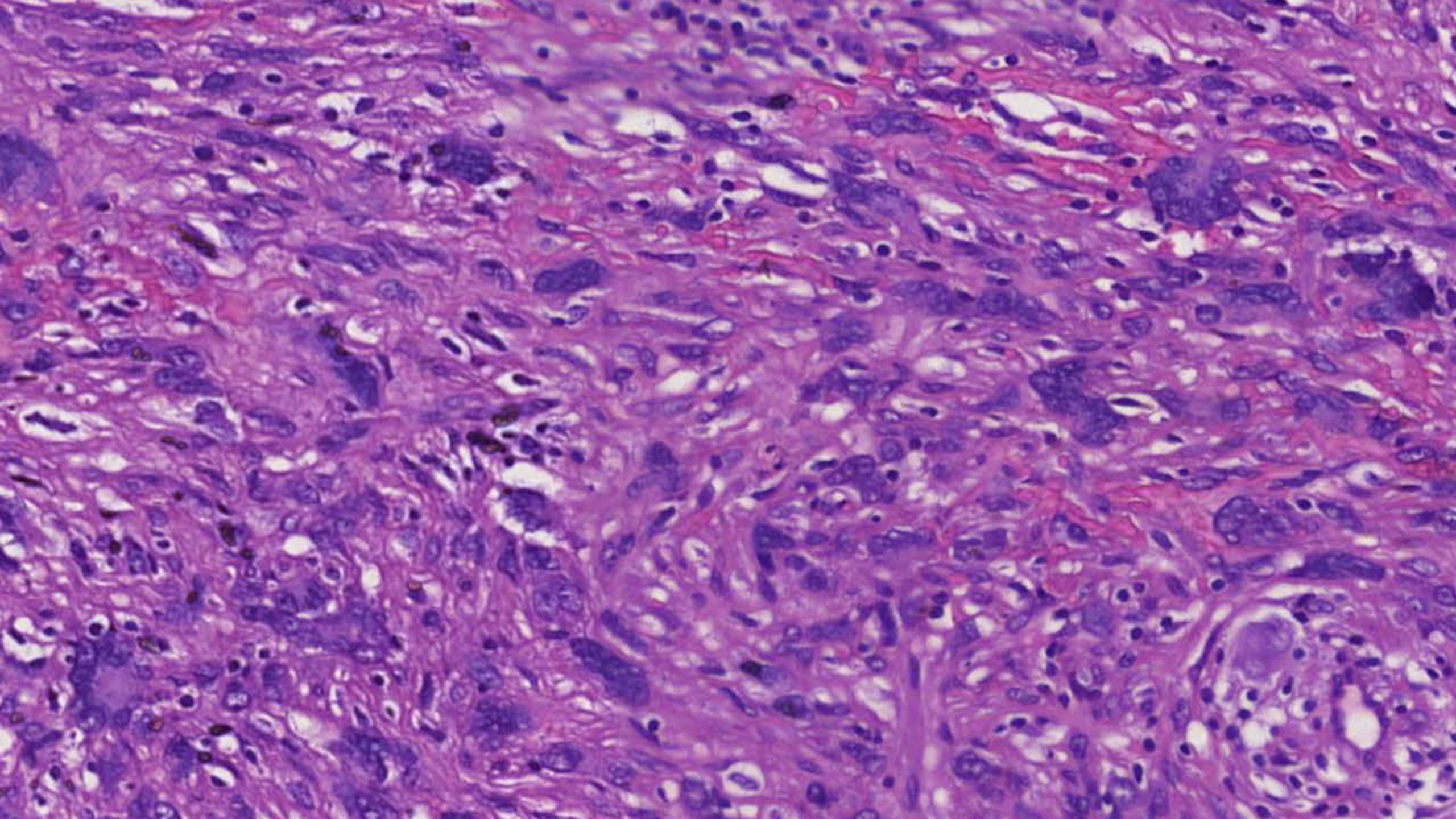
Florian Puls, MD, FRCPath, Nischalan Pillay, MB, ChB, FRCPath, PhD,†‡*
Henrik Fagman, MD, PhD, Anne Palin-Masreliez, BSc,* Fernanda Amary, MD, PhD,†*
Magnus Hansson, MD, PhD, Lars-Gunnar Kindblom, MD, PhD,**
Tom A. McCulloch, BM, BS, FRCP, FRCPath,§ George Meligonis, MBBCh, FCPath(SA),‖
*Ronald Muc, MBBCh, FRCPath,¶ Pehr Rissler, MD, PhD,# Vaiyapuri P. Sumathi, FRCPath,***
Roberto Tirabosco, MD,† Jakob Hofvander, MSc,†† Linda Magnusson, MSc,††
Jenny Nilsson, MSc,†† Adrienne M. Flanagan, MB, BCh, PhD, FRCPath,†‡
and Fredrik Mertens, MD, PhD#††

Abstract: Gene fusion transcripts containing *PRDM10* were recently identified in low-grade undifferentiated pleomorphic sarcomas (UPS). Here, we describe the morphologic and clinical features of 9 such tumors from 5 men and 4 women (age: 20 to 61 y). Three cases had previously been diagnosed as UPS, 3 as superficial CD34-positive fibroblastic tumor (SCD34FT), 2 as pleomorphic liposarcoma, and 1 as pleomorphic hyalinizing angiectatic tumor. The tumors were located in the superficial and deep soft tissues of the thigh/knee region (4 cases), shoulder (2 cases), foot, trunk, and perineum (1 case each) ranging in size from 1 to 6 cm. All showed poorly defined cellular fascicles of pleomorphic cells within a fibrous stroma with frequent myxoid change and a prominent inflammatory infiltrate. All displayed for cytokeratins was seen in 5/6 cases. PRDM10 immunoreactivity was evaluated in 50 soft tissue tumors that could mimic *PRDM10*-rearranged tumors, including 4 cases exhibiting histologic features within the spectrum of SCD34FT. Except for 2/6 pleomorphic liposarcomas and 1/4 myxofibrosarcomas, other tumors did not show nuclear positivity but displayed weak to moderate cytoplasmic immunoreactivity. In conclusion, *PRDM10*-rearranged soft tissue tumor is characterized by pleomorphic morphology and a low mitotic count. Its morphologic spectrum overlaps with SCD34FT. Clinical features of this small series suggest an indolent behavior, justifying its distinction from UPS and other sarcomas.

