Mesenchymal tumours of the GI tract

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12. Mesenchymal tumours of the digestive system

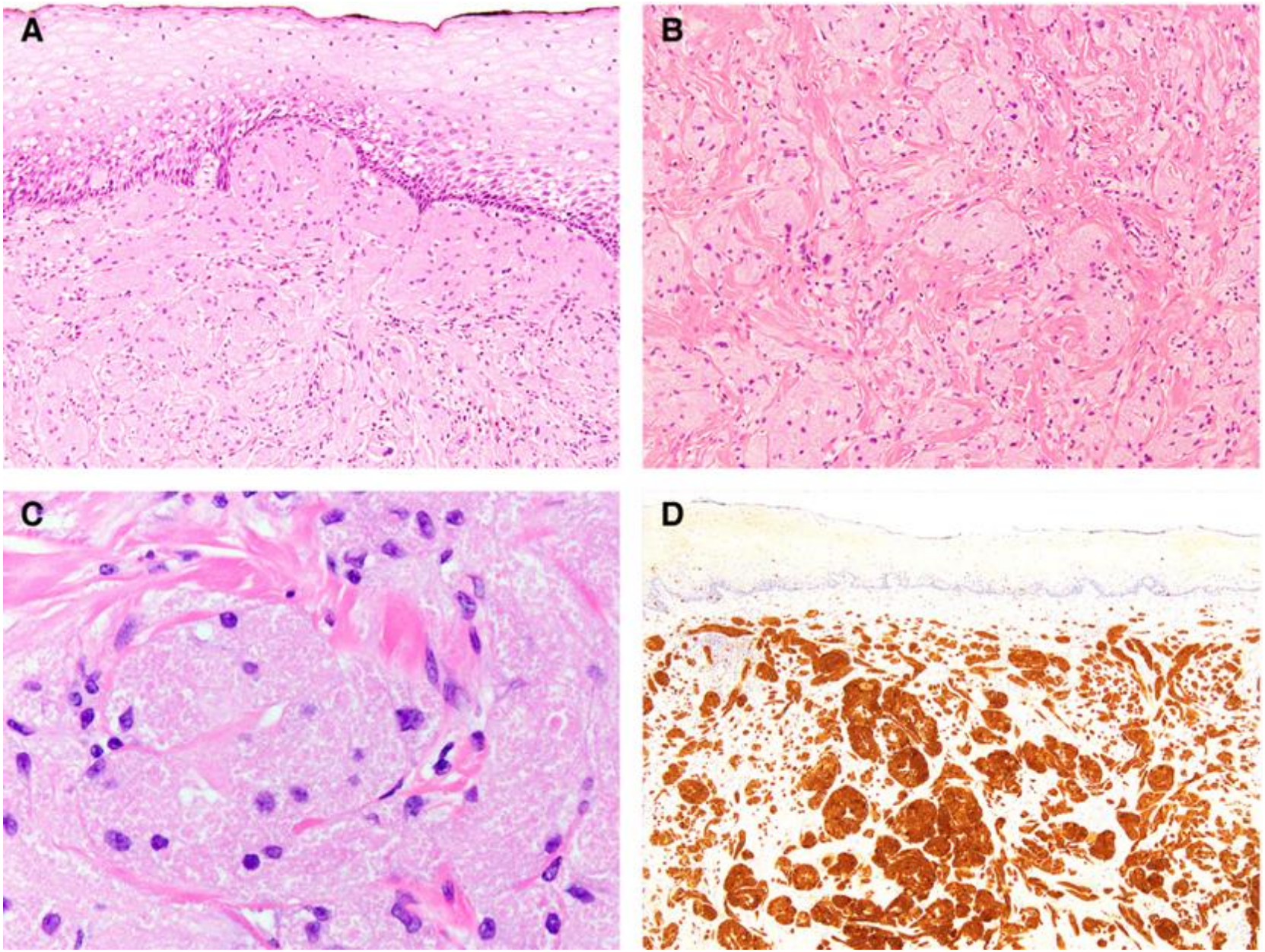
Recent developments in classification and in understanding of tumour biology

- Granular cell tumour
- Well-differentiated liposarcoma (“giant fibrovascular polyp”)
- Plexiform fibromyxoma
- Gastroblastoma
- Gastrointestinal stromal tumour
- Inflammatory fibroid polyp

Granular cell tumour

- More common in females
- Oesophagus > colorectum > anus > stomach > appendix > small bowel
- Usually incidental finding, < 1 cm
- 5% multiple lesions in the oesophagus
- SOX10+, S-100+, CD68+, NKI-C3+
- Clinically malignant granular cell tumours are exceptionally rare

