Bioptická laboratoř
CYTOLOGIE | BIOPSIE | MOLEKULÁRNÍ GENETIKA

PLZEŇ ŠIKLŮV ÚSTAV PATOLOGIE

Mesenchymální nádory GIT

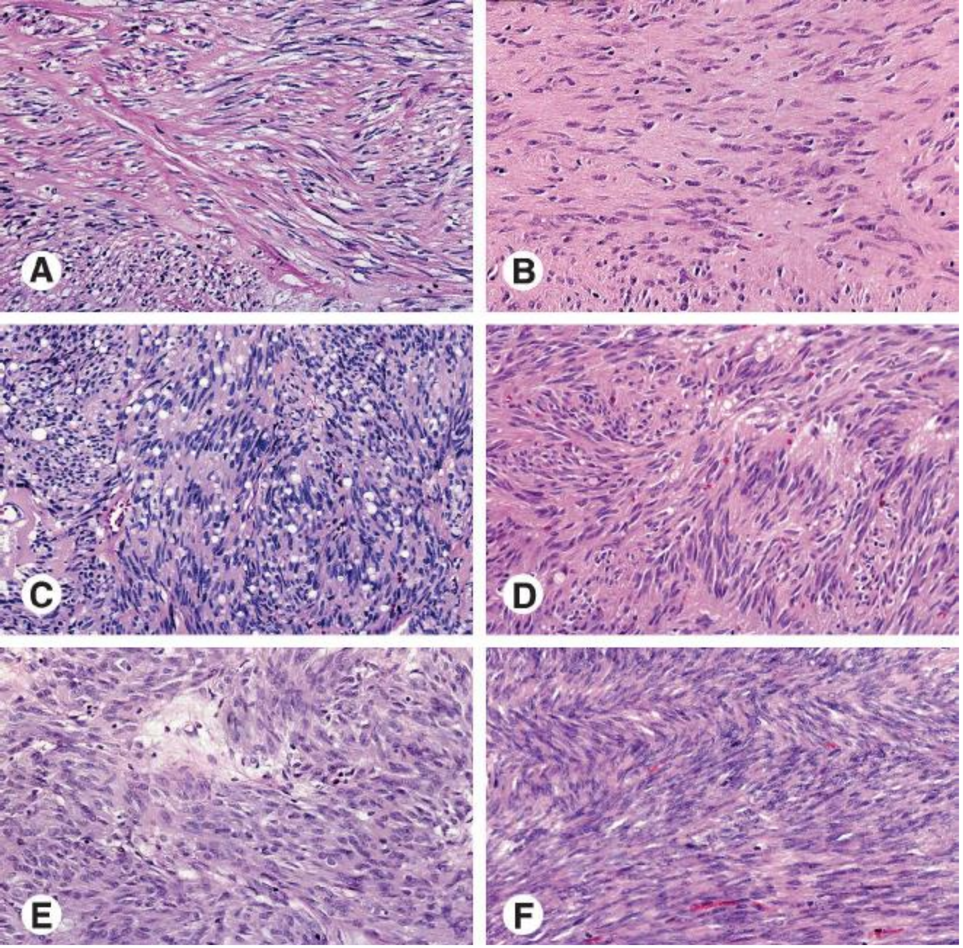
Ondřej Daum

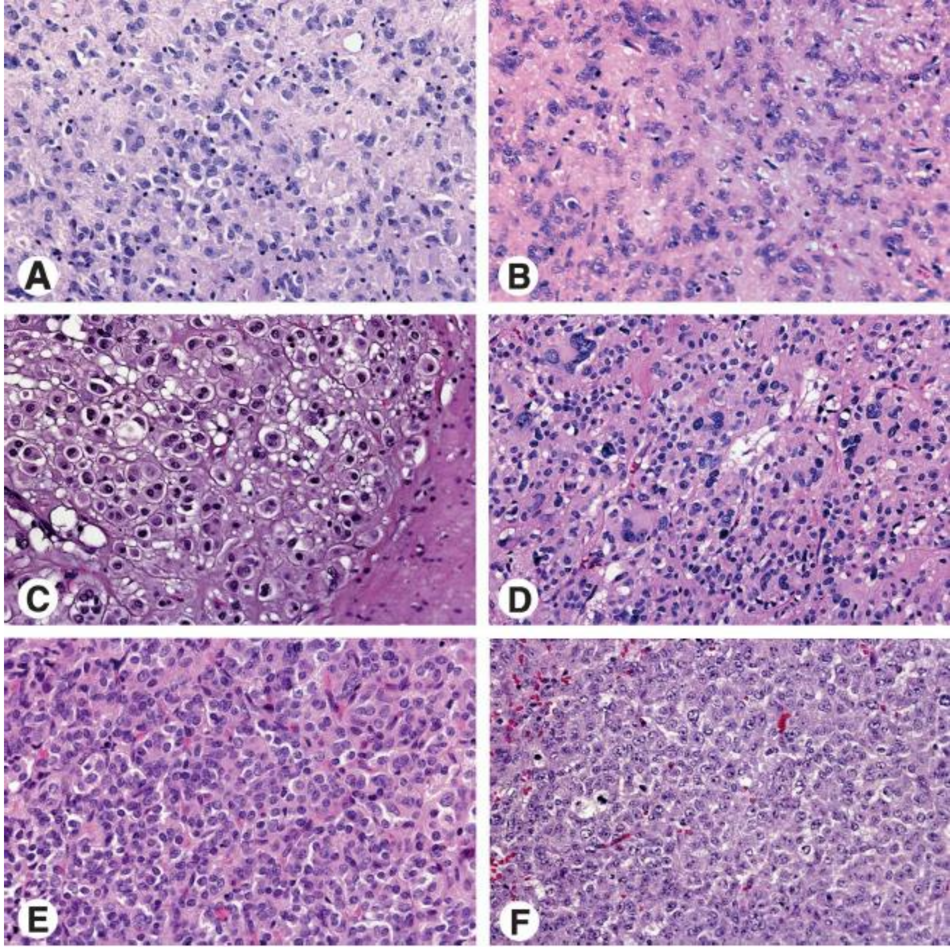
Plzeň, ČR

9.
Východoslovenský
BIOPTICKÝ SEMINÁR

Nie som v konflikte záujmov vo vzťahu k vyššie uvedenej vzdelávacej aktivite a jej organizátorovi


SPECIMEN
DATE





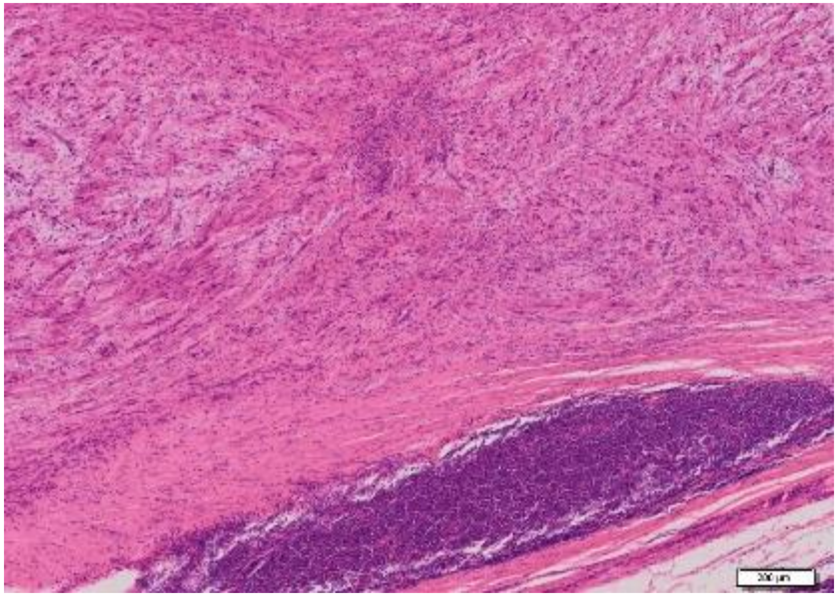
Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. *Am. J. Surg. Pathol.* 2005 Jan;**29**(1);52-68.

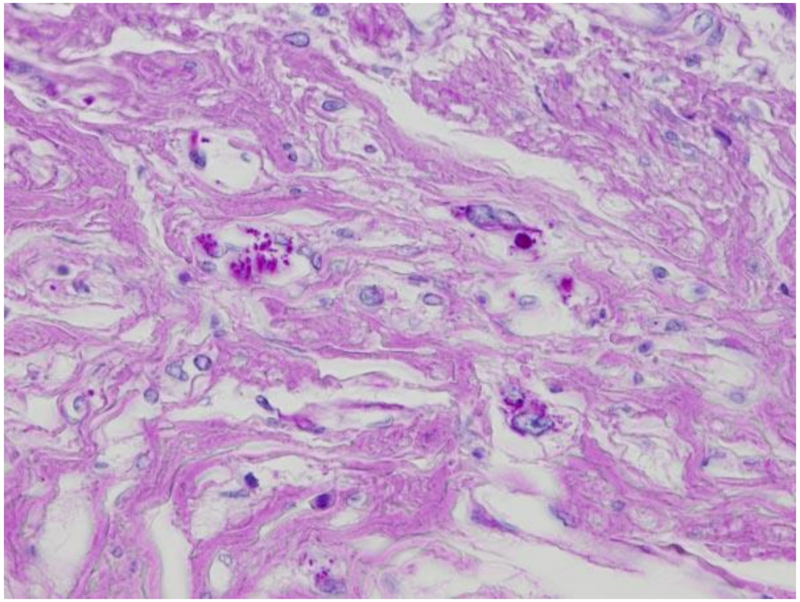
- KIT (CD117)
- (DOG1)
- Desmin
- S100

KIT+, S100-, desmin- → GIST → stanovení rizika
druhé čtení
(mol. gen.)

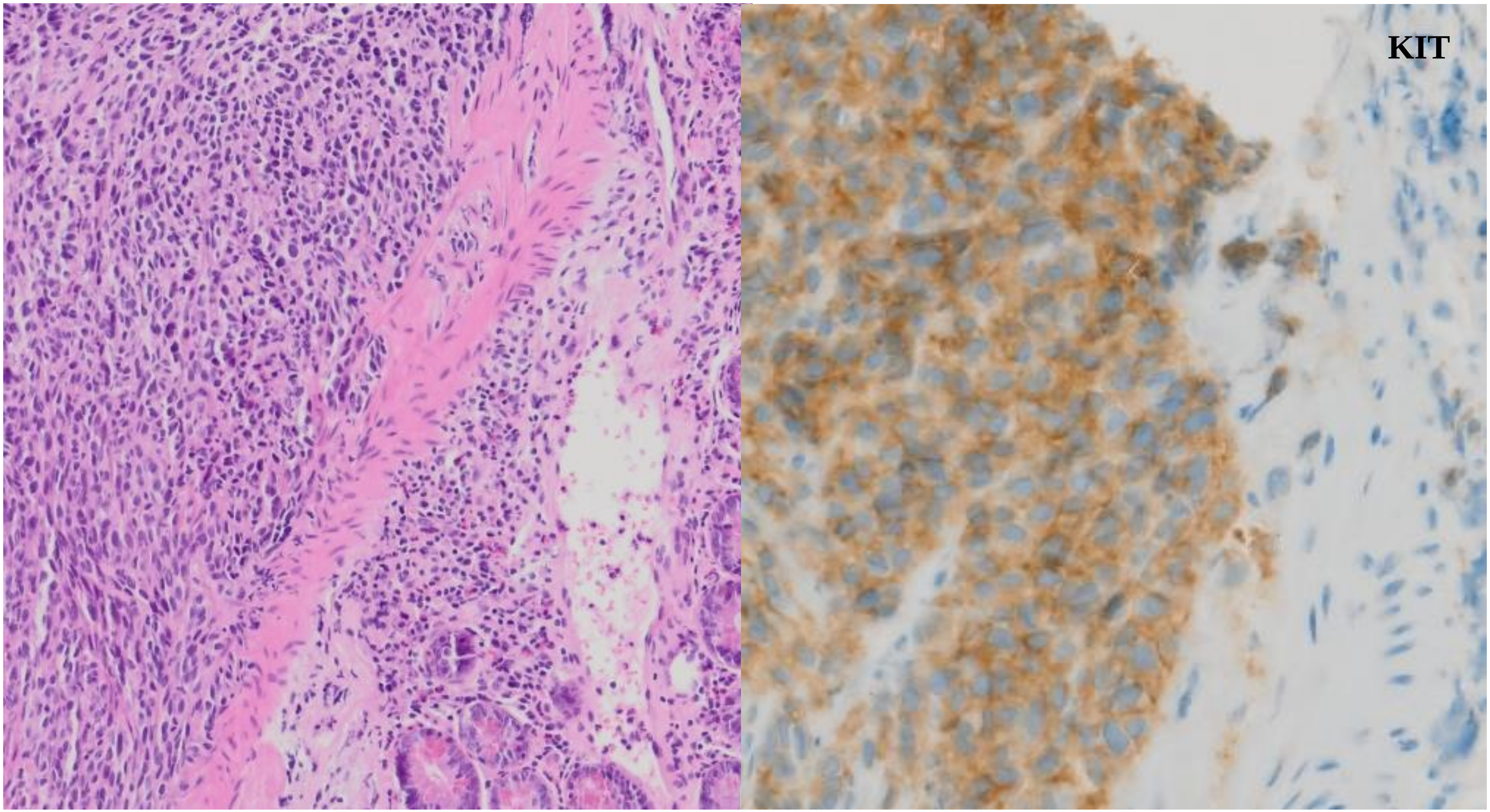
KIT-, S100-, desmin+ → leiomyom /
leiomyosarkom