Key Words: *PRDM10*, sarcoma, superficial CD34-positive

MED12-PRMD10
CITED2-PRDM10





Lipofibromatosis

The American Journal of Surgical Pathology 24(11): 1491–1500, 2000

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Lippincott Williams & Wilkins Printed in U.S.A.

A Clinicopathologic Study of 45 Pediatric Soft Tissue Tumors With an Admixture of Adipose Tissue and Fibroblastic Elements, and a Proposal for Classification as Lipofibromatosis

John F. Fetsch, M.D., Markku Miettinen, M.D., William B. Laskin, M.D., Michal Michal, M.D., and Franz M. Enzinger, M.D.

The tumor described here as lipofibromatosis is a rare pediatric neoplasm that has been variously interpreted as a type of infantile or juvenile fibromatosis, a variant of fibrous hamartoma of infancy, and a fibrosing lipoblastoma. This report details the clinicopathologic features associated with 45 cases of this soft tissue entity. The study group consisted of 32 males, 12 females, and one person of unstated gender. The patients presented with a soft tissue mass (range, 1–7 cm) involving the hand (n = 18), arm (n = 8), leg (n = 7), foot (n = 6), trunk (n = 5), or head (n = 1). Eight tumors were evident at birth. The individuals ranged in age from 11 days to 12 years (median age, 1 yr) at the time of initial biopsy or resection. Microscopic examination revealed abundant adipose tissue with a spindled fibroblastic element that chiefly involved the septa of fat and skeletal muscle. The process generally did not cause extensive architectural effacement of fat as is common with conventional fibromatoses, and it did not have a primitive nodular fibromyxoid component as is characteristic of fibrous hamartoma of infancy. The fibroblastic element exhibited focal fascicular no reactivity was detected for desmin (D33 and D-ER-11 clones), keratins, or CD57. Follow-up data were available for 25 individuals (median follow-up period, 6 yrs 7 mos) with regrowth of the tumor or persistent disease documented in 17 (72%). The following events were more common in the group with recurrent or persistent disease: congenital onset, male sex, hand and foot location, incomplete excision, and mitotic activity in the fibroblastic element. Although it is likely this tumor comprises part of the spectrum of what has been referred to in the literature as infantile/juvenile fibromatosis, its clinicopathologic features and, in particular, its distinctive tendency to contain fat as an integral component, warrant separate classification as a "lipofibromatosis."

Key Words: Calcifying aponeurotic fibroma—Congenital fibromatosis—Fibrous hamartoma of infancy—Juvenile fibromatosis—Immunohistochemistry—Lipoblastoma(tosis)—Lipofibromatosis—Soft tissue neoplasms.

Am J Surg Pathol 24(11): 1491–1500, 2000.

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ARTICLE

Aberrant receptor tyrosine kinase signaling in lipofibromatosis: a clinicopathological and molecular genetic study of 20 cases

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Abstract

Lipofibromatosis is a rare pediatric soft tissue tumor with predilection for the hands and feet. Previously considered to represent "infantile fibromatosis", lipofibromatosis has distinctive morphological features, with mature adipose tissue, short fascicles of bland fibroblastic cells, and lipoblast-like cells. Very little is known about the genetic underpinnings of lipofibromatosis. Prompted by our finding of the *FN1-EGF* gene fusion, previously shown to be a characteristic feature of calcifying aponeurotic fibroma (CAF), in a morphologically typical case of lipofibromatosis that recurred showing features of CAF, we studied a cohort of 20 cases of lipofibromatosis for this and other genetic events. The cohort was composed of 14 males and 6 females (median age 3 years; range 1 month–14 years). All primary tumors showed classical lipofibromatosis morphology. Follow-up disclosed three local recurrences, two of which contained calcifying aponeurotic fibroma-like nodular calcifications in addition to areas of classic lipofibromatosis, and no metastases. By FISH and RNA sequencing, four cases were positive for *FN1-EGF* and one case each showed an *EGR1-GRIA1, TPR-ROS1, SPARC-PDGFRB, FN1-TGFA*, *EGFR-BRAF*, *VCL-RET*, or *HBEGF-RBM27* fusion. *FN1-EGF* was the only recurrent fusion, suggesting that some cases of "lipofibromatosis" may represent calcifying aponeurotic fibroma lacking hallmark calcifications. Several of the genes involved in fusions (*BRAF*, *EGFR*, *PDGFRB*, *RET*, and *ROS1*) encode receptor tyrosine kinases (RTK), or ligands to the RTK EGFR (EGF, HBEGF, TGFA), suggesting a shared deregulation of the PI3K–AKT–mTOR pathway in a large subset of lipofibromatosis cases.

Introduction

TPR-ROS1
VCL-RET
EGFR-BRAF
SPARC-PDGFRB
HBEGF-RBM27
FN1-EGF

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

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Abstract: The family of pediatric fibroblastic and myofibroblastic proliferations encompasses a wide spectrum of pathologic entities with overlapping morphologies and ill-defined genetic abnormalities. Among the superficial lesions, lipofibromatosis (LPF), composed of an admixture of adipose tissue and fibroblastic elements, in the past has been variously classified as infantile fibromatosis or fibrous hamartoma of infancy. In this regard, we have encountered a group of superficial soft tissue tumors occurring in children and young adults, with a notably infiltrative growth pattern reminiscent of LPF, variable cytologic atypia, and a distinct immunoprofile of S100 protein and CD34 reactivity, suggestive of neural differentiation. SOX10 and melanocytic markers were negative in all cases tested. In contrast, a control group of classic LPF displayed bland, monomorphic histology and lacked S100 protein immunor- positive only in *NTRK1*-rearranged S100-positive LPF-NT but negative in classic LPF. These results suggest that NTRK1 oncogenic activation through gene fusion defines a novel and distinct subset of soft tissue tumors resembling LPF, but displaying cytologic atypia and a neural immunophenotype, provisionally named LPF-like neural tumors.

