Two “softish” pancreatic tumors

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Lab of Hepatology, KULeuven

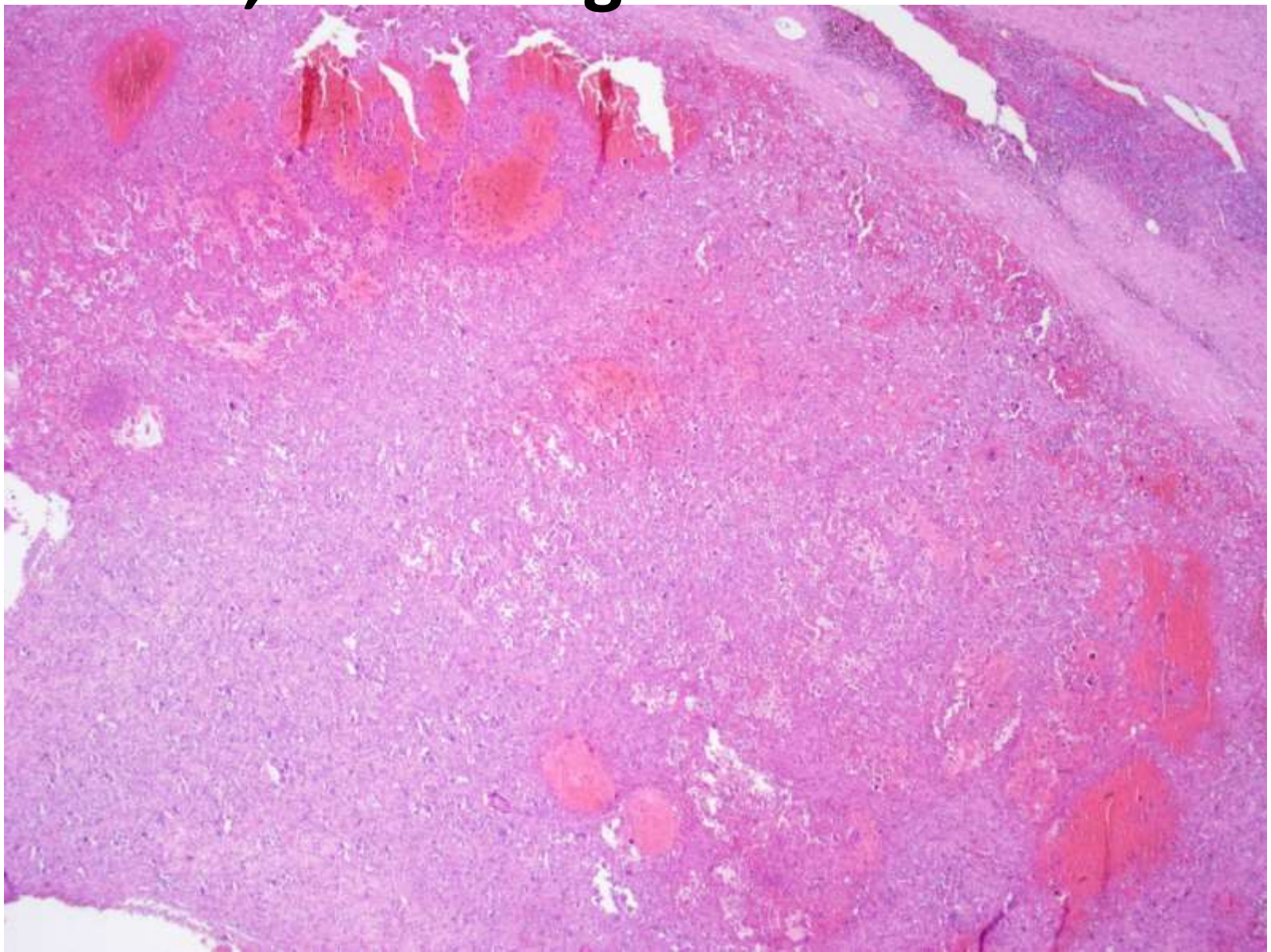
20B4315

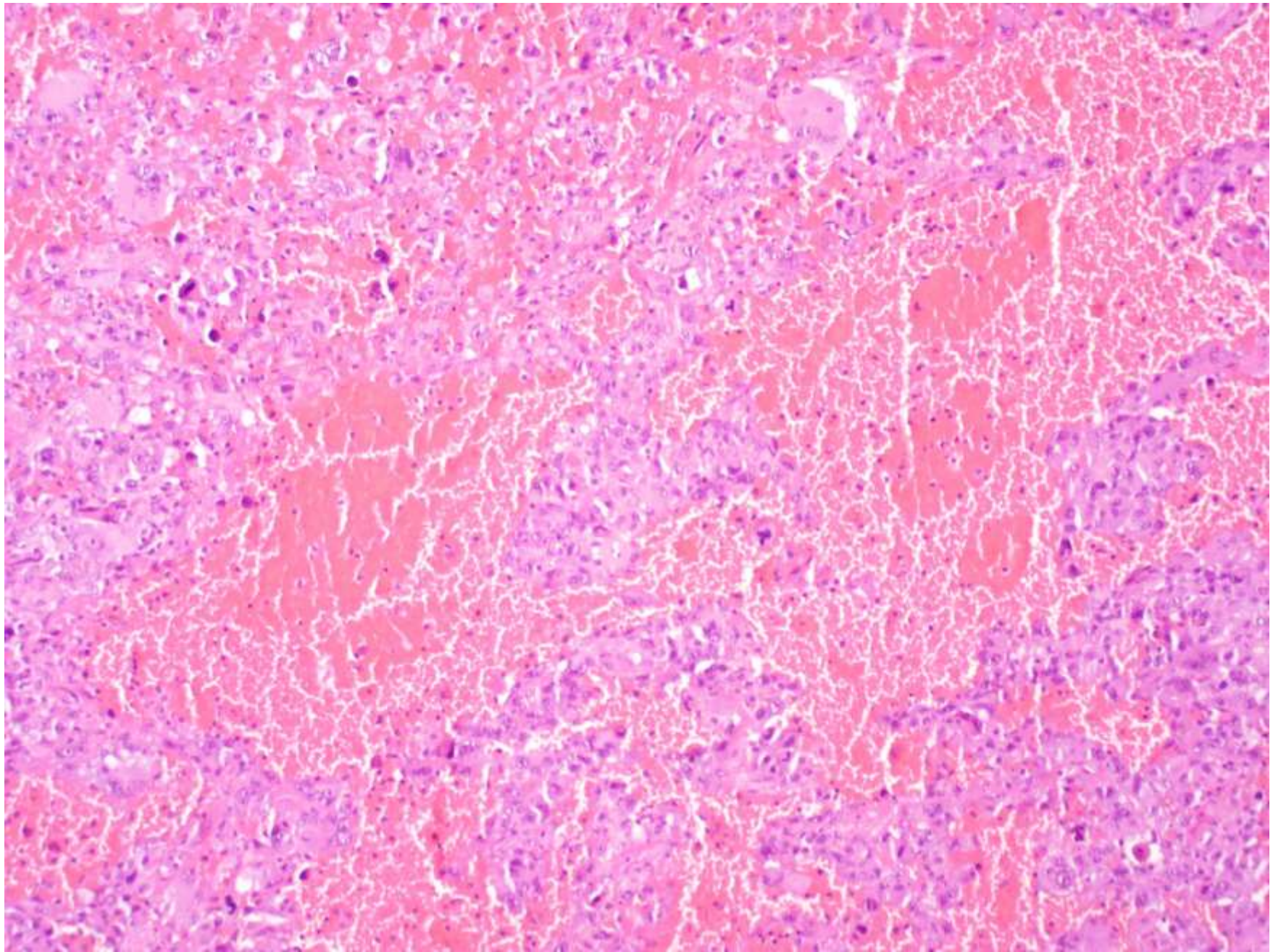
03/2020

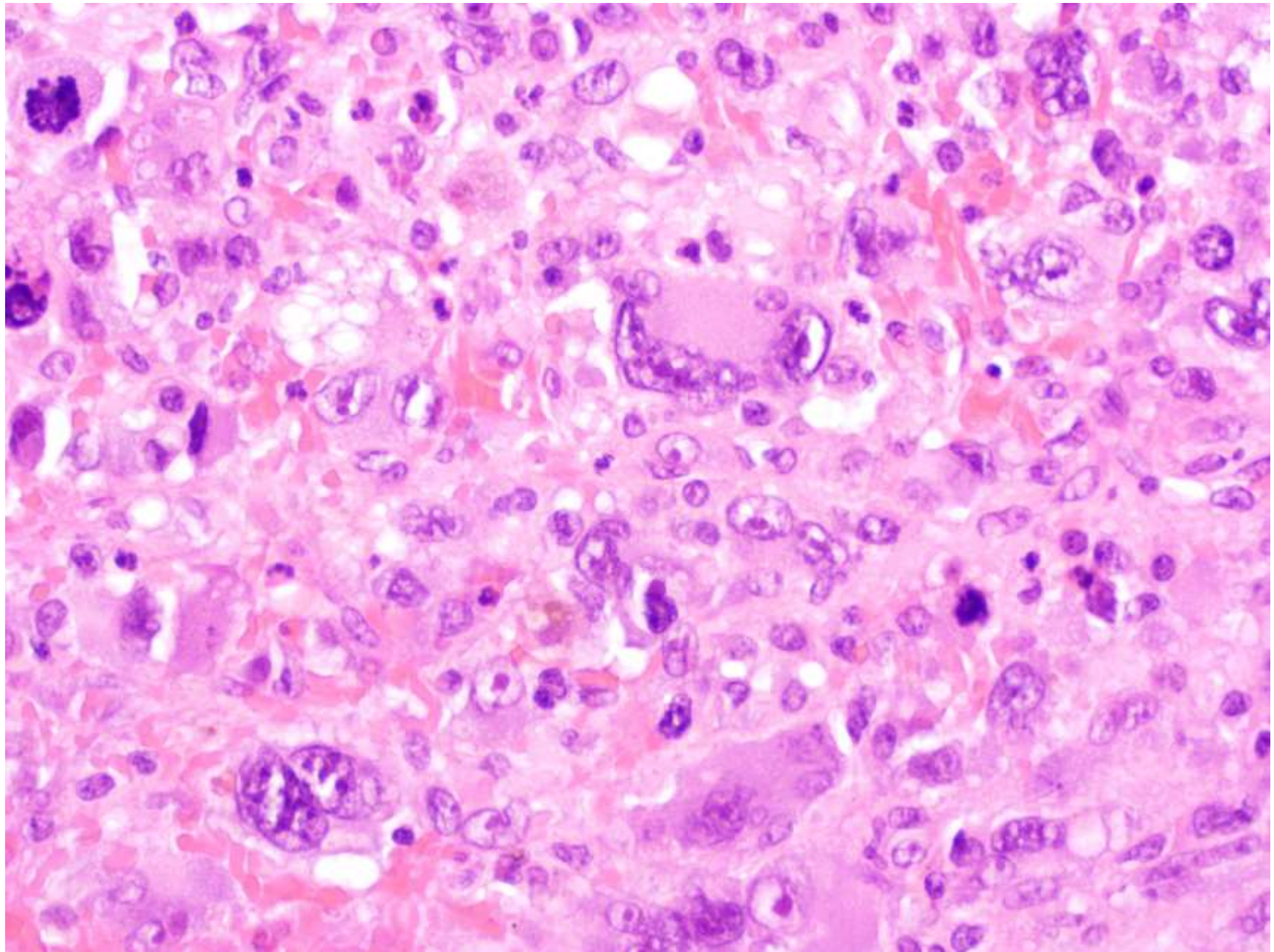
male, 61 y.

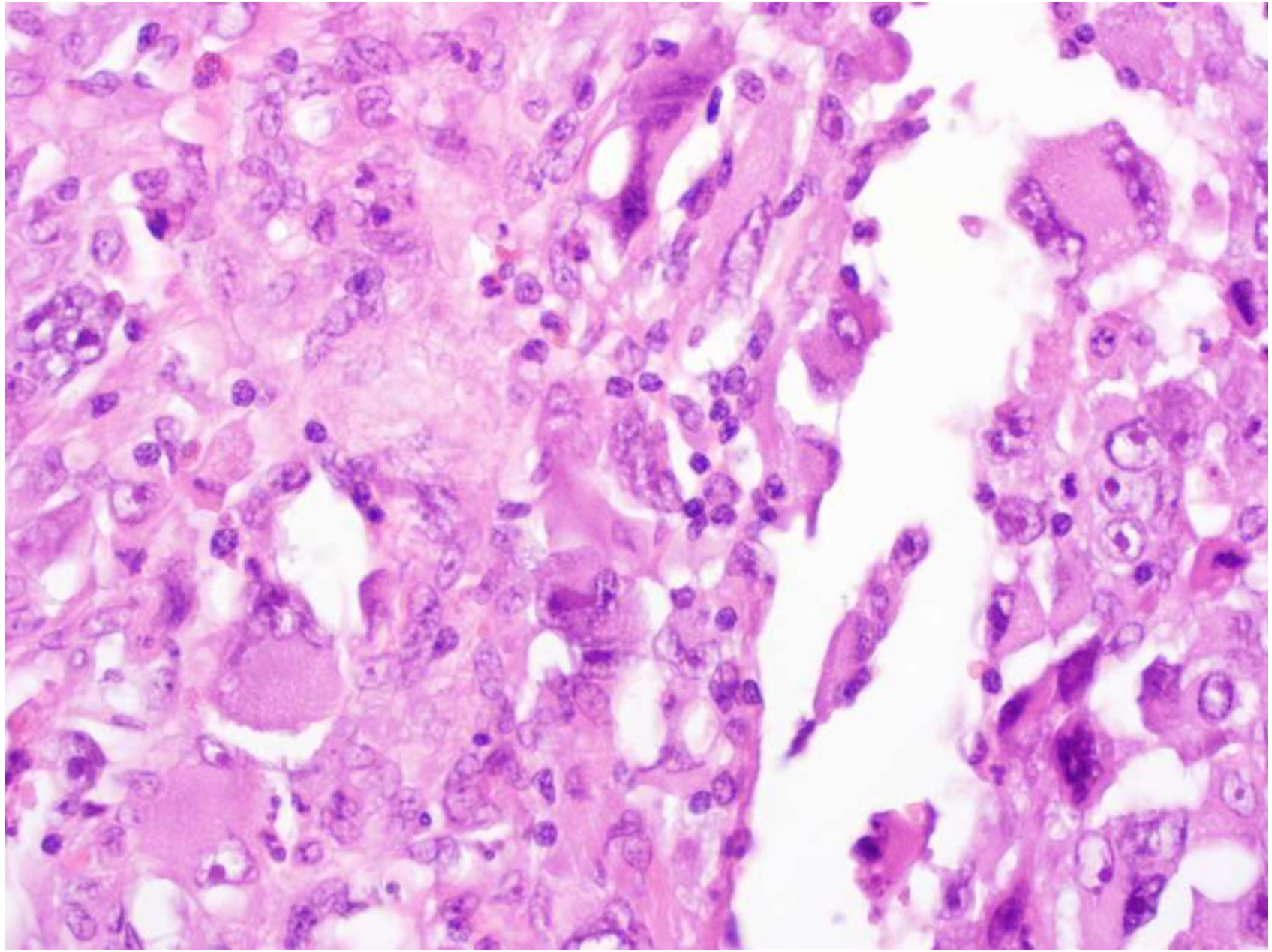
pancreatic tumor with rhabdoid phenotype

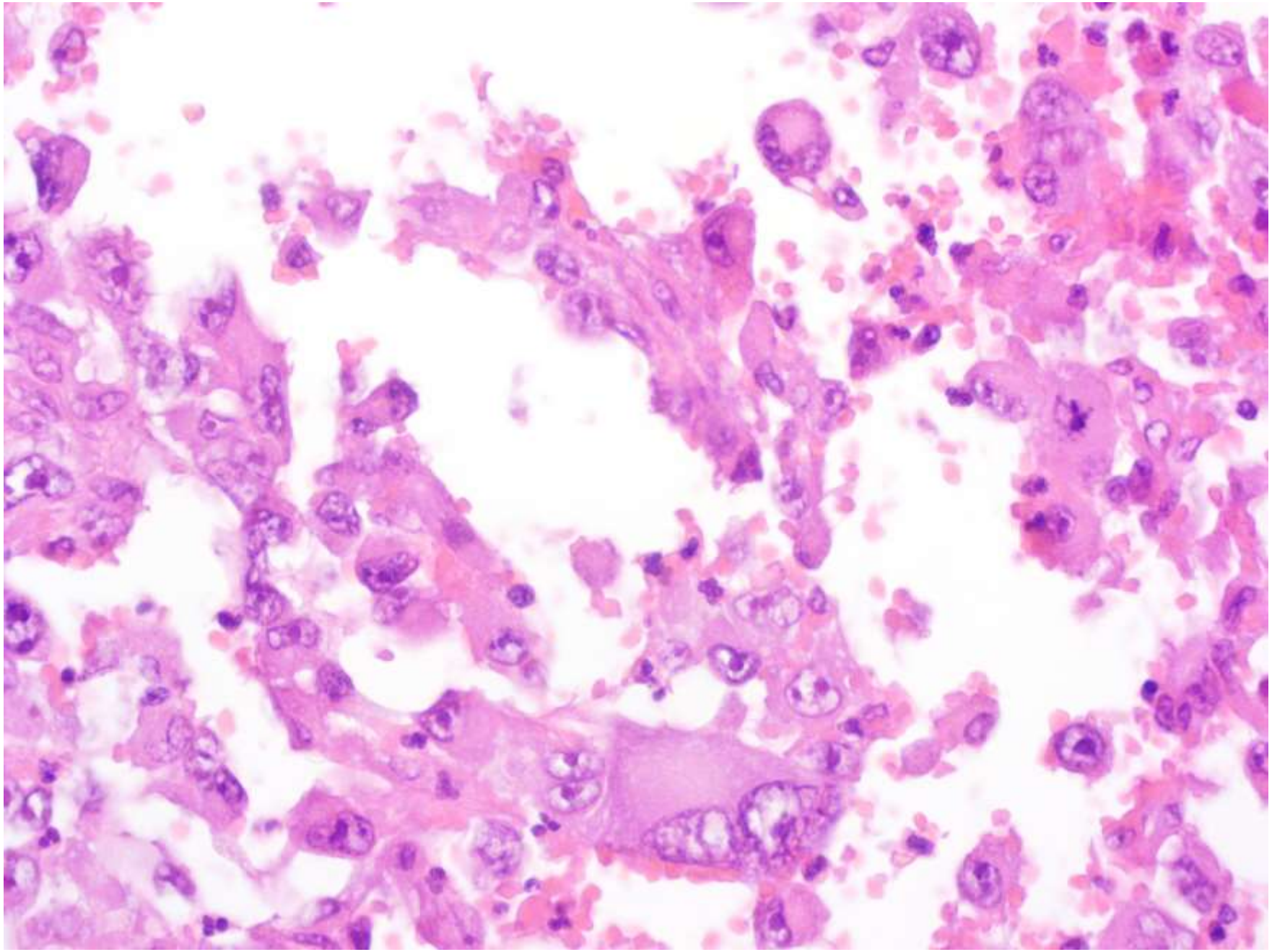
Solid to poorly cohesive to pseudovascular growth pattern, without glandular structures