KIT-, S100+, desmin- → schwannom

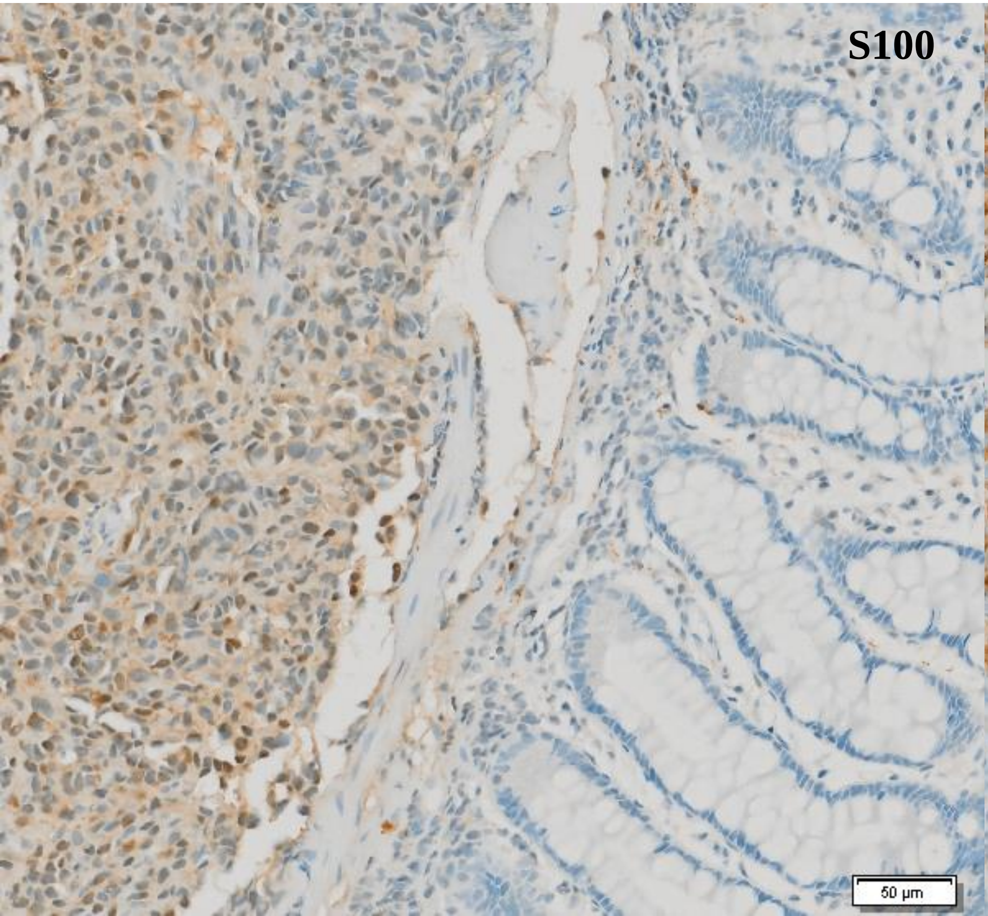


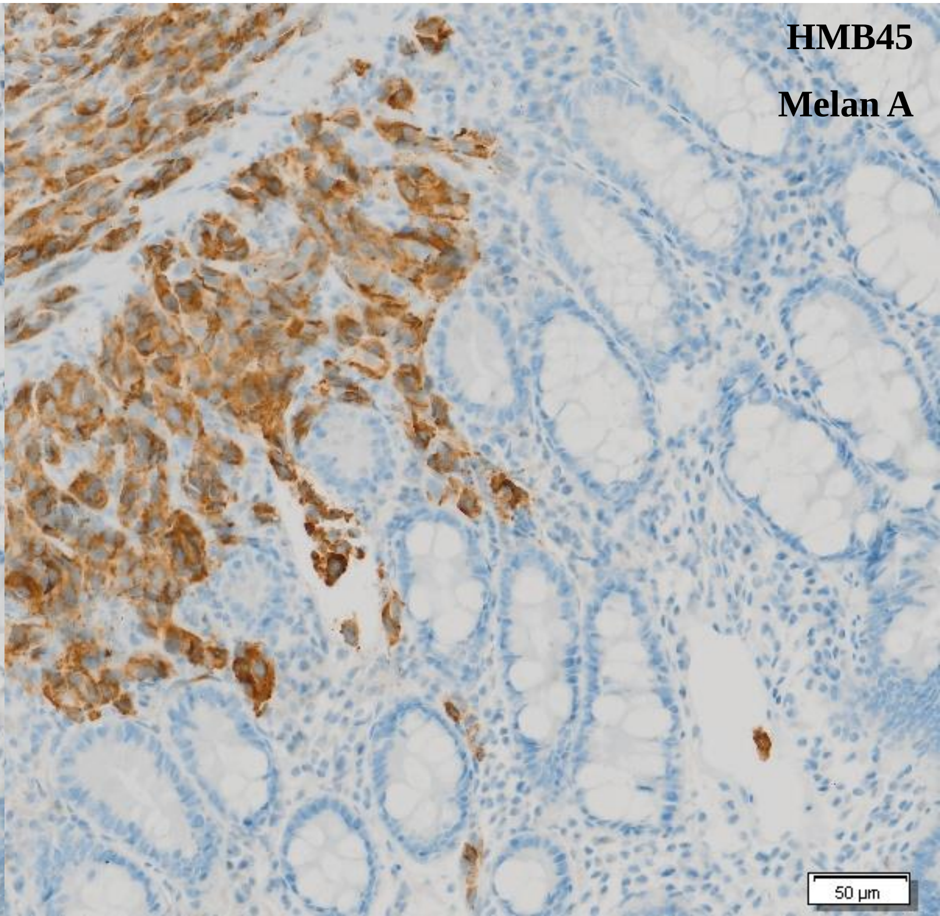


KIT+, S100+, desmin-

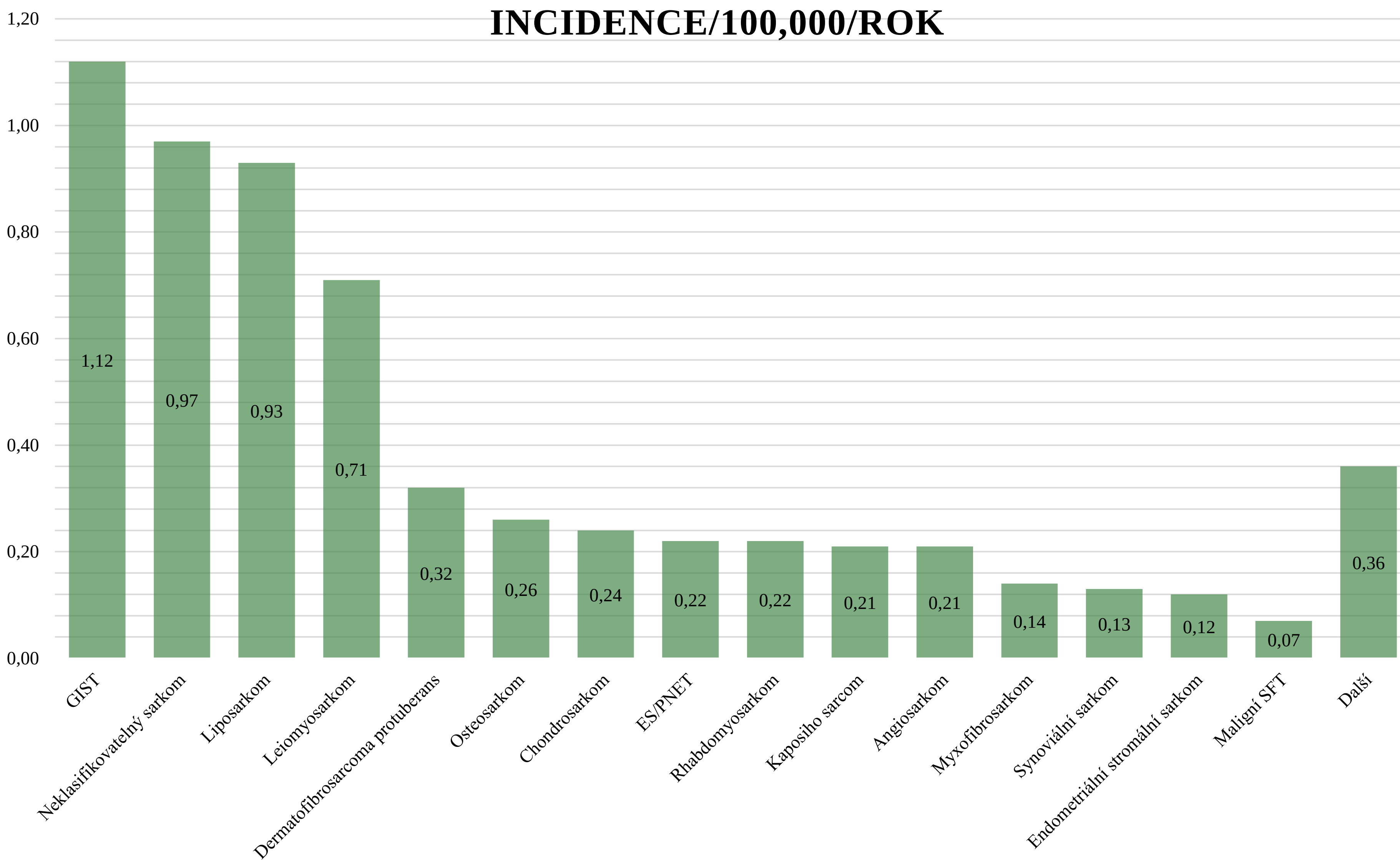


HMB45+, melan A+,... → maligní melanom





1. GIST

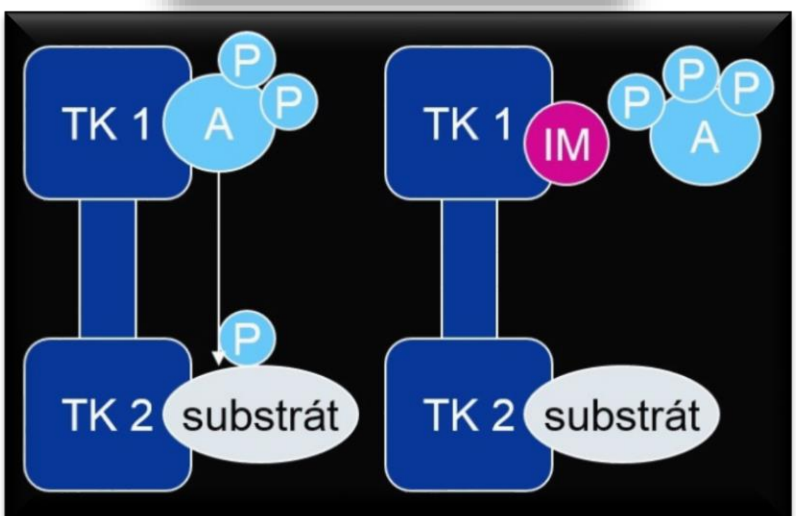


Ducimetière F. et al. (2011) PLoS ONE 6(8): e20294. doi: 10.1371/journal.pone.0020294

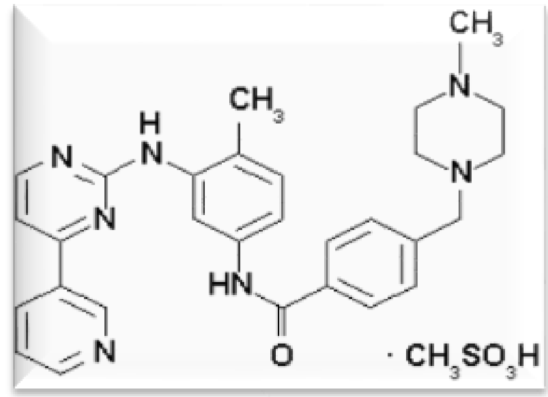
Science 1998; 279(5350): 577-580.

Gain-of-function mutations of *c-kit* in human gastrointestinal stromal tumors.

Hirota S et al.



Měkkotkáňové sarkomy



GIST
„Ty ostatní“

•Může GIST být IHC KIT (CD117) negativní?

•Může být GIST *KIT* wt?

Gastroenterology 2003; 125: 660-667.

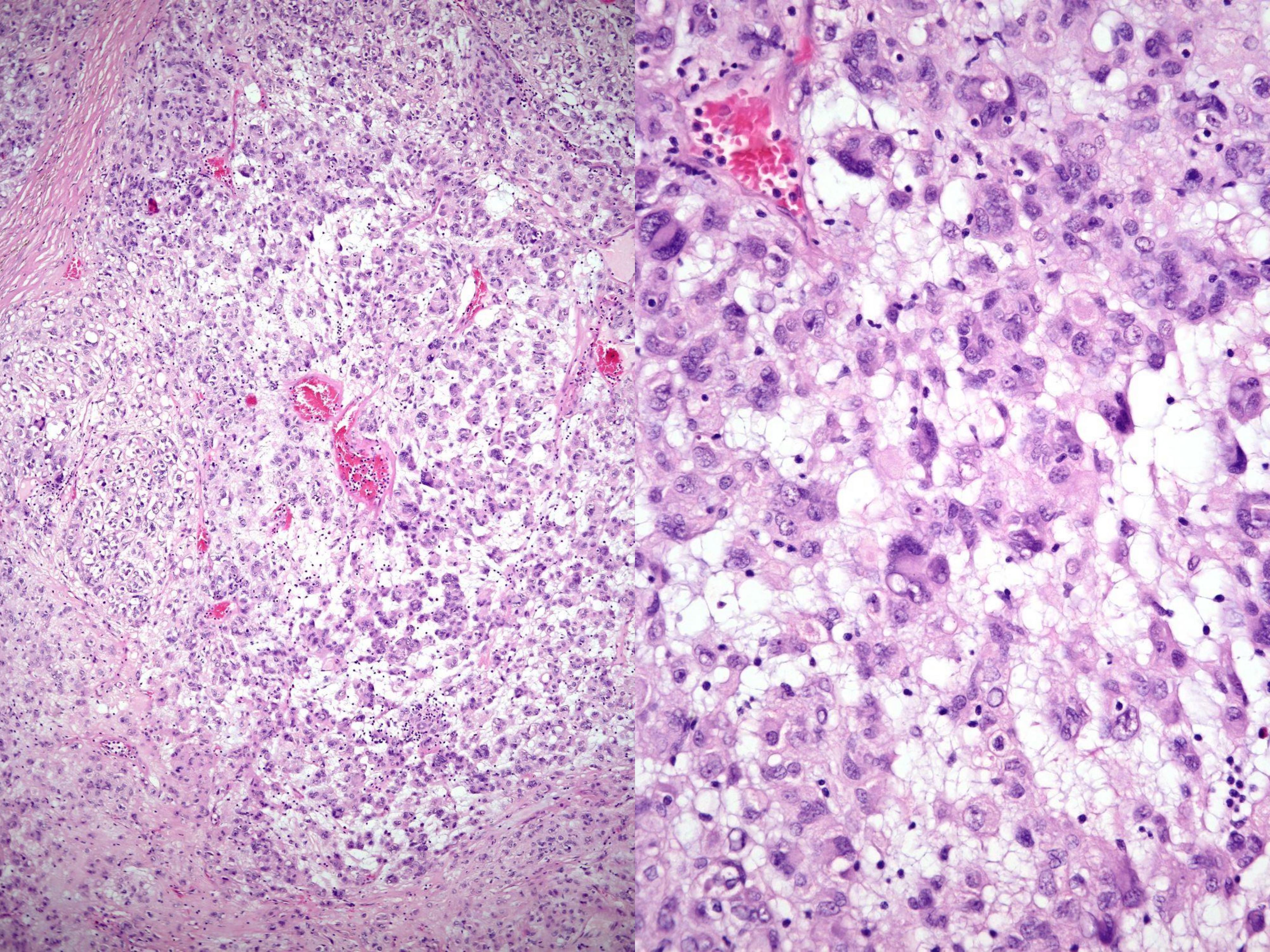
Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors.

Hirota S et al.

Science 2003; 299(5607): 708-710.

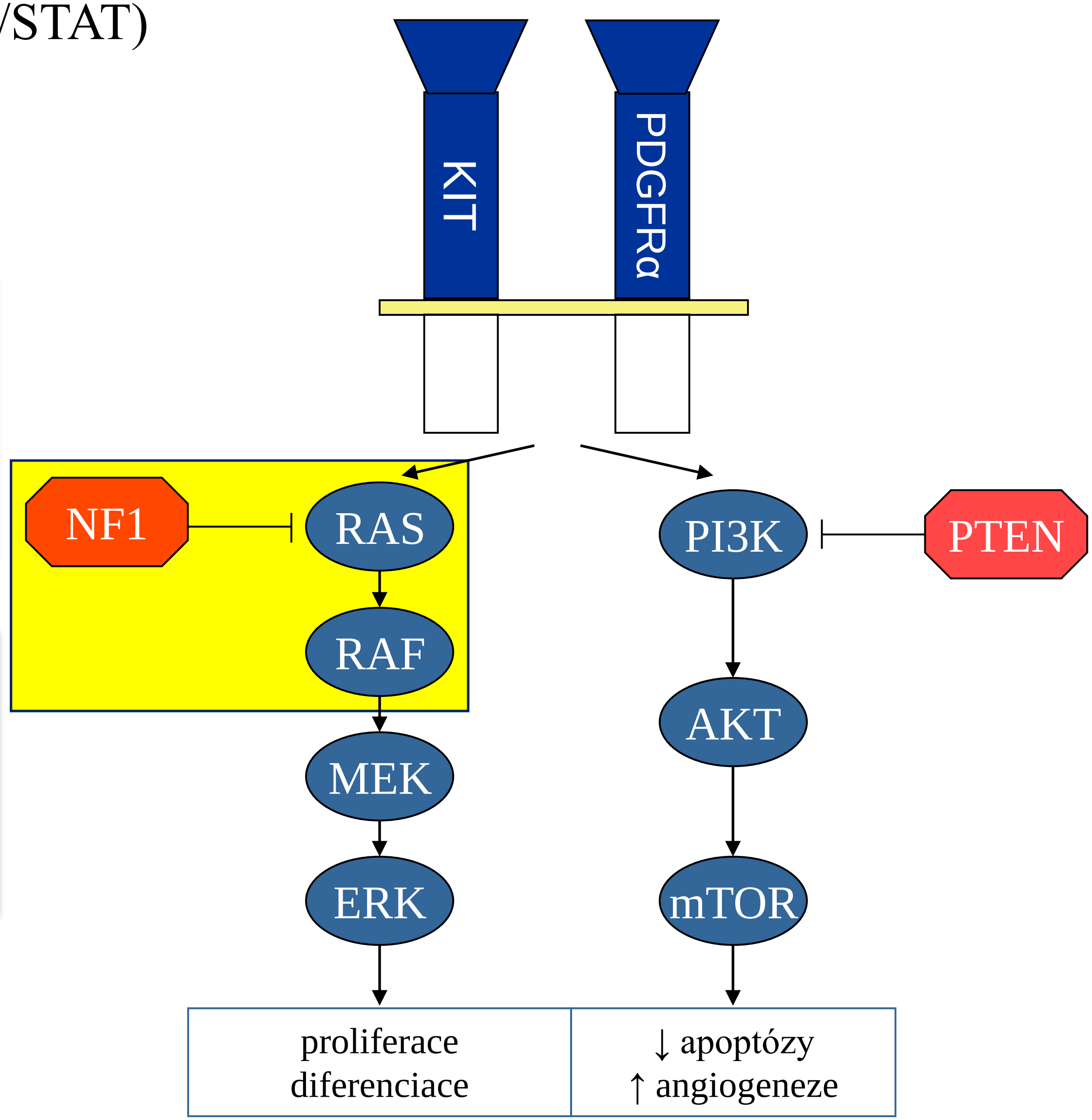
***PDGFRA* activating mutations in gastrointestinal stromal tumors.**

Heinrich MC et al.



GIST a signální dráha MAPK

- (s přispěním PI3K a JAK/STAT)



Hum Mol Genet. 2006; 15(6): 1015-1023.

Molecular pathogenesis of multiple gastrointestinal stromal tumors in NF1 patients.

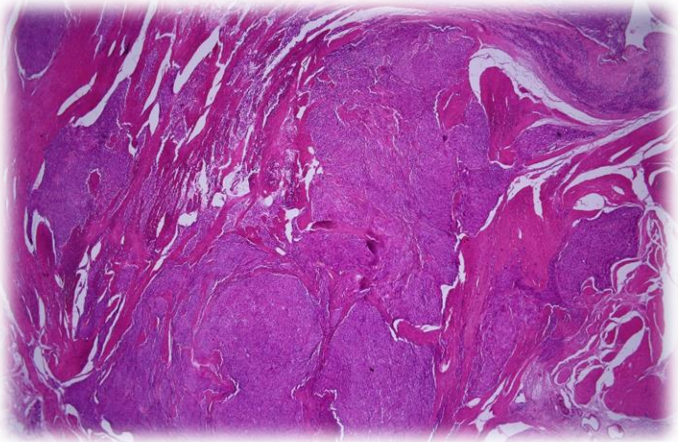
Maertens O et al.

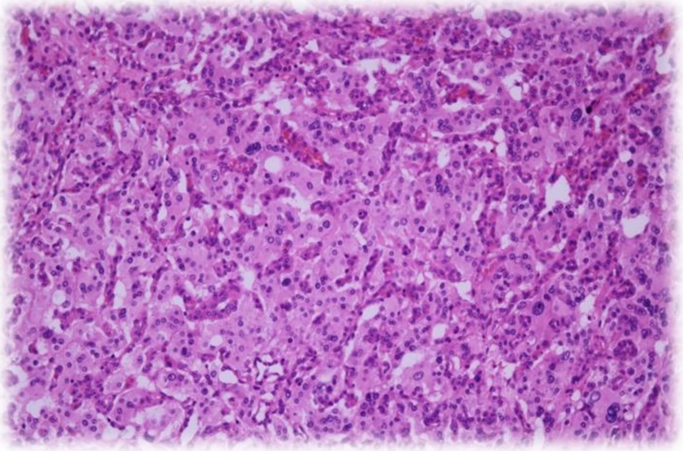
Clin Cancer Res. 2012; 18(6): 1769–1776.

***KRAS* and *BRAF* mutations predict primary resistance to imatinib in gastrointestinal stromal tumors.**

Miranda C et al.

GIST, Carney, Stratakis, děti a paragangliom

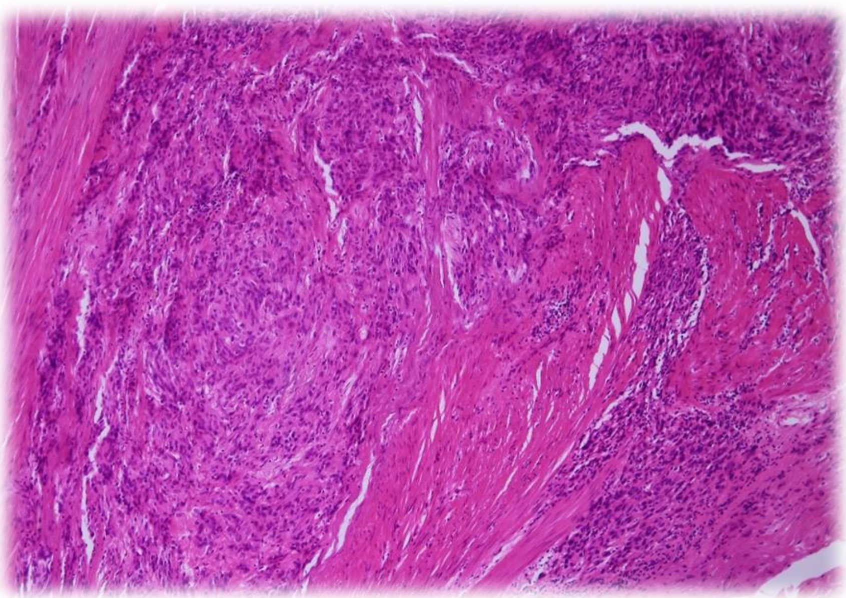


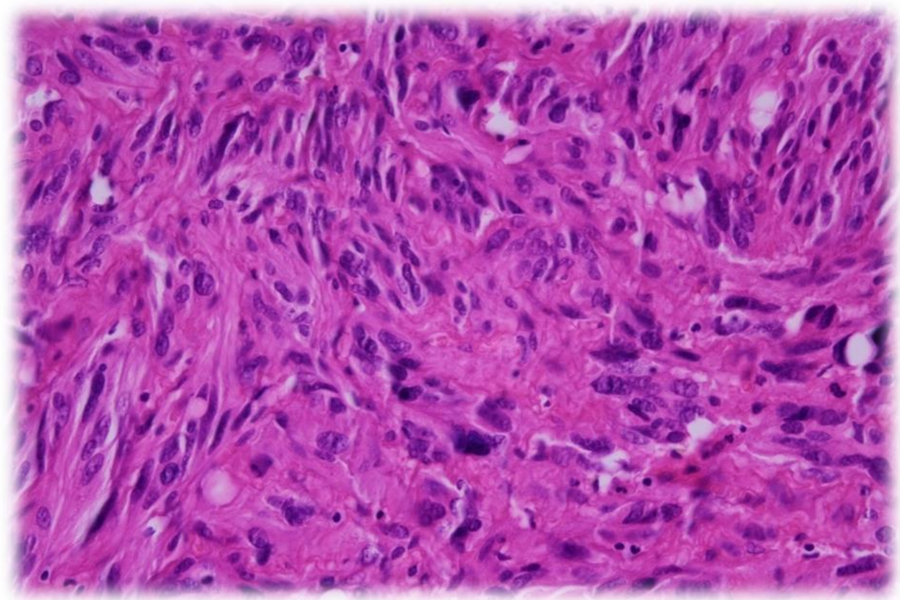


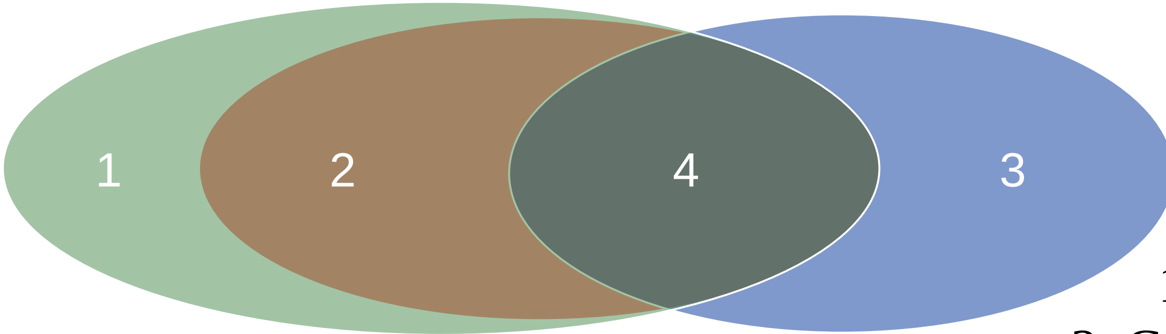
nefamiliární
Carneyho
trias

Carney JA et al. (1977) N Engl J Med 296(26): 1517-1518.
Carney JA et al.. (2002) Am J Med Genet 108(2): 132-139.