Key Words: lipofibromatosis, neural, NTRK1, TPR, TPM3, LMNA

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

Pediatric fibroblastic/myofibroblastic mesenchymal neoplasms are a morphologically diverse group of often locally aggressive soft tissue tumors that encompass a

„Nová generace“ RET inhibitorů

NCOA4-RET and *TRIM27-RET* Are Characteristic Gene Fusions in Salivary Intraductal Carcinoma, Including Invasive and Metastatic Tumors

Is "Intraductal" Correct?

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Abstract: Intraductal carcinoma (IC) is the new WHO designation for tumors previously encompassed by "low-grade cribriform cystadenocarcinoma" and "low-grade salivary duct carcinoma." The relationship of IC to salivary duct carcinoma (SDC) is controversial, even though they are considered to be distinct entities. IC is a rare low-grade malignant salivary gland neoplasm with histopathological features reminiscent of atypical ductal hyperplasia or ductal carcinoma in situ of the breast, showing diffuse S100 protein and mammaglobin positivity, while it is partially defined genetically. Recently, *RET* rearrangements including *NCOA4-RET* and *TRIM27-RET* have been described in IC. Here, we genetically characterize the largest cohort of IC to date (33 cases) including 8 cases with focal or widespread invasive growth and 1 case with lymph node metastasis. Thirty-three cases of IC were analyzed by next-generation sequencing (NGS) using the FusionPlex Solid Tumor kit (ArcherDX). Identified gene fusions were confirmed using fluorescence in situ hybridization break-apart and fusion probes and an reverse transcription polymerase chain reaction designed specifically for the detected breakpoints. Ten cases of SDC were analyzed for comparison using NGS panels that detect mutations and fusion transcripts. NGS analysis detected an *NCOA4-RET* fusion transcript in 11 cases of intercalated duct-type IC joining exon 7 or 8 of *NCOA4* gene and exon 12 of the *RET* gene. Eight cases of IC had an invasive growth pattern, including one with widespread invasion and lymph node metastasis. Three invasive ICs harbored an *NCOA4-RET* fusion

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BRIEF REPORT

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

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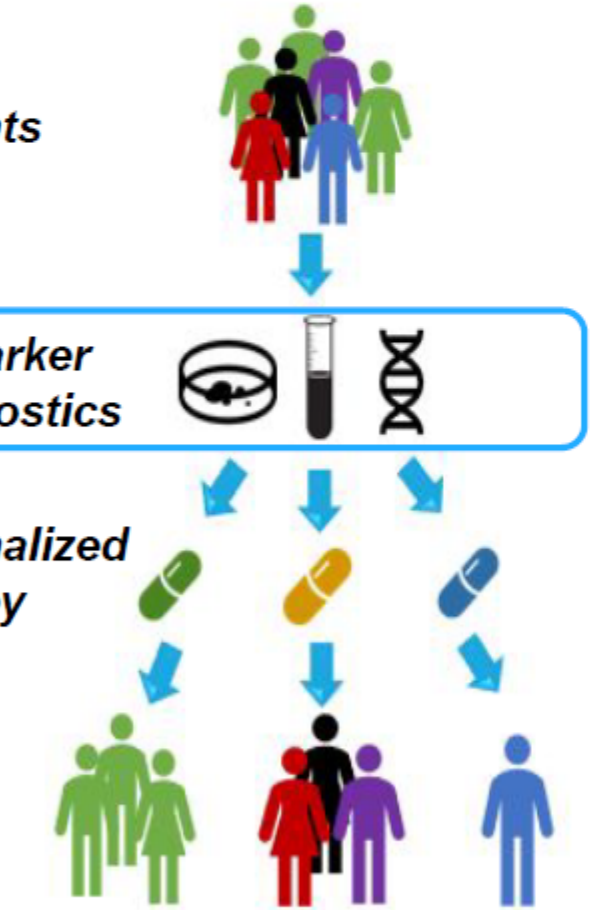
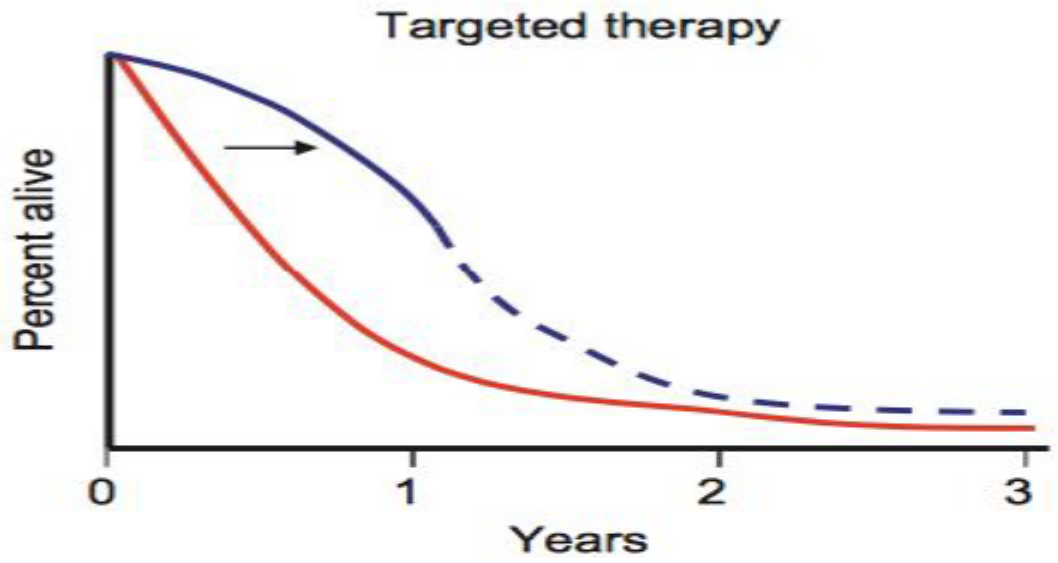
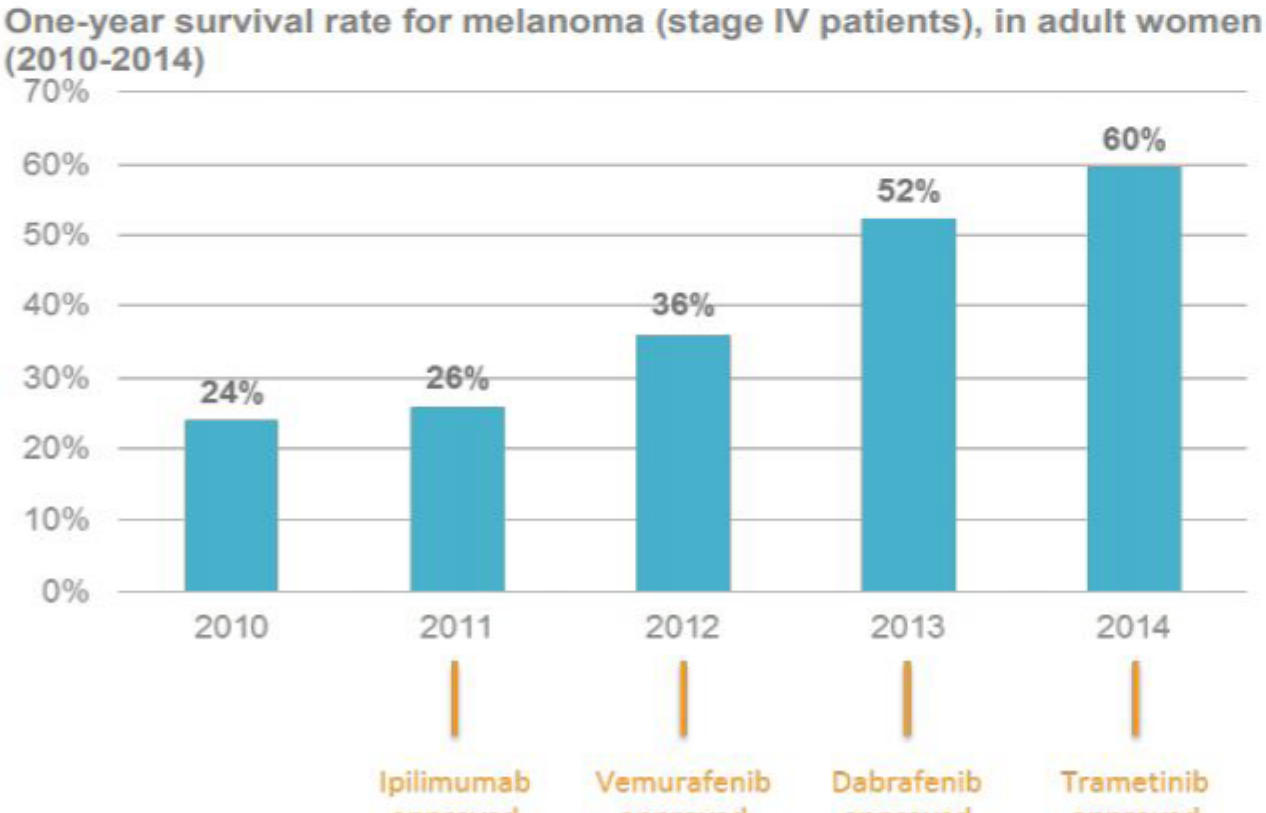
Abstract