Johnston MJ, *Dig Dis Sci* 1981
Fanburg-Smith JC, *Am J Surg Pathol* 1998
Voskuil JH, *Dig Dis Sci* 2001



S-100

Papke DJ, *Histopathology* 2021

Granular cell tumour

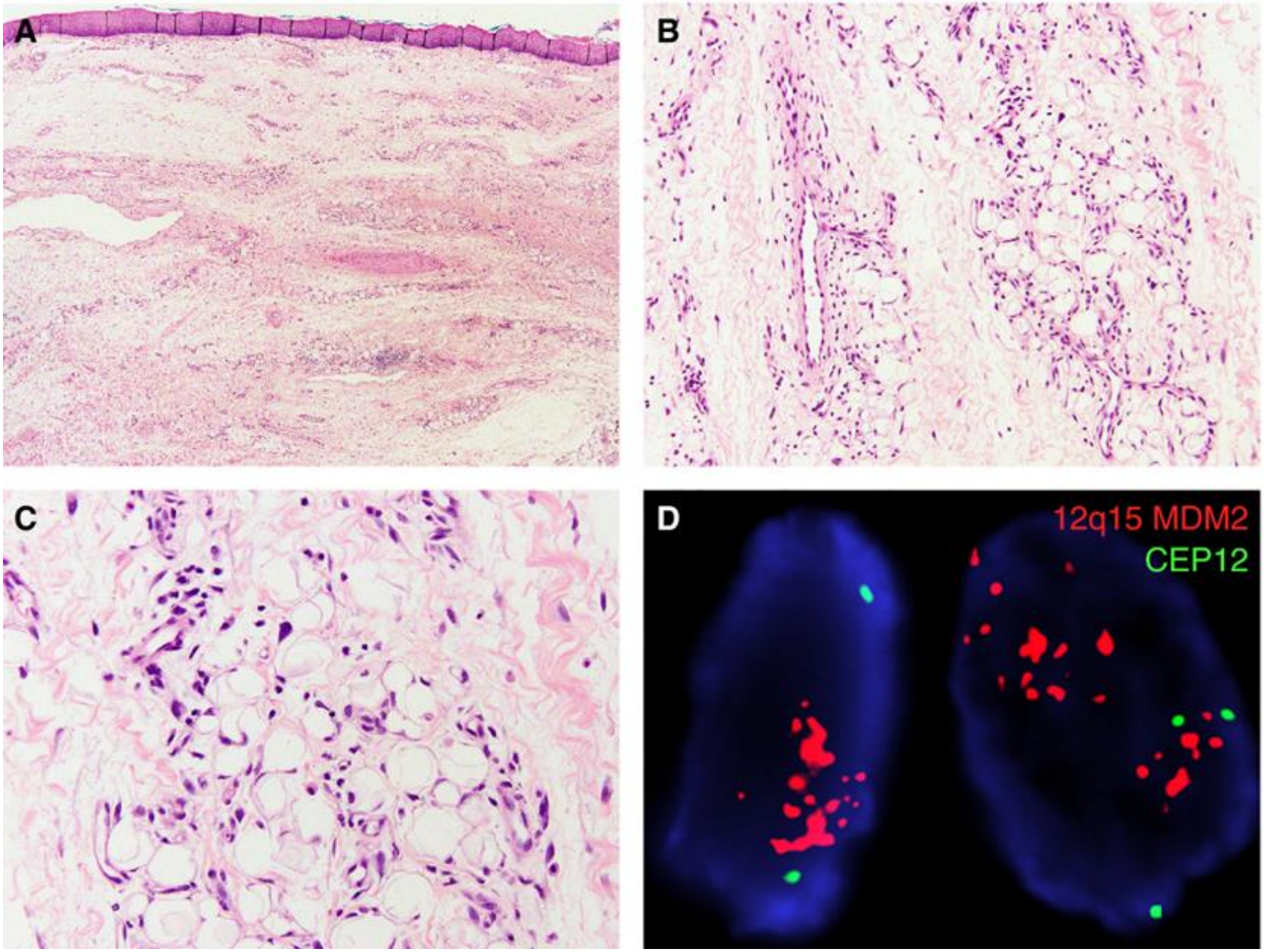
- Inactivating mutations in *ATP6AP1* and *ATP6AP2* in 70%
- Both genes located on the X-chromosome
- Mutations lead to accumulation of endosomes with abnormally high pH
- Additional mutations in granular cell tumours with aggressive tumour biology