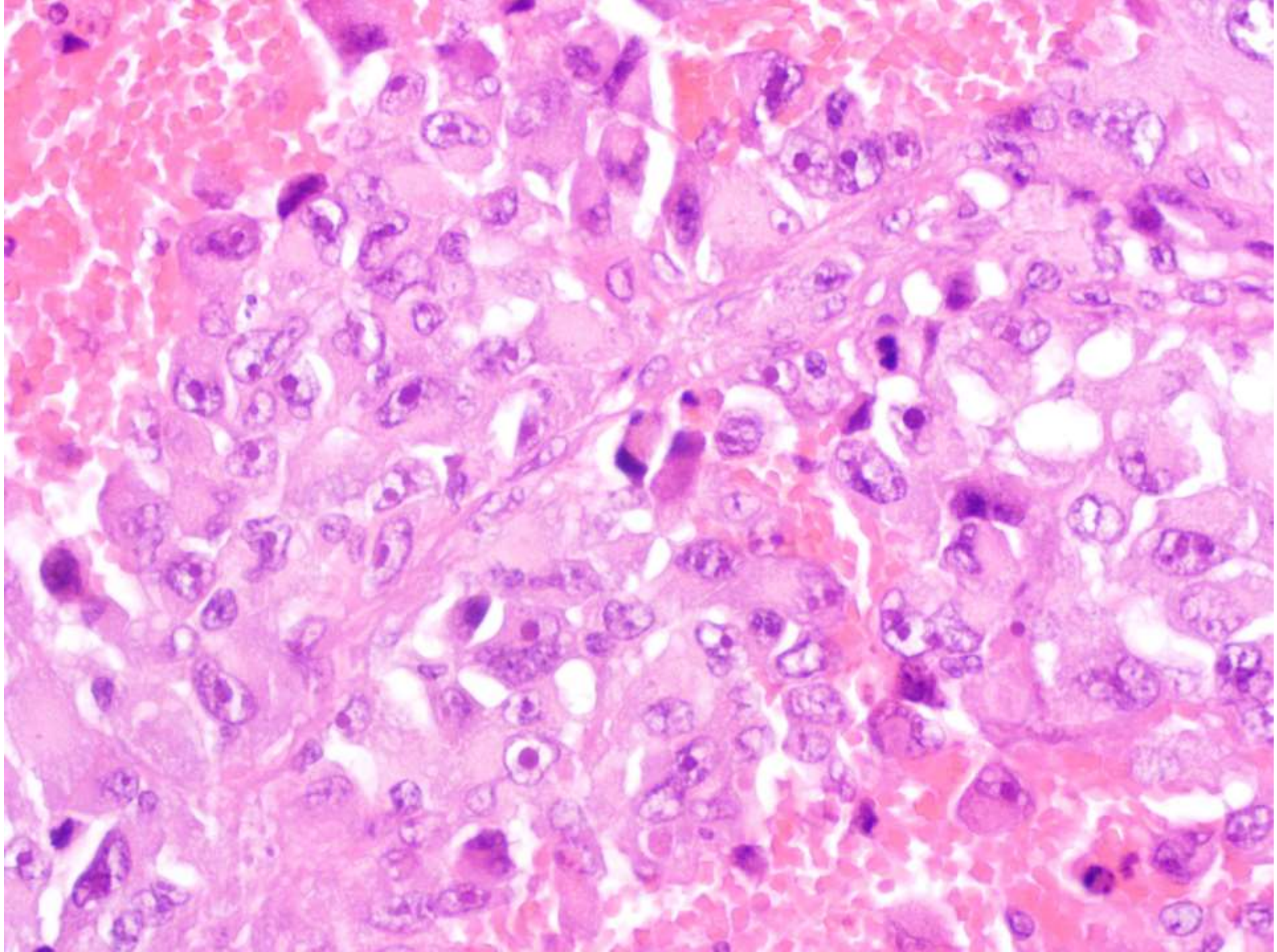




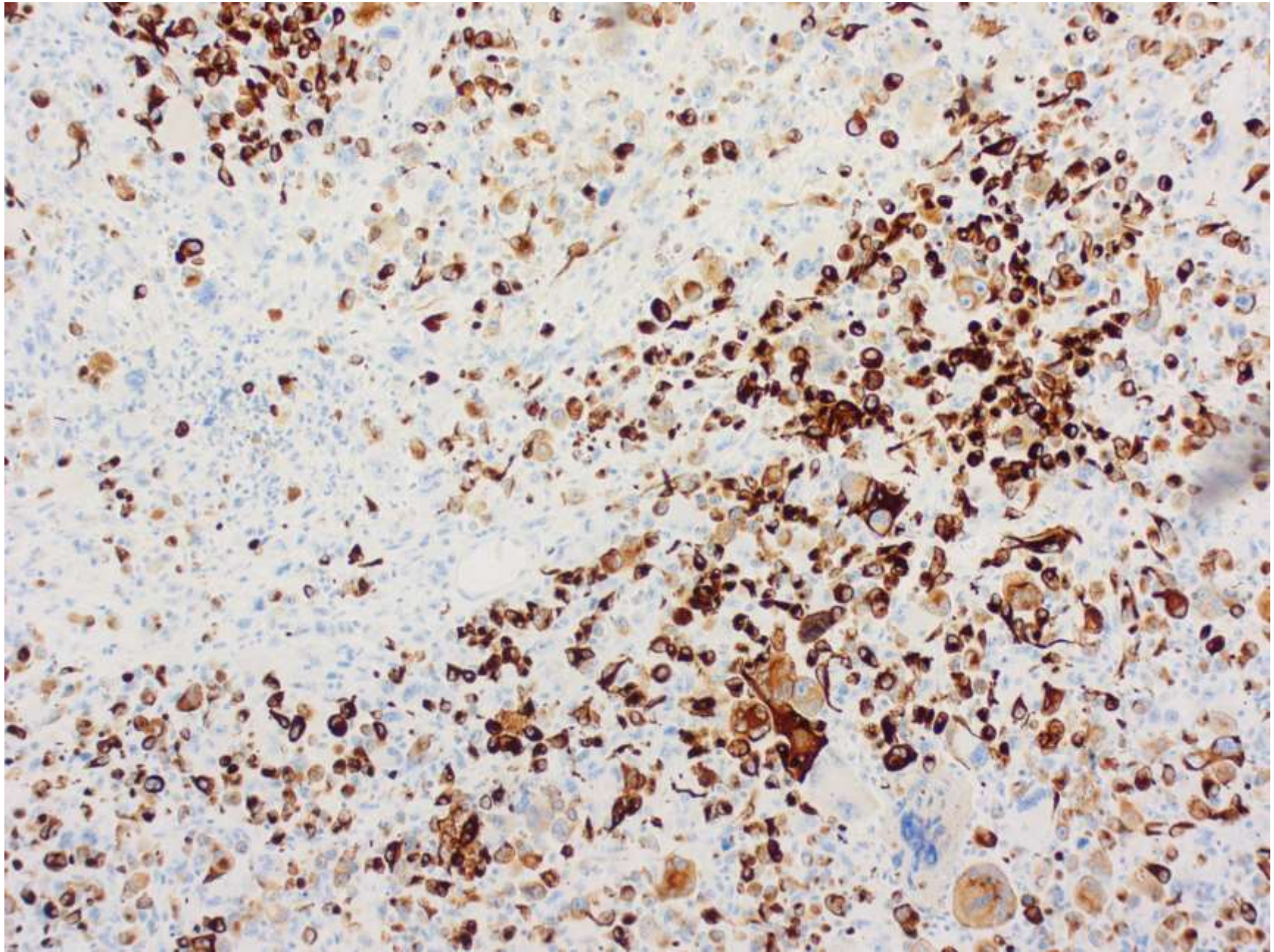




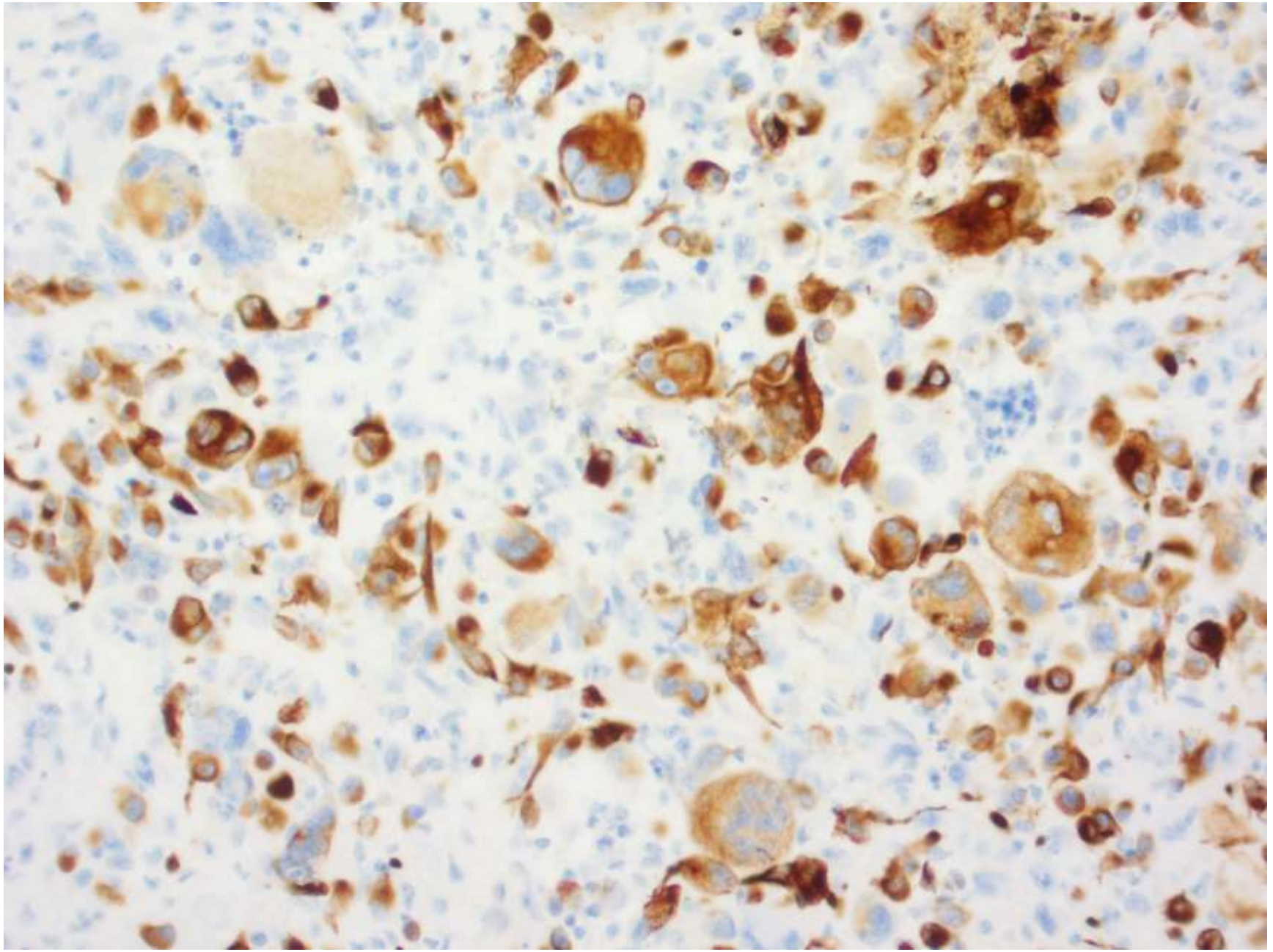


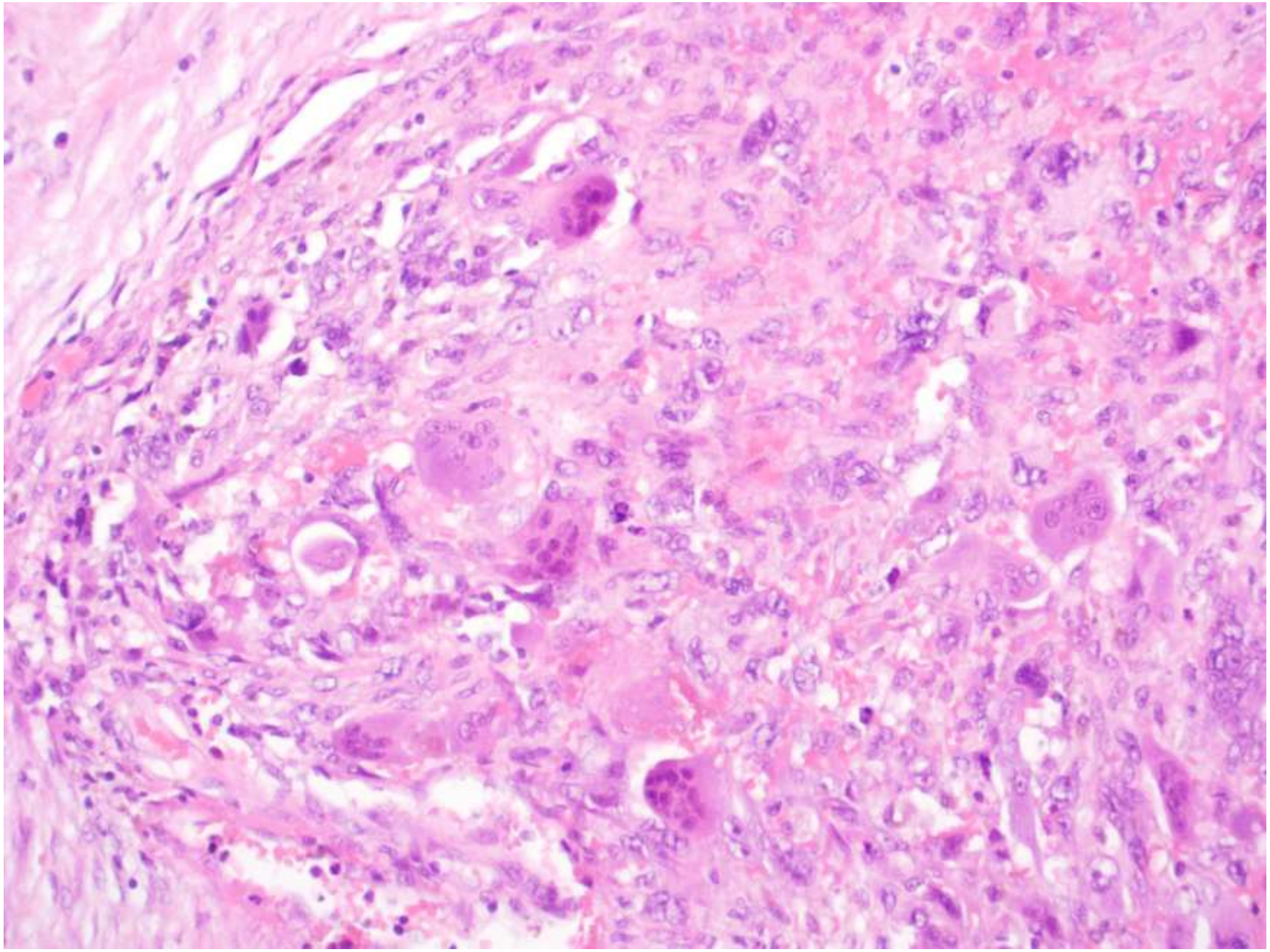


CKpan

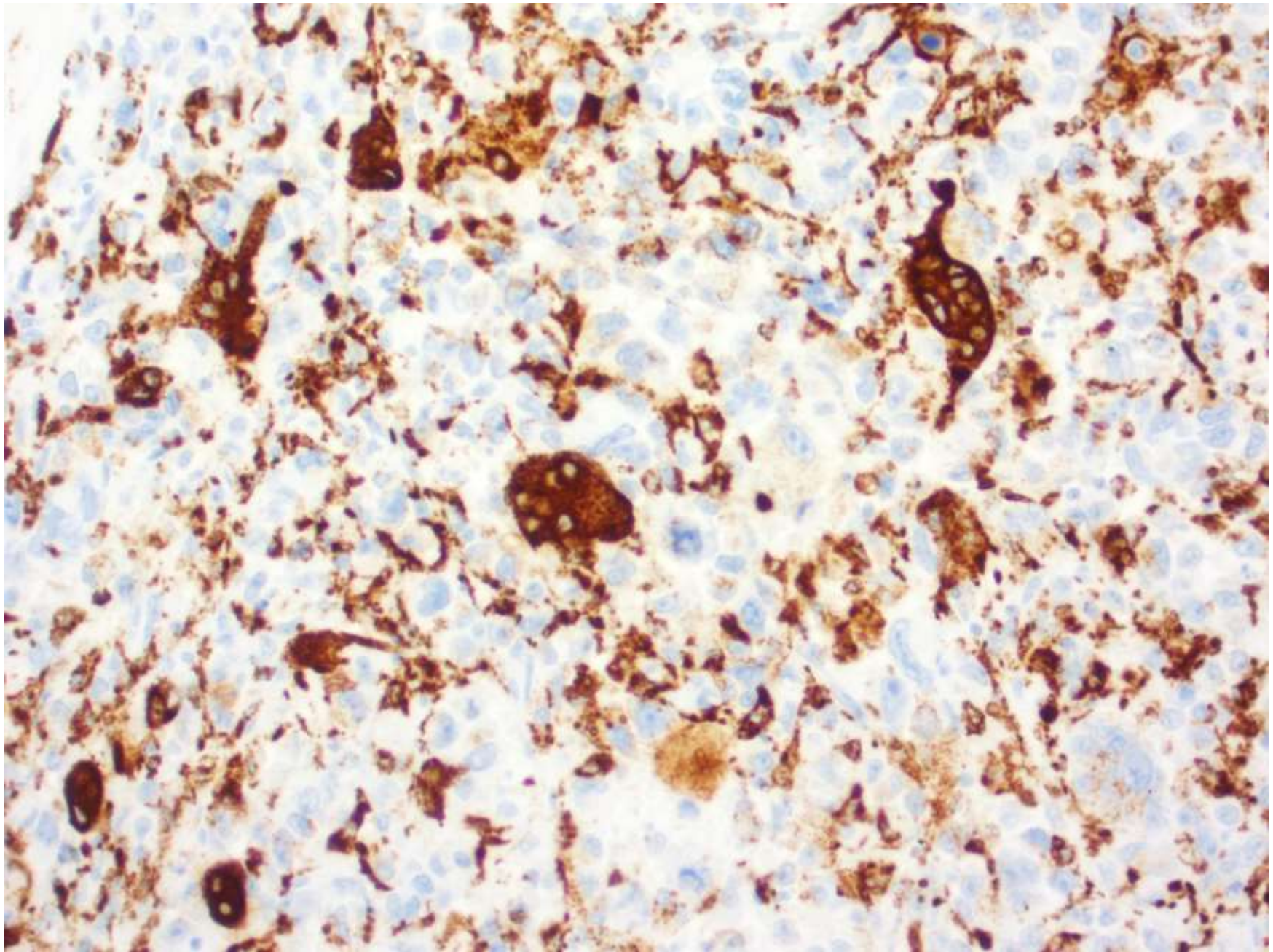


CKpan

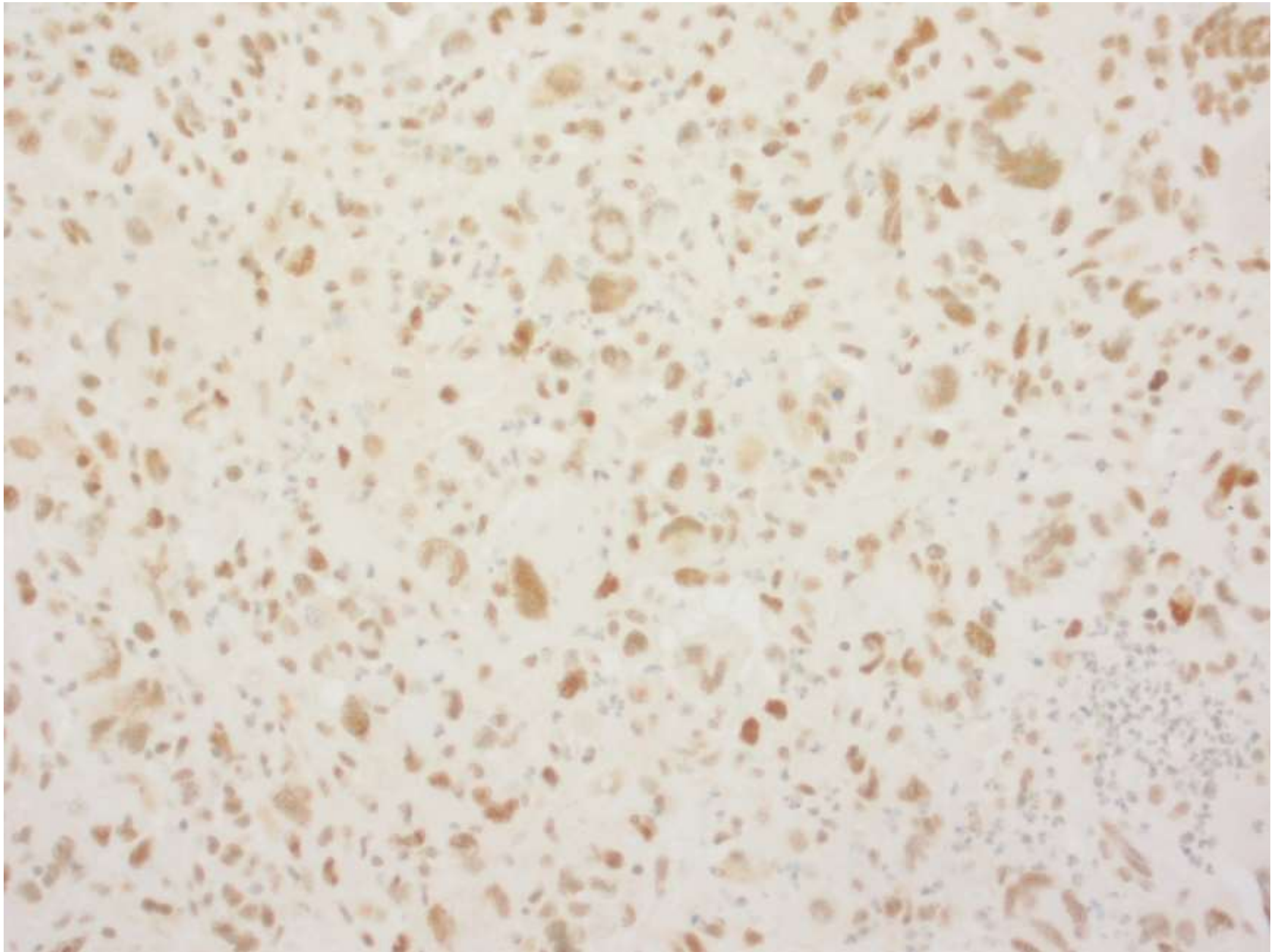




CD68



INI-1 (SMARCB1)



Other IHC markers

- **ERG, CD34, CD31: negative.**
- **CK7, EMA: focally positive.**
- **E-cadherine: completely negative.**
- **Beta-catenin: focal membranous expression.**

MODERN PATHOLOGY (2015) 28, 248–260

Pancreatic undifferentiated rhabdoid carcinoma: *KRAS* alterations and SMARCB1 expression status define two subtypes

Abbas Agaimy[1], Florian Haller[1], Judith Frohnauer[1], Inga-Marie Schaefer[2,3], Philipp Ströbel[3], Arndt Hartmann[1], Robert Stoehr[1] and Günter Klöppel[4]

Pleomorphic versus monomorphic undifferentiated rhabdoid pancreatic carcinoma

Pancreatic undifferentiated carcinoma is a heterogeneous group of neoplasms, including pleomorphic giant cell, sarcomatoid, round cell, and rhabdoid carcinomas, the molecular profiles of which have so far been insufficiently characterized. We studied 14 undifferentiated carcinomas with prominent rhabdoid cells, occurring as advanced tumors in seven females and seven males aged 44–96 years (mean: 65 years). Histologically, 10 tumors qualified as pleomorphic giant cell and 4 as monomorphic anaplastic carcinomas. A glandular component, either in the primary or in the metastases, was seen in 5 out of 14 tumors (4 out of 10 pleomorphic giant cell and 1 out of 4 monomorphic anaplastic subtypes, respectively). Osteoclast-like giant cells were absent. Immunohistochemistry revealed coexpression of cytokeratin and vimentin, and loss of membranous β-catenin and E-cadherin staining in the majority of cases. Nuclear SMARCB1 (INI1) expression was lost in 4 out of 14 cases (28%), representing all 4 tumors of the monomorphic anaplastic subtype. FISH and mutation testing of ***KRAS*** revealed ***KRAS*** amplification in 5 out of 13 (38%) and exon 2 mutations in 6 out of 11 (54%) successfully analyzed cases. A strong correlation was found between ***KRAS*** alterations (mutation and/or copy number changes) and intact SMARCB1 expression (7 out of 8; 87%). On the other hand, loss of SMARCB1 expression correlated with the absence of ***KRAS*** alterations (3 out of 5 cases; 60%). The results suggest that rhabdoid phenotype in pancreatic undifferentiated rhabdoid carcinomas has a heterogeneous genetic background. SMARCB1 loss is restricted to the anaplastic monomorphic subtype and correlates with the absence of ***KRAS*** alterations, whereas the pleomorphic giant cell subtype is characterized by ***KRAS*** alterations and intact SMARCB1 expression. Recognition and appropriate subtyping of these rare variants might become necessary for future therapeutic strategies.