We report a case of a 35-year old male patient with a tumor located in the deep dermis on his forearm. The lesion was completely excised but recurred 4 years later. The patient showed no signs of neurofibromatosis type 1. The morphology and immunophenotype of the tumor corresponded to the recently characterized group of soft tissue spindle cell lesions defined by a relatively uniform cytomorphology, patternless architecture, conspicuous stromal and perivascular hyalinization, S100 and CD34 coexpression and recurrent fusions involving *RAF1*, *BRAF*, and *NTRK1/2* genes. Using a 592-gene panel and massively parallel next-generation sequencing platform, we initially detected only *NF1* gene mutation in our case. However, further molecular







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Undifferentiated Sarcomas in Children Harbor Clinically Relevant Oncogenic Fusions and Gene Copy-Number Alterations: A Report from the Children's Oncology Group

Theodore W. Laetsch[1], Angshumoy Roy[2], Lin Xu[1], Jennifer O. Black[3], Cheryl M. Coffin[4], Yueh-Yun Chi[5], Jing Tian[5], Sheri L. Spunt[6], Douglas S. Hawkins[7], Julia A. Bridge[8], D. Williams Parsons[2], and Stephen X. Skapek[1]

Abstract

Purpose: A comprehensive analysis of the genomics of undifferentiated sarcomas (UDS) is lacking. We analyzed copy-number alterations and fusion status in patients with UDS prospectively treated on Children's Oncology Group protocol ARST0332.

Experimental Design: Copy-number alterations were assessed by OncoScan FFPE Express on 32 UDS. Whole-exome and transcriptome libraries from eight tumors with sufficient archived material were sequenced on HiSeq (2 × 100 bp). Targeted RNA-sequencing using Archer chemistry was performed on two additional cases.

Results: Five-year overall survival for patients with UDS was 83% (95% CI, 69%–97%) with risk-adapted therapy (surgery, chemotherapy, and radiotherapy). Both focal and arm-level occurred more often in clinically defined high-risk tumors. Tumors with both loss of 1p and gain of 1q carried an especially poor prognosis with a 5-year event-free survival of 20%. GISTIC analysis identified recurrent amplification of FGF1 on 5q31.3 ($q = 0.03$) and loss of *CDKN2A* and *CDKN2B* on 9p21.3 ($q = 0.07$). Known oncogenic fusions were identified in eight of 10 cases analyzed by next-generation sequencing.