Klinické varianty	Carneyho trias, Syndrom Carney - Stratakis, sporadický pediatrický GIST, sporadický adultní GIST
Distribuce	Žaludek, často multifokálně
Architektura	Nodulární, plexiformní, s vazivovými septy
Buněčný typ	Převážně epiteloidní
Imunohistochemie	KIT pozitivní
Metastázy	Často v lymfatických uzlinách
Biologické chování	Nekoreluje s velikostí tumoru a mitotickým indexem

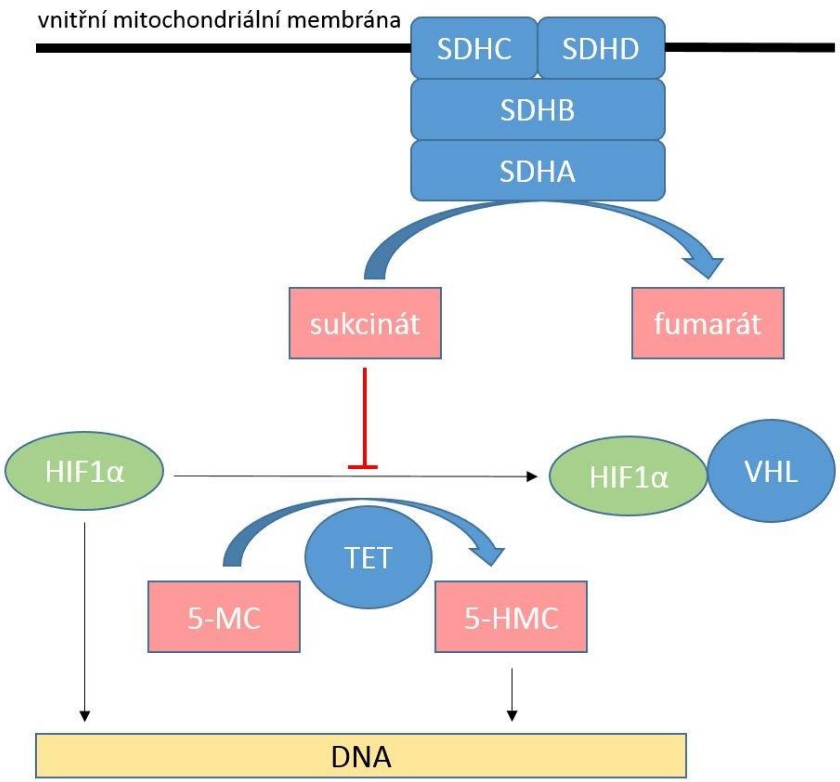


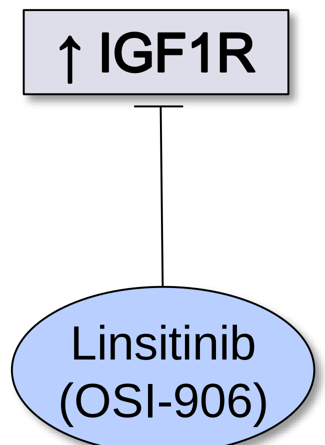


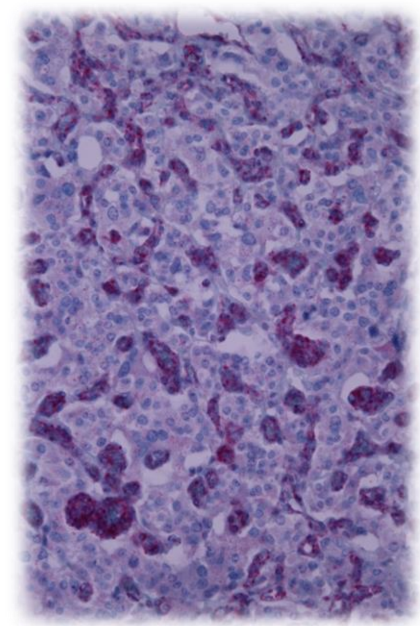


1: SDHB-deficientní GIST
2: GIST s germinální mutací *SDHx*
3: hereditární paragangliom
4: syndrom Carneyho a Stratakise

…aneb GIST a SDH







<u>Carney trias:</u> metylace SDHC
<u>ostatní:</u> mutace SDHx

X

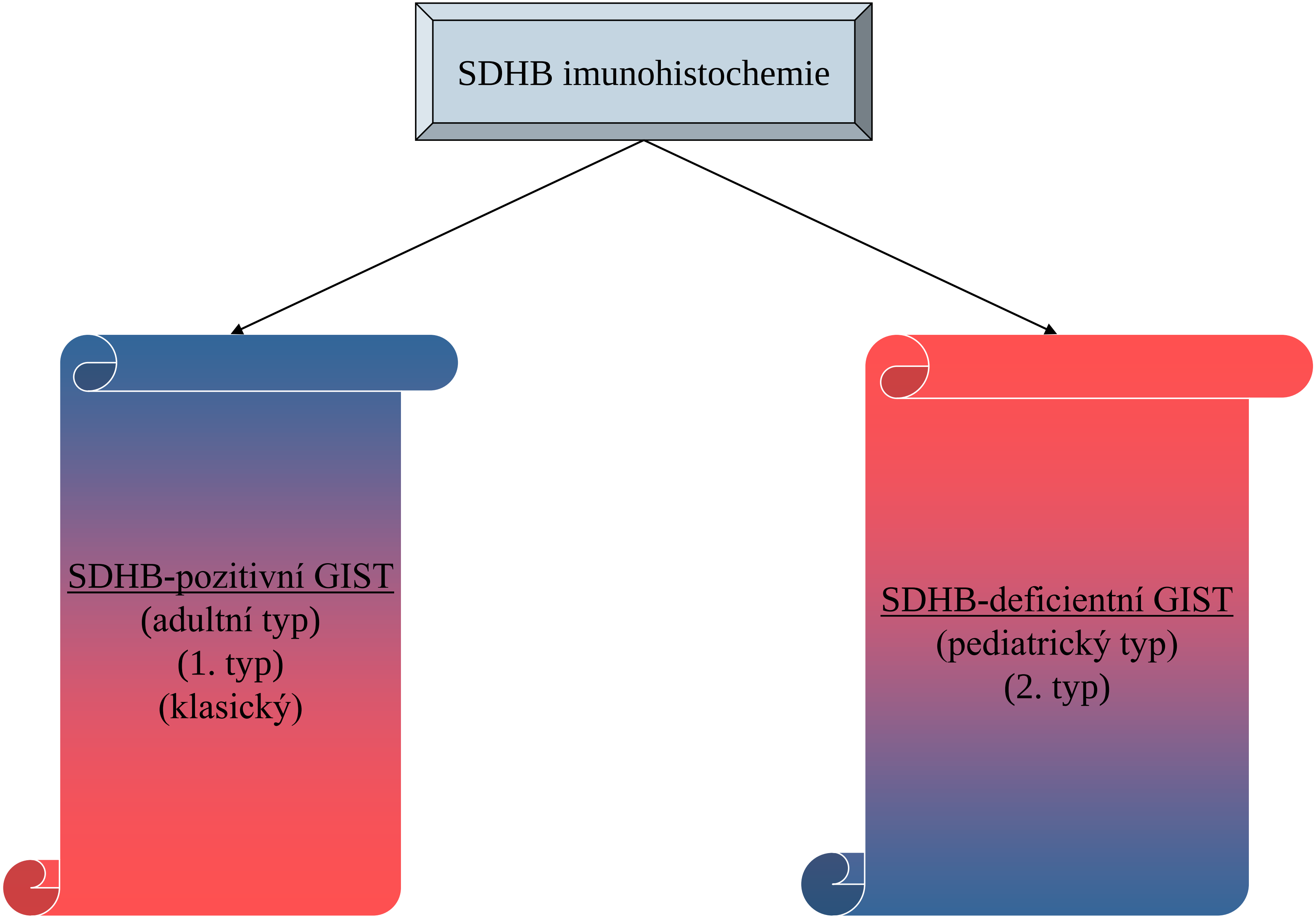
Conventional Risk Stratification Fails to Predict Progression of Succinate Dehydrogenase–deficient Gastrointestinal Stromal Tumors

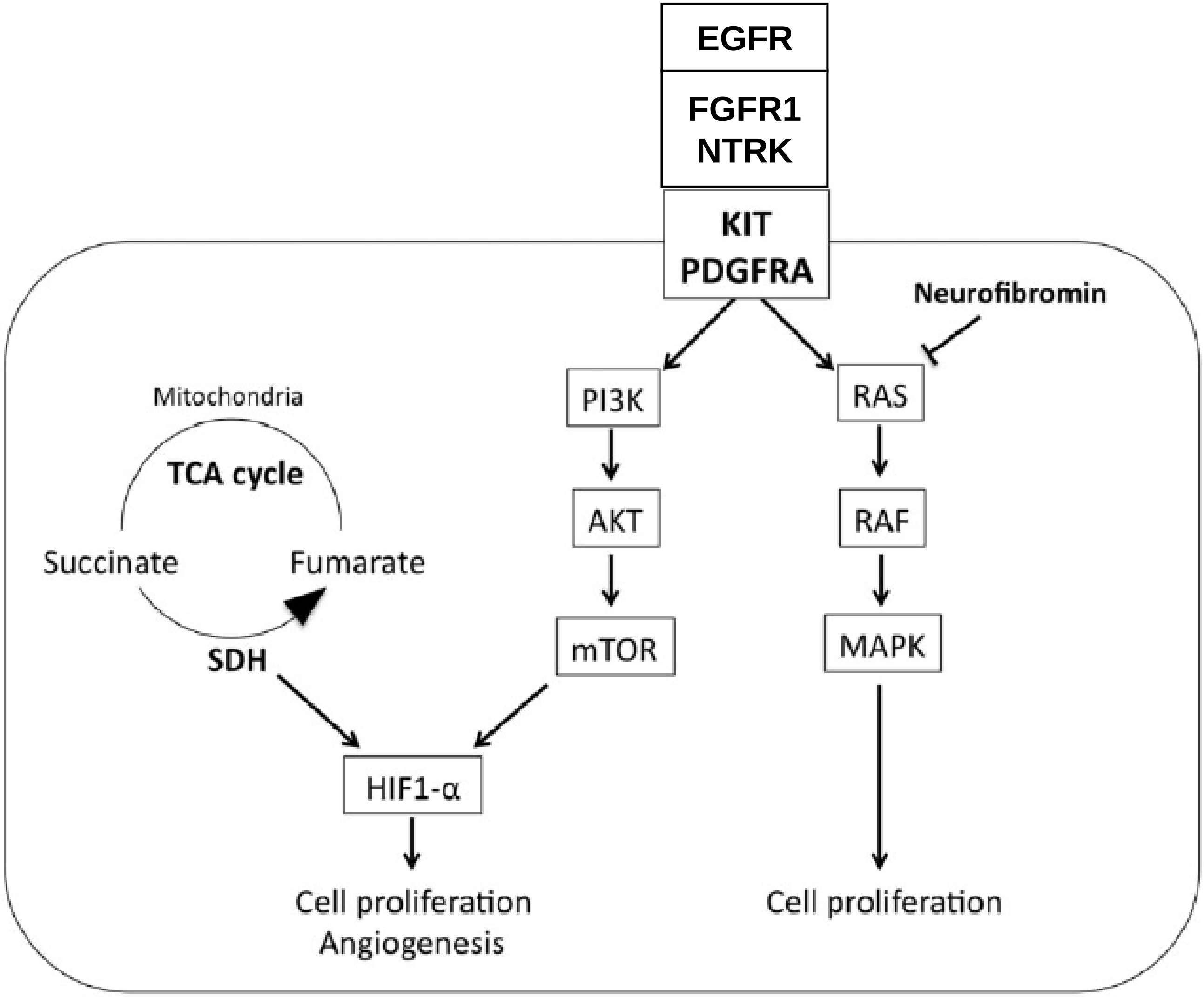
A Clinicopathologic Study of 76 Cases

Emily F. Mason, MD, PhD and Jason L. Hornick, MD, PhD

Am J Surg Pathol 2016;40:1616–1621

- 76 případů
- 8 % žaludečních GISTů
- nejčastěji *SDHA* mut
- 4 ze 7 případů Carneyho trias mají mutace SDHx


SDHB imunohistochemie
SDHB-pozitivní GIST
(adultní typ)
(1. typ)
(klasický)
SDHB-deficientní GIST
(pediatrický typ)
(2. typ)



Yamamoto H et al. (2015) Pathol Int 65(1): 9–18

Hlavní mutace signální dráhy MAPK
• *KIT*
• *PDGFRA*
Další mutace signální dráhy MAPK a PI3K
• *BRAF*
• *NF1*
• *RAS*
• *PIK3CA*
• *NTRK1* nebo *NTRK3* fúze
• *FGFR1* fúze
• *EGFR*
SDH deficience
• mutace *SDHx*
• metylace promotoru *SDHC (Carney trias)*

Možnost familiárního výskytu

Killian JK et al. (2014) Sci Transl Med 6(268): 268ra177.
Haller F et al. (2014) Endocr Relat Cancer 21(4):567-577.

Journal of Pathology
J Pathol 2016; **238:** 543–549
Published online 25 January 2016 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.4677

ORIGINAL PAPER

Transcriptome sequencing identifies *ETV6–NTRK3* as a gene fusion involved in GIST

Monica Brenca,[1#] Sabrina Rossi,[2#] Maurizio Polano,[1] Daniela Gasparotto,[1] Lucia Zanatta,[2] Dominga Racanelli,[1] Laura Valori,[2] Stefano Lamon,[3] Angelo Paolo Dei Tos[2##] and Roberta Maestro[1##*]

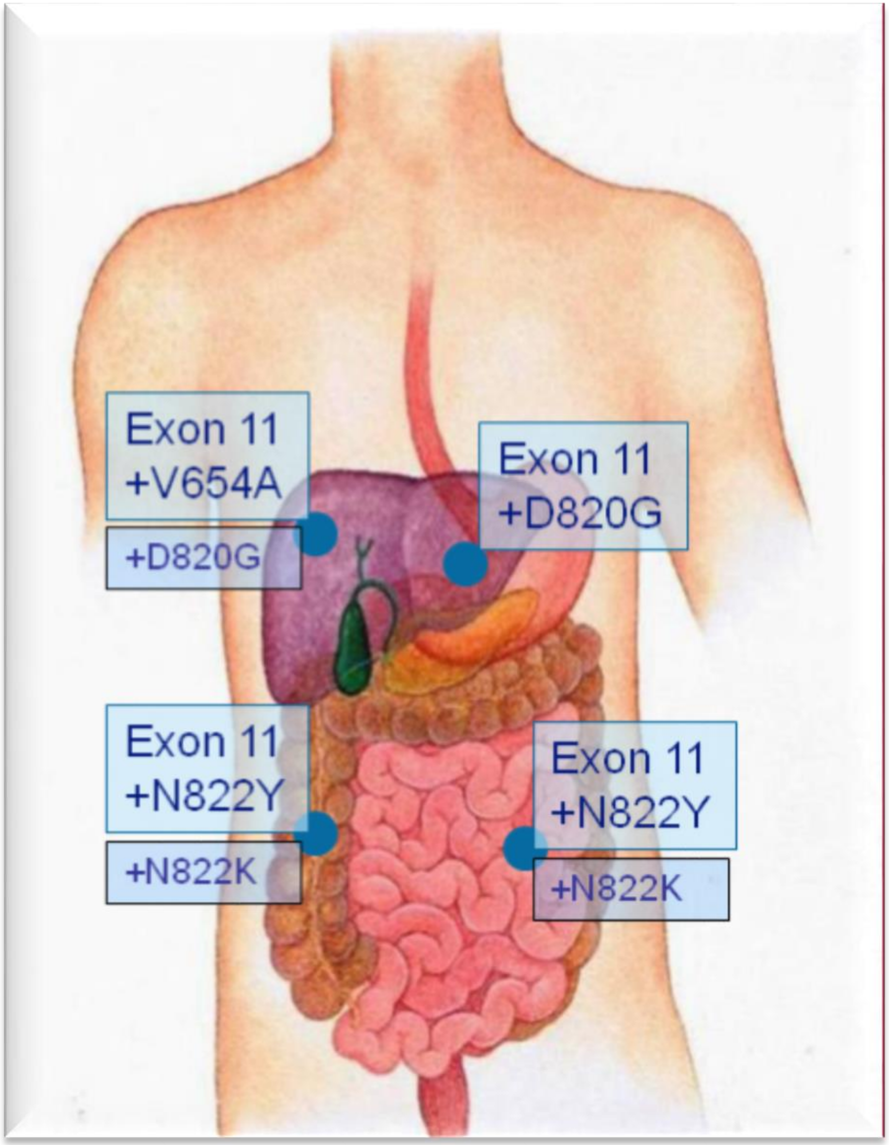
- fúzní transkript indukuje fosforylaci IRS1 → aktivace IGF1R pathway
- → možnost inhibice inhibitory IGF1R a ALK

Neurofibromin C terminus-specific antibody (clone NFC) is a valuable tool for the identification of *NF1*-inactivated GISTs

Sabrina Rossi[1,8], Daniela Gasparotto[2,8], Matilde Cacciatore[1], Marta Sbaraglia[1], Alessia Mondello[2], Maurizio Polano[2], Alessandra Mandolesi[3], Alessandro Gronchi[4], David E Reuss[5,6], Andreas von Deimling[5,6], Roberta Maestro[2,9] and Angelo Paolo Dei Tos[1,7,9]

MODERN PATHOLOGY (2018) 31, 160–168

- protilátka proti C-konci neurofibrominu
- možnost léčby inhibitory MEK



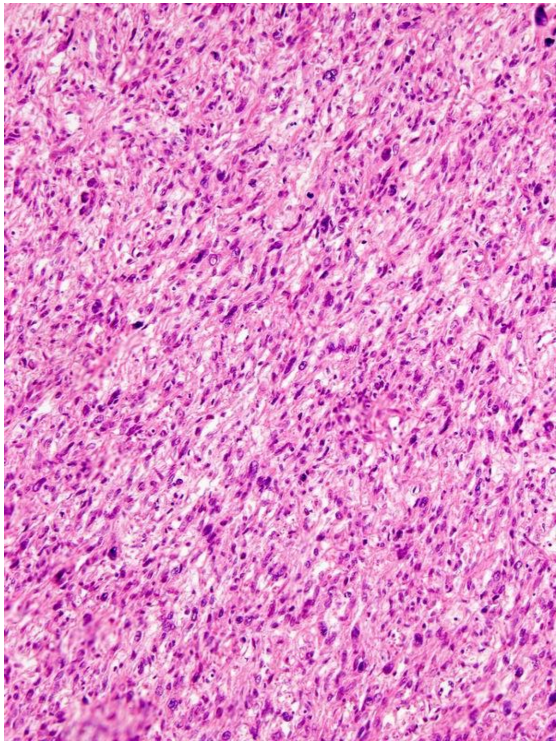
Liegl B. et al. Heterogeneity of kinase inhibitor resistance mechanisms in GIST. J Pathol 2008:216(1):64-74.