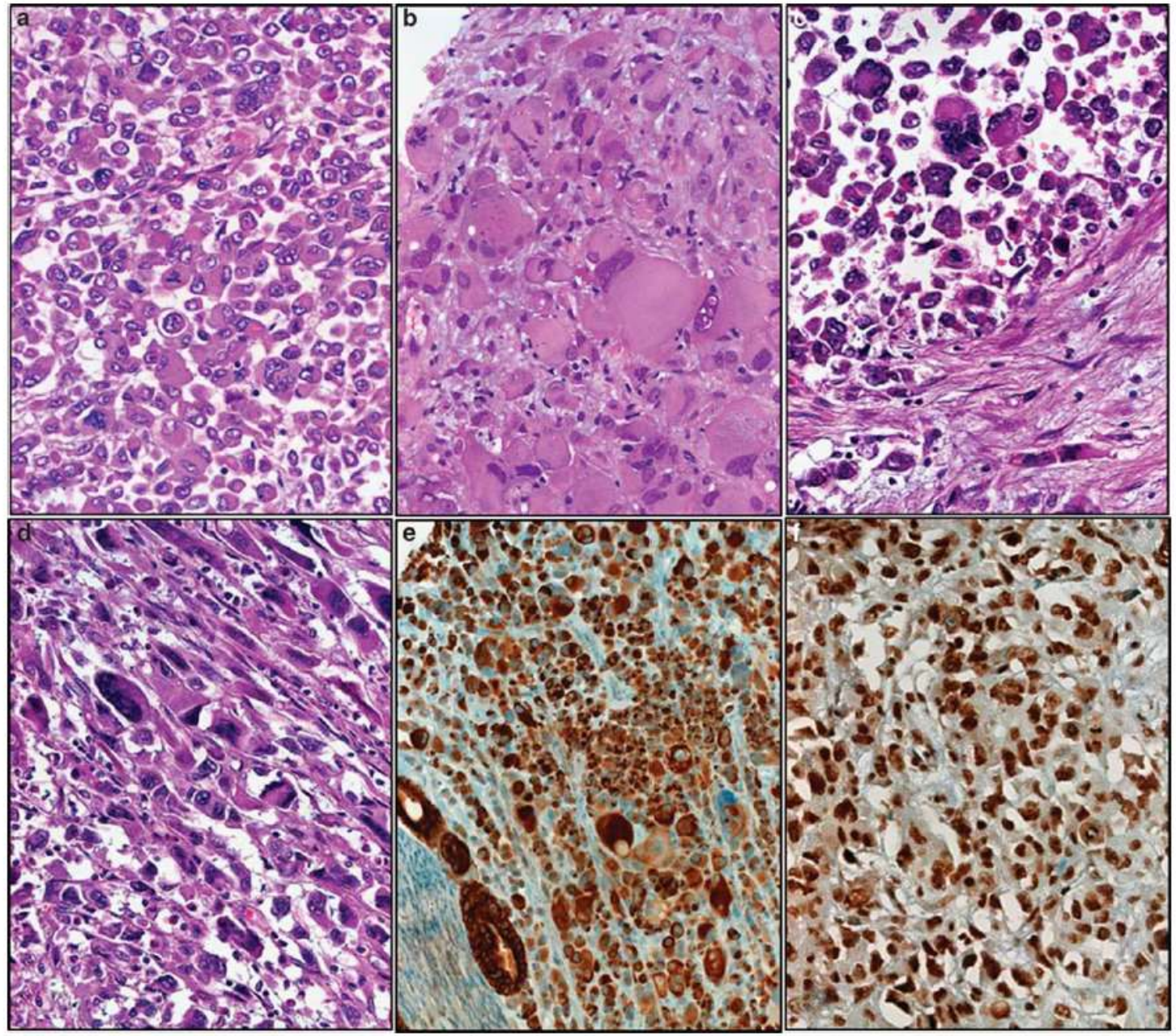


Figure 1 Examples of the pleomorphic giant cell subtype of undifferentiated rhabdoid pancreatic carcinoma. (**a**) Highly pleomorphic tumor cells with variable nuclear sizes and frequent bi- and multinucleation. Note prominent cytoplasmic eosinophilia with rhabdoid inclusions. (**b**) Extreme example of cell size variation and eosinophilic cytoplasm. (**c**) Non-cohesive pseudoalveolar pattern. (**d**) Sarcomatoid spindle cells. (**e**) Cell size variation highlighted by pancytokeratin (note perineural carcinomatous glands lower left). (**f**) Intact nuclear SMARCB1 expression was seen in all cases of this subtype.

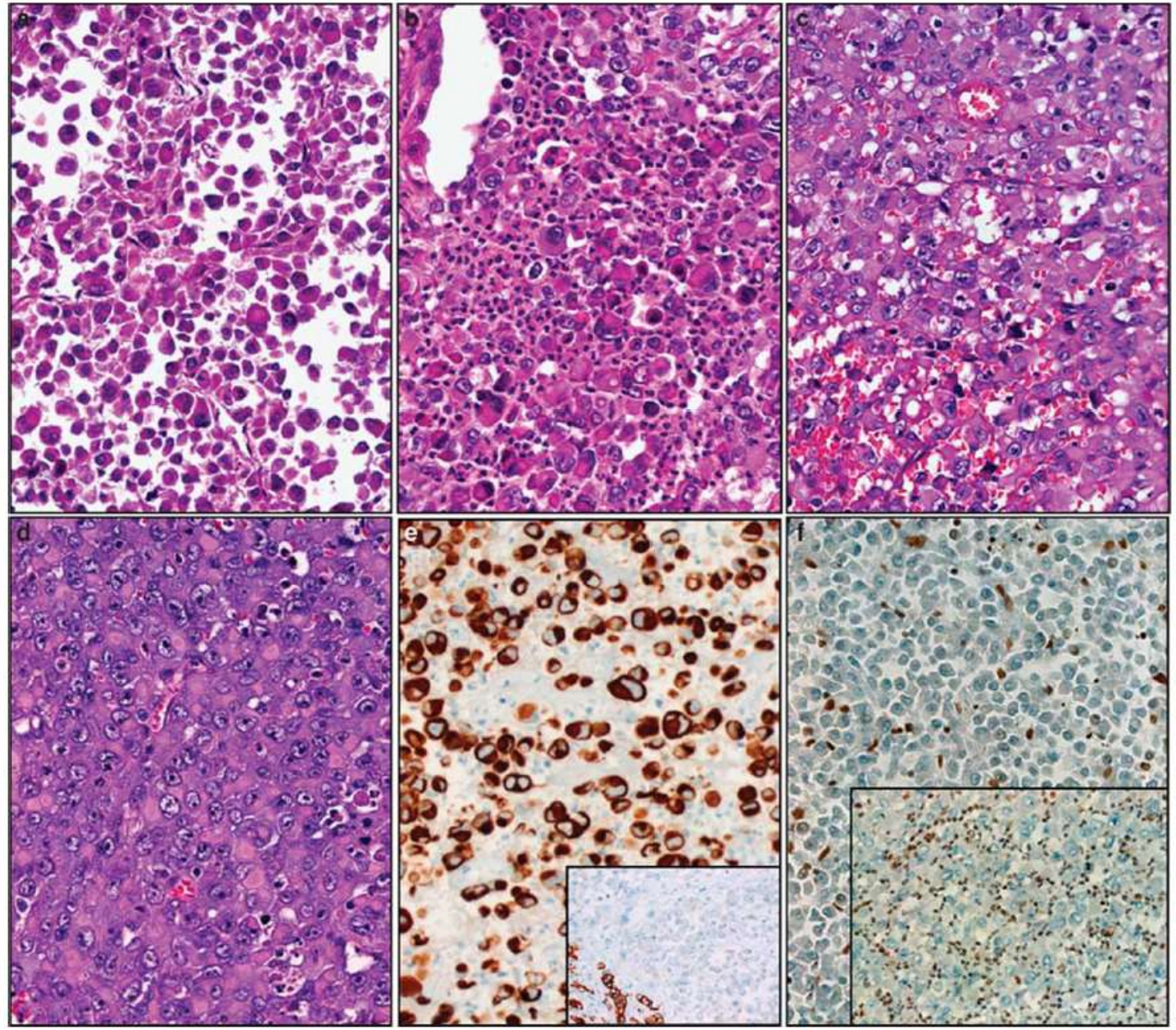


Figure 3 Examples of the SMARCB1-deficient monomorphic subtype. (**a**) Small to medium sized monotonous rhabdoid cells in pseudoalveolar pattern. (**b**) Another case showed prominent neutrophilia and focal gland formation (upper left). (**c**) Epithelioid large cell pattern mimicking angiosarcoma. (**d**) Compact sheets of large cells with frequent rhabdoid inclusions mimicking proximal-type epithelioid sarcoma. (**e**) Characteristic paranuclear cytokeratin expression (KL1). Inset: loss of pancytokeratin in another case with focal expression in gland-like areas. (**f**) Complete loss of nuclear SMARCB1 expression (main image: same case as in **a** with retained expression in endothelial and stromal cells; inset: same case as in **b**, with prominent nuclear staining of neutrophils and stromal cells).

Table 3 Immunohistochemical features of undifferentiated rhabdoid pancreatic carcinomas ($n = 14$)

No	*Vimentin*	*KL-1*	*CK7*	*EMA*	*E-cadherin*	*β-Catenin*	*TP53*	*SMARCB1 IHC*
1	+ + +	+	−	−	−	−	−	Intact
2	+ + +	+ + +	+ +	+	−	−	NR	Intact
3	+ + +	+ +	+	+ +	−	−	NR	Intact
4	+ +	+ + +	+ + +	+	−	−	−	Intact
5	+ + +	+ +	+	+	−	−	NR	Intact
6	+ + +	+ + +	+ +	+ +	−	+ Membranous	−	Intact
7	+ +	+	+	+	−	−	40%	Intact
8	+ + +	+ + +	+ + +	+ +	−	−	20%	Intact
9	+ + +	+ +	−	−	−	+ Membranous	5%	Intact
10	−	+ + +	+ +	+ +	−	−	10%	Intact
11	+ + +	+ +	−	+	−	−	−	Complete loss
12	+ + +	+ + +	+	+	−	−	NR	Complete loss
13	+ + +	+ +	−	+ +	−	−	NR	Complete loss
14	+ +	+ + +	−	+ + +	−	+ + Cytoplasmic + Membranous	50%	Complete loss

Abbreviations: IHC, immunohistochemistry; NR, no results due to artifacts or poor preservation.

09/2021:

clinician asks DNA NGS

motivation: search for predictive markers for targeted therapy

Resultaat

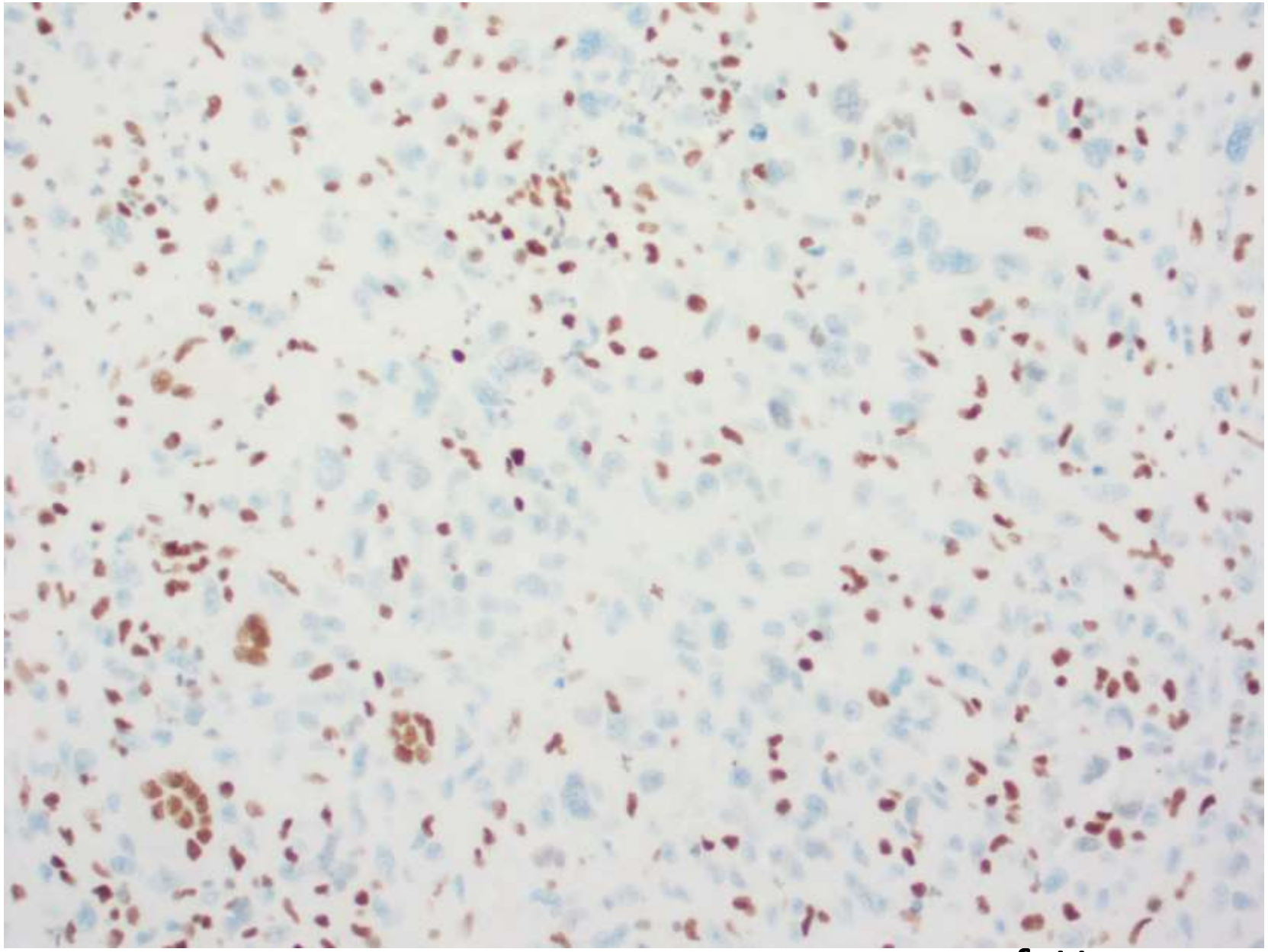
(Vermoedelijk) pathogene varianten:

Gen	Variant	%*	Bio.klasse	Klin.Klasse
KRAS_exon2	c.35G>A (p.(Gly12Asp))	51.0	pathogeen	klasse II
SMARCA4_exon29	c.4025_4035del (p.(Glu1342Valfs*15))	16.0	vermoedelijk pathogeen	klasse III

VAF/MAF SMARCA4 x 3 = VAF/MAF KRAS

prof. Vanden Bempt, CME UZ Leuven

SMARCA4 IHC



prof. Hoorens, APO UZ Gent

MODERN PATHOLOGY (2013) 26, 1346–1354

KRAS mutant allele-specific imbalance is associated with worse prognosis in pancreatic cancer and progression to undifferentiated carcinoma of the pancreas

Alyssa M Krasinskas[1], A James Moser[2], Burcu Saka[3], N Volkan Adsay[3] and Simion I Chiosea[1]

KRAS codon 12 mutations are present in about 90% of ductal adenocarcinomas and in undifferentiated carcinomas of the pancreas. The role of ***KRAS*** copy number changes and resulting ***KRAS*** mutant allele-specific imbalance (MASI) in ductal adenocarcinoma ($n=94$), and its progression into undifferentiated carcinoma of the pancreas ($n=25$) was studied by direct sequencing and ***KRAS*** fluorescence ***in situ*** hybridization (FISH). Semi-quantitative evaluation of sequencing electropherograms showed ***KRAS*** MASI (ie, mutant allele peak higher than or equal to the wild-type allele peak) in 22 (18.4%) cases. ***KRAS*** FISH (performed on 45 cases) revealed a trend for more frequent ***KRAS*** amplification among cases with ***KRAS*** MASI (7/20, 35% ***vs*** 3/25, 12%, $P=0.08$). ***KRAS*** amplification by FISH was seen only in undifferentiated carcinomas (10/24, 42% ***vs*** 0/21 pancreatic ductal adenocarcinoma, 0%, $P=0.0007$). In 6 of 11 cases with both undifferentiated and well-differentiated components, transition to undifferentiated carcinoma was associated with an increase in ***KRAS*** copy number, due to amplification and/or chromosome 12 hyperploidy. Pancreatic carcinomas with ***KRAS*** MASI (compared to those without MASI) were predominantly undifferentiated (16/22, 73% ***vs*** 9/97, 9%, $P<0.001$), more likely to present at clinical stage IV (5/22, 23% ***vs*** 7/97, 7%, $P=0.009$), and were associated with shorter overall survival (9 months, 95% confidence interval, 5–13, ***vs*** 22 months, 95% confidence interval, 17–27; $P=0.015$) and shorter disease-free survival (5 months, 95% confidence interval, 2–8 ***vs*** 13 months, 95% confidence interval, 10–16; $P=0.02$). Our findings suggest that in a subset of ductal adenocarcinomas, ***KRAS*** MASI correlates with the progression to undifferentiated carcinoma of the pancreas.

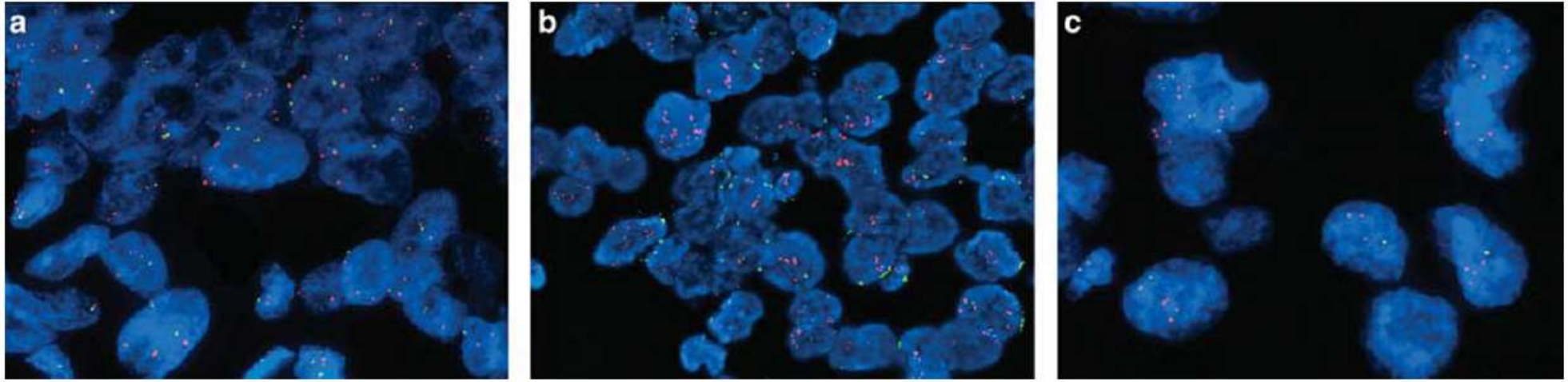


Figure 2 *KRAS* fluorescence *in situ* hybridization. (**a**) *KRAS* amplification; numerous *KRAS* (orange) signals and two CEP12 (green) signals per nucleus. (**b**) Example of a case with *KRAS* amplification and chromosome 12 hyperploidy; numerous orange and green signals in each nucleus. (**c**) Example of a case with *KRAS* amplification and chromosome 12 monosomy; numerous *KRAS* (orange) signals and only one CEP12 (green) signal per nucleus.