Pareja F, *Nat Commun* 2018
Kinouchi K, *Circ Res* 2010
Machado I, *Virchows Arch* 2016

Well-differentiated liposarcoma

- “Giant fibrovascular polyp” first described in 1957 as a non-neoplastic, reactive lesion
- Peak incidence in 5th decade, no gender predilection
- > Proximal oesophagus near the cricopharyngeus muscle
- Large polypoid mass, dysphagia

Levine MS, *AJR Am J Roentgenol* 1996
Sargent RL, *Arch Pathol Lab Med* 2006
Park JS, *Clin Endosc* 2014



Papke DJ, *Histopathology* 2021

Polypoid fibroadipose tumors of the esophagus: 'giant fibrovascular polyp' or liposarcoma? A clinicopathological and molecular cytogenetic study of 13 cases

Rondell P Graham[1,2,4], Saba Yasir[1,4], Karen J Fritchie[1], Michelle D Reid[3], Patricia T Greipp[2] and Andrew L Folpe[1]

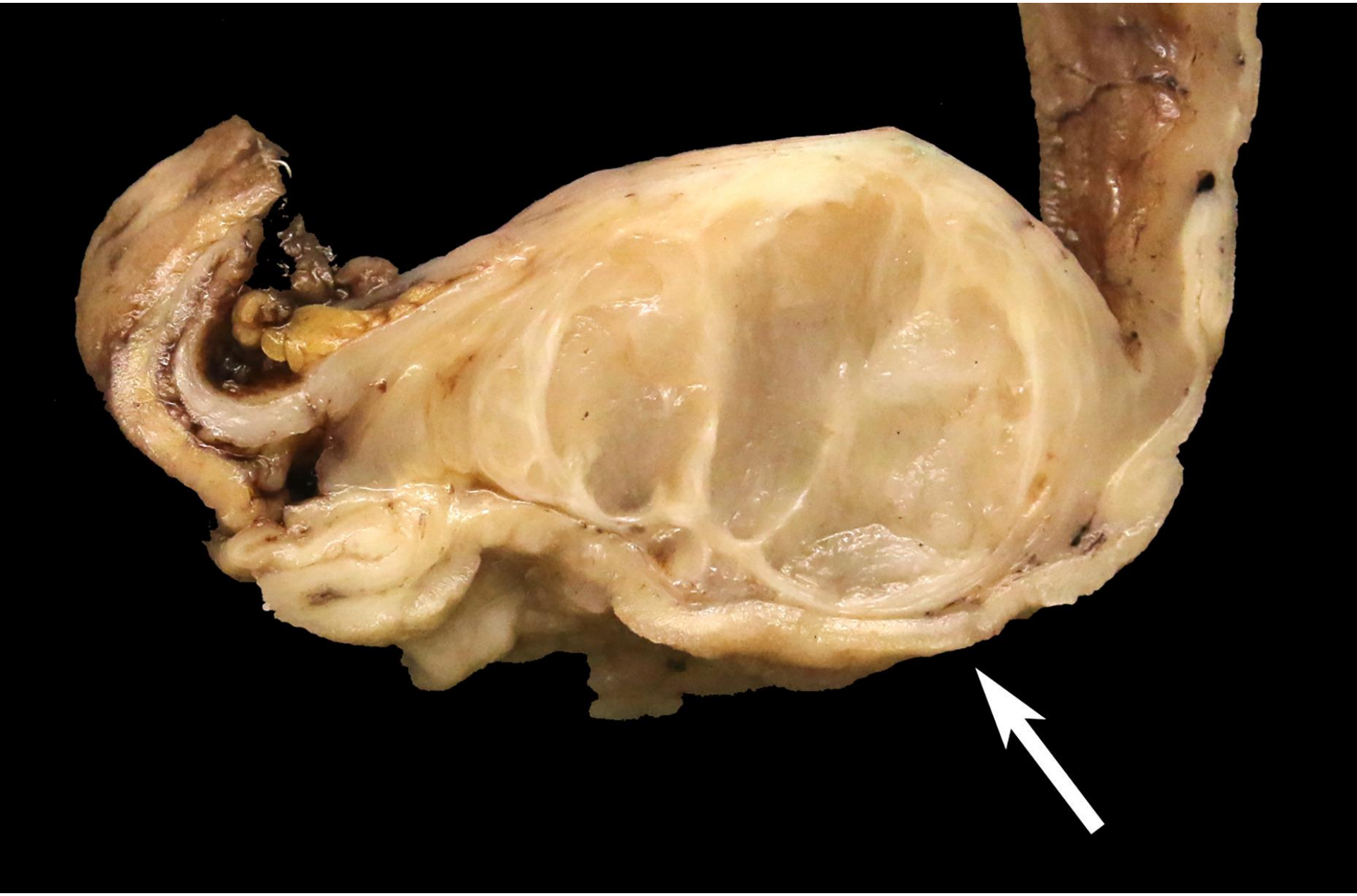
[1]*Division of Anatomic Pathology, Mayo Clinic, Rochester, MN, USA;* [2]*Division of Laboratory Genomics, Mayo Clinic, Rochester, MN, USA and* [3]*Department of Pathology, Emory University, Atlanta, GA, USA*