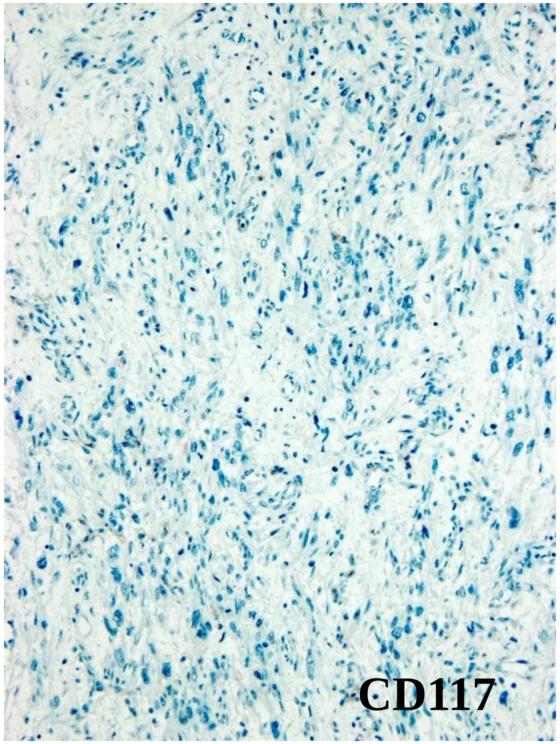
2. Leiomyocelulární nádory

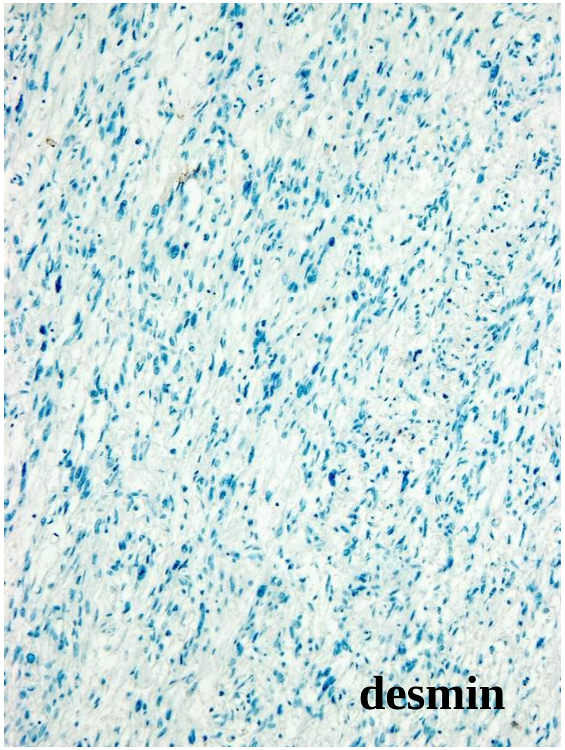
KIT-, S100-, desmin+

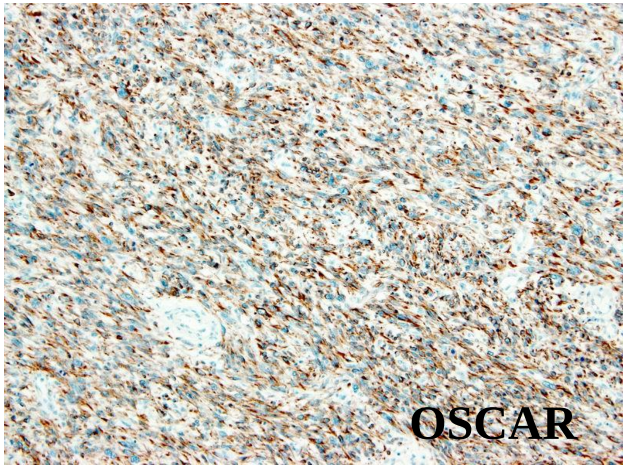
+ další leiomyocelulární markery (SMA, h-caldesmon …)

!!! ALE:







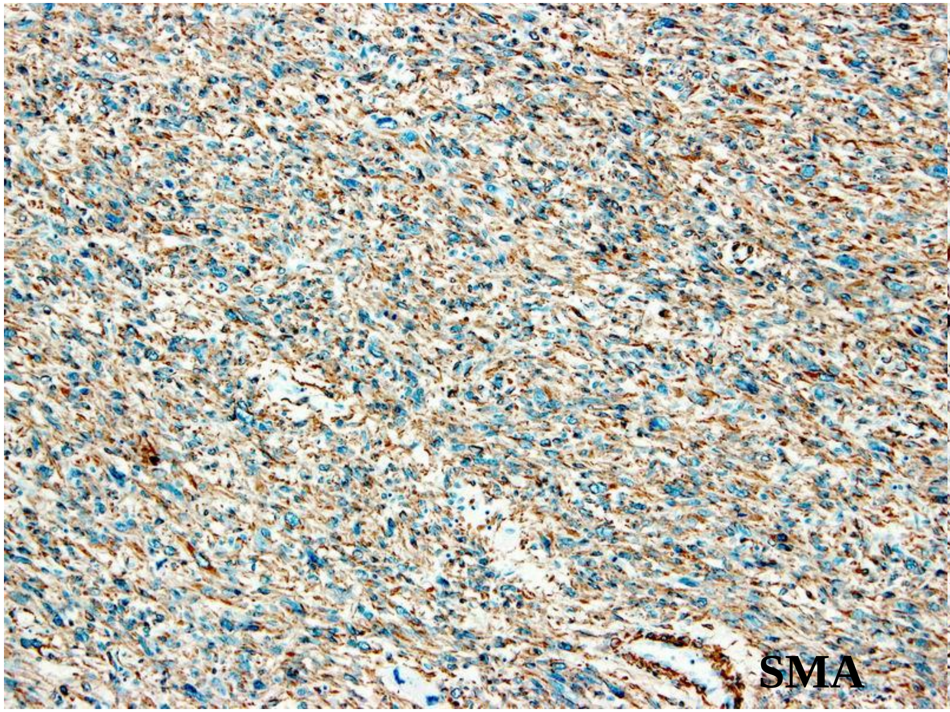


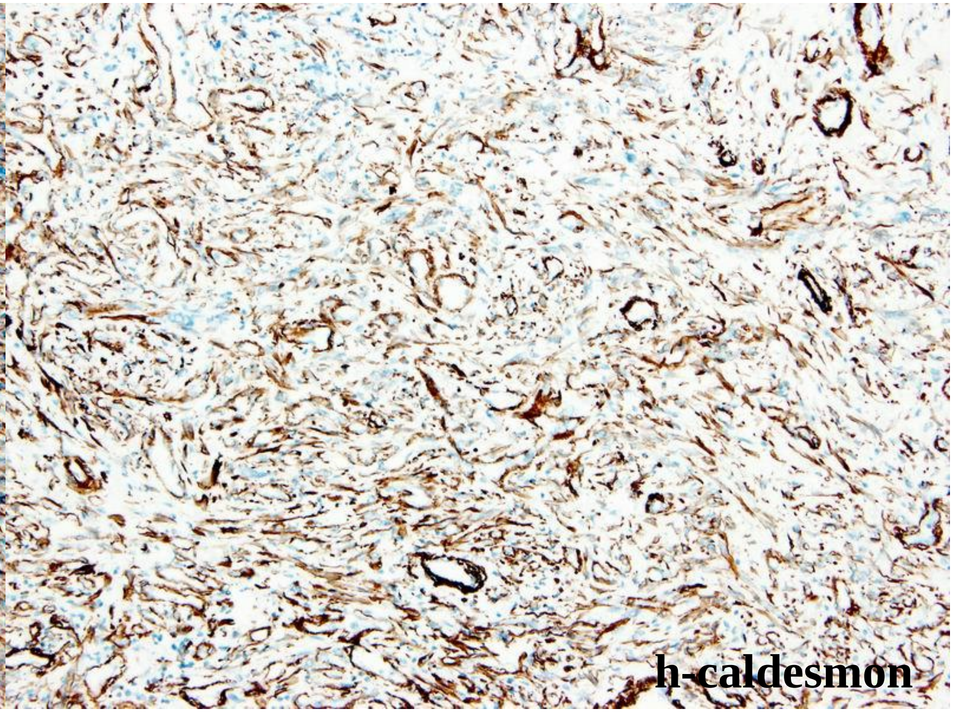
Immunohistochemical detection of cytokeratin and epithelial membrane antigen in leiomyosarcoma: A systematic study of 100 cases

Jun Iwata[1] and Christopher D. M. Fletcher[2]

Pathology International 2000; **50**: 7–14

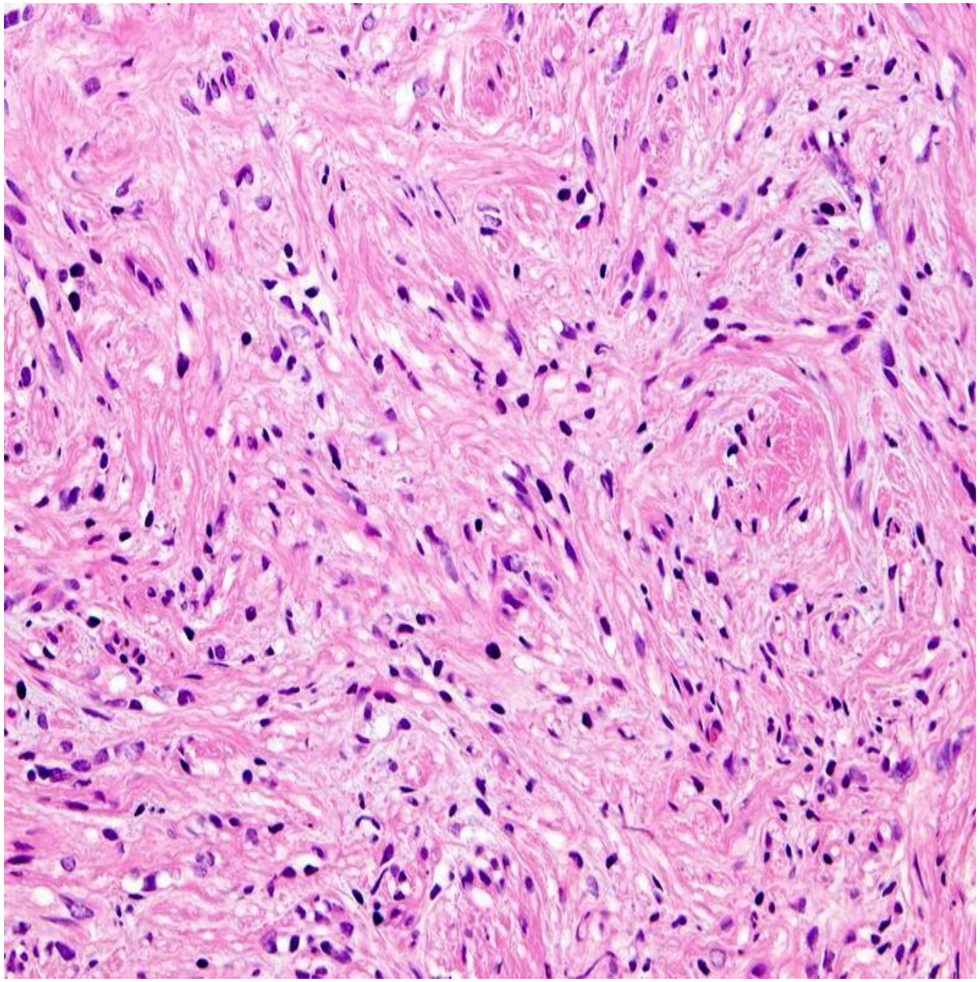
alespoň 2 leiomyocelulární markery





Leiomyom

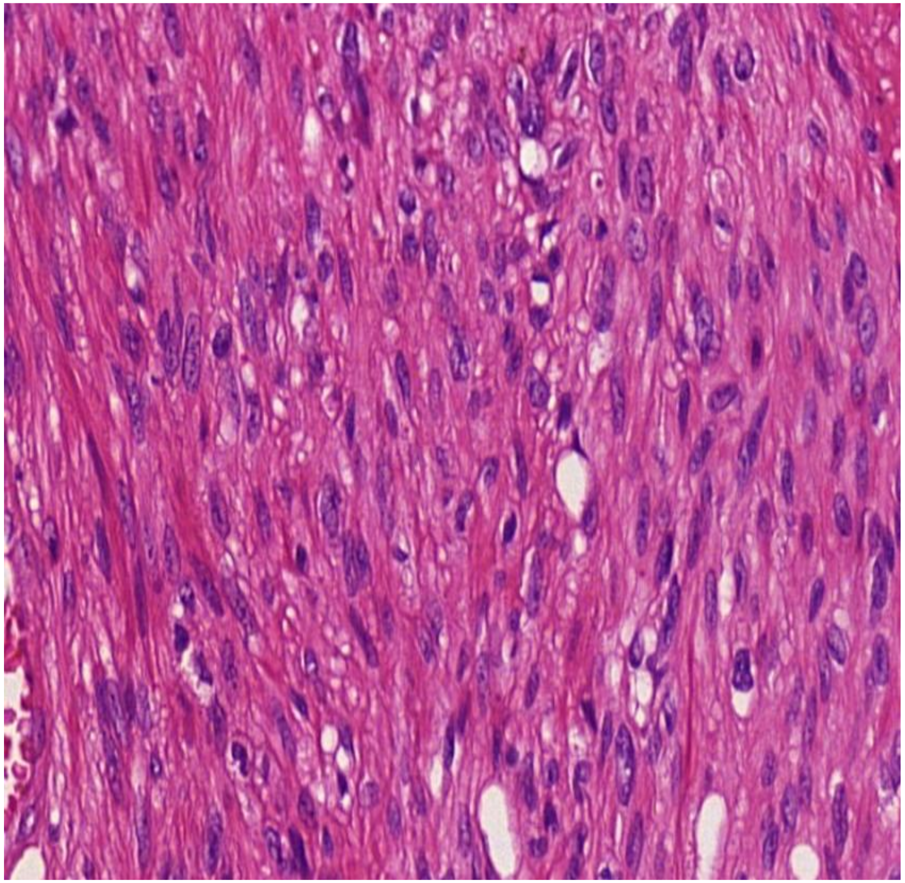
- Vzácné, častěji v jícnu a tlustém střevě (z muscularis mucosae)
- Sporadické/v rámci MEN1, Alport sy. (*COL4A5, COL4A3, COL4A4*)
- SMA, h-caldesmon, desmin +



Heidet, L., Boye, E., Cai, Y., et al. Somatic deletion of the 5' ends of both the COL4A5 and COL4A6 genes in a sporadic leiomyoma of the esophagus. *Am J Pathol*, 1998, 152(3): 673-8.

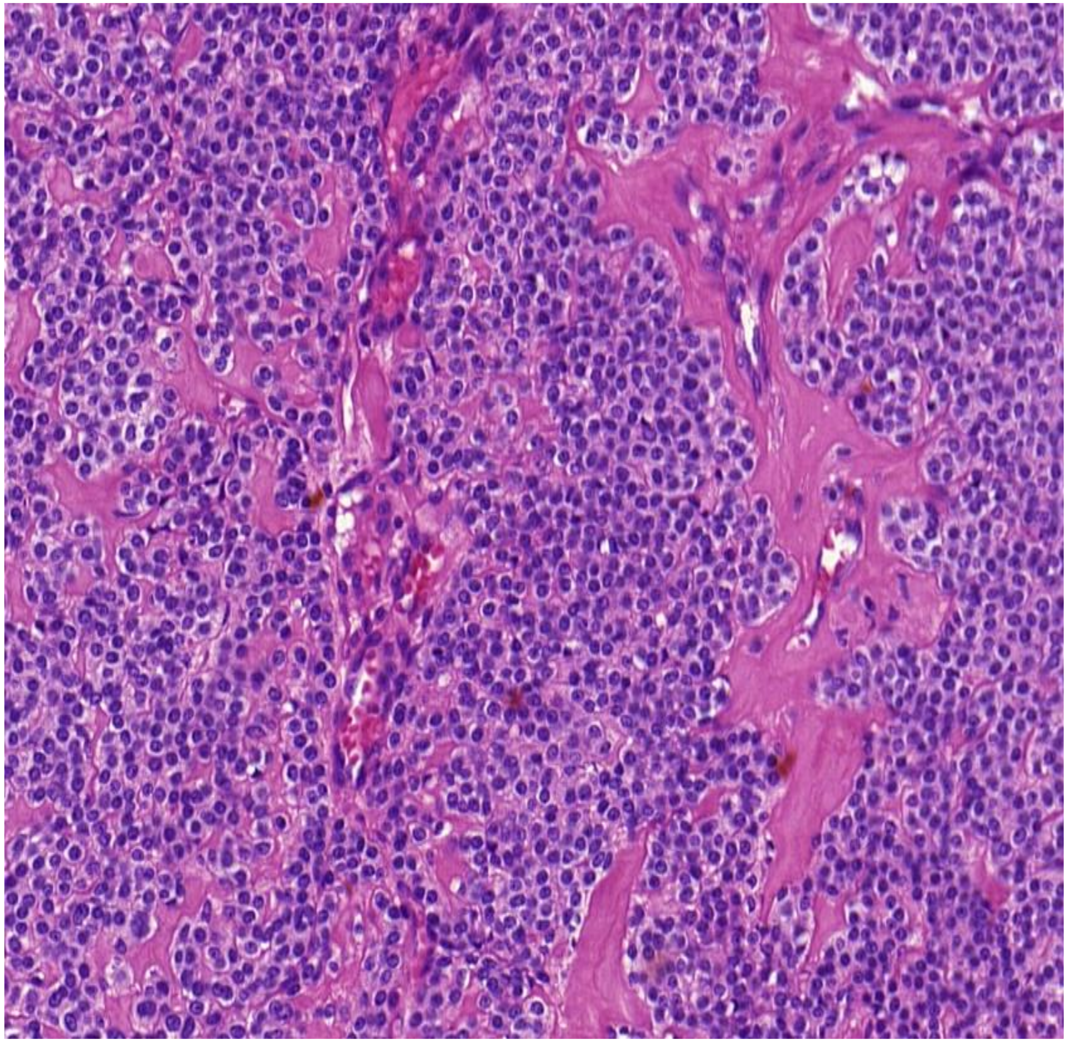
EBV-asociované leiomyocelulární nádory

- Imunokompromitovaní pacienti
- Mnohočetné (GIT, plíce, játra)
- Dobrá prognóza
- <u>Imuno:</u>
  - hladkosvalové markery
  - CD21 (EBV receptor)
  - EBNA2
- <u>ISH</u> (EBER)