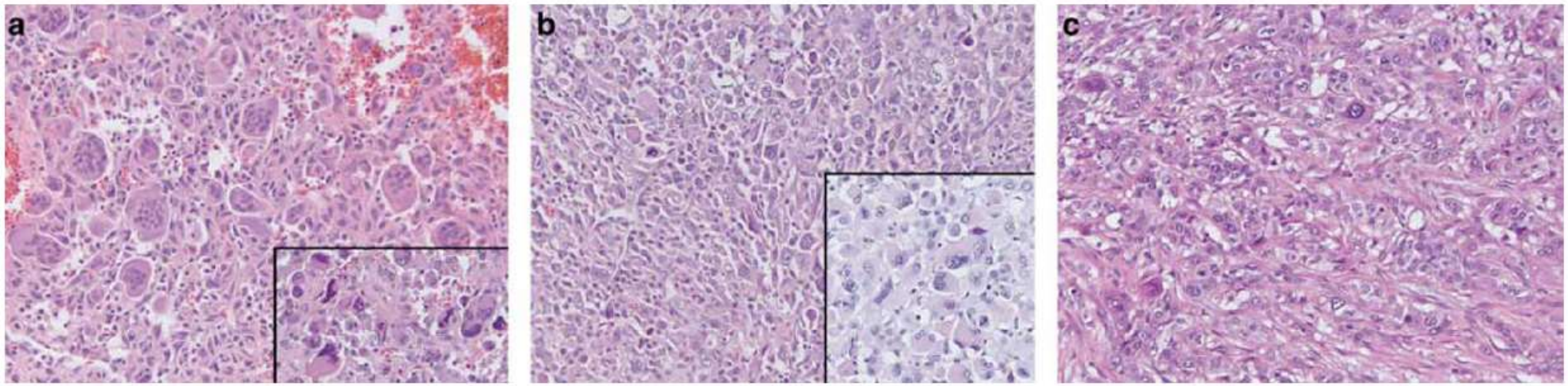
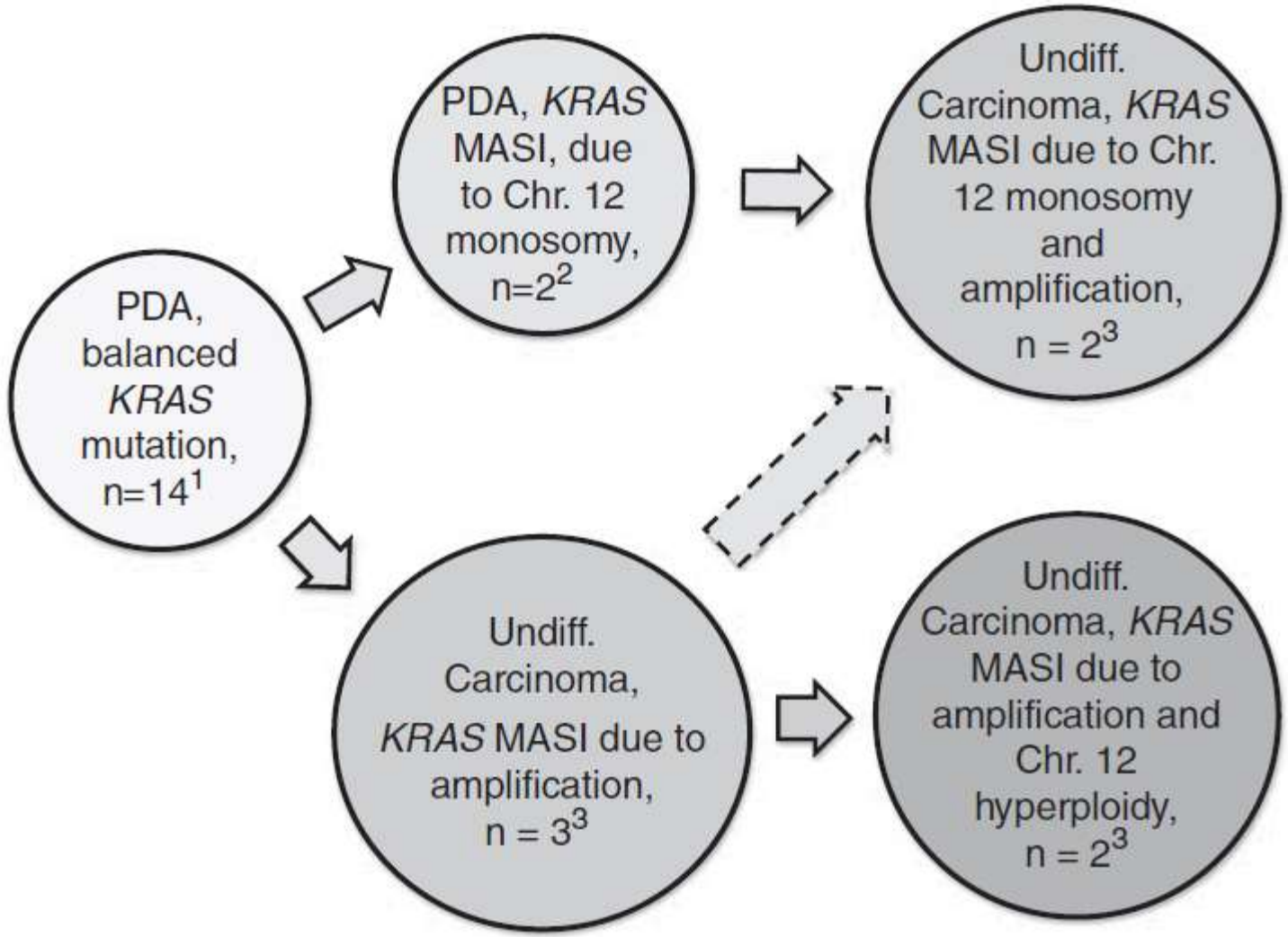


Figure 3 Representative examples of the undifferentiated carcinomas of the pancreas included in this study (H&E, ×200). (**a**) Undifferentiated carcinoma with osteoclast-like giant cells; some cases also contained anaplastic giant cells (inset) (H&E, ×200); (**b**) Undifferentiated carcinoma containing sheets of medium-to-large anaplastic cells (anaplastic carcinoma); in some cases, the malignant cells contained abundant pink cytoplasm creating a rhabdoid appearance (inset) (H&E, ×200). (**c**) Five cases contained epithelioid cells admixed with anaplastic cells that formed vague nests and trabeculae (H&E, ×200).


PDA, balanced *KRAS* mutation, n=14[1]
PDA, *KRAS* MASI, due to Chr. 12 monosomy, n=2[2]
Undiff. Carcinoma, *KRAS* MASI due to Chr. 12 monosomy and amplification, n = 2[3]
Undiff. Carcinoma, *KRAS* MASI due to amplification, n = 3[3]
Undiff. Carcinoma, *KRAS* MASI due to amplification and Chr. 12 hyperploidy, n = 2[3]

JCI insight

CLINICAL MEDICIN

SWI/SNF complex alterations as a biomarker of immunotherapy efficacy in pancreatic cancer

Gregory P. Botta,[1,2] Shumei Kato,[1,2] Hitendra Patel,[2] Paul Fanta,[2] Suzanna Lee,[1] Ryosuke Okamura,[3] and Razelle Kurzrock[1,2]

[1]Center for Personalized Cancer Therapy, Department of Medicine, and [2]Division of Hematology/Oncology, Department of Medicine, UCSD, La Jolla, California, USA. [3]Department of Surgery, Kyoto University Hospital, Kyoto, Japan.

BACKGROUND. Immune checkpoint inhibitors (ICIs) fail to demonstrate efficacy in pancreatic cancer. Recently, genomic biomarkers have been associated with response to ICIs: microsatellite instability high (MSI-H) and tumor mutation burden (TMB) > 10 mutations/Mb. Alterations in Switch/Sucrose Nonfermentable (SWI/SNF) chromatin remodeling genes may predispose to improved outcomes with immunotherapy. The current study examined a possible role for SWI/SNF complex abnormalities in pancreatic cancer responsiveness to ICIs.

METHODS. A database of 6831 cancer patients that had undergone next-generation sequencing (NGS) was filtered for advanced pancreatic cancer, SWI/SNF alterations, and outcomes depending on immunotherapy treatment.

RESULTS. Nine patients had metastatic pancreatic adenocarcinoma harboring SWI/SNF chromatin remodeling gene alterations and had received ICIs: 7 had an ARID1A alteration (77%); 2, ARID1B (22%); 3, SMARCA4 (33%); 1, SMARCB1 (11%); and 1, PBRM1 (11%). Three patients possessed more than 1 SWI/SNF complex alteration. Only 3 tumors were microsatellite unstable. Eight of 9 patients (89%) achieved an objective response, including a complete remission, with the 2 longest responses ongoing at 33+ and 36+ months. Median progression-free and overall survival was 9 and 15 months, respectively. Responses occurred even in the presence of microsatellite stability, low TMB, and/or low PD-L1 expression.

CONCLUSION. A small subset of patients with pancreatic cancer have genomic alterations in SWI/SNF chromatin remodeling components and appear to be responsive to ICIs, suggesting the need for prospective trials.

Authorship note: GPB and SK contributed equally to this work.

Conflict of interest: GPB serves on the Advisory Board of Natera and as a consultant to TumorGen Inc. and CEND Therapeutics. SK serves as a consultant for Foundation Medicine and receives speaker fees from Roche, as well as research funding from ACT Genomics, Sysmex, Konica Minolta, and OmniSeq. RK has research funding from Incyte, Genentech, Merck

Immunotherapy in SMARCA4-deficient NSCLC and UT: variable results, sometimes good response, but PDL1 IHC not predictive

Conversion Surgery for Advanced Thoracic SMARCA4-Deficient Undifferentiated Tumor With Atezolizumab in Combination With Bevacizumab, Paclitaxel, and Carboplatin Treatment: A Case Report

Kei Kunimasa, MD, PhD,[a,*] Jiro Okami, MD, PhD,[b] Satoshi Takenaka, MD, PhD,[c] Keiichiro Honma, MD, PhD,[d] Yoji Kukita, PhD,[e] Shigenori Nagata, MD, PhD,[d] Takahisa Kawamura, MD, PhD,[a] Takako Inoue, MD,[a] Motohiro Tamiya, MD,[a] Hanako Kuhara, MD, PhD,[a] Kazumi Nishino, MD, PhD,[a] Hideaki Tahara, MD, PhD,[f,g] Toru Kumagai, MD, PhD[a]

JTO Clinical and Research Reports Vol. 2 No. 11: 100235

10/2021:

Given supra, my suggestion to clinician was: maybe try immunotherapy?

Response: not now, maybe later.

11/2021:

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journal homepage: www.elsevier.com/locate/semdp

Pleomorphic (giant cell) carcinoma revisited: A historical perspective and conceptual reappraisal

Abbas Agaimy *

Institute of Pathology, Friedrich-Alexander-University Erlangen-Nürnberg, University Hospital, Erlangen, Germany

The term *pleomorphic "giant cell" carcinoma* was coined by Sommers and Meissner in 1954 for a pancreatic carcinoma variant showing a "*sarcoma-like transformation*" and characterized by an admixture of undifferentiated cells with striking variation in size and shape. Based on the predominant cell type, four patterns were recognized: spindle cell (sarcomatoid), pleomorphic "giant cell", osteoclastic giant cell-rich, and anaplastic round cell. These four basic patterns frequently coexisted within same tumor, albeit to a significantly variable extent. Follow-up series further characterized the entity, expanded its topographic distribution to include almost all organ systems, and illustrated its morphological and phenotypic homology among different organs. Although resemblance of the neoplastic cells to rhabdomyoblasts was already pointed out by Stout in 1958, the term "rhabdoid" (introduced in 1978 for specific kidney tumors) was not used for carcinomas until 1993. Review of the old and recent literature indicates pleomorphic "giant cell" carcinoma is not an entity but a morphological pattern in the spectrum of undifferentiated (anaplastic) and sarcomatoid carcinoma that can originate in any organ, either in a pure form or as a dedifferentiated carcinoma component. These tumors fall into two major categories: a monomorphic (variable admixture of small or larger "gemistocyte-like" rhabdoid cells and epithelioid cells) and a pleomorphic (bizarre large polygonal, spindled, or multinucleated malignant cells) subtype. The few available genetic studies suggest close association of the monomorphic type with SWI/SNF pathway defects, while bizarre-looking pleomorphic tumors usually harbor complex and heterogeneous genetic alterations. Most tumors dominated by the pleomorphic "giant cell" pattern are extremely aggressive, resulting in death, soon after diagnosis, irrespective of treatment modalities. This review gives an historical account on the evolution of the pleomorphic "giant cell" carcinoma concept with special reference to their relationship to SWI/SNF complex alterations.

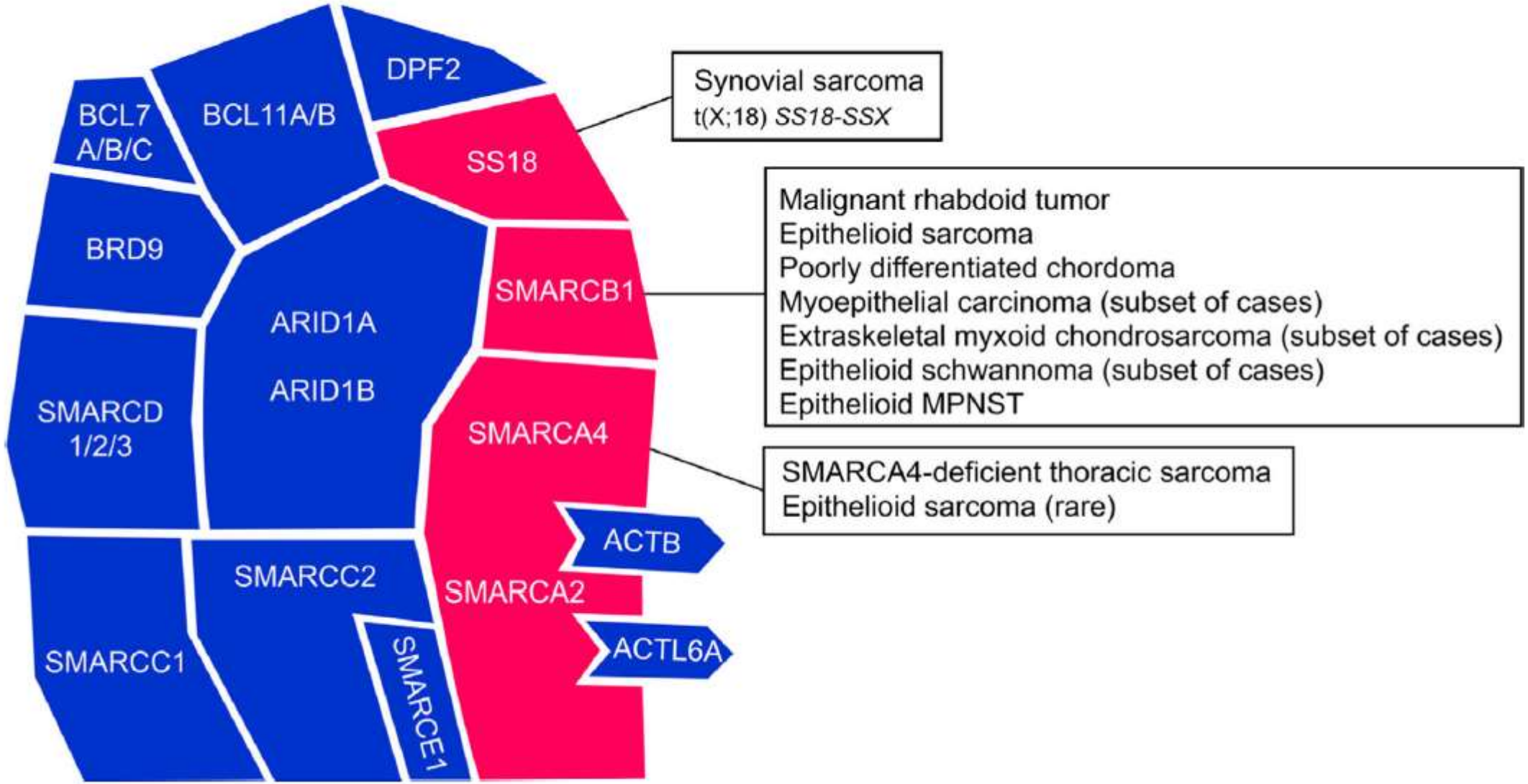
In summary, all these observations are consistent with the notion that pleomorphic giant cell carcinoma represents a shared morphological pattern in the wide spectrum of sarcomatoid dedifferentiation occurring across different histological carcinoma subtypes in different organs and not an entity. A modified approach to sarcomatoid and undifferentiated carcinomas comparable to the one adopted by the previous and the current WHO classification for pancreatic undifferentiated carcinoma seems more valuable and can be applied to different organ systems. Such an approach can help to maintain terminological uniformity for undifferentiated carcinoma variants originating from different carcinoma types in different organs. Separation of these highly lethal diseases into monomorphic and pleomorphic subcategories would facilitate recognition of specific genetic alterations underlying their morphological dedifferentiation and might pave the way for a better molecular, prognostic, and therapeutic stratification in the future.

Semin Diagn Pathol. 2021 May ; 38(3): 222–231. doi:10.1053/j.semdp.2020.05.005.

SWI/SNF complex-deficient soft tissue neoplasms: An update

Inga-Marie Schaefer, **Jason L. Hornick***

Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA


DPF2
BCL7 A/B/C
BCL11A/B
SS18
BRD9
SMARCB1
ARID1A
ARID1B
SMARCD 1/2/3
SMARCA4
ACTB
SMARCC2
SMARCA2
SMARCC1
SMARCE1
ACTL6A
Synovial sarcoma
t(X;18) SS18-SSX
Malignant rhabdoid tumor
Epithelioid sarcoma
Poorly differentiated chordoma
Myoepithelial carcinoma (subset of cases)
Extraskeletal myxoid chondrosarcoma (subset of cases)
Epithelioid schwannoma (subset of cases)
Epithelioid MPNST
SMARCA4-deficient thoracic sarcoma
Epithelioid sarcoma (rare)

MODERN PATHOLOGY (2017) 30, 539–548

Claudin-4 expression distinguishes SWI/SNF complex-deficient undifferentiated carcinomas from sarcomas

Inga-Marie Schaefer[1], Abbas Agaimy[2], Christopher DM Fletcher[1] and Jason L Hornick[1]

[1]*Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA and* [2]*Institute of Pathology, Friedrich-Alexander University Erlangen-Nuremberg, University Hospital of Erlangen, Erlangen, Germany*

Rhabdoid and/or SMARC* tumors

=

the “Agaimy tumors”