Conclusions: Pediatric UDS generally has a good outcome with risk-adapted therapy. A high-risk subset of patients whose tumors have copy-number loss of 1p and gain of 1q was identified with only 20% survival. Oncogenic fusions are common in UDS, and next-generation sequencing should be considered for children with UDS to refine

Diagnostika pankreatobiliárních nádorů pomocí NGS a LBC-Cellient technologií

Pankreatobiliární NGS panel

		serous cystadenoma	IPMN	oncocytic-IPMN	ITPN	MCN	PDCa	Acinar cell Ca	Pancreatoblastoma	Solid pseudopapillary	WD-NET	NEC	extrahepatic BD carcinoma
2	***VHL (syndrome, +germline)***	50%											
3	**LOH 3p**	90%											
4	**LOH 10q**	50%											
5	***KRAS***		60-80%			50-70%	>90%						
6	***GNAS***		50-70%										
7	***RNF43***		50%										
8	***ZNRF3***		BD IPMN										
9	***TP53***		10-40% HG IPMN, 40-60% Ca			v.s. malignant							
10	***SMAD4, +LOH***		v.s. invasive				55%						
11	***NOTCH1***						only in malignant cysts						
12	***NOTCH2***												
13	***ARHGAP26***												
14	***ASXL1***												
15	***EPHA8***												
16	***ERBB4***												
17	***KMT2A (MLL1)***												
18	***KMT2B (MLL2)***												
19	***KMT2C (MLL3)***												
20	***KMT2D***												
21	***BAP1***												
22	***PIK3CA + CNV***												
23	***PIK3R3 + CNV***												
24	***PTEN***												
25	***FGFR2 fusion***												
26	***CDKN2A (p16), + prom methylation, LOH***												
27	***BRCA2 (*PARB inhibitors)***												
28	***BRCA1 (*PARB inhibitors)***												
29	***PALB2 (*PARB inhibitors)***												
30	***CHEK2***												
31	***RAD51***												
32	***KDM6A***												
33	***ARID1A***												
34	***PBRM1***												
35	***SMARCA4 (BRG1)***												

35	***SMARCA4 (BRG1)***													
36	***SMARCB1 (INI1)***													
37	***ATM*** *(*targetable platinum based Th)*													
38	***MYC amp, polysomy 8***													
39	***LOH 18q***													
40	***RASSF1 prom methylation***													
41	***APC, + prom methylation, LOH***							8%						
42	***CTNNB1***							7%						
43	***BRAF*** *(*targetable)*		only in HG IPMN					rare						
44	***BRAF (SND1-BRAF), RAF reaarangements*** *(*MEK inhibitors)*													
45	***ID3***													
46	***11p LOH***								>80%					
47	***MEN1*** *(syndrome, +germline)*										40%			
48	***DAXX***													
49	***ATRX***													
50	***TSC1***													
51	***TSC2***													
52	***HIF1A***													
53	***NF1*** *(syndrome, +germline)*													
54	***GCGR*** *(glucagonoma syndrome, +germline)*													
55	***MAFA*** *(syndrome, +germline)*													
56	***Rb1***													
57	***SETD2***													
58	***HRAS***													
59	***RET***													
60	***NRAS***													
61	***FBXW7***													
62	***ARID1B***													
63	***ELF3***													
64	**PRKACA/PRKACB fusion**													
65	***EGFR*** *(*targetable),* **+CNV?**													
66	***FOXL2***													
67	***IDH1*** *(*targetable)*													
68	***IDH2*** *(*targetable)*													

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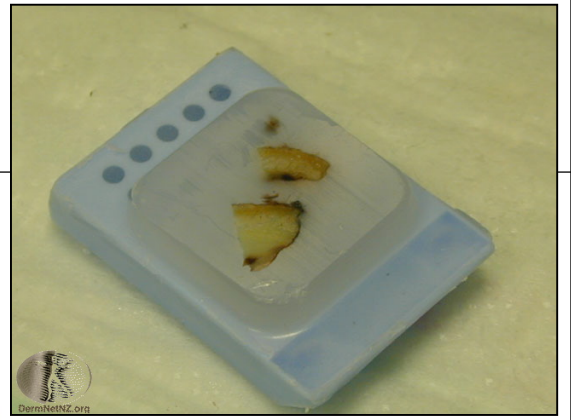