Dívka (12 let), mesenterium
Terapie: Cyclosporin, kortikosteroidy

Glomus tumor



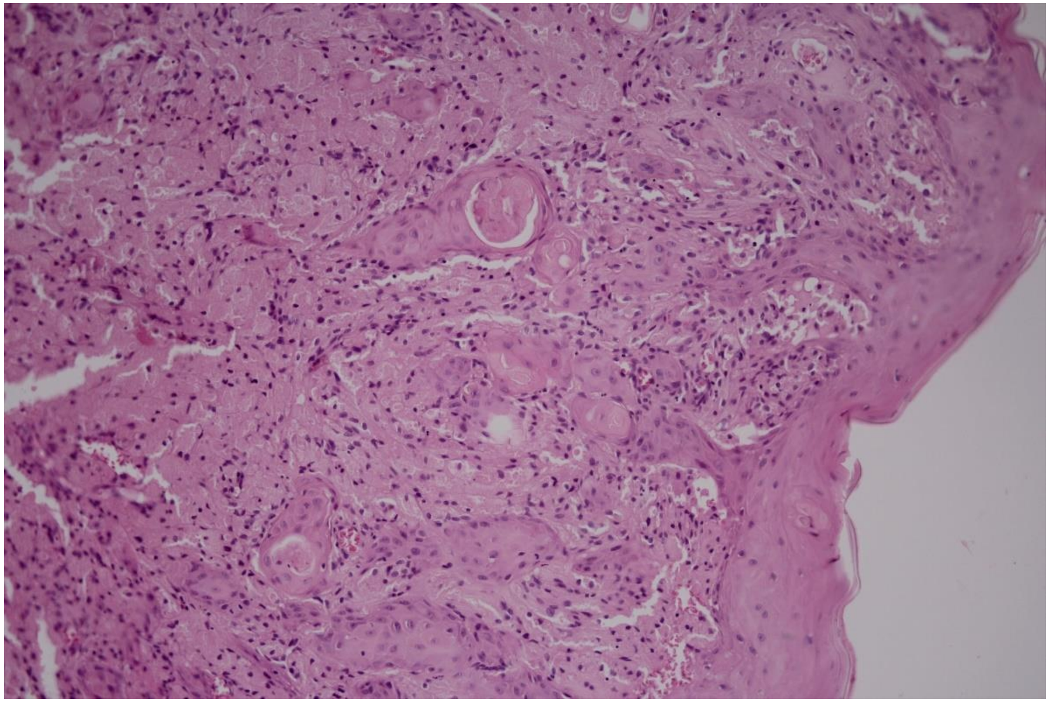
- žaludek (antrum)
- Imuno:
  - SMA
  - kolagen IV
  - ! fokálně může synaptofyzin

3. Neurální nádory

KIT-, S100+, desmin-

(kromě schwannomu)

Granular cell tumor



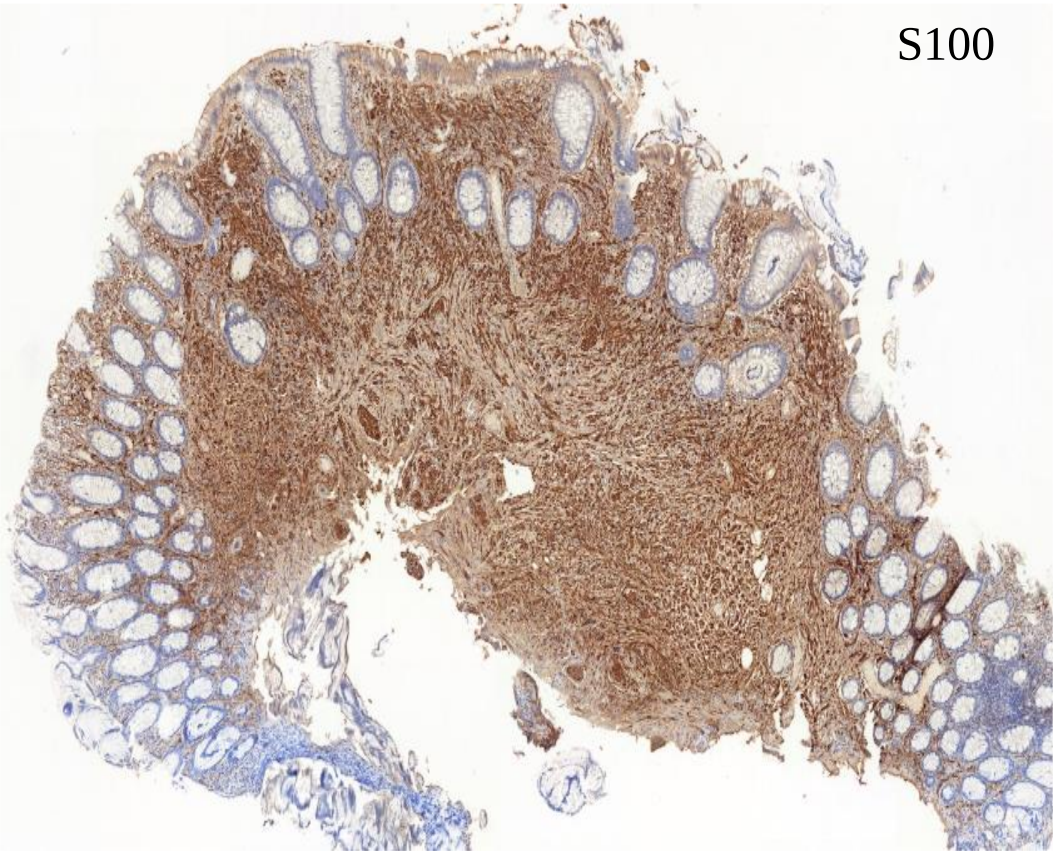
Loss-of-function mutations in *ATP6AP1* and *ATP6AP2* in granular cell tumors

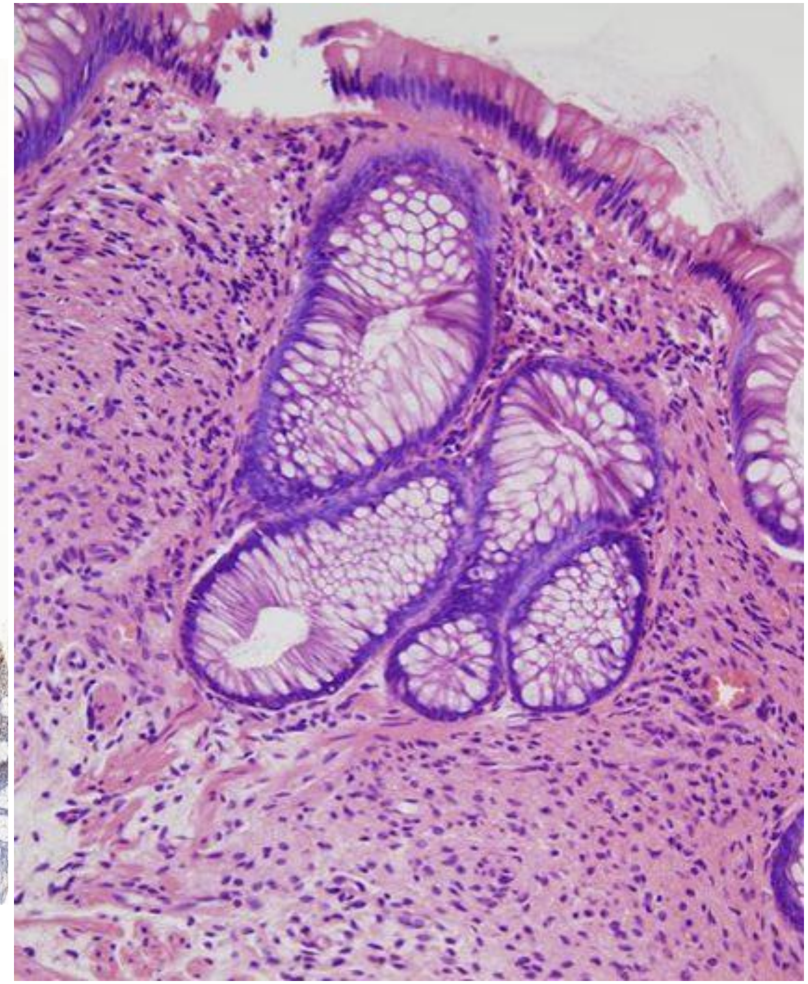
Fresia Pareja[1], Alissa H. Brandes[1], Thais Basili[1], Pier Selenica[1], Felipe C. Geyer[1], Dan Fan[1], Arnaud Da Cruz Paula[1], Rahul Kumar[1], David N. Brown[1], Rodrigo Gularte-Mérida[1], Barbara Alemar[1,2], Rui Bi[1,3], Raymond S. Lim[1], Ino de Bruijn[1], Sho Fujisawa[4], Rui Gardner[5], Elvin Feng[4], Anqi Li[1,3], Edaise M. da Silva[1], John R. Lozada[1], Pedro Blecua[6], Leona Cohen-Gould[7], Achim A. Jungbluth[1], Emad A. Rakha[8], Ian O. Ellis[8], Maria I.A. Edelweiss[9], Juan Palazzo[10], Larry Norton[11], Travis Hollmann[1], Marcia Edelweiss[1], Brian P. Rubin[12], Britta Weigelt[1] & Jorge S. Reis-Filho[1]

NATURE COMMUNICATIONS | (2018)9:3533 | DOI: 10.1038/s41467-018-05886-y

- geny kódující endosomální pH regulázy
- inaktivační mutace → narušení acidifikace vesikul, akumulace intracytoplasmatických granul

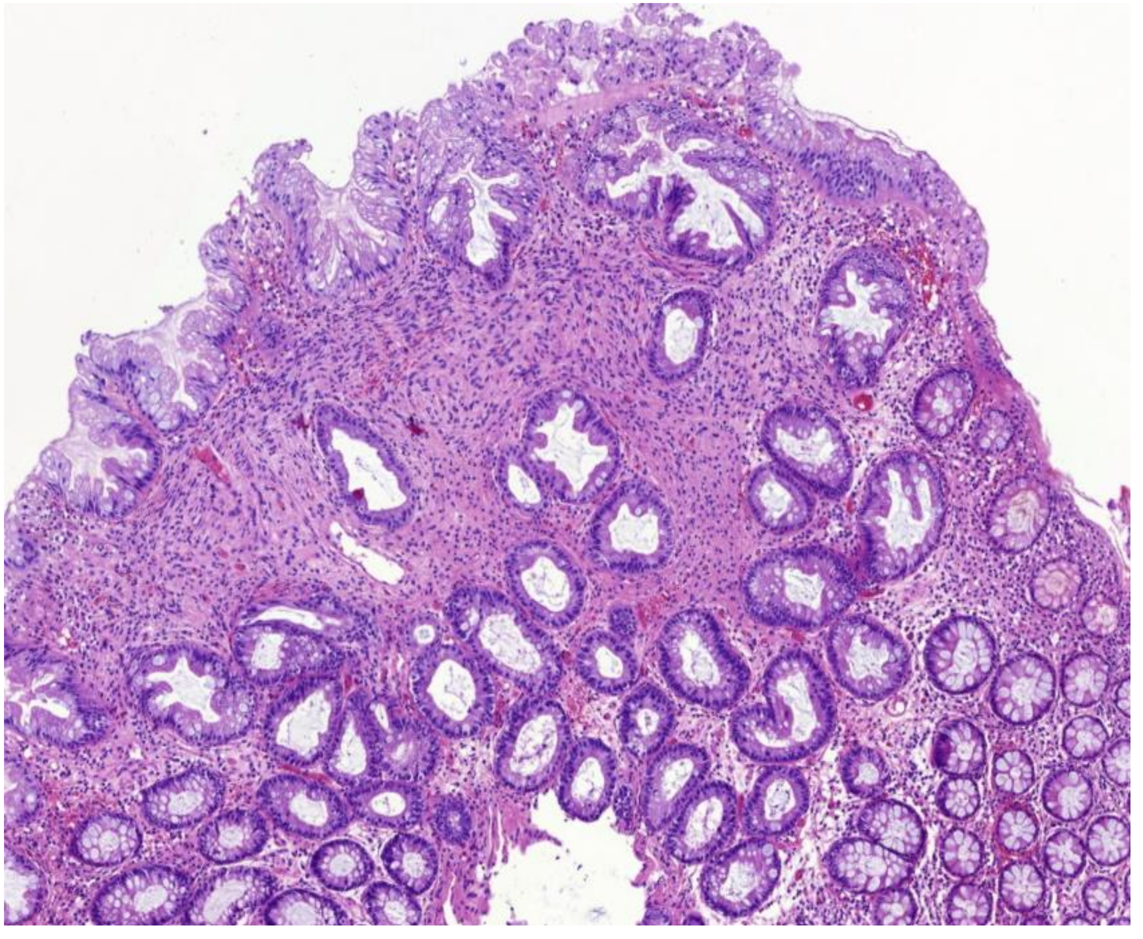
Slizniční hamartom ze Schwannových buněk





„slizniční neurom“
IHC neurofilamenta neg. (vs. neurofibrom)

Slizniční „perineuriom“



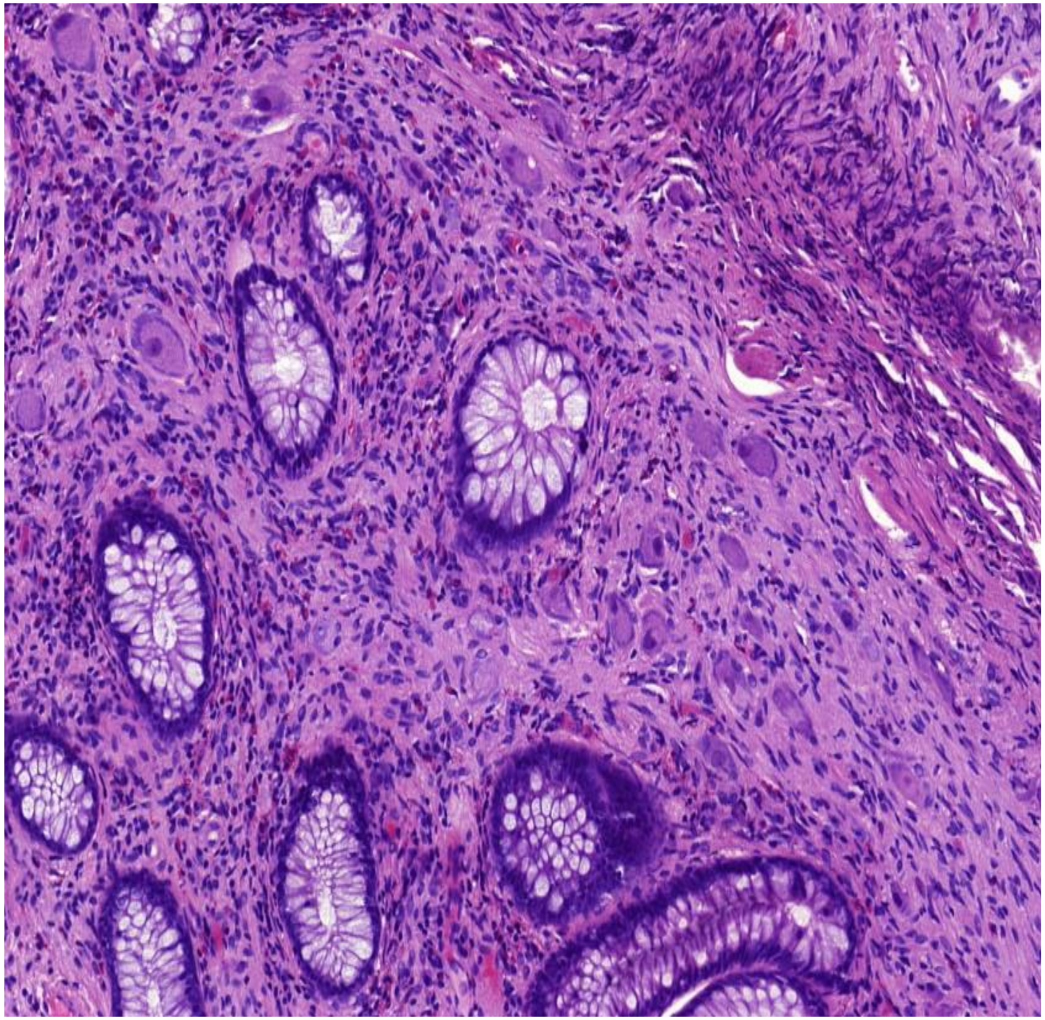
- dříve benigní „*fibroblastický polyp colon*“
- v budoucnu snad „*serrated polyp s perineuriálním stromatem*“

- smíšené epiteliálně-stromální polypy
  - **stromální komponenta:** proliferace perikryptálních fibroblastů (EMA, claudin-1, GLUT1)
  - **epitelová komponenta:** *BRAF* V600E

Agaimy, A., Stoehr, R., Vieth, M., et al. Benign serrated colorectal fibroblastic polyps/intramucosal perineuriomas are true mixed epithelial-stromal polyps (hybrid hyperplastic polyp/mucosal perineurioma) with frequent BRAF mutations. *Am J Surg Pathol, 2010, 34(11): 1663-71.*

Erlenbach-Wünsch, K., Bihl, M., Hartmann, A., et al. Serrated epithelial colorectal polyps (hyperplastic polyps, sessile serrated adenomas) with perineurial stroma: Clinicopathological and molecular analysis of a new series. *Ann Diagn Pathol, 2018, 35: 48-52.*

Ganglioneurom

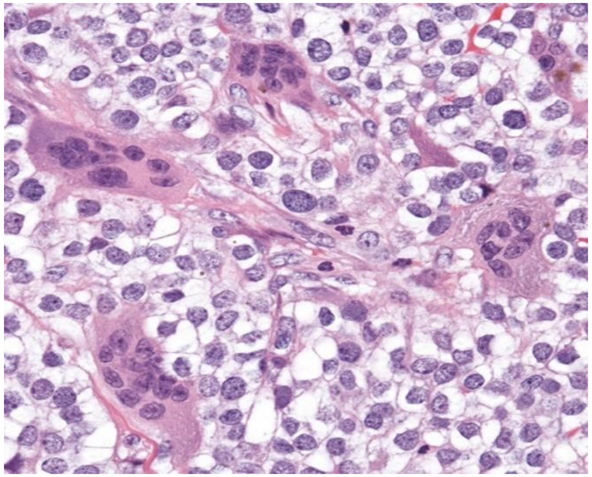
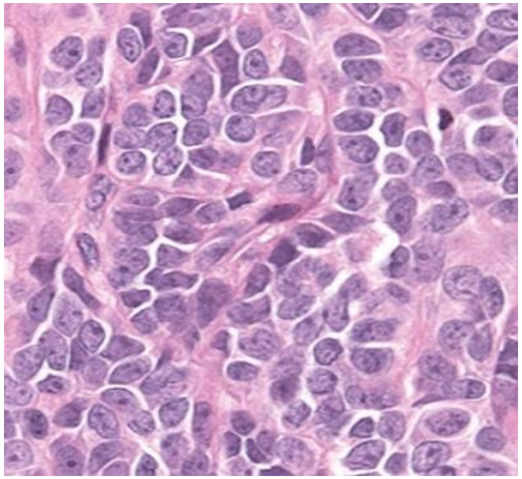
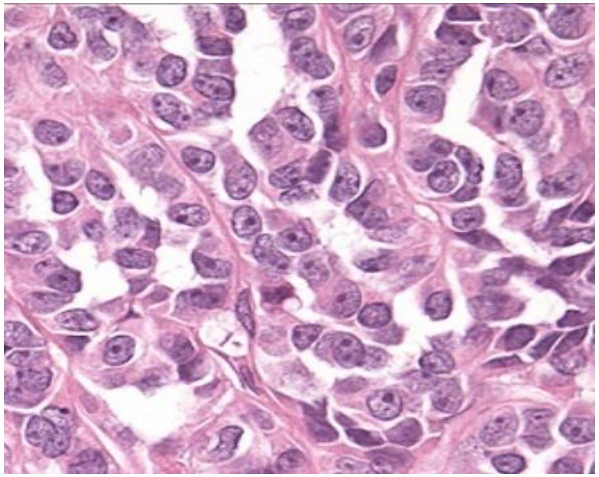