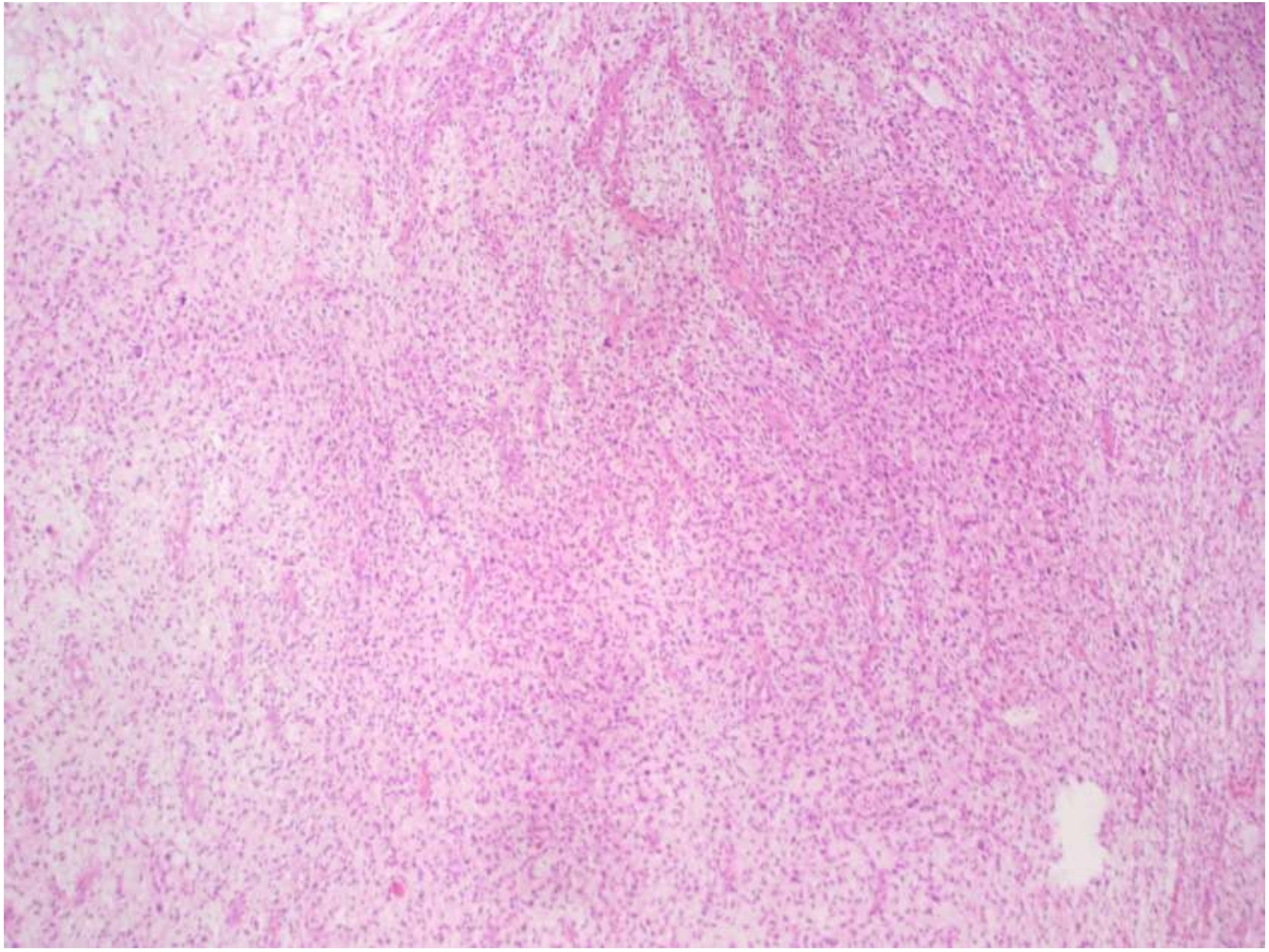
20B8409 and 20B13783

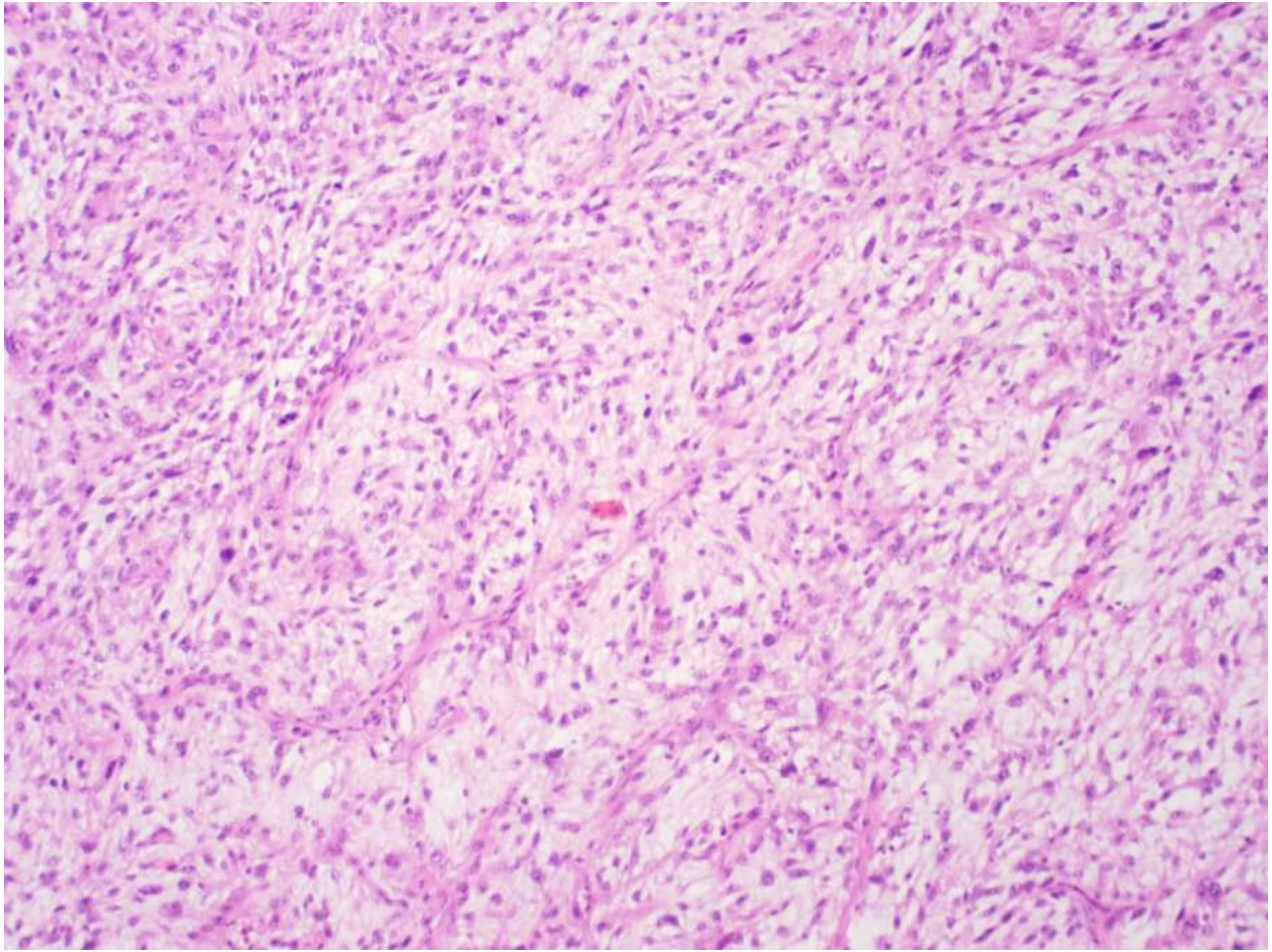
06/2020 and 05/2021

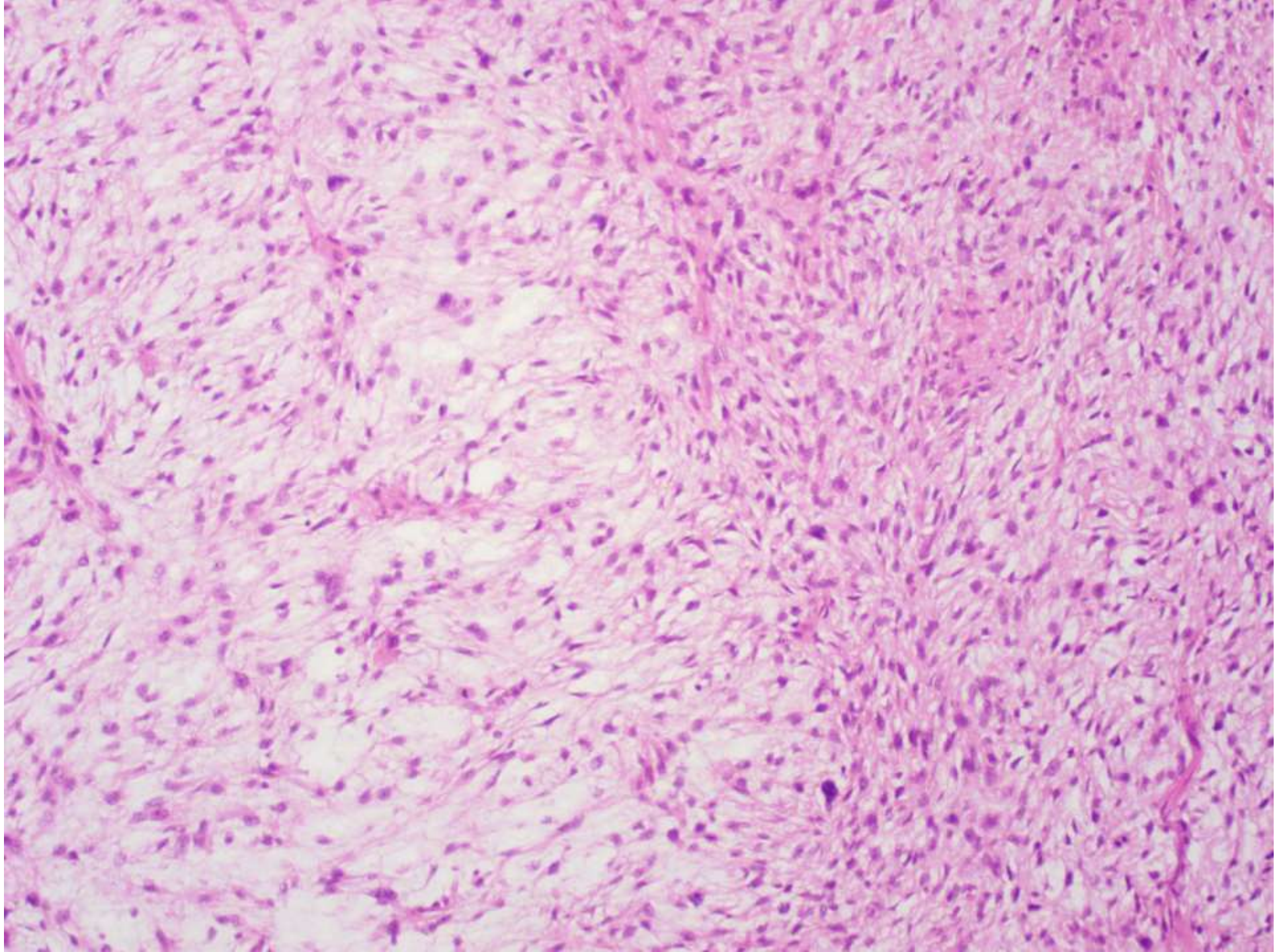
male, 86 y.

Inguinal canal tumor (2020) + pancreatic tumor (2021)

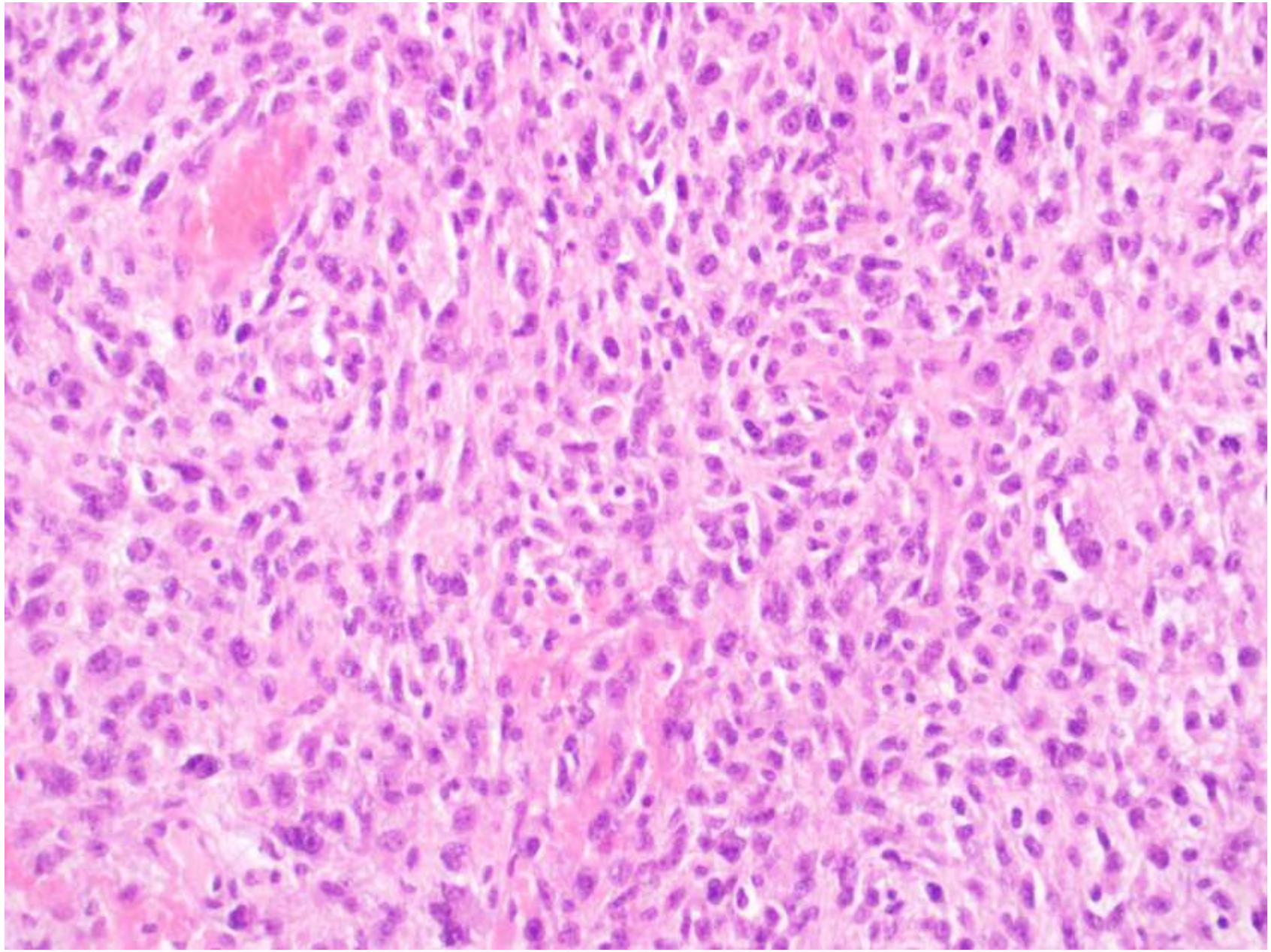
Myxofibrosarcoma-like; no lipomatous areas

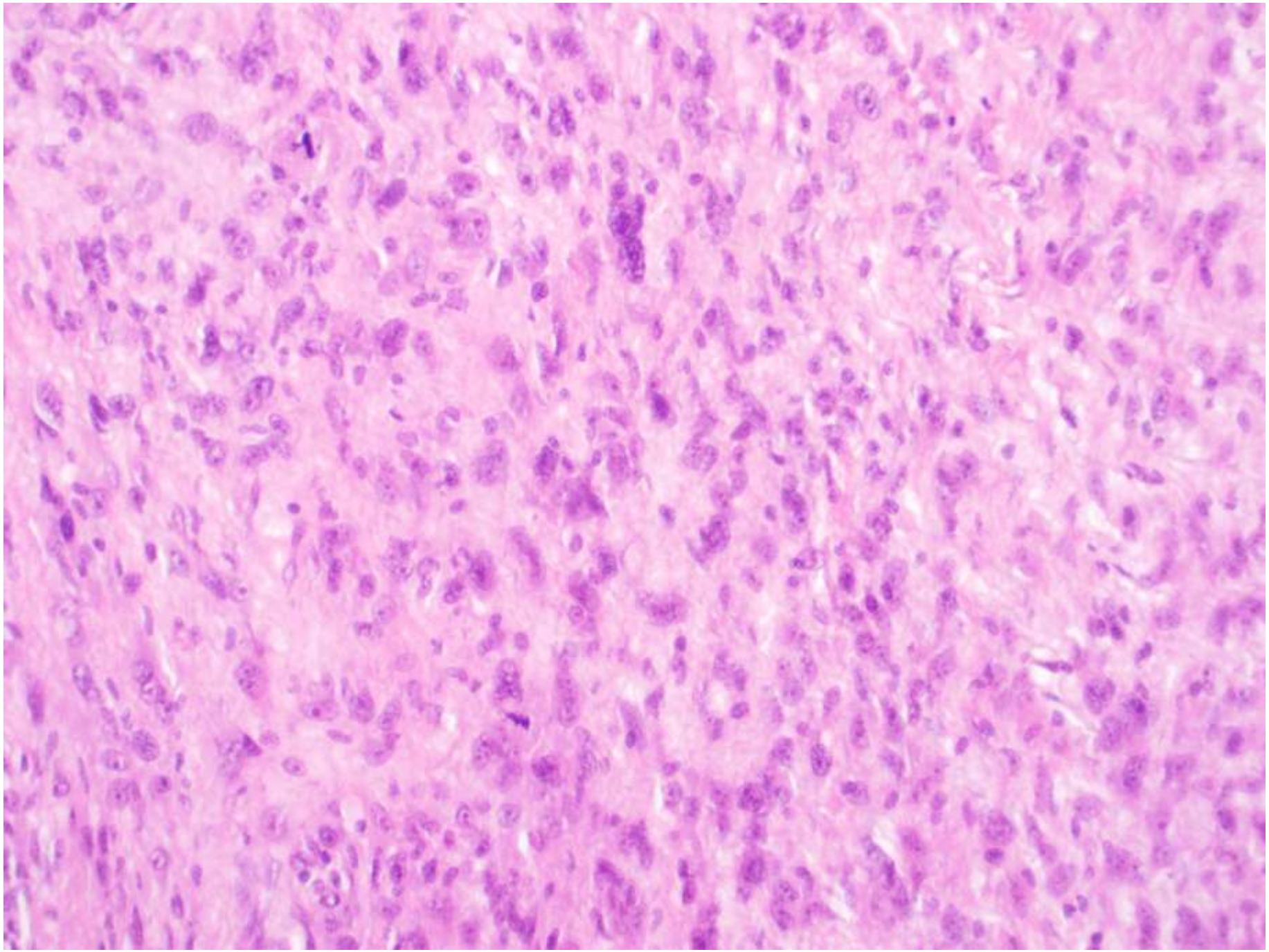






Areas that are more pleomorphic/epithelioid than spindle





IHC markers

- **All tested markers were completely negative.**
- **Desmin, caldesmon, CKpan, CD34, ASMA, EMA, SOX10.**

High-level MDM2 amplification in 79% of cells

Probe resultaten

Probe	Resultaat
MDM2 (SO) / SE 12 (SG)	100 kernen: 1R 1G: 7% 2R 2G: 14% >15R 2-3G (amplificatie): 79%

Resultaat

FISH werd uitgevoerd op een tumorbiopt, op paraffine coupe B-2024492-01.
Volgende probe(s) werd(en) gebruikt: MDM2 (SO) / SE 12 (SG)[12q15, Kreatech].
Het preparaat was goed evalueerbaar.

Dit onderzoek toont:
- Positief voor MDM2 amplificatie in 79% van de kernen.

prof. Vanden Bempt, CME UZ Leuven

Comparison of retroperitoneal liposarcoma extending into the inguinal canal and inguinoscrotal liposarcoma

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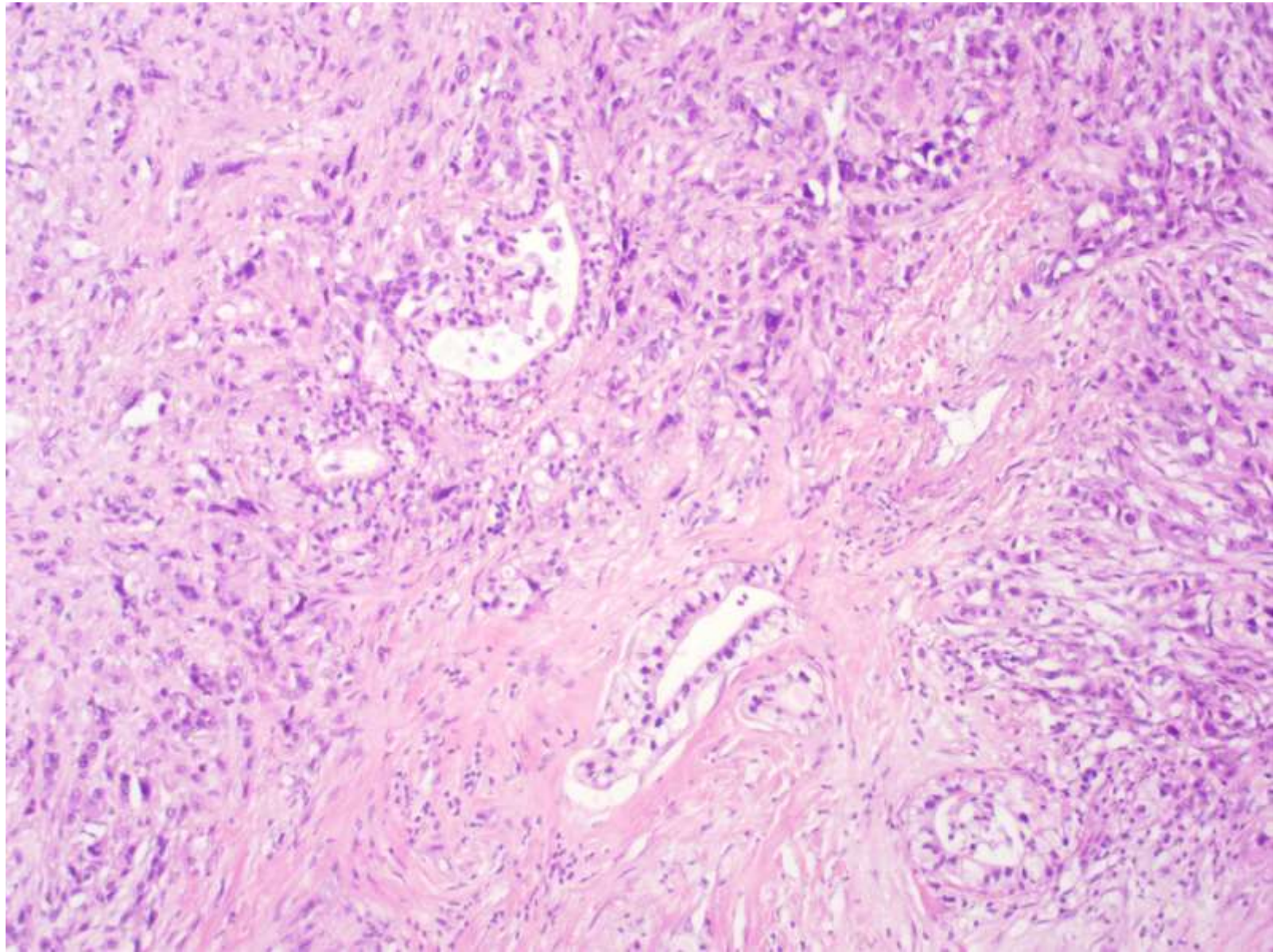
Background: This study was designed to analyze differences between retroperitoneal liposarcoma (RLPS) extending into the inguinal canal and inguinoscrotal liposarcoma.

Methods: We retrospectively reviewed the records for patients who were managed for inguinal liposarcoma at Samsung Medical Center, a tertiary hospital, between January 1998 and December 2016. Patient data on demographics, tumour location, surgery, adjuvant therapy, histology, recurrence and death were collected. We used Mann–Whitney, Fisher exact and Kaplan–Meier log-rank tests to analyze differences between groups.

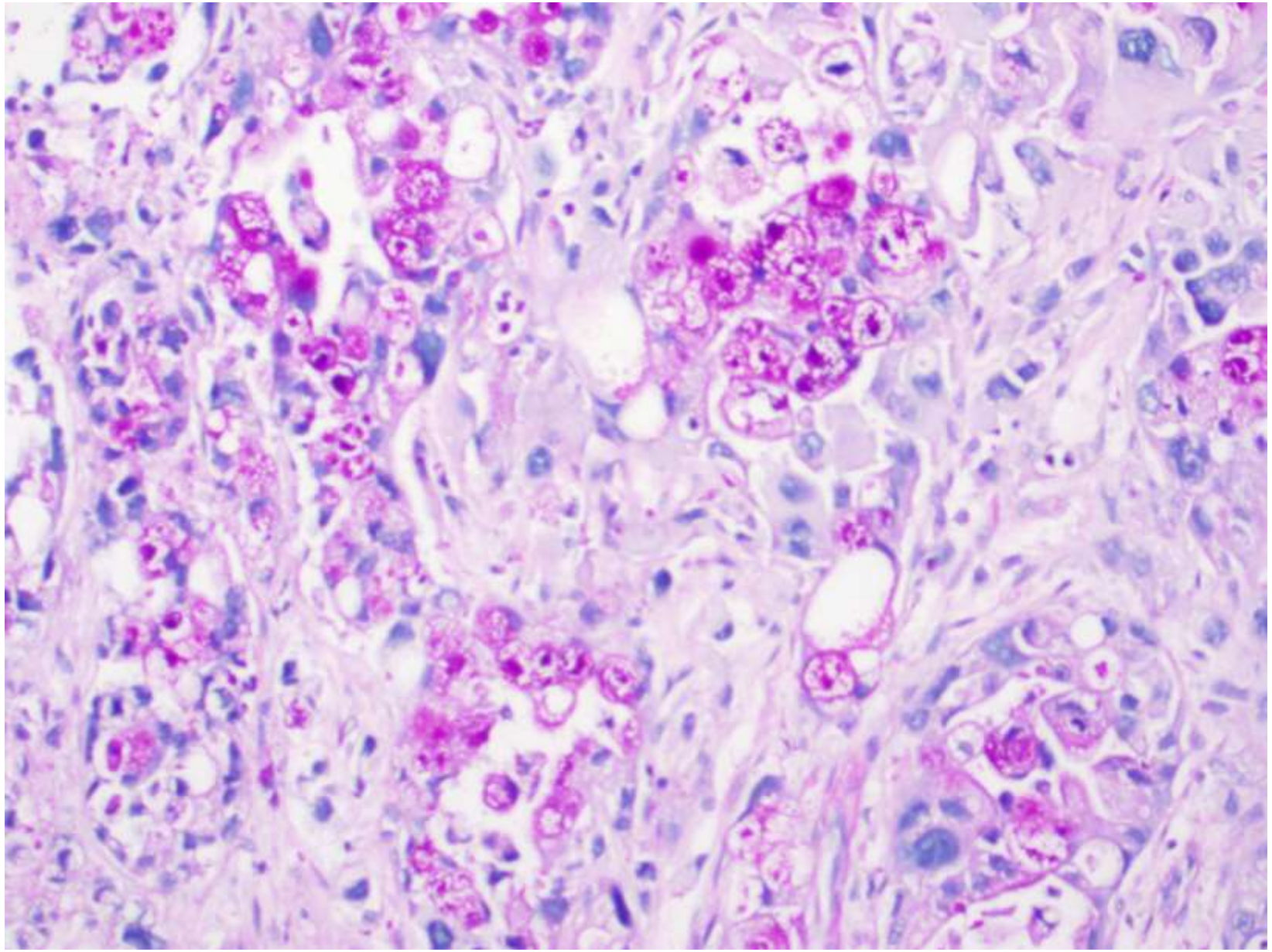
Results: Seven of 179 (3.9%) patients with abdominal liposarcoma had inguinoscrotal liposarcoma, and 6 of 168 (3.6%) patients with RLPS had extension to the inguinal canal. No differences were observed between groups in sex ($p > 0.99$), mean age (49.7 ± 6.4 yr v. 52.1 ± 12.5 yr, $p = 0.37$), laterality ($p > 0.99$) or scrotal involvement (40.0% v. 66.7%, $p = 0.57$). The RLPS group had significantly larger tumours than the inguinoscrotal group (27.9 ± 6.8 cm v. 7.8 ± 4.2 cm, $p = 0.001$). Postoperative complications were significantly more common in the RLPS group ($n = 4$, 83.3%); patients in the inguinoscrotal group experienced no postoperative complications ($p = 0.021$). Log-rank tests showed that the groups had no statistical differences in disease-free survival ($p = 0.94$) or overall survival ($p = 0.10$). However, inoperable disease-free survival was significantly poorer in the RLPS group ($p = 0.010$).