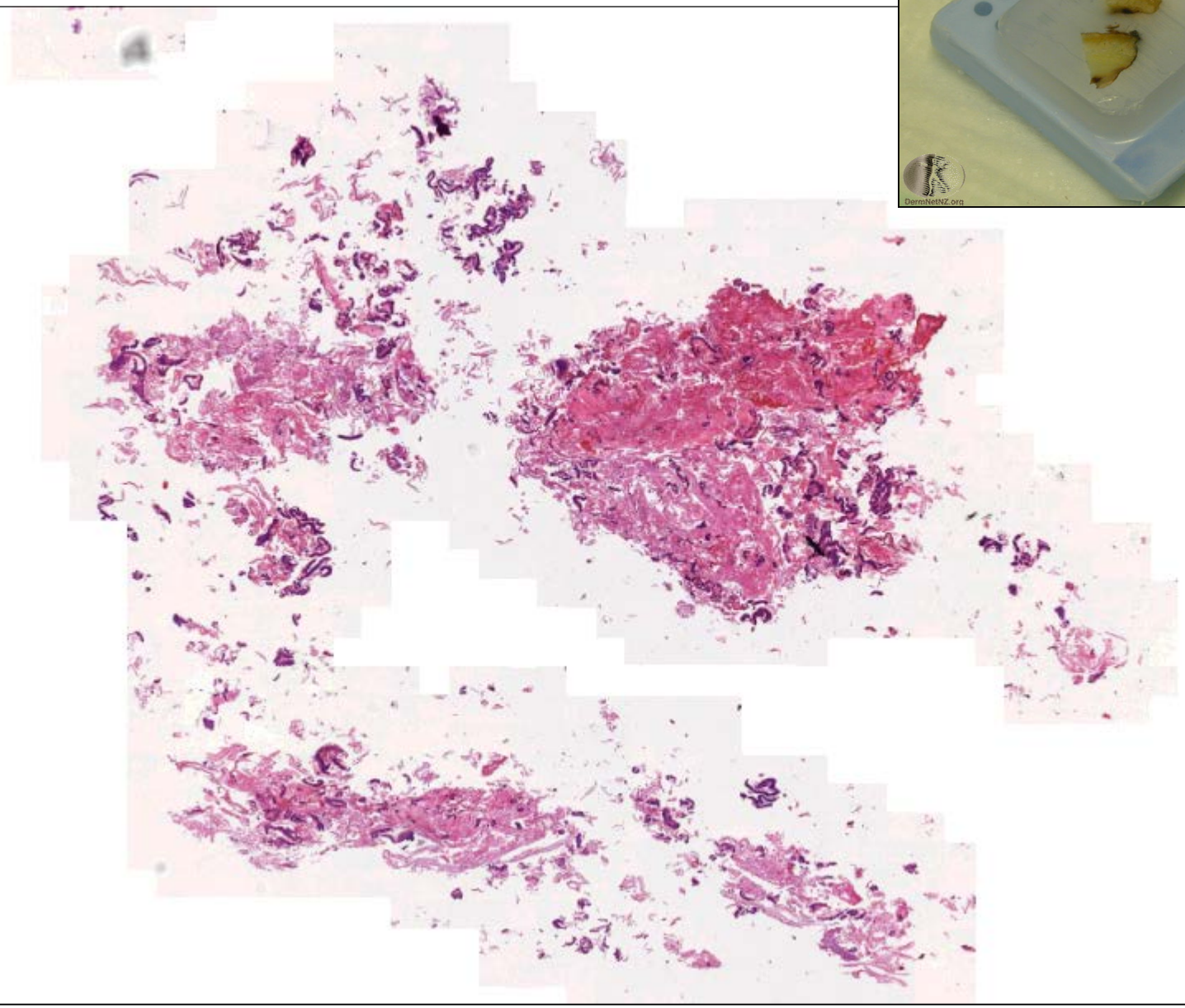

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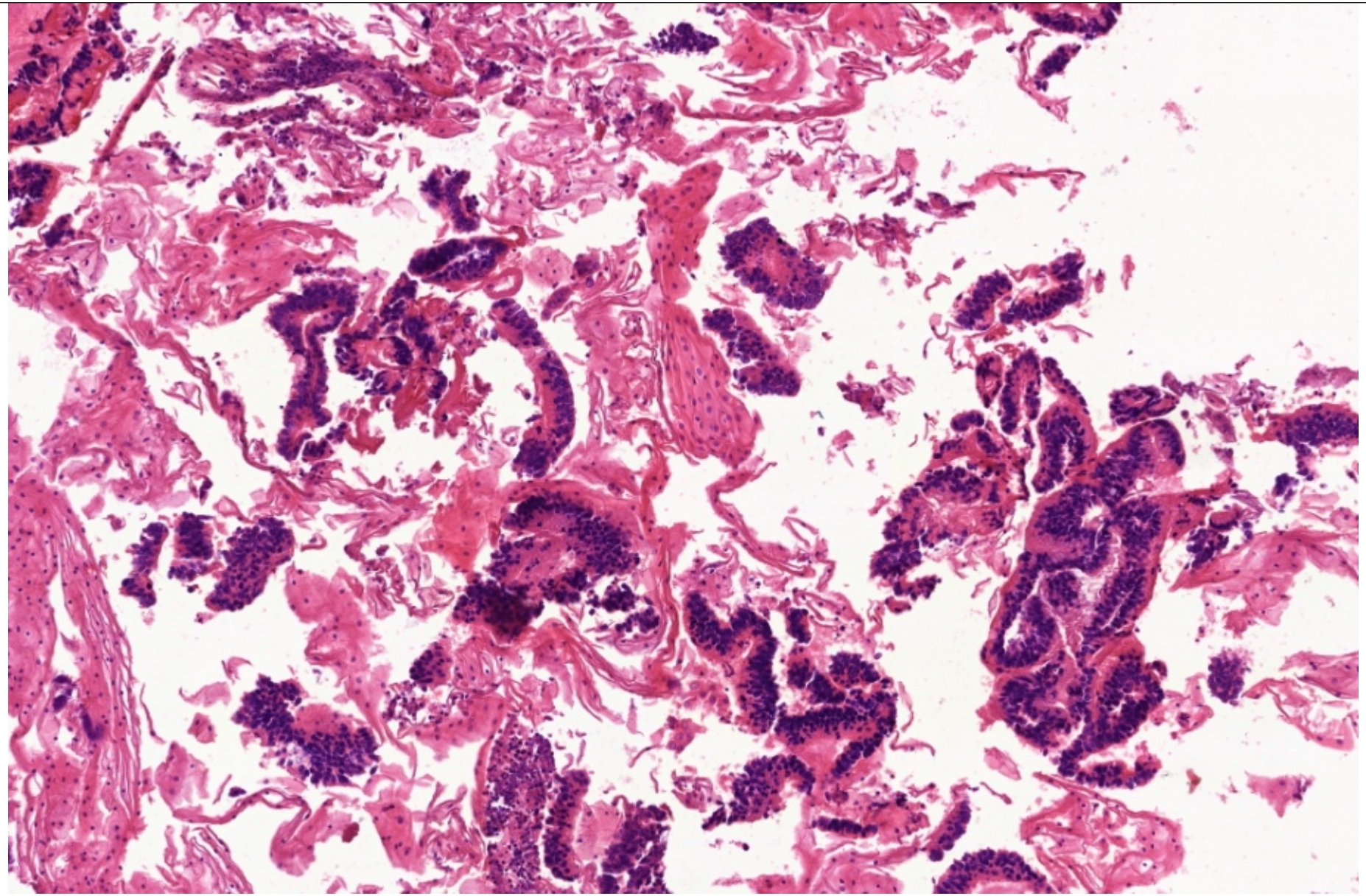