Giant fibrovascular polyp of the esophagus is a descriptive diagnostic term intended to encompass rare, large, polypoid esophageal masses composed of fibroadipose tissue. Despite sometimes dramatic clinical presentations, they have historically been considered to represent reactive, non-neoplastic proliferations. Recently, however, a small number of reports have described well-differentiated liposarcomas of the esophagus, mimicking giant fibrovascular polyps. In order to clarify the relationship between esophageal liposarcoma and giant fibrovascular polyp, we retrieved esophageal cases coded as 'giant fibrovascular polyp,' 'lipoma' and 'liposarcoma' from our archives and re-examined their clinicopathologic features and *MDM2* amplification status. Thirteen cases were identified (lipoma ($n=1$), giant fibrovascular polyp ($n=5$), well-differentiated liposarcoma ($n=3$), dedifferentiated liposarcoma ($n=3$)). The tumors ranged from 5.2 to 19.5 cm and arose predominantly in the cervical esophagus. All consisted chiefly of mature adipose tissue, with a variable component of fibrous septa. In all cases, close inspection of these fibrous septa showed them to contain an increased number of slightly enlarged spindled cells with irregular, hyperchromatic nuclei, similar to those seen in some well-differentiated liposarcomas. Three cases, all previously classified as dedifferentiated liposarcoma, showed in addition solid zones of non-lipogenic spindle cell sarcoma. By fluorescence *in situ* hybridization (FISH), all cases showed *MDM2* amplification, confirming diagnoses as well-differentiated ($N=10$) and dedifferentiated ($N=3$) liposarcoma. Clinical follow-up (8 cases, range 22–156 months, median 33 months) showed 3 patients with local recurrences (1 well-differentiated and 2 dedifferentiated liposarcomas), 1 patient with liver metastases (dedifferentiated liposarcoma) and 2 deaths from disease (both dedifferentiated liposarcomas). These results suggest that the great majority of large, polypoid, fat-containing masses of the esophagus represent well and dedifferentiated liposarcoma, rather than 'giant fibrovascular polyps.' We suggest that the diagnosis of 'giant fibrovascular polyp' should be made with great caution in the esophagus, and only after careful morphological study and *MDM2* FISH has excluded the possibility of liposarcoma.