Conclusion: Although initial signs and symptoms can be similar, RLPS extending into the inguinal canal was associated with significantly higher morbidity and mortality than inguinoscrotal liposarcoma.

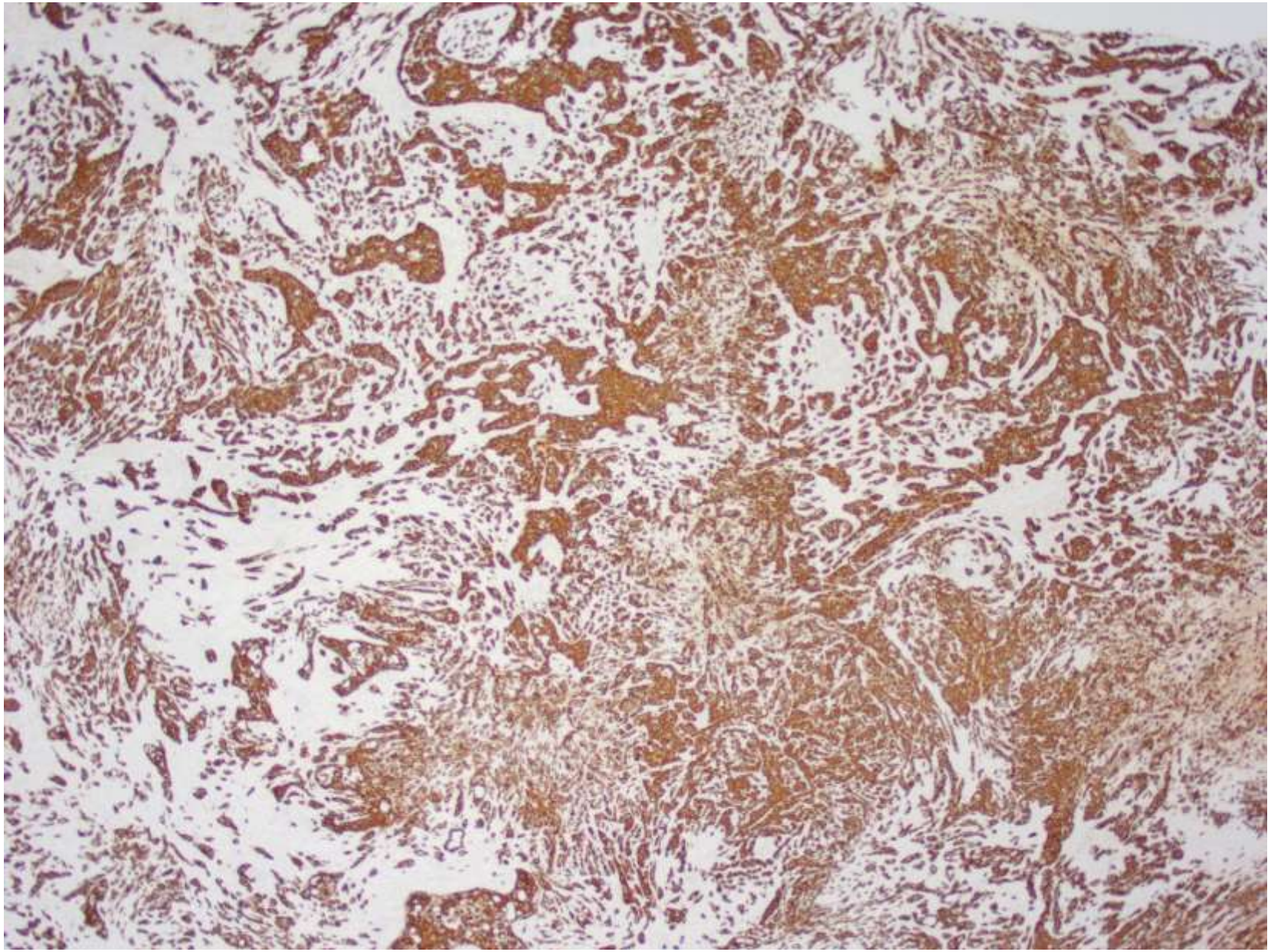
05/2021: resection of the pancreatic tumor focal glandular areas



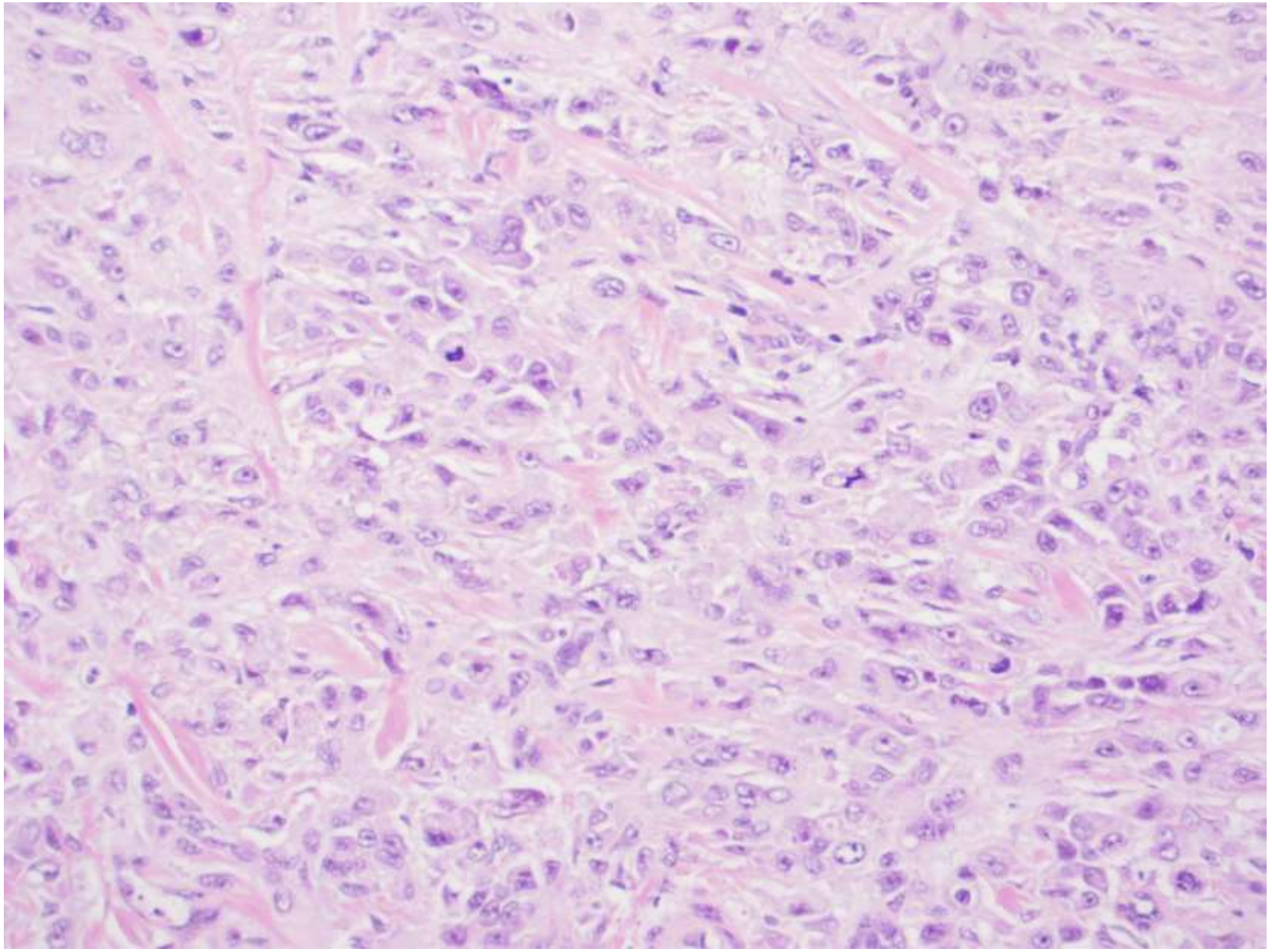
Pas-diastase

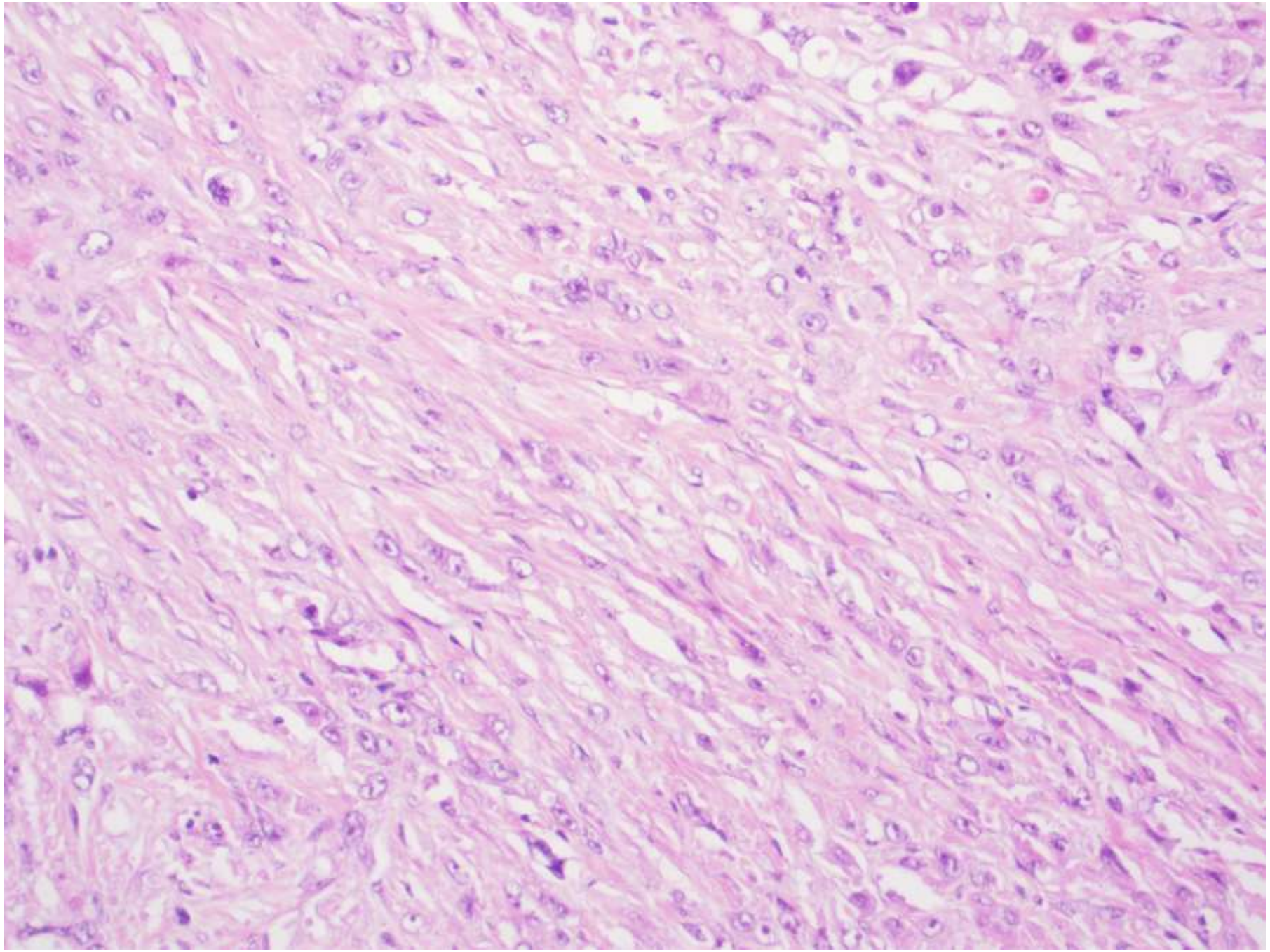


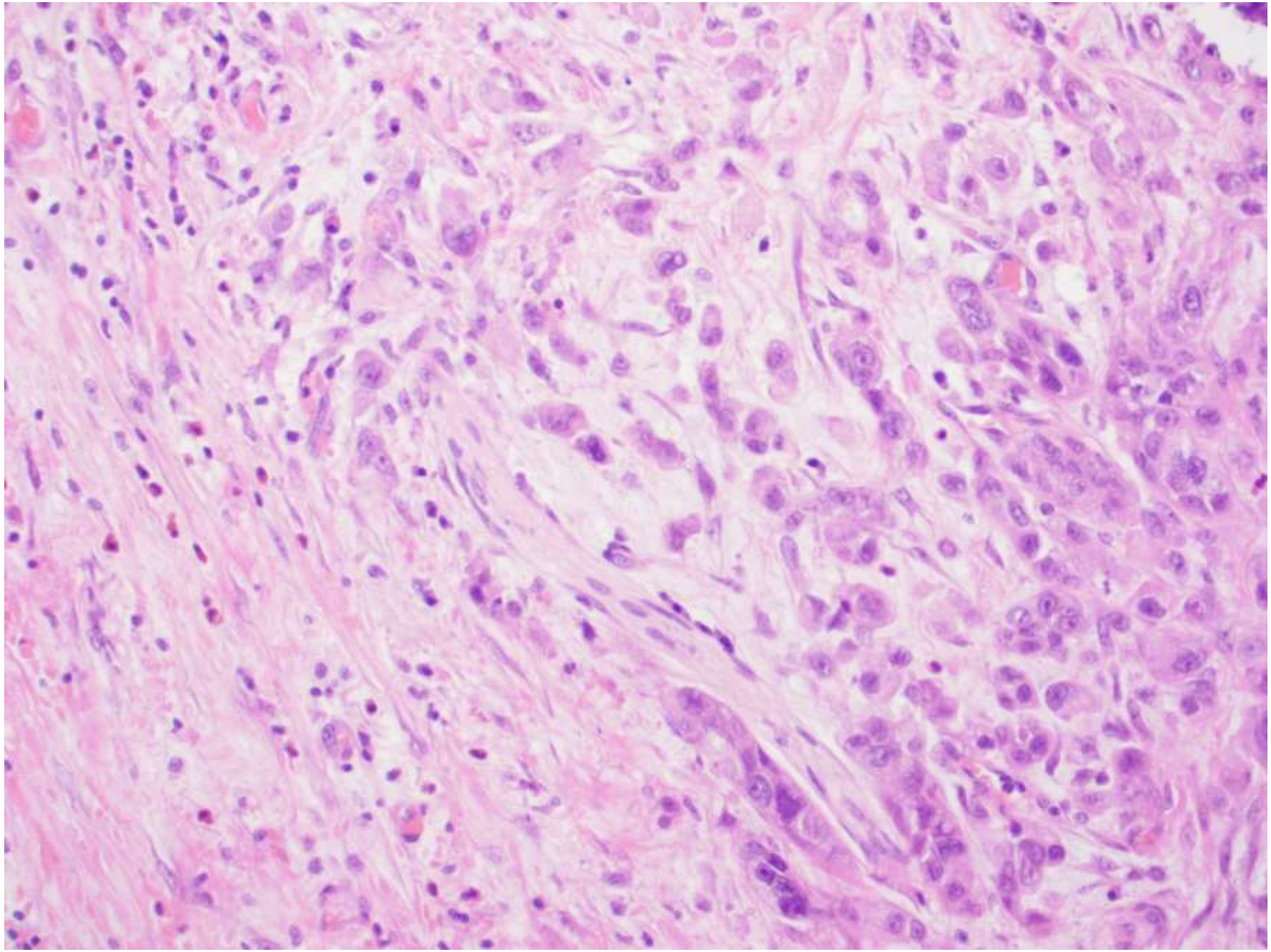
CKpan



Mainly more epitheloid/pleomorphic/sarcomatoid areas







High-level MDM2 amplification in 6% of cells

Probe resultaten

Probe	Resultaat
MDM2 (SO) / SE 12 (SG)	100 kernen: 1R 1G: 39% 2R 2G: 44% 1R 2G: 4% >15R 3-5G: 6% 2R 3G: 3% 3R 3G: 2% 3-5R 2G: 2%

Resultaat

FISH werd uitgevoerd op een tumorbiopt, op paraffine coupe B-2035961-01 (20B13783).
Volgende probe(s) werd(en) gebruikt: MDM2 (SO) / SE 12 (SG)[12q15, Kreatech].
Het preparaat was goed evalueerbaar.
De aangeduide tumorzone werd volledig onderzocht.
Dit onderzoek toont:
- Positief voor sterke MDM2 amplificatie in 6% van de kernen.

prof. Vanden Bempt, CME UZ Leuven

Idylla KRAS testing on the pancreatic and inguinal canal tumor

Idylla™ KRAS Mutation Test

KRAS GENOTYPE	KRAS-MUTATIE GEDETECTEERD IN CODON 12
Mutatie	G12R
Proteïne	p.Gly12Arg
Nucleotideverandering	c.34G>C

Idylla™ KRAS Mutation Test

KRAS GENOTYPE	GEEN KRAS MUTATIE GEDETECTEERD IN CODON 12,13,59,61,117,146

APO AZ Groeninge

GENES, CHROMOSOMES & CANCER 50:456–465 (2011)

Genome Profiling of Pancreatic Adenocarcinoma

David J. Birnbaum,[1] José Adélaïde,[1] Emilie Mamessier,[2] Pascal Finetti,[1] Arnaud Lagarde,[1] Geneviève Monges,[3] Frédéric Viret,[4] Anthony Gonçalvès,[4] Olivier Turrini,[5] Jean-Robert Delpero,[5] Juan Iovanna,[6] Marc Giovannini,[7] Daniel Birnbaum,[1] and Max Chaffanet[1]*

MDM2 gain/amplification in approx. 10% of pancreatic adenocarcinomas, sometimes without KRAS mutation

TABLE 2. Summary of aCGH and Sequencing Results on Tumor Samples

Tumors	Deleted genes												Amplified genes								Mutated genes	
	ARID1A	*TRIM33*	*TGFBR2*	*CTNNB1*	*FHIT*	*CDKN2A/B*	*PTEN*	*RB1*	*TP53*	*SMAD4*	*STK11*	*MACROD2*	*CCND3*	*SMURF1*	*MYC*	*CDK4*	*MDM2*	*GATA6*	*AKT2*	*FOXA2*	*KRAS*	*ARID1A*
13659																A					No	No
13773																					Yes	No
13900															A						No	No
14122																		A	A		na	na
14233																	A				Yes	No
14288																					Yes	No
14293															A			A			Yes	No
14462																					No	No
14482																					na	Na
14558																					Yes	No
14563																					Yes	No
17582																					Yes	No
17653																					No	No
17719																		A			Yes	No
17724																					Yes	No
17846																		A		A	na	Na
17848																					Yes	Yes[b]
17904														A							Yes	No
17917																					No	No
17936																					Yes	Yes[b]
17982																					na	Na
17994																					na	Na
18169															A						na	na
18177																					Yes	No
18397																					na	na
18446						HOMO															Yes	No
18459														A				A			Yes	No
18520																					No	No
18574																					na	na
18610																					Yes	No
18647																					No	No
18708																					na	na
18812																					Yes	No
18978																					No	No
19045																					Yes	No
19096																					na	na
19286						HOMO												A			Yes	No
20219																					Yes	No
20220															A						Yes	No
TOTAL	13	6	6	5	8	18	3	2	23	23	10	6	1	6	11	3	3	11	8	5	21	2
	33.3%	15.4%	15.4%	12.8%	20.5%	46.1%	7.7%	5.1%	59.0%	59.0%	25.6%	15.4%	2.56%	15.4%	28.2%	7.7%	7.7%	28.2%	20.5%	12.8%	72.4%	6.9%

HOMO, homozygous deletion; A, amplification; na, non-applicable. Losses and gains are marked in grey.

This is an accidental association of a DDLPS and a focally MDM2-amplified pancreatic adenocarcinoma.

Since 10% of pancreas adca have MDM2 amplification, sooner or later it will be seen together with a DDLPS, especially if you look hard enough for it

Let us search a bit further and deeper on the this topic…

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Human
PATHOLOGY
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Original contribution

MDM2 amplification and immunohistochemical expression in sarcomatoid renal cell carcinoma☆,☆☆

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Keywords:
Sarcomatoid;
RCC;
MDM2 Amplification;
FISH;
Renal

Summary The sarcomatoid variant of renal cell carcinoma is a highly aggressive tumor with propensity for metastasis and limited therapeutic options. Metastases of sarcomatoid renal cell carcinoma can sometimes be mistaken for a variety of spindle cell sarcomas, particularly at soft tissue sites in the absence of a history of a kidney tumor. Immunoreactivity for markers associated with certain types of soft tissue sarcomas can, therefore, pose a pitfall for diagnosis under such circumstances. We evaluated the immunohistochemical and molecular features of 49 cases of sarcomatoid renal cell carcinoma with special emphasis on the expression of MDM2 by immunohistochemistry and *MDM2* amplification by fluorescence in situ hybridization. Of the 49 sarcomatoid renal cell carcinoma cases evaluated by fluorescence in situ hybridization, 5 (10%) were positive for *MDM2* gene amplification and 5 (10%) contained polysomy 12. Immunohistochemical nuclear expression for MDM2 was also observed in 30/49 (61%) cases; of these, 15/19 (78%) were metastatic and 15/30 (50%) were primary. MDM2 expression by immunohistochemistry has been previously reported in conventional clear cell renal cell carcinoma; however, occurrence of this phenomenon has not yet been properly assessed in the sarcomatoid variant of renal cell carcinoma. Our study demonstrates that alterations of the *MDM2* pathway are relatively frequent in sarcomatoid renal cell carcinoma, and nuclear positivity for MDM2 by immunohistochemistry, as well as *MDM2* amplification by fluorescence in situ hybridization may pose a potential pitfall for diagnosis with dedifferentiated liposarcoma at metastatic sites. A panel approach to immunohistochemical testing is recommended for the diagnosis of these lesions. Also, identification of cases of sarcomatoid renal cell carcinomas harboring *MDM2* copy number gain or gene amplification may also have potential therapeutic implications.