Především tlusté střevo

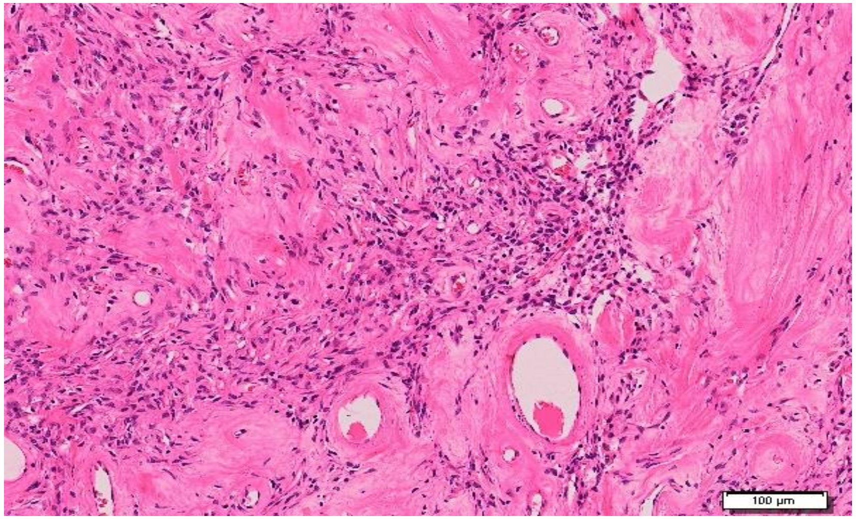
- Polypoidní ganglioneurom
- Ganglioneuromatózní polypóza
  - > 20 polypů
  - + ex-GIT lipomy a acrochordony
- Difúzní ganglioneuromatóza
  - MEN2B
  - NF1
  - syndrom Cowdenové (PTEN)
  - tuberozní skleróza
  - JPS

CCS/GNET

- Spektrum nádorových obrazů vycházející v. s. z primitivních nádorových buněk autonomního nervového systému z neurální lišty
- *EWSR*/*ATF1*, *EWSR1*/*CREB1*
- Společná IHC: S100, SOX10
  - **CCS:** diferenciace melanocytárním směrem (HMB45, melan A)
  - **GNET:** primitivní neuroektodermální/neurální (synaptofyzin, chromogranin, CD56)

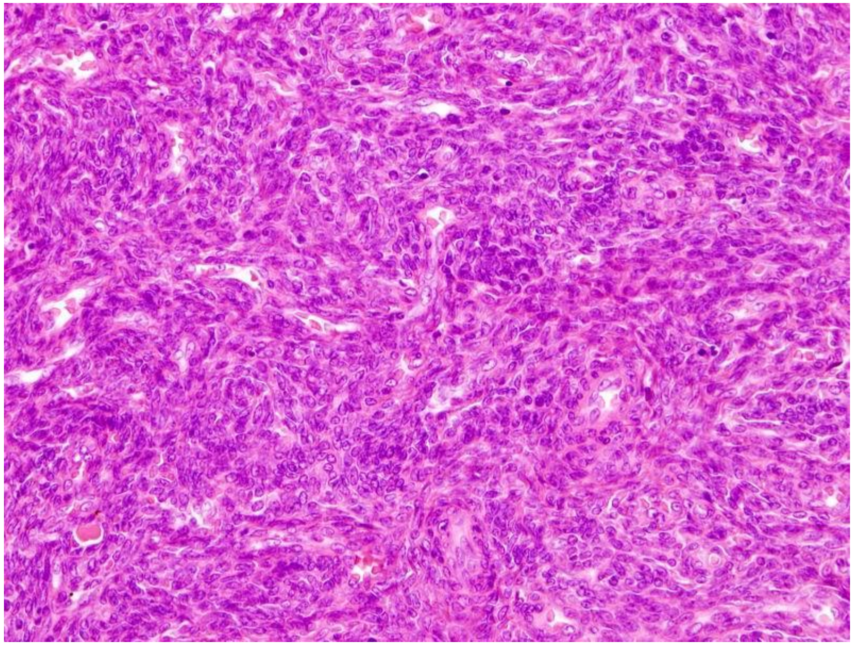




KIT-, S100-, desmin-



SFT ?

~~CD34, bcl2, CD99~~
druhé čtení
STAT6
NAB2/*STAT6*

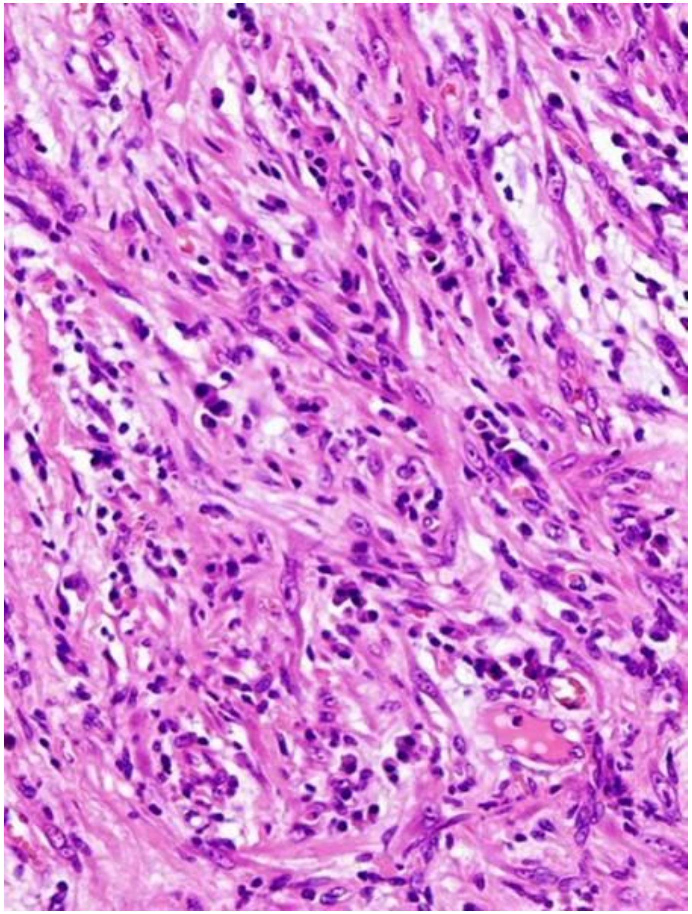


CD10+, ER+
anamnéza
gynekologické vyšetření

? druhé čtení
KIT / *PDGFRA*
JAZF1-JJAZ1

ESS

KIT-, S100-, „zánětlivá histologie“



Intimní kontakt vřetenitých buněk s lymfocyty

Desmin -

CD21+, CD35+

→ FDC tumor

SMA, calponin +

Desmin +/-

ALK1 +/-

Systémové příznaky +/-

→ IMT

Histopathology

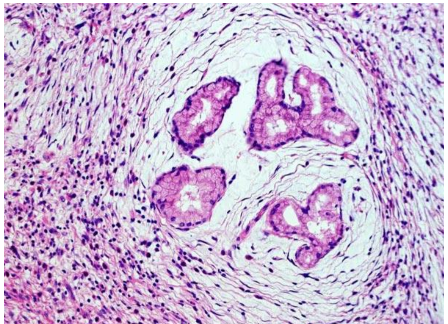
Histopathology 2016, 69, 72–83. DOI: 10.1111/his.12910

ALK, *ROS1* and *NTRK3* gene rearrangements in inflammatory myofibroblastic tumours

Hidetaka Yamamoto, Akihiko Yoshida,[1] Kenichi Taguchi,[2] Kenichi Kohashi, Yui Hatanaka, Atsushi Yamashita,[3] Daisuke Mori[4] & Yoshinao Oda

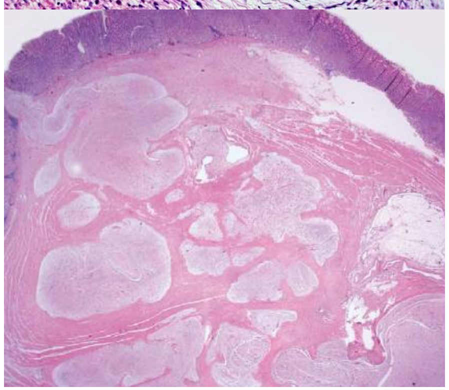
- Děti, mladí dospělí
- Lokální recidivy až u ¼ případů, maligní chování vzácné (vysoká celularita a mitotická aktivita)
- Široké spektrum translokací:
  - ***ALK*** (fúzními partnery *TPM3/4*, *RANBP2*, *TFG*, *CARS*, *ATIC*, *LMNA*, *PRKAR1A*, *CLTC*, *FN1*, *SEC31A*, *EML4* …)
  - a další genové fúze: *ROS1* (*YWHAE – ROS1*, *TGF-ROS1*), *PDGFRB* (*NAB2-PDGFRB*), *ETV6* (*ETV6-NTRK3*) , *RET* …

KIT-, S100-, desmin-, netypická histologie, (pod)slizniční lokalizace



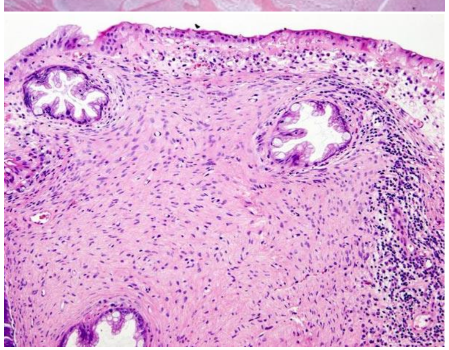
CD34+
PDGFRA mut

Vaňkův tumor



CD34-
PDGFRA wt

plexiformní fibromyxom



EMA, claudin 1, GLUT1+
BRAF mut

slizniční „perineuriom“

GASTRIC SUBMUCOSAL GRANULOMA WITH EOSINOPHILIC INFILTRATION *

J. VANĚK, M.D.
(*From the First Department of Pathology, Charles University, Prague, Czechoslovakia*)

Am J Pathol 1949; 25(3): 397-411

J Pathol 2008; **216**: 176–182
Published online 13 June 2008 in Wiley InterScience
(www.interscience.wiley.com) **DOI:** 10.1002/path.2393

Original Paper

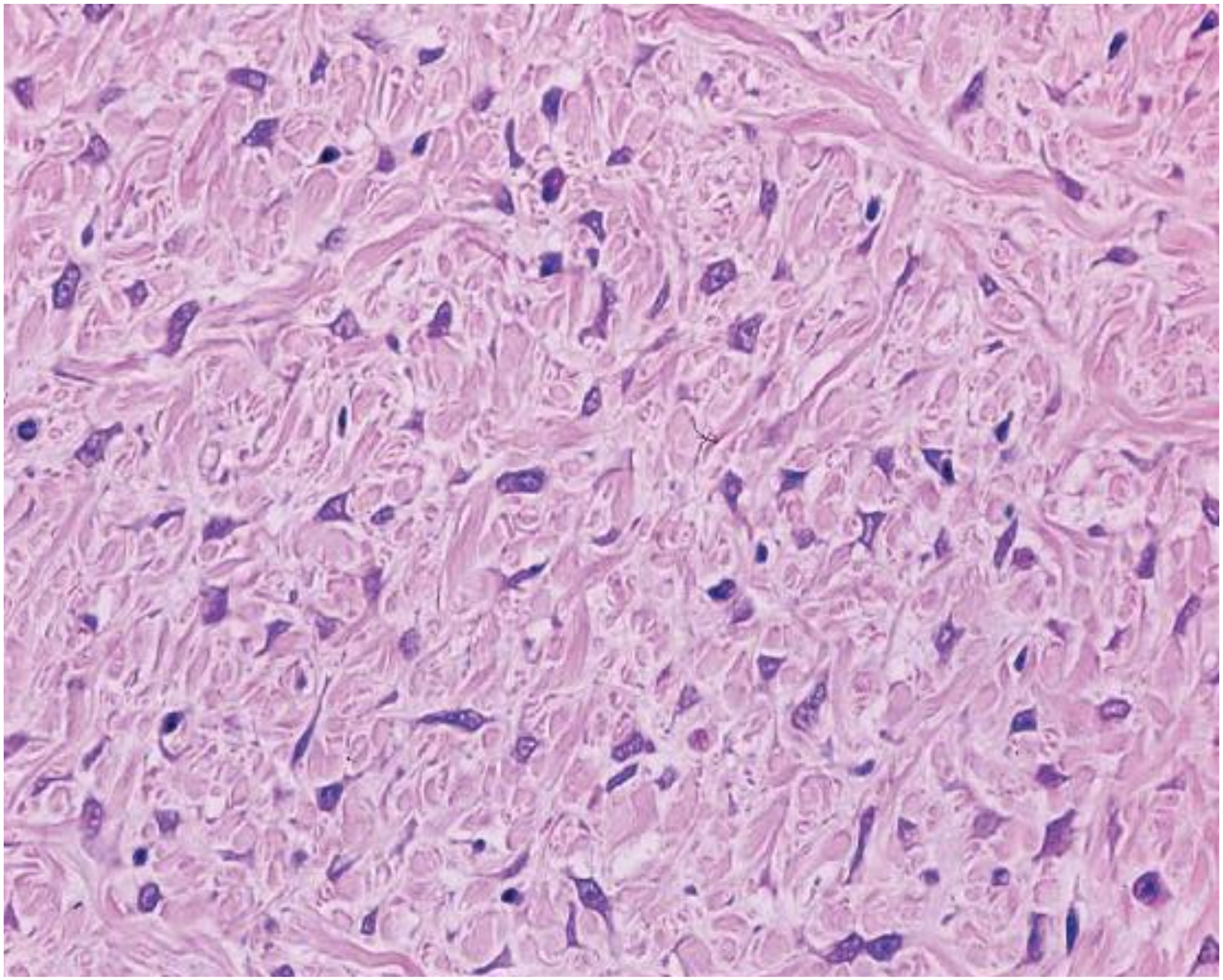
Inflammatory fibroid polyps harbour mutations in the *platelet-derived growth factor receptor alpha* (*PDGFRA*) gene

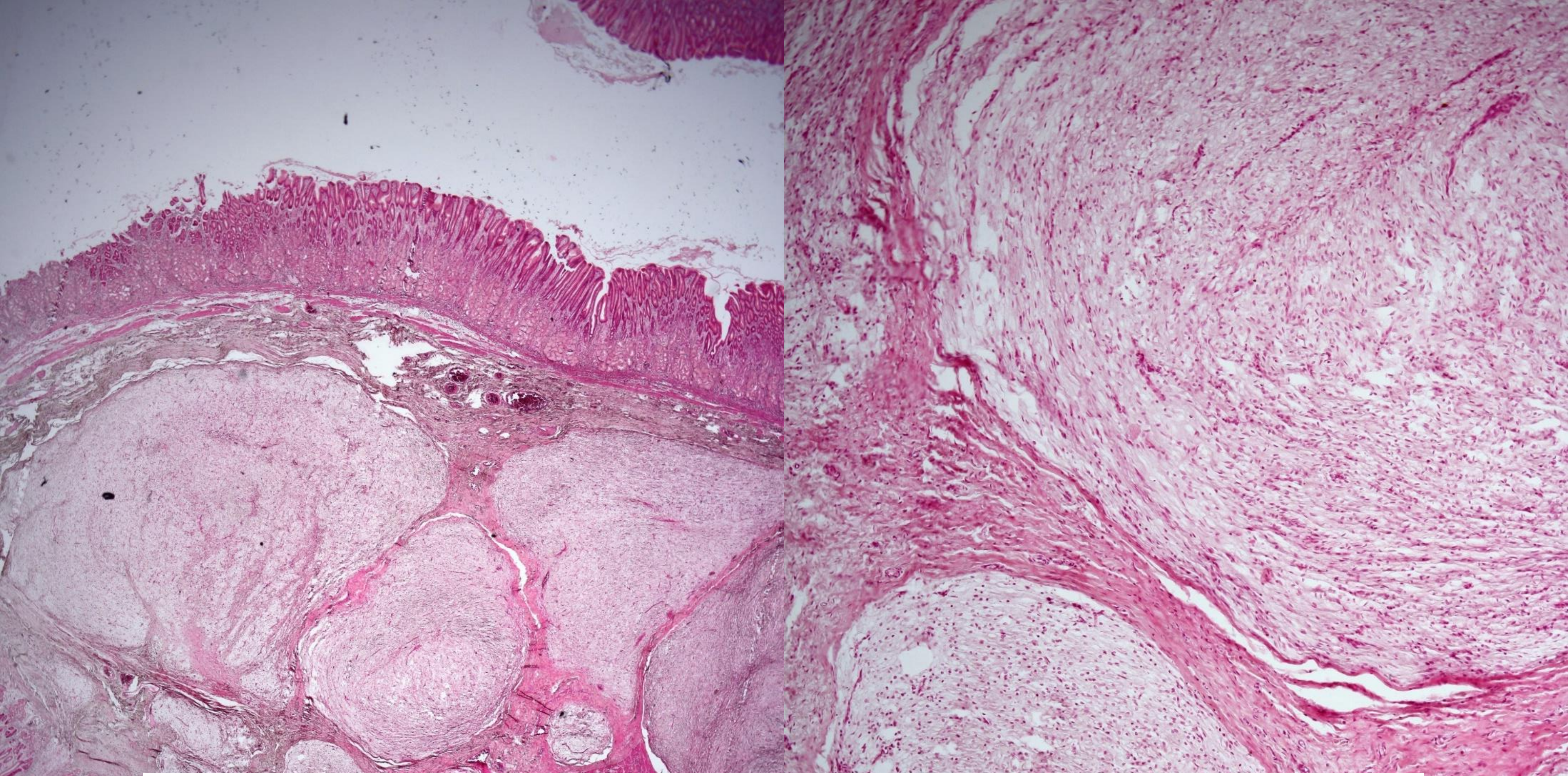
H-U Schildhaus, T Cavlar, E Binot, R Büttner, E Wardelmann* and S Merkelbach-Bruse
Institute of Pathology, University of Bonn Medical School, Bonn, Germany

Stromal, Fibrous, and Fatty Gastrointestinal Tumors in a Patient With a *PDGFRA* Gene Mutation

J. Aidan Carney, MD, PhD, FRCPI, FRCP and Constantine A. Stratakis, MD, D(Med)Sci†*

(*Am J Surg Pathol* 2008;32:1412–1420)