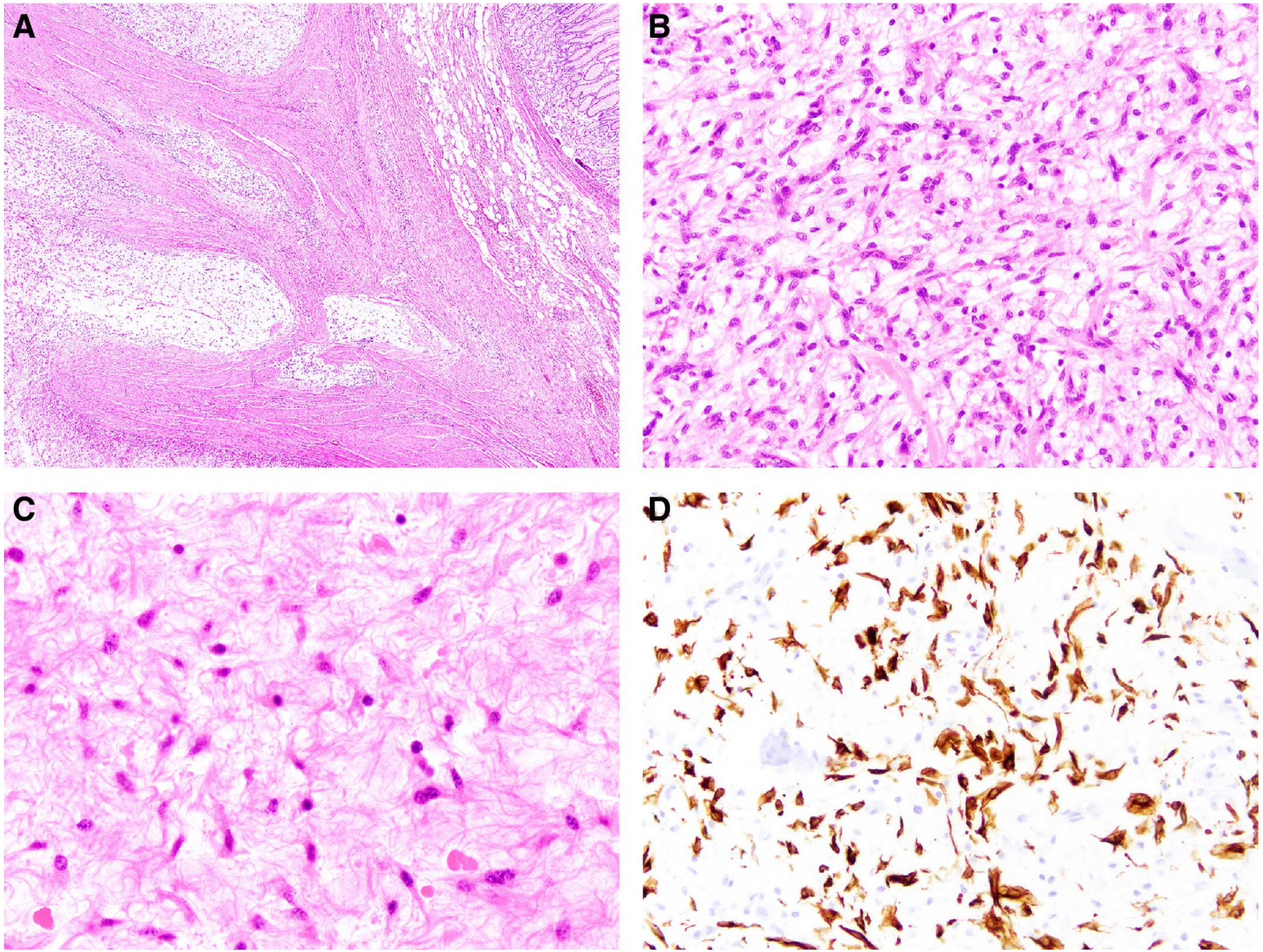
Modern Pathology (2018) **31,** 337–342; doi:10.1038/modpathol.2017.140; published online 6 October 2017

Plexiform fibromyxoma

- Formerly called “gastric fibromyxoma” or “plexiform angiomyxoid myofibroblastic tumour”
- Predilection for gastric antrum and pylorus
- Gastrointestinal bleeding, gastric outlet obstruction, perforation, abdominal distention, pain
- Centred in the muscularis propria, multinodular, gelatinous



Papke DJ, *Histopathology* 2021



desmin

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Plexiform fibromyxoma: immunohistochemistry