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https://doi.org/10.1007/s00428-019-02703-9

BRIEF REPORT

MDM2-positive papillary sarcomatoid renal cell carcinoma: a potential diagnostic pitfall

Jera Jeruc[1] · Tanja Čugura[1] · Aleš Tomažič[2] · Emanuela Boštjančič[1]

Received: 19 July 2019 / Revised: 12 September 2019 / Accepted: 17 October 2019 / Published online: 16 November 2019

Abstract

Sarcomatoid renal cell carcinoma is a highly aggressive form of carcinoma, histologically showing both carcinomatous and mesenchymal component in different proportions. We present a case of advanced type 1 papillary sarcomatoid renal cell carcinoma infiltrating adjacent organs and showing positivity for MDM2 by immunohistochemistry and *MDM2* amplification by fluorescence in situ hybridization. This finding, together with sarcomatoid morphology, poses a potential pitfall for diagnosis with dedifferentiated liposarcoma. MDM2 is known to be altered in various human sarcomas. Only recently, MDM2 alterations have been reported in carcinomas. The presented case illustrates the need of thorough sampling with clinic-pathological correlation before making a final diagnosis in sarcomatoid retroperitoneal tumours. Additionally, the potential clinical implications of *MDM2* amplification in renal cell carcinoma are discussed.

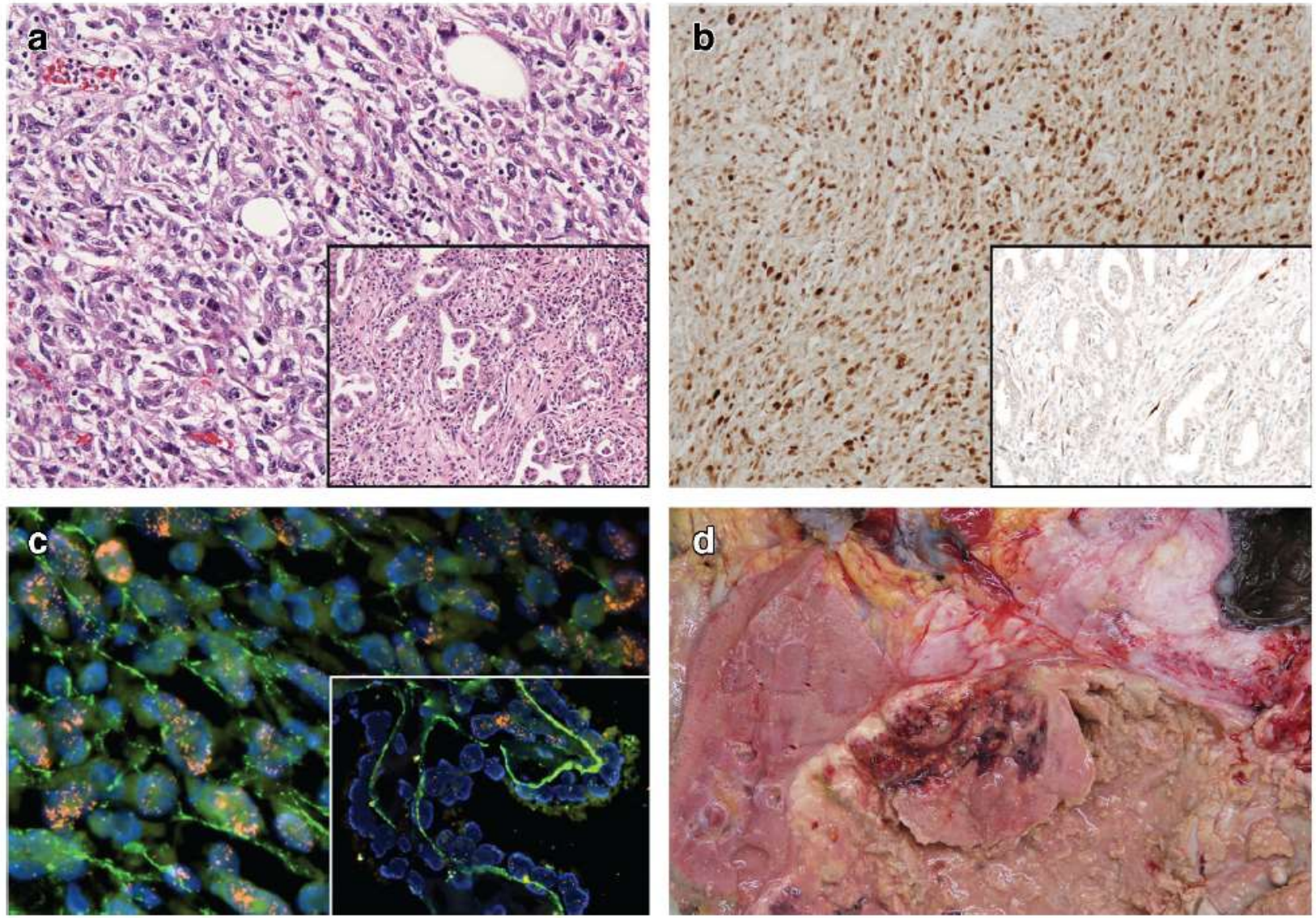

Fig. 1 **a** Sarcomatoid RCC and transition area between papillary RCC and sarcomatoid RCC (inset) (both H&E, ×200). **b** Sarcomatoid RCC showing strong MDM2 nuclear expression with only scattered sarcomatoid cells in the transition area showing *MDM2* expression (inset) (both MDM2, ×200). **c** MDM2/CEP12 FISH showing increased signals consistent with amplification in sarcomatoid RCC in contrast to papillary RCC (inset). **d** Gross picture of sarcomatoid RCC infiltrating descending colon (top right) with relatively sharp demarcation from the left kidney (left)

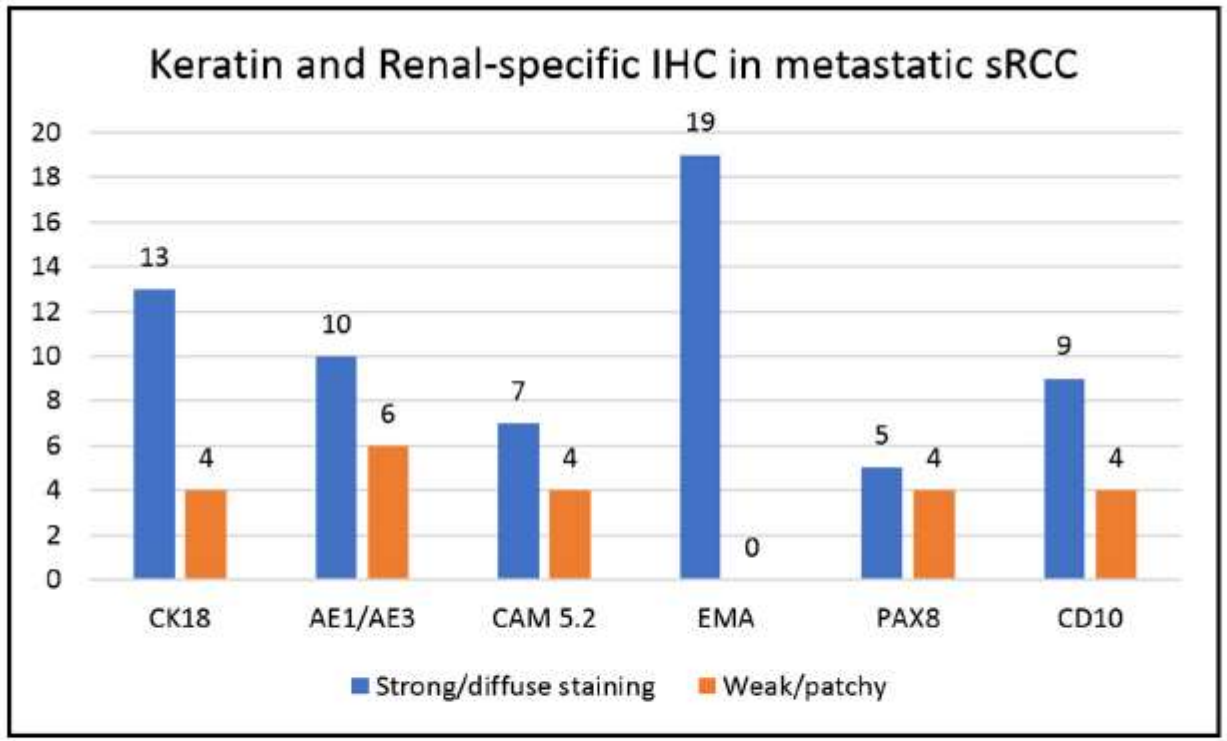

Fig. 5 Summary of differential expression patterns in the metastatic cohort of sRCC for epithelial and renal-specific IHC. IHC = immunohistochemistry, sRCC = sarcomatoid renal cell carcinoma.

MDM2 amplification in sarcomatoid lung carcinoma

Cancer Genetics 250–251 (2021) 12–19

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Cancer Genetics

journal homepage: www.elsevier.com/locate/cancergen

Genetic heterogeneity and predictive biomarker for pulmonary sarcomatoid carcinomas

Jing Qin[a,b,1], Bo Chen[c,1], Chenghui Li[b], Junrong Yan[d], Hongyang Lu[a,b,*]

allele frequency in 4 out of 6 patients. However, *KRAS* mutation was not detected in this study. Notably, we found *MDM2* amplification in 2/6 (33.3%) cases and *STK11* mutation in 1/6 (16.7%) cases.

Renal and other carcinomas becoming sarcomatoid, spreading and metastasizing, also to the retroperitoneum, with loss of markers like CKpan and appearance of MDM2 amplification…

…it is getting difficult to diagnose a (retroperitoneal) MDM2 DDLPS without a clear WDLPS component if there is a know carcinoma in the abdominal cavity or even elsewhere in the body…

…luckily we have the KRAS data in our patient…

MDM2 Amplification in Intrahepatic Cholangiocarcinomas

Its Relationship With Large-Duct Type Morphology and Uncommon KRAS Mutations

Sung Joo Kim, MD, Masayuki Akita, MD,† You-Na Sung, MD,* Kohei Fujikura, MD, PhD,† Jae Hoon Lee, MD, PhD,‡ Shin Hwang, MD, PhD,‡ Eunsil Yu, MD, PhD,* Kyoko Otani, MD,† Seung-Mo Hong, MD, PhD,* and Yoh Zen, MD, PhD, FRCPath†*

(*Am J Surg Pathol* 2018;42:512–521)

KRAS mutation mutually exclusive with MDM2 amplification: you only need one driver

TABLE 2. Immunohistochemical Features and Gene Mutation Analyses

	MDM2 Amplified (N = 13)	*MDM2* Nonamplified (N = 200)	*P*
Immunohistochemistry (n [%])			
p53 abnormality	3 (23)	90 (45)	0.155
Loss of SMAD4	7 (54)	51 (26)	0.047
Loss of BAP1	1 (8)	27 (19)	0.704
Gene sequencing (n [%])			
KRAS	0	7 (28)*	0.035
IDH1	0	3 (12)*	0.193
IDH2	0	0*	Identical

*Examined in 25 cases.

The *KRAS* mutation was exclusively observed in iCCAs without *MDM2* amplification (7/25 cases tested, 28%) and in none of the *MDM2*-amplified iCCAs (0/13 cases; $P = 0.035$). Similarly, all *MDM2*-amplified iCCAs

Next-generation sequencing and histological response assessment in peritoneal metastasis from pancreatic cancer treated with PIPAC

Malene Nielsen,[1,2] Martin Graversen ,[3] Signe Bremholm Ellebæk,[3] Thomas Kielsgaard Kristensen,[1] Claus Fristrup,[3] Per Pfeiffer,[2,4] Michael Bau Mortensen,[2,3] Sönke Detlefsen [1,2]

Nielsen M, *et al*. *J Clin Pathol* 2021;**74**:19–24. doi:10.1136/jclinpath-2020-206607

Table 4 Results of NGS analyses of cytological and histological specimens from primary tumour and metastases from 16 patients with PM from pancreatic cancer

	Primary tumour	Histological biopsy prior to PIPAC*	PF before PIPAC	Histological peritoneal biopsy after PIPAC	PF after PIPAC
Patient 1	*KRAS* (p.Gly12Asp)	*KRAS* (p.Gly12Asp)	*KRAS* (p.Gly12Asp)	ND (PIPAC 3 and 4)	NA
Patient 2	*KRAS* (p.Gly12Val) *TP53* (p.Cys275Tyr)	*KRAS* (p.Gly12Val)	NA	*KRAS* (p.Gly12Val) (PIPAC 2 and 3)	NA
Patient 3	ND	ND	NA	ND (PIPAC 2, 3, 4 and 5)	ND (PIPAC 5)
Patient 4	ND	*KRAS* (p.Gly12Val)	ND	*KRAS* (p.Gly12Val) (PIPAC2)	*KRAS* (p.Gly12Val) (PIPAC 2)
Patient 5	*KRAS* (p.Gly12Asp) *SMAD4* (p.Arg135Ter)	NA	NA	*KRAS* (p.Gly12Asp) (PIPAC 2) *SMAD4 (p.Arg135Ter) (PIPAC 2)* ND (PIPAC 3) *KRAS (p.Gly12Asp) (PIPAC 4)*	*KRAS* (p.Gly12Asp) (PIPAC 5)
Patient 6	*KRAS* (Gly12Asp)	NA	NA	NA	NA
Patient 7	*KRAS* (p.Gly12Val)	*KRAS (p.Gly12Val) (lymph node)*	NA	NA	NA
Patient 8	NA	ND	*KRAS* (p.Gly12Asp)	NA	NA
Patient 9	*MET* (p.Arg988Cys)	*MET* (p.Arg988Cys) (found in PM biopsy and lymph node biopsy)	NA	NA	NA
Patient 10	ND	*KRAS* (p.Gln61Arg) *SMAD4* (p.Arg361Cys)	*KRAS* (p.Gln61Arg)	*KRAS* (p.Gln61Arg) (PIPAC 2)	*KRAS* (p.Gln61Arg) (PIPAC 2)
Patient 11	*FGFR2 (p.Asn549Lys)*	*KRAS (p.Gly12Asp)*	NA	NA	NA
Patient 12	*KRAS* (p.Gly12Asp)	NA	NA	NA	ND (PIPAC 3 and 4)
Patient 13	*KRAS* (p.Gly12Val)	NA	NA	NA	NA
Patient 14	*KRAS* (p.Gly12Val) *TP53* (p.Arg273His)	NA	NA	NA	NA
Patient 15	NA	*KRAS* (p.Gly12Arg)	*KRAS* (p.Gly12Arg)	*KRAS* (p.Gly12Arg)	*KRAS* (p.Gly12Arg) (PIPAC 2)
Patient 16	NA	*KRAS* (p.Gly12Ala)	ND	ND	ND (PIPAC 2)

*NGS of histological biopsy from peritoneum, unless something else is stated.
NA, not available; ND, not detected; NGS, next-generation sequencing; PF, peritoneal fluid; PM, peritoneal metastasis.

patients. A *KRAS* mutation was found in both the primary tumour and at least one metastasis in 4/11 patients (36.36%). In three patients, a *KRAS* mutation was detected in a metastasis but not in the primary tumour. In one patient, a *KRAS* mutation was detected in the primary tumour but not in the metastases.

KRAS is in the driver seat of the pancreatic adenocarcinoma

MDM2 takes over the driver seat: appearance of a focus of MDM2 amplification; KRAS is not needed anymore in this focus and disappears gradually

The very aggressive MDM2 amplified/KRAS- clone metastasizes to the inguinal canal/retroperitoneum, accompagnied by CKpan loss and acquisition of a DDLPS-like morphology and diffuse presence of the MDM2 amplification

Human Pathology (2022) 119, 85–93

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Original contribution

Differential immunohistochemical and molecular profiling of conventional and aggressive components of chromophobe renal cell carcinoma: pitfalls for diagnosis☆,☆☆

Constance V. Chen MD, Nicole A. Croom MD [1], Jeffry P. Simko PhD MD, Bradley A. Stohr MD PhD [2], Emily Chan MD PhD*,[2]

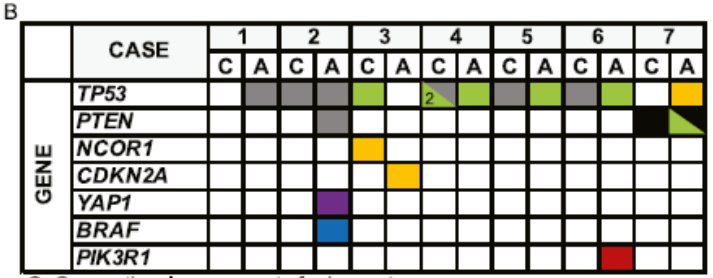
tases. In the primary conventional components, a typical ChRCC IHC pattern (CK7+, CD117+, and CAIX-) was observed in 8 of 10 cases; 2 cases had rare CK7 staining. In the aggressive components, CD117 and/or CK7 was lost in 7 of 10 cases; 3 cases showed loss of both. Two of 10 cases showed significant CAIX staining in the aggressive component. All 7 cases that had molecular profiling performed showed characteristic chromosomal losses reported for ChRCC, with the aggressive components generally demonstrating more copy number complexity. Recurrent *TP53* mutations (*TP53*m) were also seen; however, surprisingly, the conventional and aggressive components had no shared *TP53*m: a *TP53*m was private to aggressive components in 2 cases and to the conventional component in 1 case, and in 4 cases, components demonstrated different *TP53*m. Of the 21 pathogenic alterations identified in 7 tumors, only a *PTEN* splicing alteration was shared between both components in one case. In conclusion, ChRCC can have IHC staining patterns and molecular profile that differ between conventional and aggressive components. Interpretation of stains on metastases or small biopsies to

A

CASE	Conventional Component (primary tumor)	AF^ (%)	Aggressive Component#	AF^ (%)
1			*TP53* p.D208F	81
2	*TP53* p.K351E	23	*PTEN* p.I101dup	31
			TP53 p.R213Q	28
			YAP1 amplification	
			BRAF-KD duplication	
3	*NCOR1* p.E1077*	20	*CDKN2A* p.E88*	27
	TP53 p.L130fs	4		
4	*TP53* p.M237K	8	*TP53* p.R209fs	30
	TP53.R65fs	8		
	TP53 p.T18fs	13		
5	*TP53* p.R175H	94	*TP53* p.S15fs	54
6	*TP53* p.V157L	81	*TP53* p.Q192fs	68
			PIK3R1 deletion	
7	*PTEN* c.209+1_209+2delGT	82	*PTEN* c.209+1_209+2delGT	29
			PTEN p.P248fs	41
			TP53 p.R306*	49

^AF: Allele frequency.
#Metastatic component tested: cases 1, 2, 4, 5 and 6. Sarcomatoid component in primary tumor tested: cases 3 and 7.

B



C: Conventional component of primary tumor
A: Aggressive component

Alteration Type
Missense
Nonsense
Frameshift
Kinase domain duplication
Deletion
Amplification
Splicing mutation
Frameshift and Splicing mutations
Frameshift and Missense mutations

Fig. 3 Molecular findings in conventional and aggressive chromophobe renal cell carcinoma components. **A.** Comparison of pathogenic and likely pathogenic gene alterations identified in the conventional primary tumor, primary sarcomatoid component, or metastatic tumor of 7 cases. **B.** Mutations from (A) illustrated by type.

How could one prove that the inguinal tumor does represent a metastasis from the pancreatic tumor?