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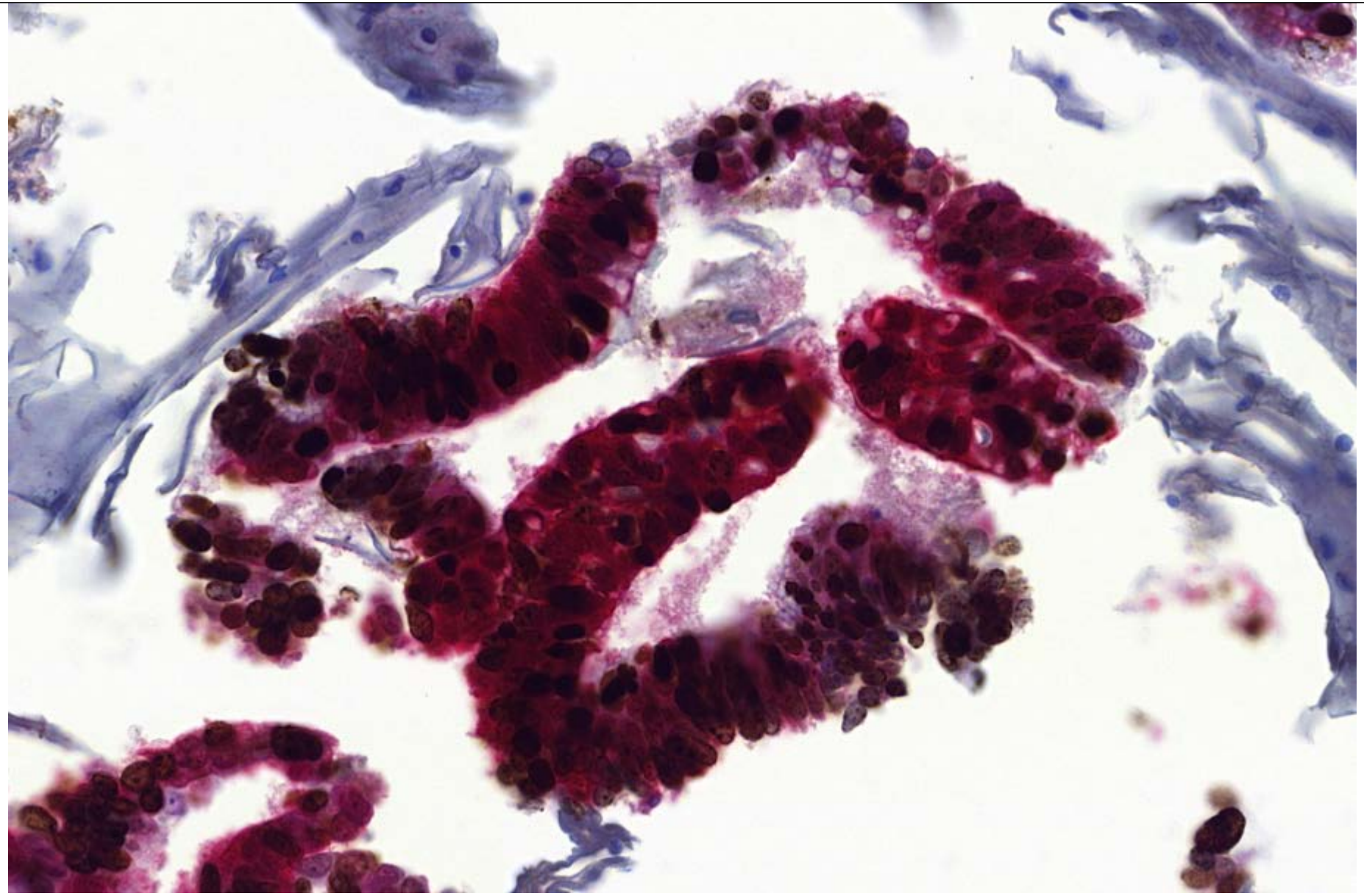

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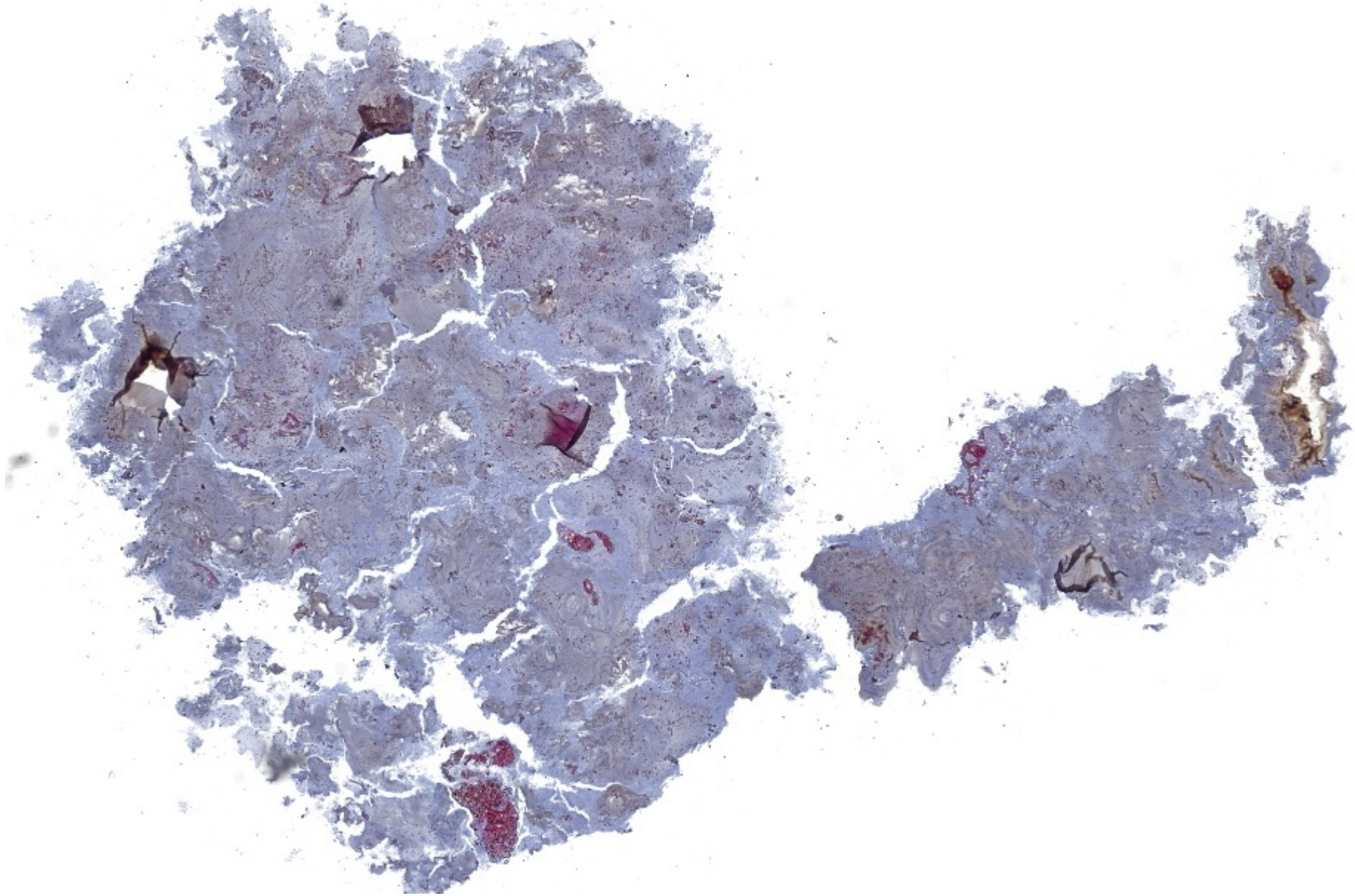