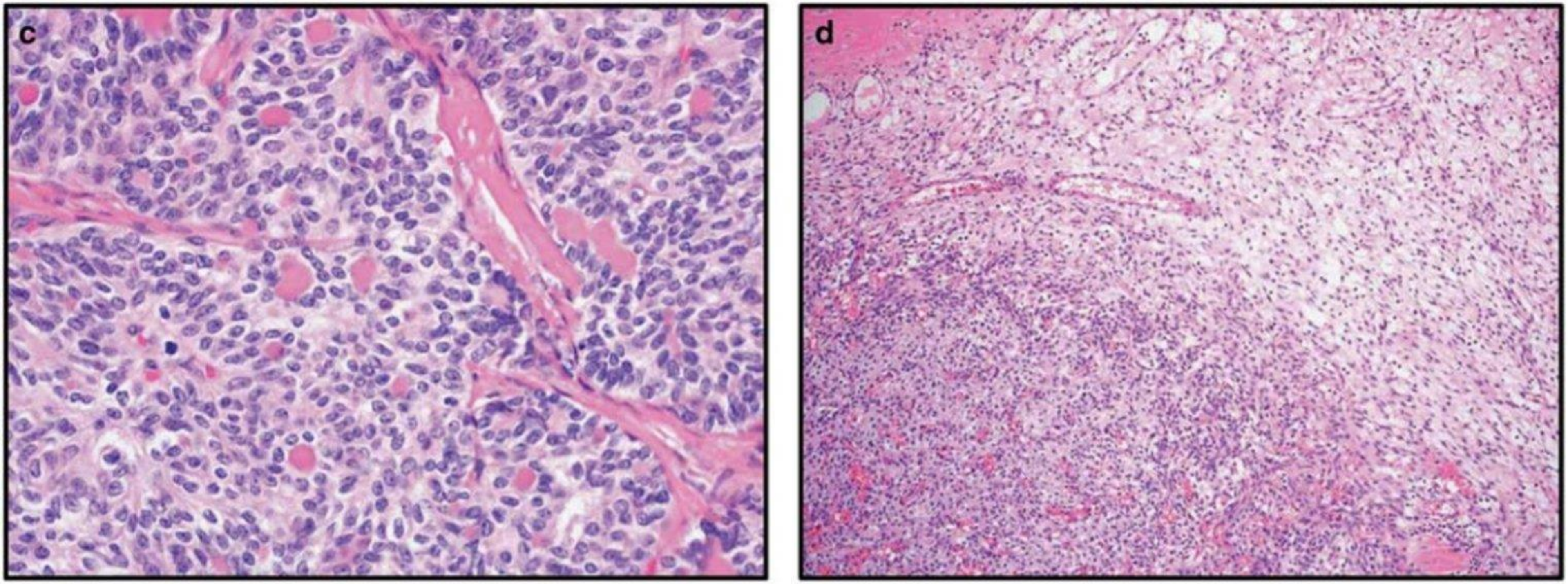


Journal of Pathology
J Pathol 2016; **239:** 335–343
Published online 20 May 2016 in Wiley Online Library
(wileyonlinelibrary.com) **DOI:** 10.1002/path.4730

ORIGINAL PAPER

Recurrent *MALAT1–GLI1* oncogenic fusion and *GLI1* up-regulation define a subset of plexiform fibromyxoma

Lien Spans,[1] Christopher DM Fletcher,[2] Cristina R Antonescu,[3] Alexandre Rouquette,[4] Jean-Michel Coindre,[5] Raf Sciot[6†] and Maria Debiec-Rychter[1*†]



Gastroblastoma harbors a recurrent somatic *MALAT1–GLI1* fusion gene

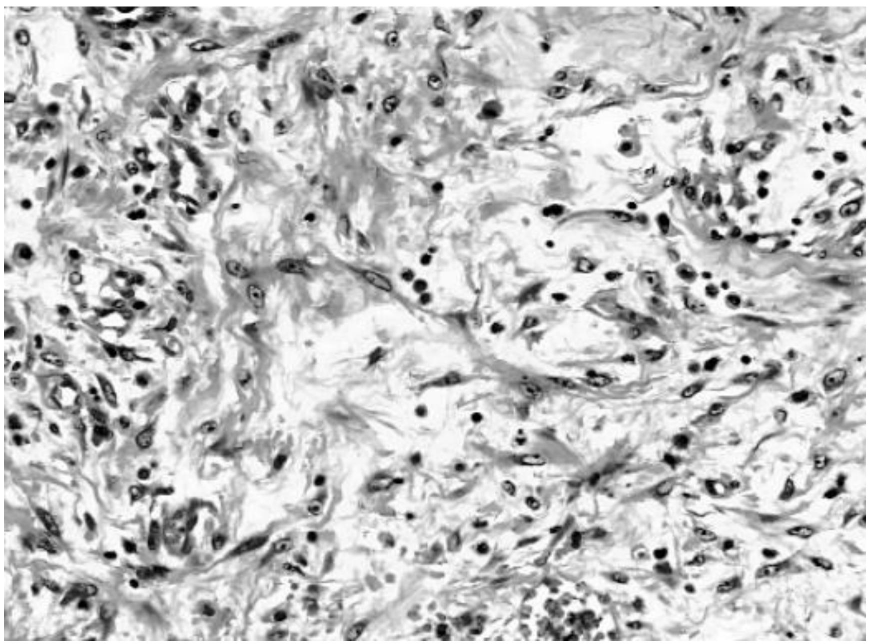
Rondell P Graham[1,2], Asha A Nair[3], Jaime I Davila[3], Long Jin[2], Jin Jen[4], William R Sukov[2], Tsung-Teh Wu[1], Henry D Appelman[5], Jorge Torres-Mora[1], Kyle D Perry[1], Lizhi Zhang[1], Sara M Kloft-Nelson[4], Ryan A Knudson[4], Patricia T Greipp[2] and Andrew L Folpe[1]

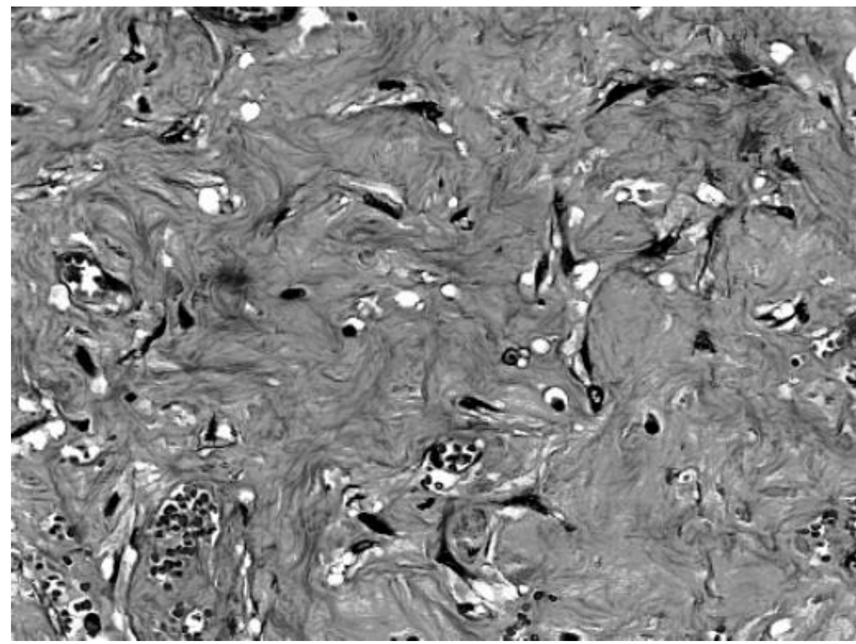
Modern Pathology (2017) **30,** 1443–1452

International Journal of Surgical Pathology 12(4):365–374, 2004

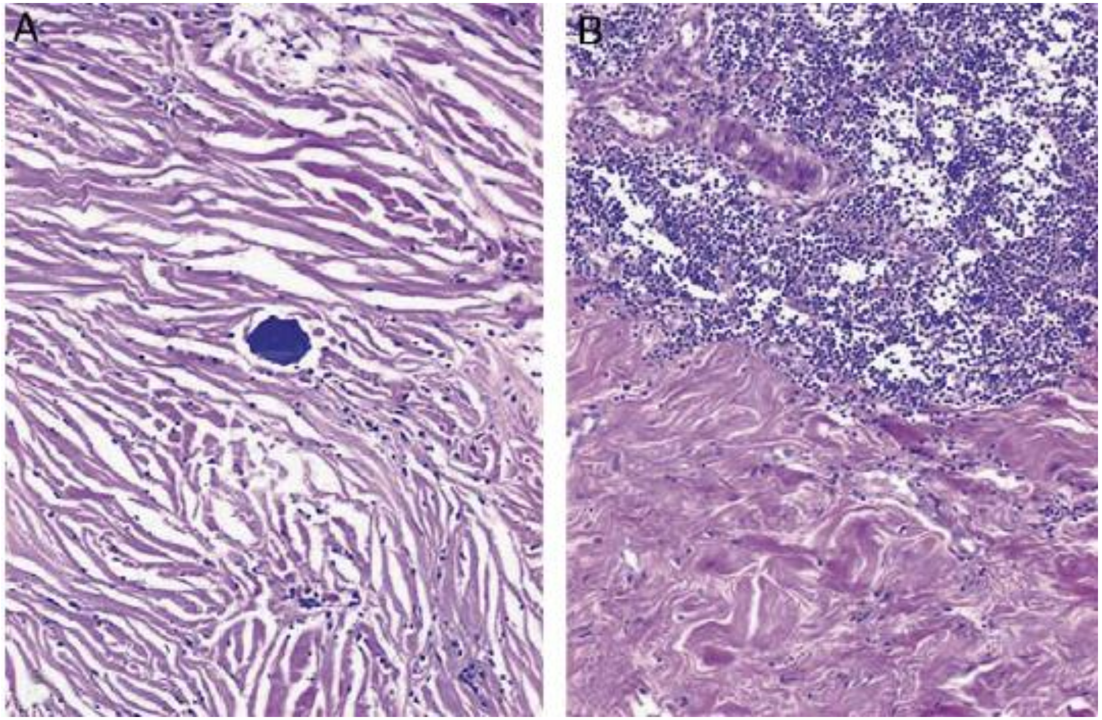
Reactive Nodular Fibrous Pseudotumors of the Gastrointestinal Tract: Report of 8 Cases

Ondrej Daum, MD,* Tomas Vanecek, Msc,* Radek Sima, Msc,*
Romuald Curik, MD,† Michal Zamecnik, MD,* Shoji Yamanaka, MD,‡
Petr Mukensnabl, MD,* Zdenek Benes, MD,§ and Michal Michal, MD*





Reaktivní proliferace multipotentních subserózních buněk schopných diferenciace v (myo)fibroblasty i epitelové (mesotelové) buňky



Human Pathology (2018) **78**, 36–43

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Human
PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

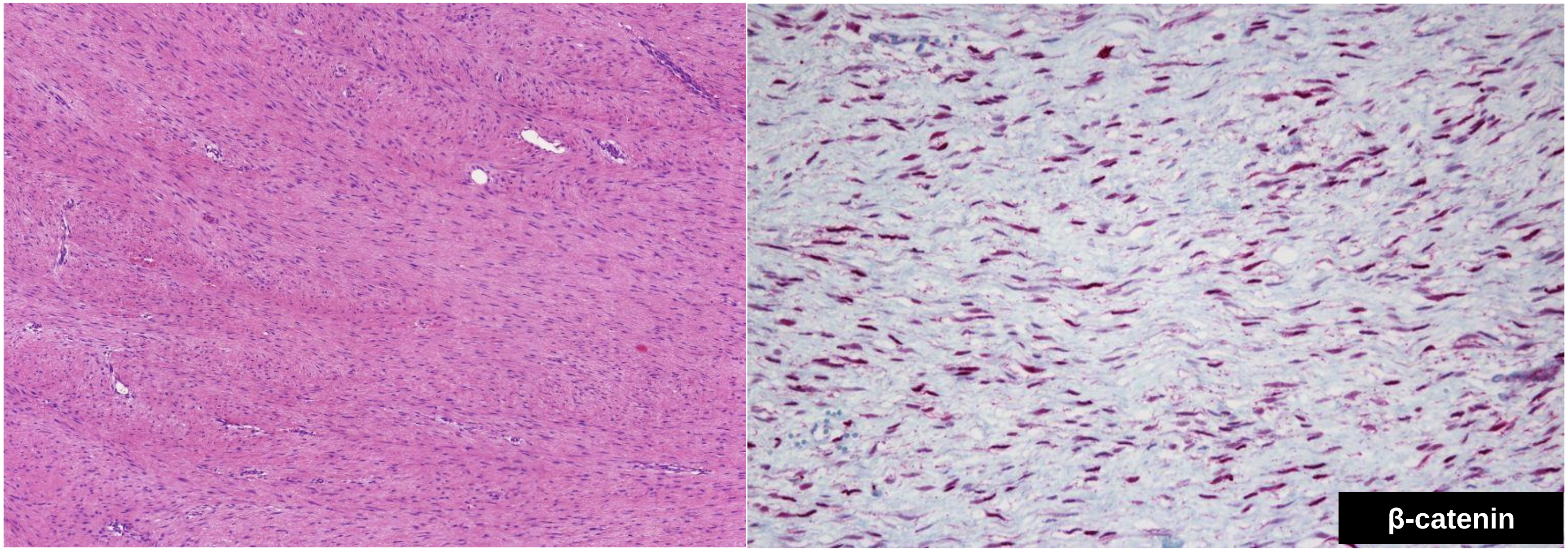
Whole-exome sequencing identifies unique mutations and copy number losses in calcifying fibrous tumor of the pleura: report of 3 cases and review of the literature☆

Mitra Mehrad MD[a,*], William A. LaFramboise PhD[b,c], Maureen A. Lyons MS[b,c], Humberto E. Trejo Bittar MD[b], Samuel A. Yousem MD[b]

mutace *ZNF717*, *FRG1*, *CDC27*
ztráta 6p22 (třeba *HFE*)

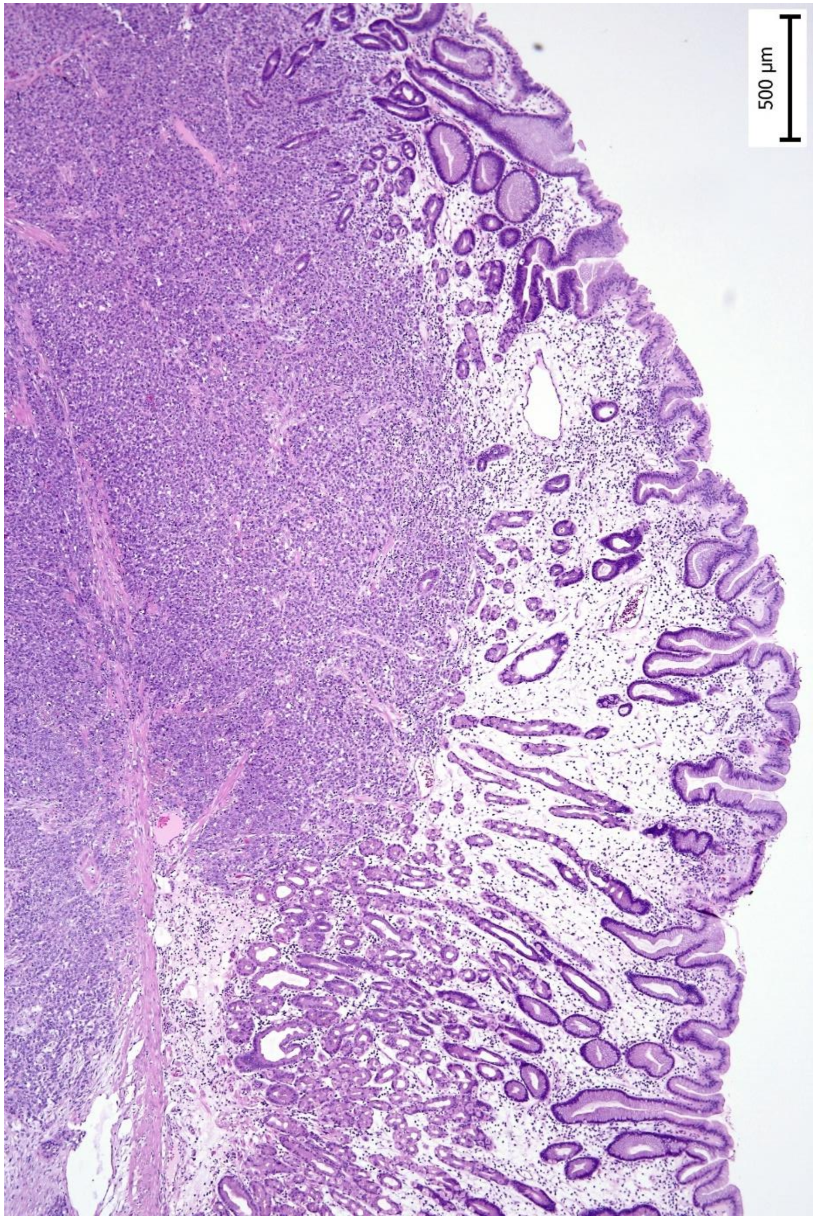
Intraabdominální fibromatóza (desmoid)

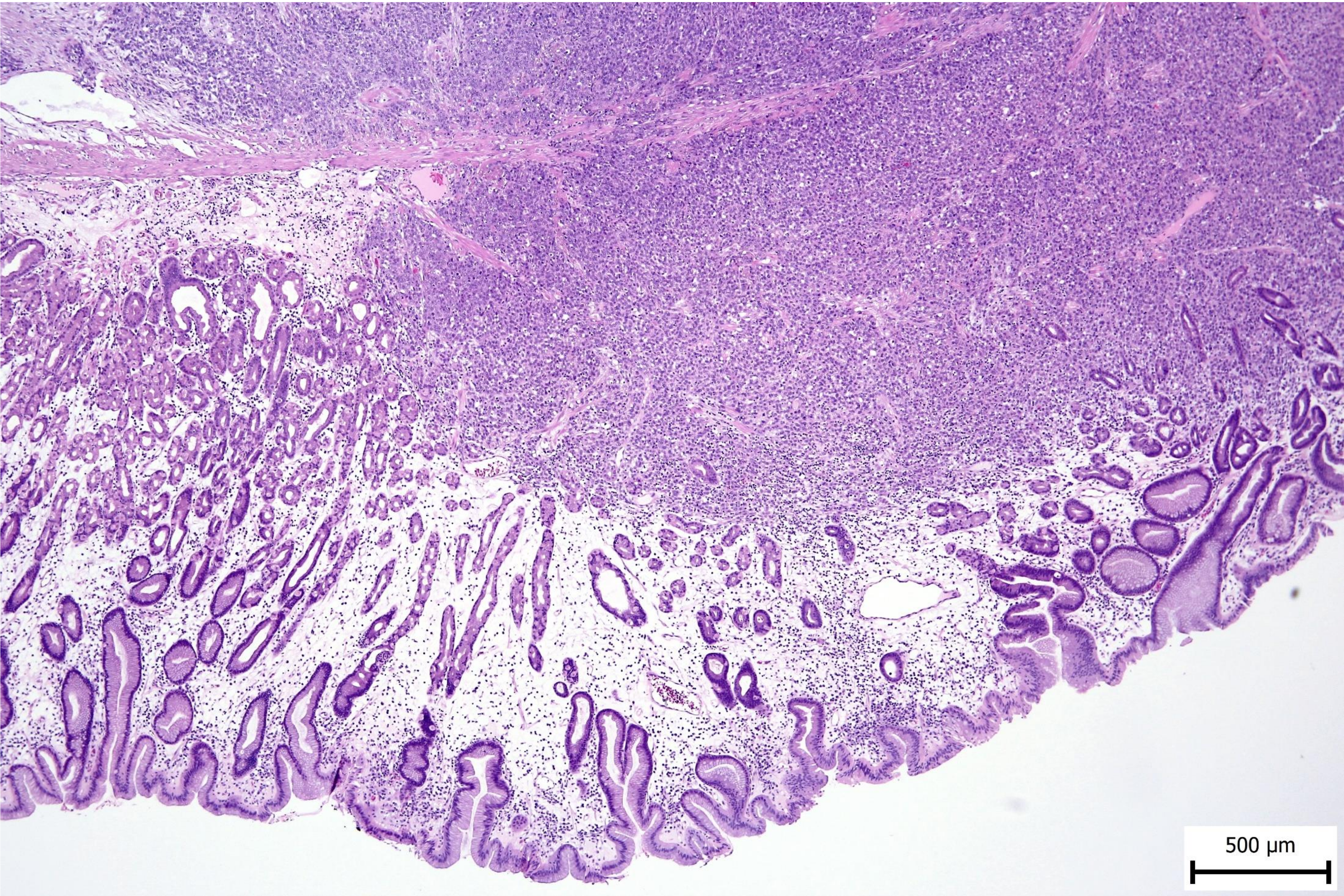
- Tumoriformní lokálně agresivní léze
- Mesenterium, retroperitoneum, vzácně stěna GIT
- Sporadicky/v asociaci s FAP (Gardner)
- Imunohistochemický profil: **jaderný β-catenin +**
- Molekulárně genetický profil: ***CTNNB1*** nebo ***APC***