Classical molecular analysis does not help since the original molecular alteration is lost and replaced by another type of molecular alteration and the tumors are at distance from each other

The only proof possible would be show that the MDM2-amplified cells/focus in the pancreas is KRAS- and is surrounded by KRAS+ and MDM2+ tumoral tissue

This could in principle be possible via mutated KRAS specific RNA ISH combined with FISH for MDM2…which we did not have access to

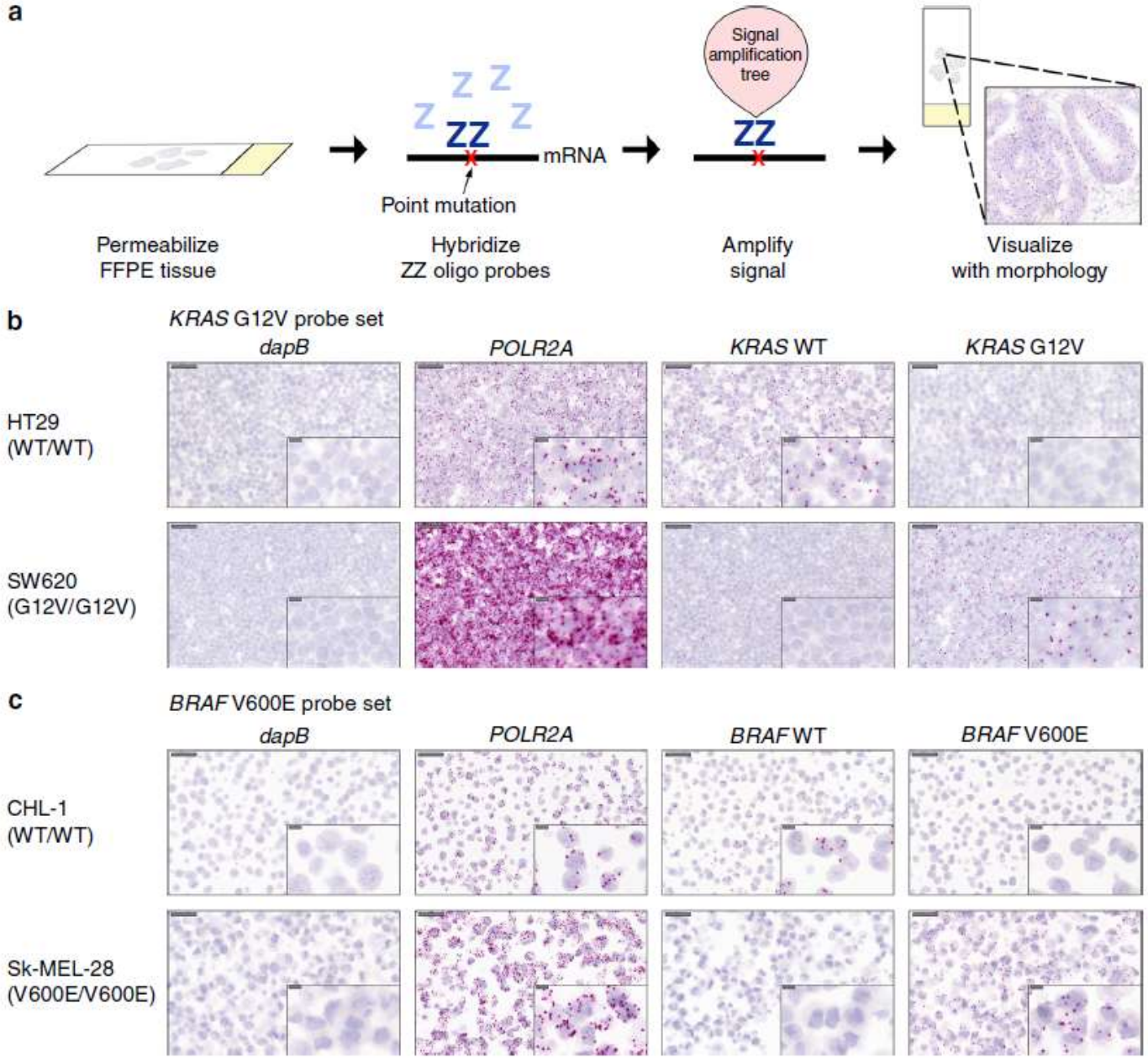
nature COMMUNICATIONS

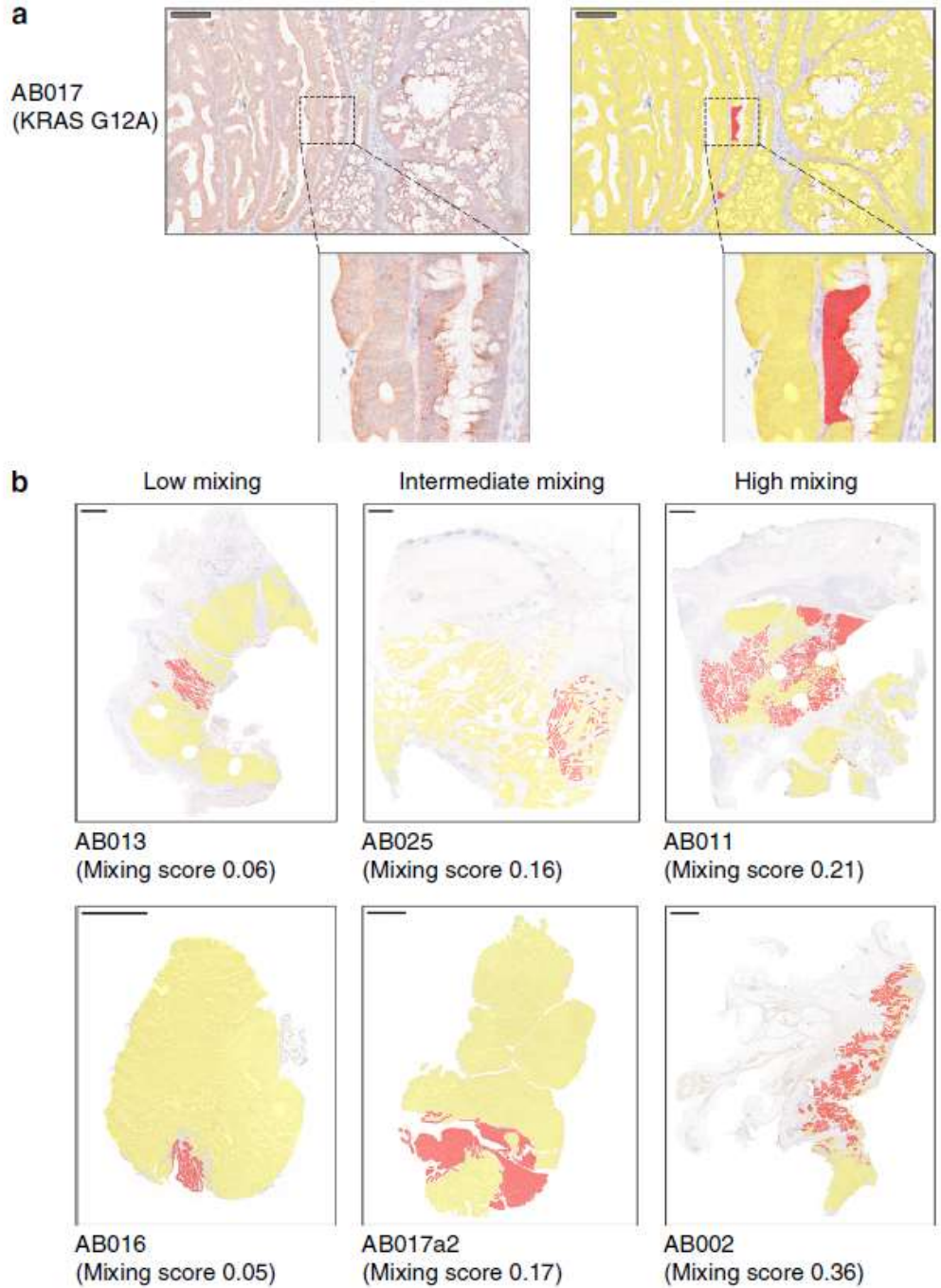
ARTICLE

DOI: 10.1038/s41467-017-02295-5 OPEN

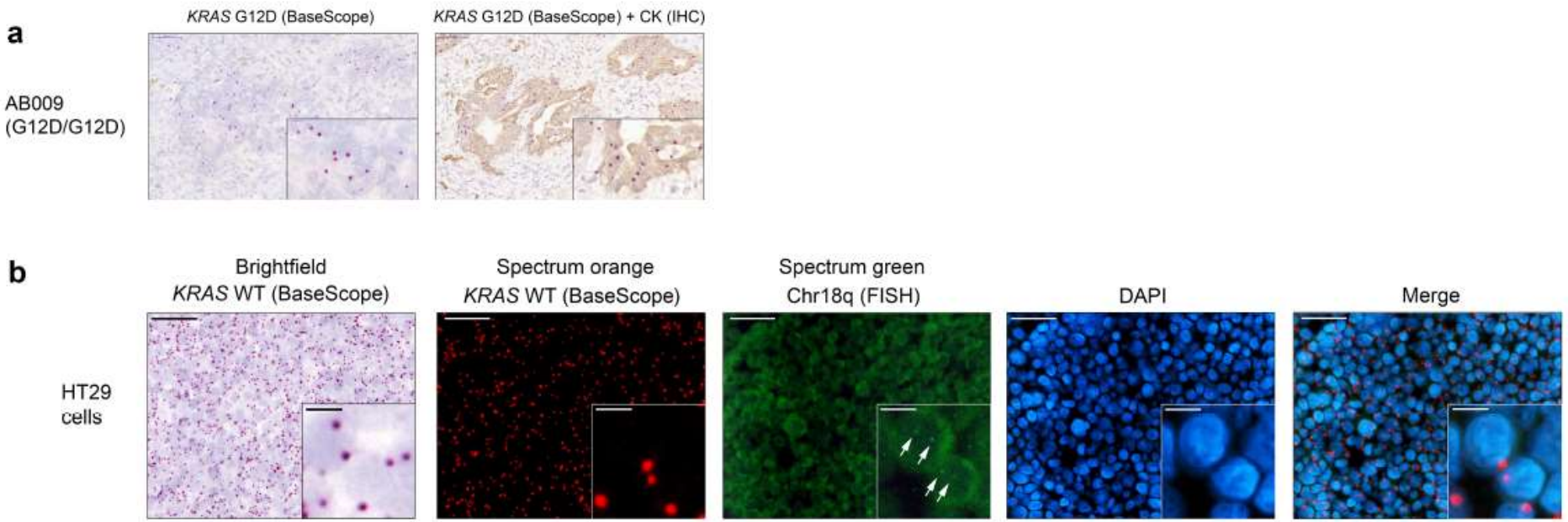
Robust RNA-based in situ mutation detection delineates colorectal cancer subclonal evolution

Ann-Marie Baker[1], Weini Huang[1], Xiao-Ming Mindy Wang[2], Marnix Jansen[3,4], Xiao-Jun Ma[2], Jeffrey Kim[2], Courtney M. Anderson[2], Xingyong Wu[2], Liuliu Pan[2], Nan Su[2], Yuling Luo[2], Enric Domingo[5], Timon Heide[6], Andrea Sottoriva[6], Annabelle Lewis[7], Andrew D. Beggs[8], Nicholas A. Wright[1], Manuel Rodriguez-Justo[3], Emily Park[2], Ian Tomlinson[9] & Trevor A. Graham[1]


a
Signal amplification tree
ZZ
mRNA
Point mutation
Permeabilize FFPE tissue
Hybridize ZZ oligo probes
Amplify signal
Visualize with morphology
b
KRAS G12V probe set
dapB
POLR2A
KRAS WT
KRAS G12V
HT29 (WT/WT)
SW620 (G12V/G12V)
c
BRAF V600E probe set
dapB
POLR2A
BRAF WT
BRAF V600E
CHL-1 (WT/WT)
Sk-MEL-28 (V600E/V600E)


a
AB017
(KRAS G12A)
b
Low mixing
Intermediate mixing
High mixing
AB013
(Mixing score 0.06)
AB025
(Mixing score 0.16)
AB011
(Mixing score 0.21)
AB016
(Mixing score 0.05)
AB017a2
(Mixing score 0.17)
AB002
(Mixing score 0.36)

Supplementary Figure 3. Baker *et al*
BaseScope can be combined with IHC or DNA-FISH



Supplementary Figure 3 – BaseScope can be combined with IHC or DNA-FISH
a. Representative images of *KRAS* G12D BaseScope signal alone (left panel) and with sequential IHC staining for pan-cytokeratin (CK, right panel).
b. Representative images of *KRAS* wild-type BaseScope signal (visible in brightfield and under the 'Spectrum orange' filter) combined with FISH for Chr18q (under the 'Spectrum green' filter, white arrows highlight location of the FISH signals). Scale bars in **a** and **b** represent 50 micron and 10 micron (inset).

MDM2 amplification is everywhere

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Dedifferentiated melanoma with MDM2 gene amplification mimicking dedifferentiated liposarcoma

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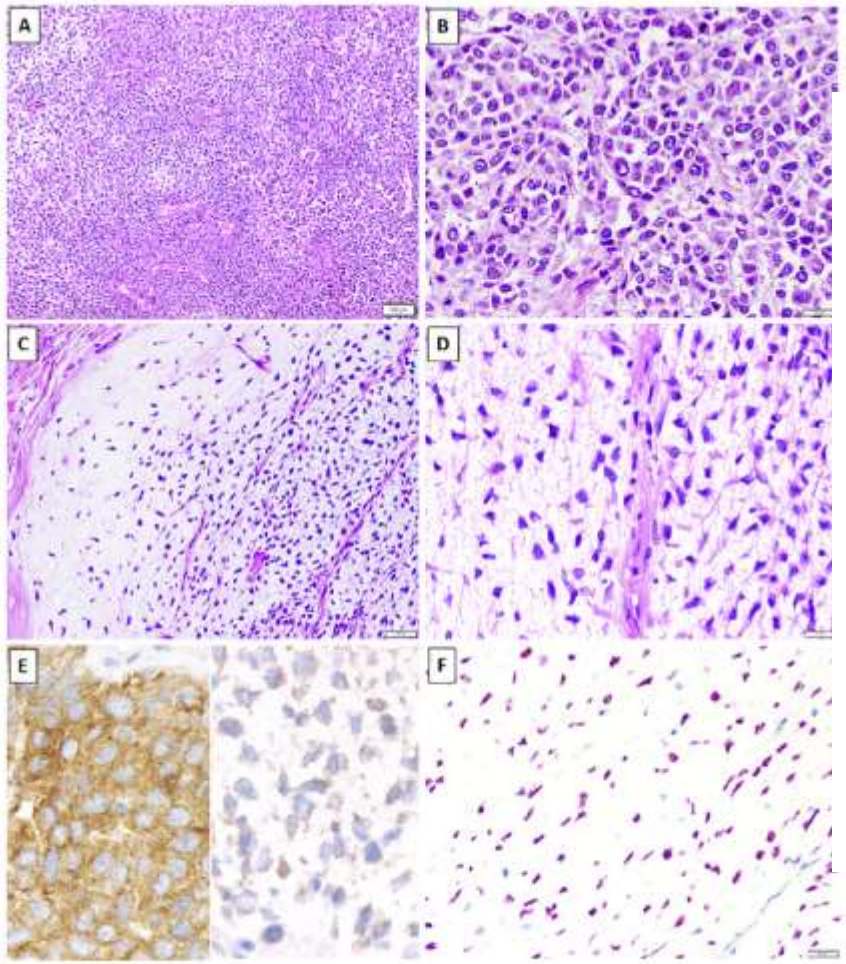

Fig. 1 (A,B) H&E images of melanoma with epithelioid morphology. (C,D) H&E stained sections of myxoid liposarcoma (ML)-like areas. (E) BRAF VE1 immunohistochemical (IHC) stain showing strong cytoplasmic expression in melanoma with epithelioid appearance (left panel) and equivocal granular cytoplasmic expression in ML-like areas (right panel). (F) PRAME IHC showing strong and diffuse expression in ML-like areas (red chromogenic stain).

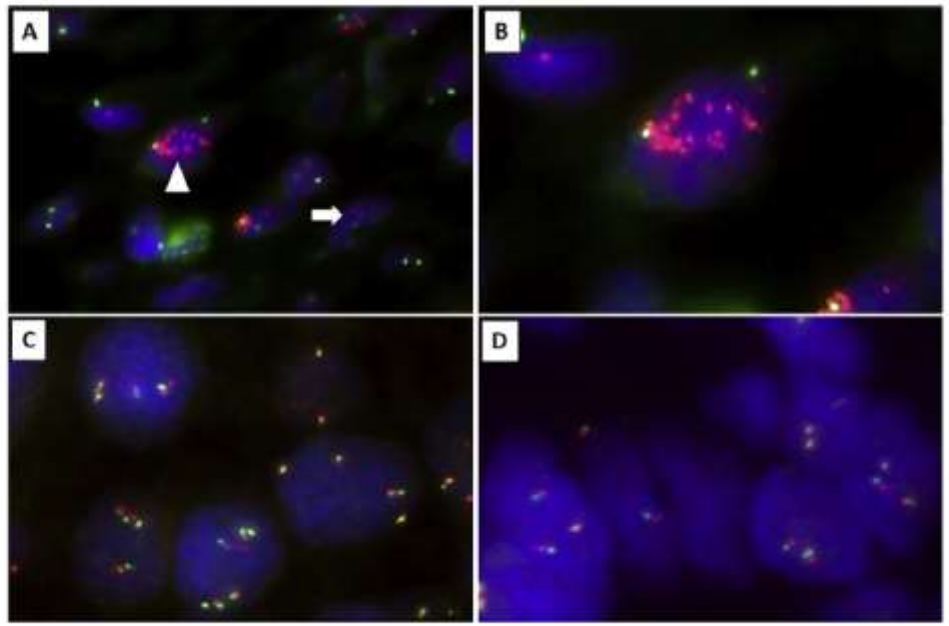

Fig. 2 (A,B) Fluorescence *in situ* hybridisation (FISH) for *MDM2* (12q15)/CC12, showing a cell (arrow head) with high level of amplification (>20 copies) in a background of cells with diploid signals (arrow). (C) FISH for *DDIT3* (12q13) and (D) *EWSR1* (22q12) break-apart probes demonstrated an average 3 extra non-rearranged copies and increased isolated red and/or green signals for both probes.

The patient presented with a rapidly growing tumour in the left breast at the 2 o'clock position suspicious for primary breast carcinoma. A core biopsy demonstrated morphological features of metastatic melanoma characterised by an epithelioid morphology and supported by immunohistochemistry (IHC) (SOX10+/HMB45+/PanCK−). A somatic *BRAF* V600E mutation was detected by a targeted next generation sequencing (NGS) panel (FIND IT Melanoma Panel; Contextual Genomics, Canada). A wide local excision was

(Fig. 1F). Although the overall appearances were thought to be compatible with a dedifferentiated melanoma, the possibility of a collision DD-LPS or high-grade ML was considered and fluorescence *in situ* hybridisation (FISH) was performed to elucidate the diagnosis. FISH for *MDM2* [*MDM2* (12q15) Red + Copy Control 12 Green FISH Probe; Biocare Medical, USA] detected gene amplification in 30% of the tumour cells including high level of amplification (>20 copies) with the remaining nuclei showing diploid and polysomic signals (Fig. 2A,B). FISH for *DDIT3* (12q13;

of *MDM2* amplified DD-LPS, *BRAF* V600E mutation testing was repeated on the same block submitted for FISH analysis. *BRAF* V600E mutation was also present in the same block tested for *MDM2* FISH analysis (in spite of the equivocal VE1 immunostain). Given the presence of shared *BRAF* V600E mutation indicative of clonal relationship between the two components with one of these representing unequivocal melanoma together with the focal (rather than diffuse) nature of *MDM2* amplification, the final diagnosis rendered was dedifferentiated melanoma.

To make things even more complex:
cases that are not DDLPS-like carcinoma, but carcinoma-like DDLPS
(Agaimy again, of course)

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In this issue

Dedifferentiated liposarcoma composed predominantly of rhabdoid/epithelioid cells: a frequently misdiagnosed highly aggressive variant☆,☆☆

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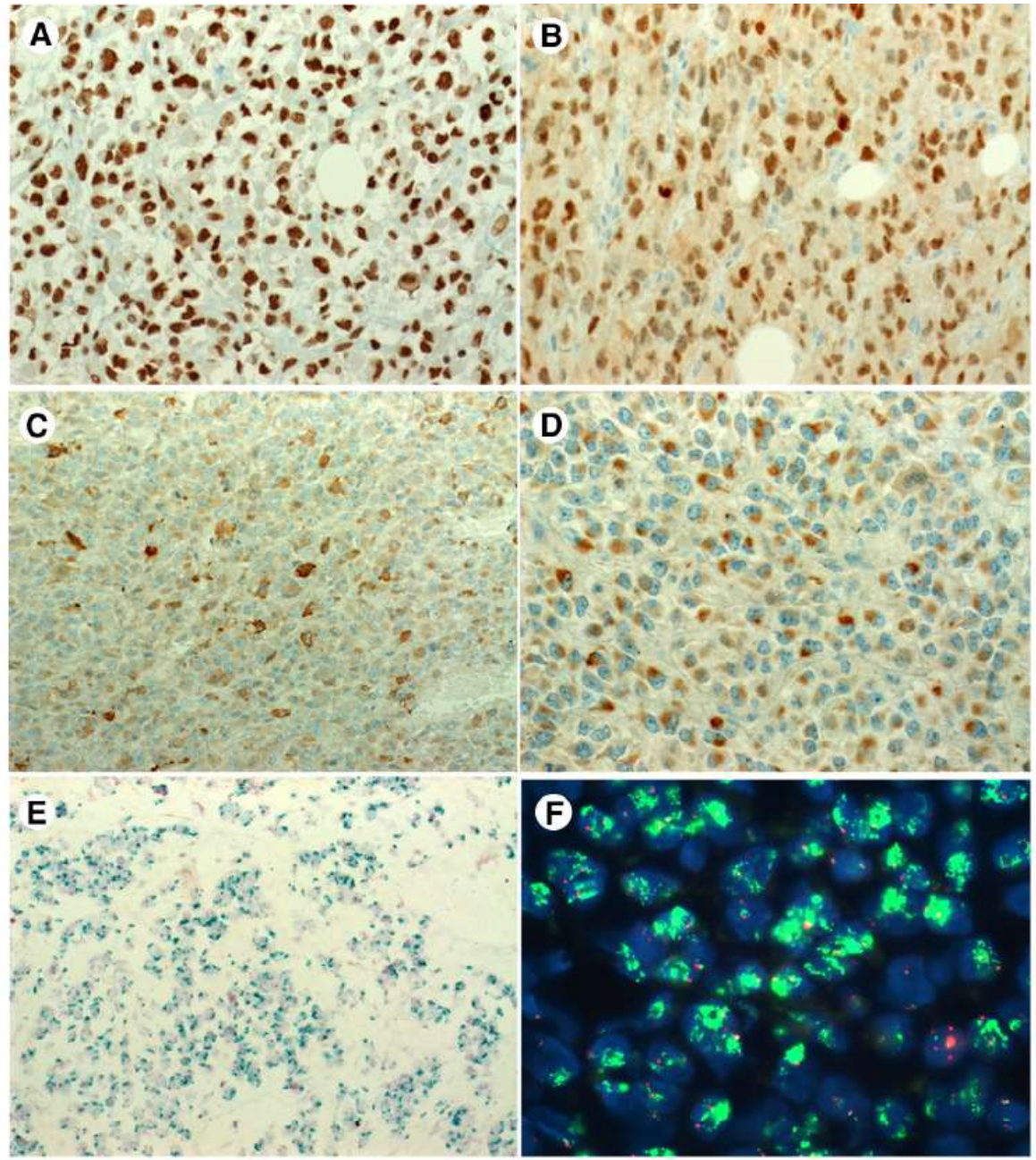

Fig. 4 Strong expression of CDK4 (A) and MDM2 (B) was seen in all cases (images: Case 2). AE1/AE3 was positive in scattered numerous cells (C) with focally prominent dot-like pattern highlighting rhabdoid morphology (D, images Case 1). E, Amplification of *MDM2* (CISH, Case 3) and CDK4 (F, FISH, Case 6) was a constant feature.

Thank you for your attention