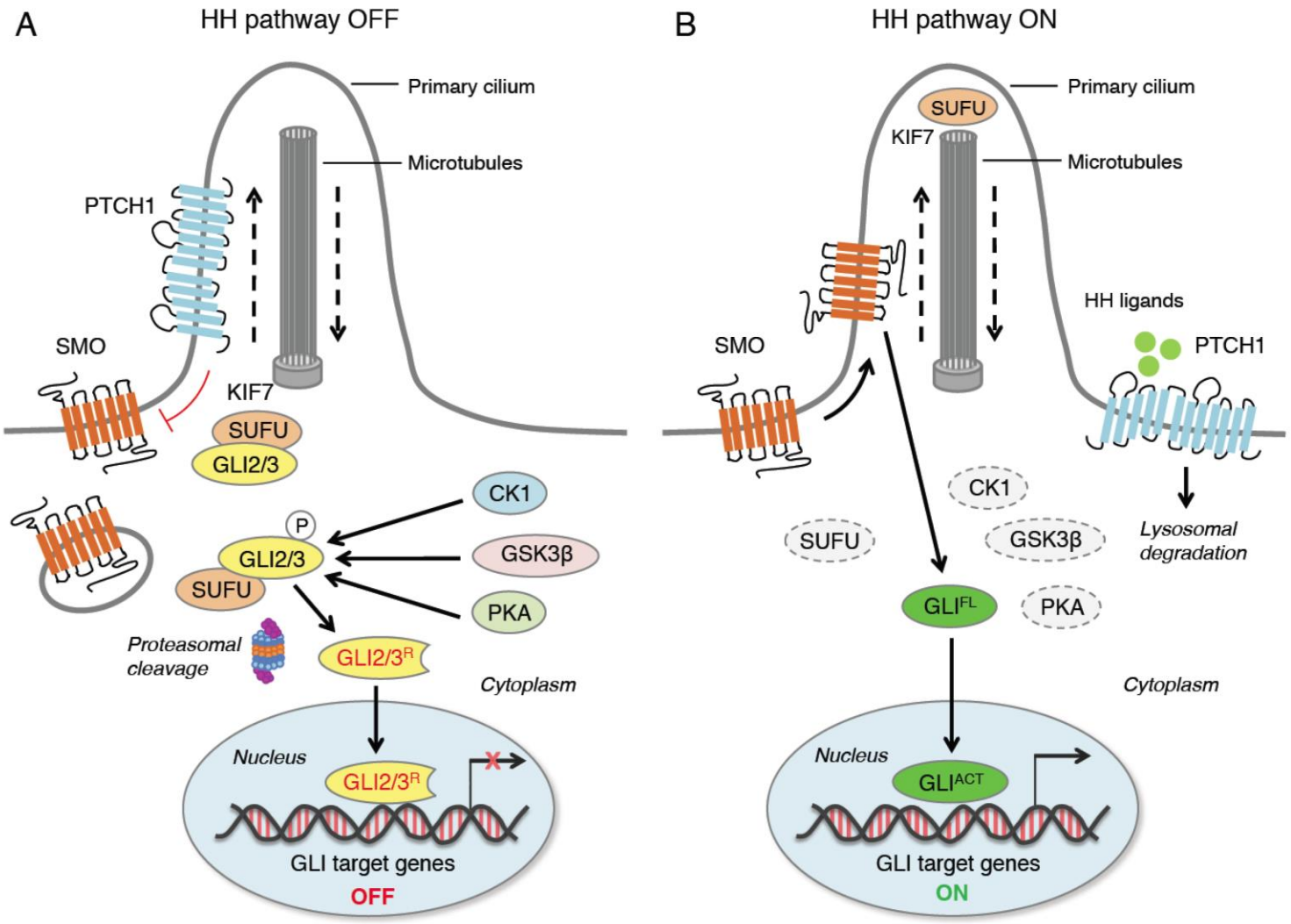
positive

- Smooth muscle actine (SMA)
- Desmin

negative

- KIT
- ANO1 (DOG1)
- S-100 protein

Hedgehog signalling pathway



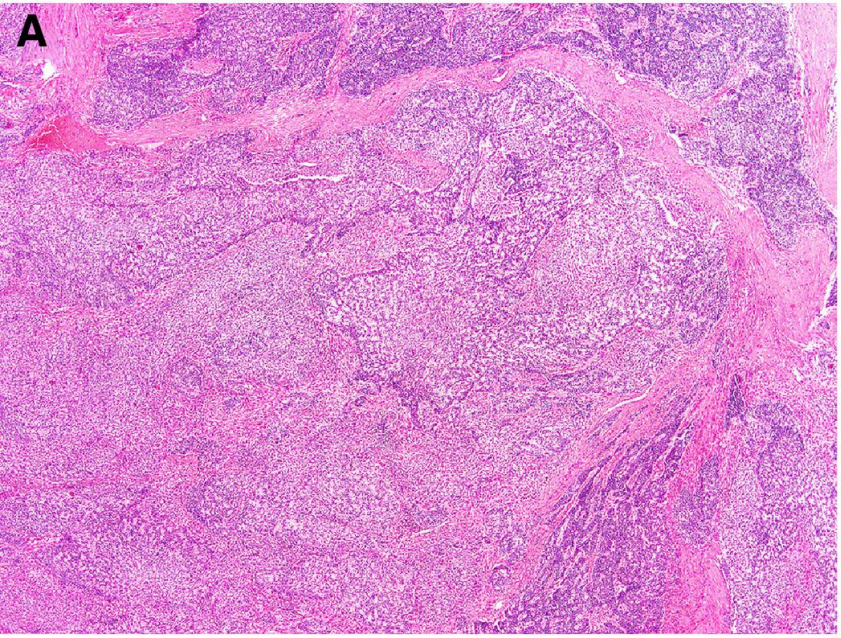
Plexiform fibromyxoma

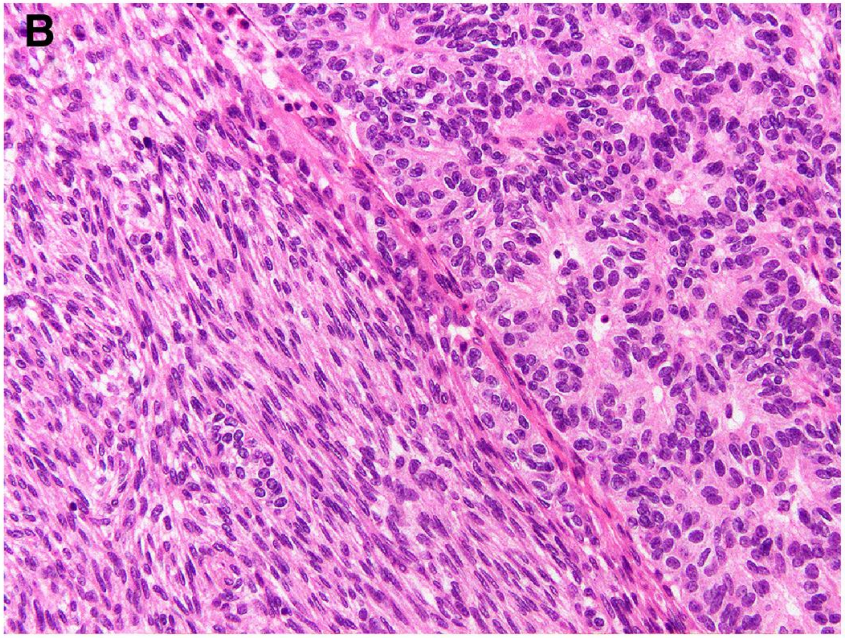