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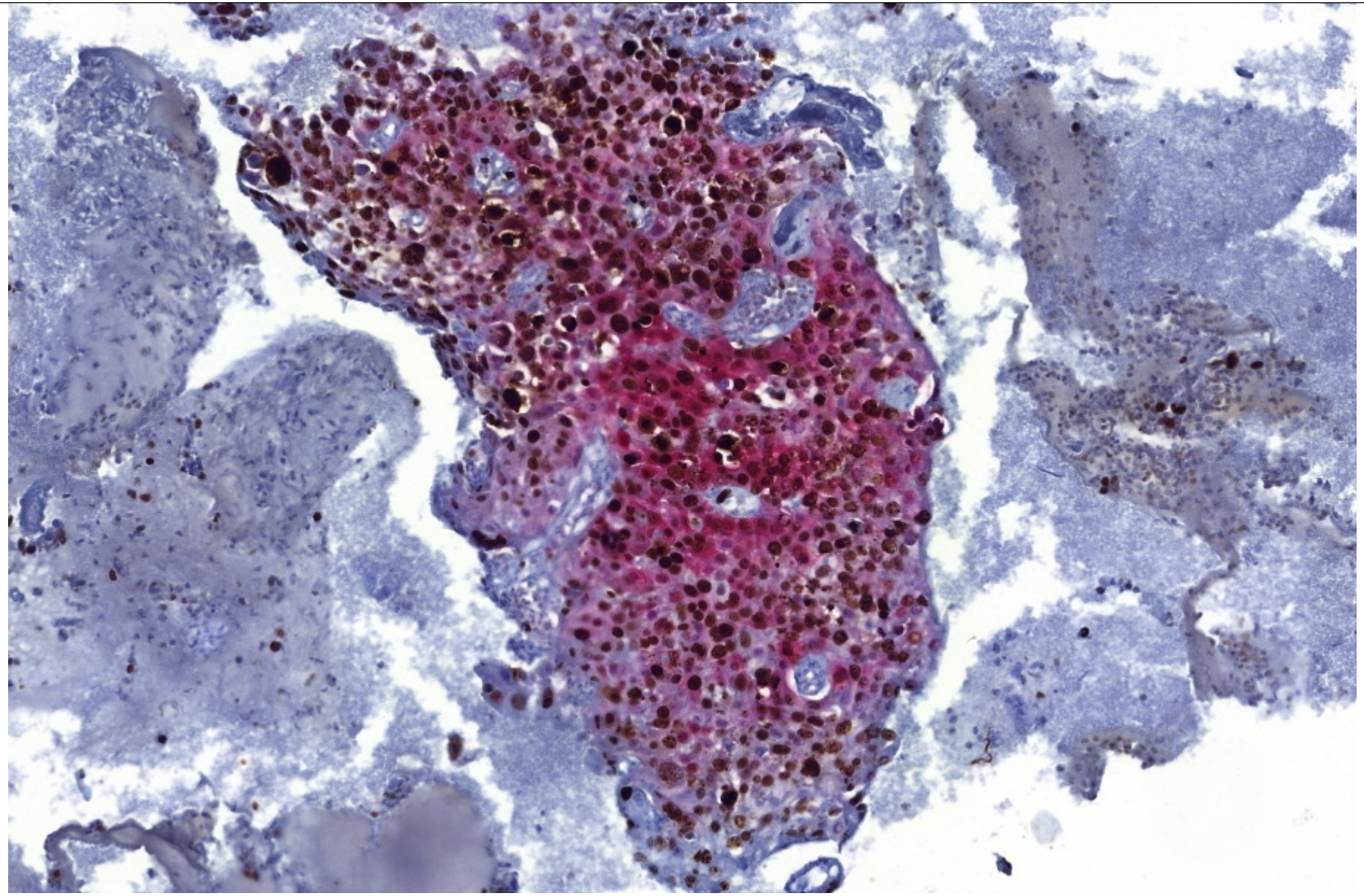

TABLE 3. Syndrome-associated Pancreatic Neuroendocrine Neoplasms

Syndrome	Inheritance	Gene Location	Gene	Incidence of Pancreatic Tumor (%)
Multiple endocrine neoplasia type 1	Autosomal dominant	11q13	*MEN1*	40-80
von Hippel-Lindau	Autosomal dominant	3p25	*VHL*	10-17
Neurofibromatosis type 1	Autosomal dominant	17q11.2	*NF1*	< 10
Tuberous sclerosis	Autosomal dominant	9q34 16p13.3	*TSC1* *TSC2*	Rare
Glucagon cell hyperplasia and neoplasia	Autosomal recessive	17q25.3	*GCGR*	Rare