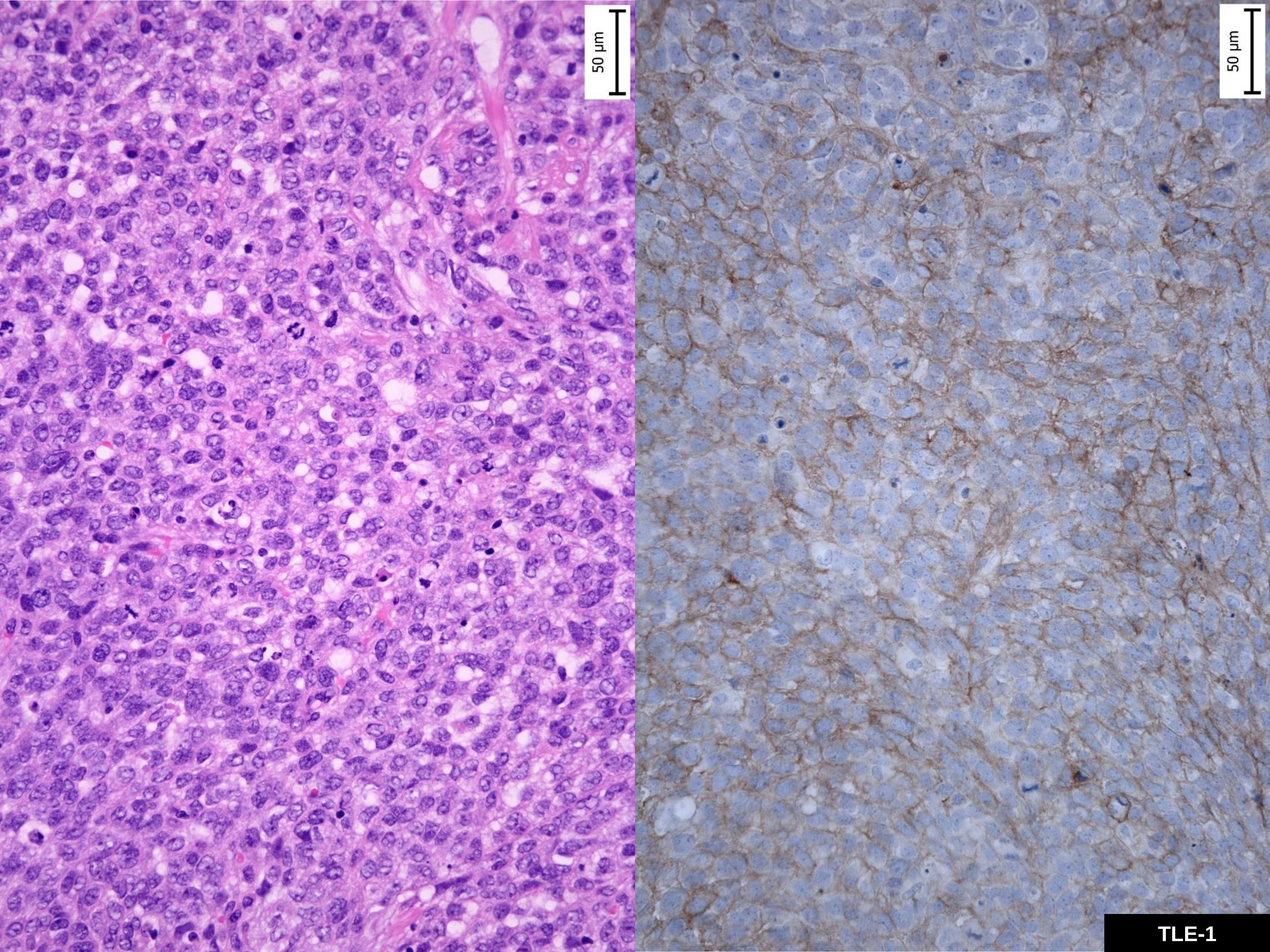


Synoviální sarkom

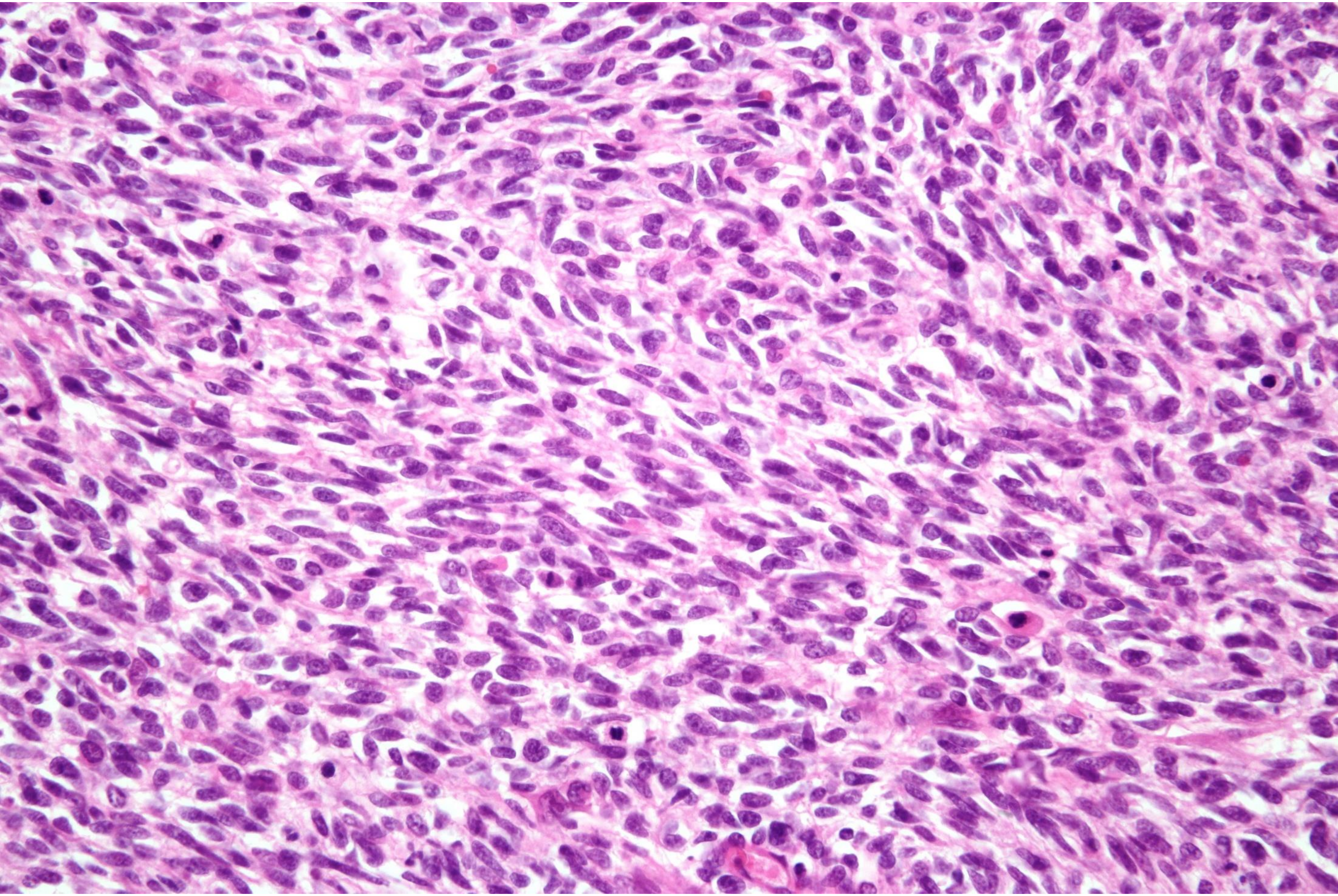
- Vzácný, nejčastěji v žaludku (monofazický) a jícnu (bifazický)
- Imuno:
  - CK (CK7, CK19)
  - EMA
  - **TLE-1**
  - **ojediněle CD117, DOG1**
- t(X;18):
  - *SS18/SSX1*, *SS18/SSX2*, *SS18/SSX4*

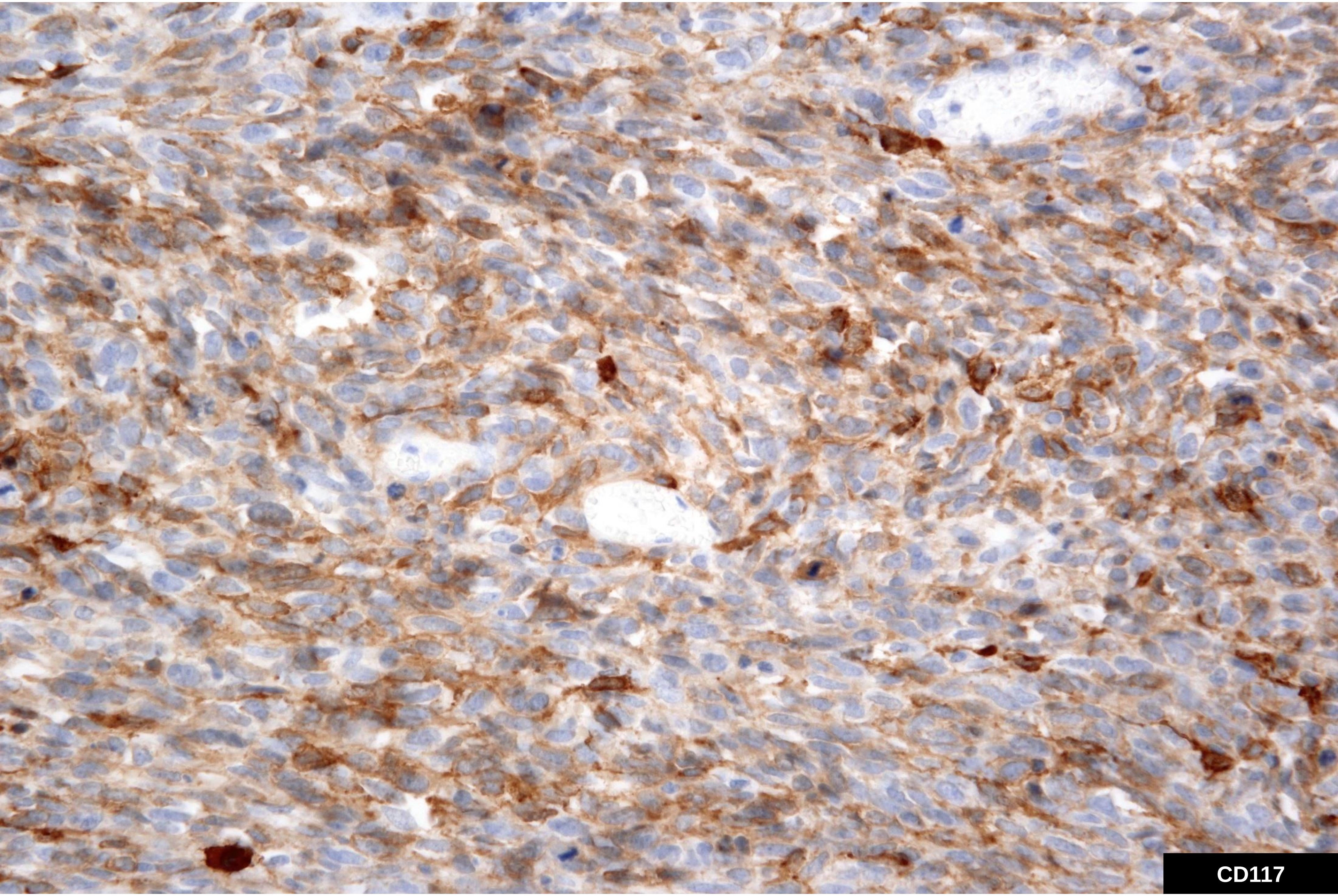


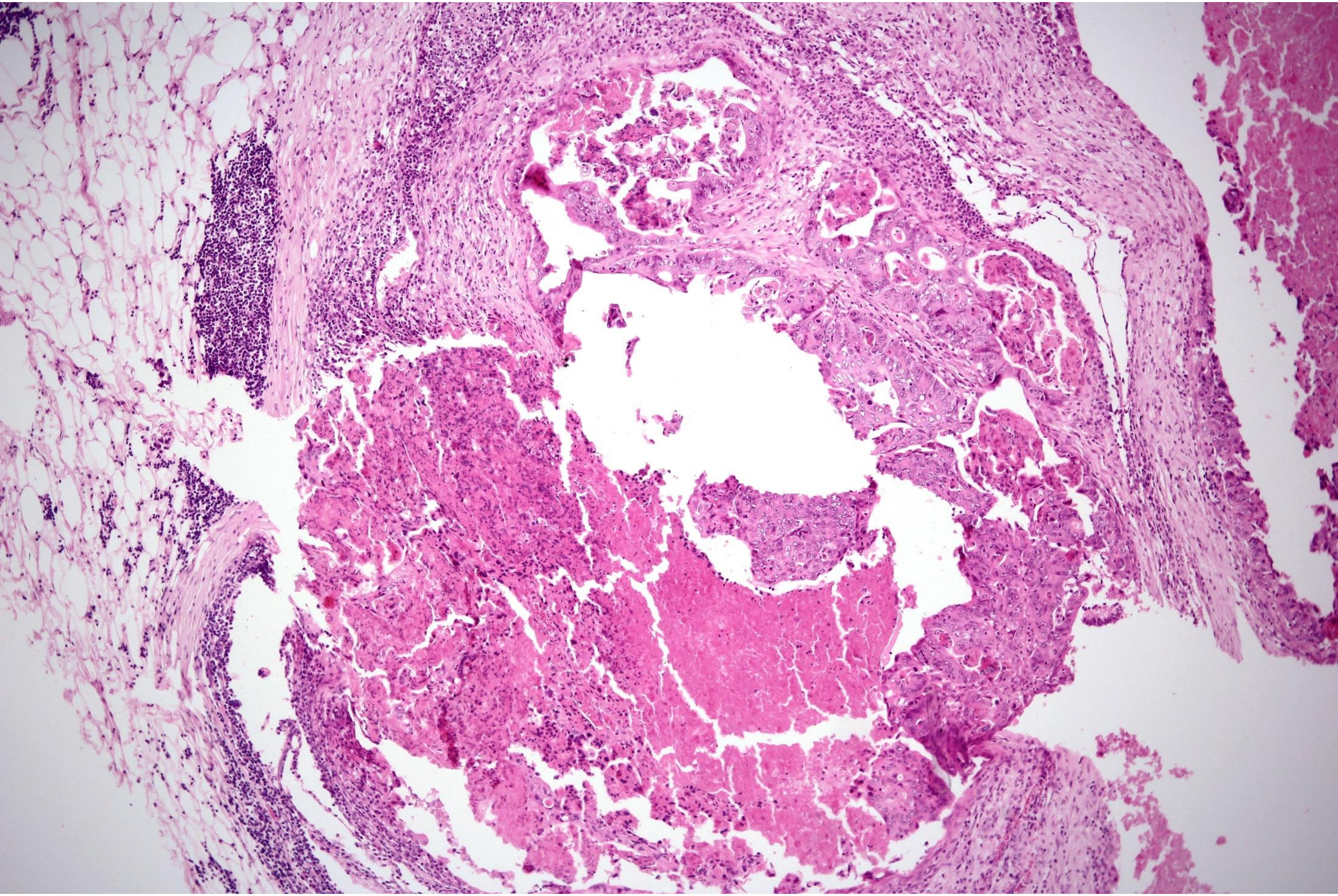

500 µm

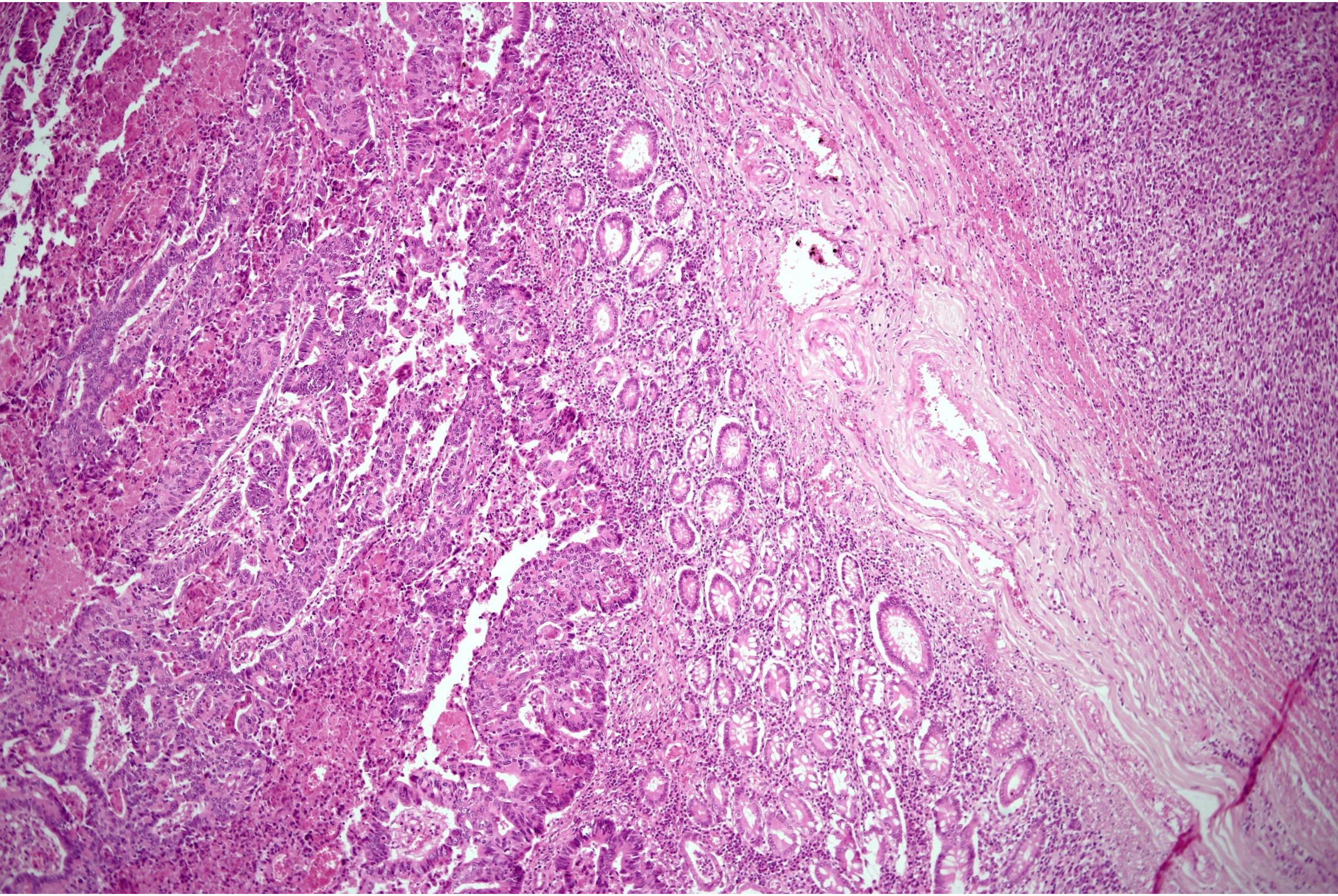

50 µm
50 µm
TLE-1

!




CD117





GIST vs.:

__KIT:__
Seminom
Maligní melanom

__PDGFRA:__
Vaňkův tumor

__RAS:__
Maligní melanom
CRC

__BRAF:__
Maligní melanom
CRC
Slizniční perineuriom

__NTRK:__
Inflamatorní myofibroblastický tumor
CRC

__PIK3CA:__
Kulatobuněčný LPS
CRC
Ca. žaludku