- *MALAT1-GLI1* gene fusions (20-40% of cases)
- *GLI1* amplifications (10-15% of cases)
- *PTCH1* deletions (20%)

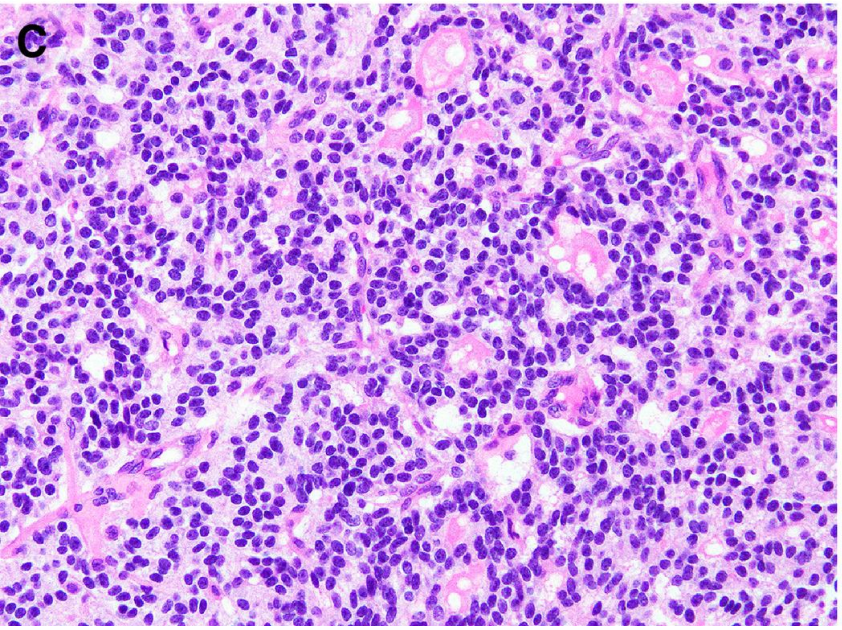
Hu G, *Int J Clin Exp Pathol* 2017
Spans L, *J Pathol* 2016
Banerjee S, *J Transl Med* 2019

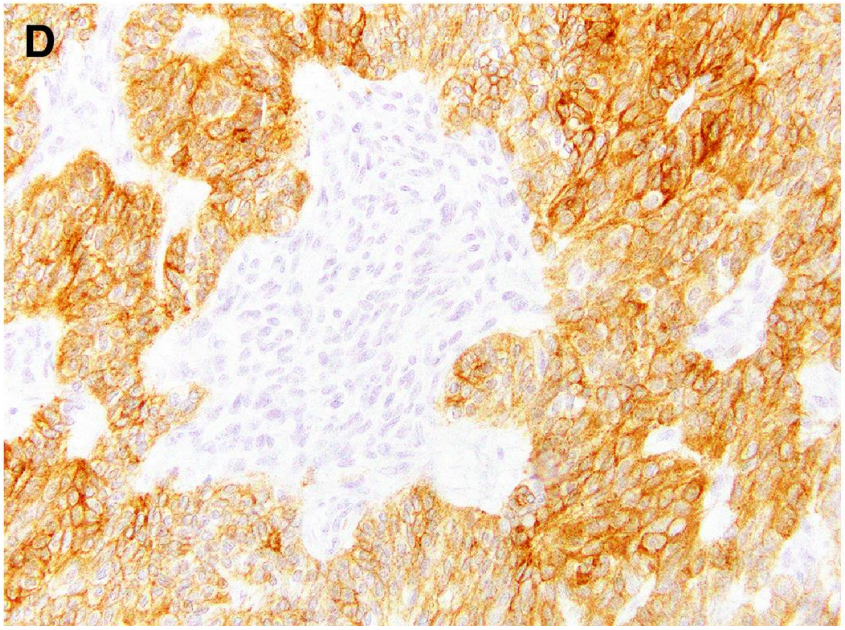
Gastroblastoma

- Centred in the muscularis propria
- Consistently contains a uniform and bland spindle cell component
- Biphasic neoplasm, with regions with epithelioid morphology
- May occasionally give rise to lymph node and peritoneal metastases









AE1/AE3

Papke DJ, *Histopathology* 2021

Gastroblastoma

Modern Pathology (2017) 30, 1443–1452

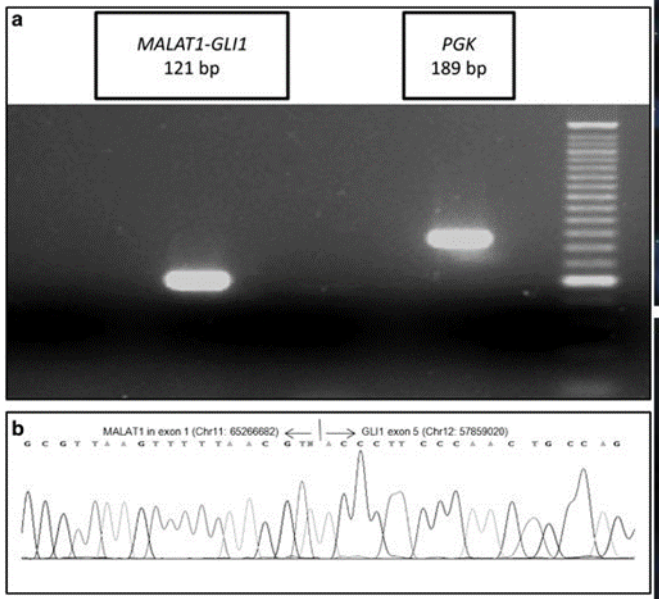
Gastroblastoma harbors a recurrent somatic *MALAT1–GLI1* fusion gene

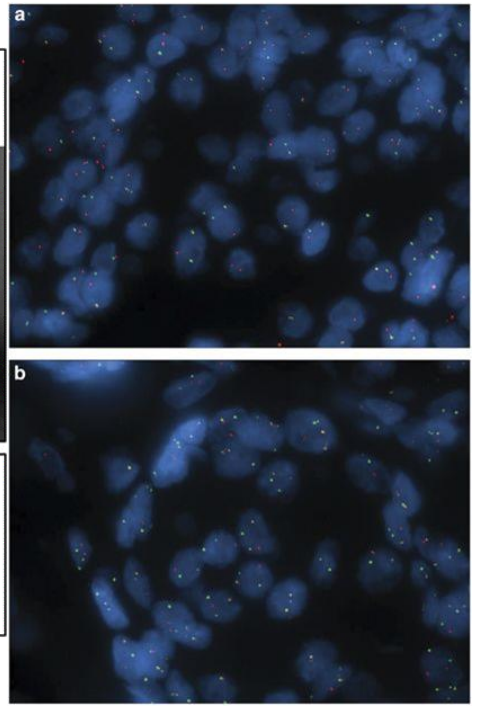
Rondell P Graham[1,2], Asha A Nair[3], Jaime I Davila[3], Long Jin[2], Jin Jen[4], William R Sukov[2], Tsung-Teh Wu[1], Henry D Appelman[5], Jorge Torres-Mora[1], Kyle D Perry[1], Lizhi Zhang[1], Sara M Kloft-Nelson[4], Ryan A Knudson[4], Patricia T Greipp[2] and Andrew L Folpe[1]

[1]*Division of Anatomic Pathology, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA;* [2]*Division of Laboratory Genetics/Genomics, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA;* [3]*Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA;* [4]*Medical Genome Facility, Mayo Clinic, Rochester, MN, USA and* [5]*Department of Pathology, University of Michigan, Ann Arbor, MI, USA*

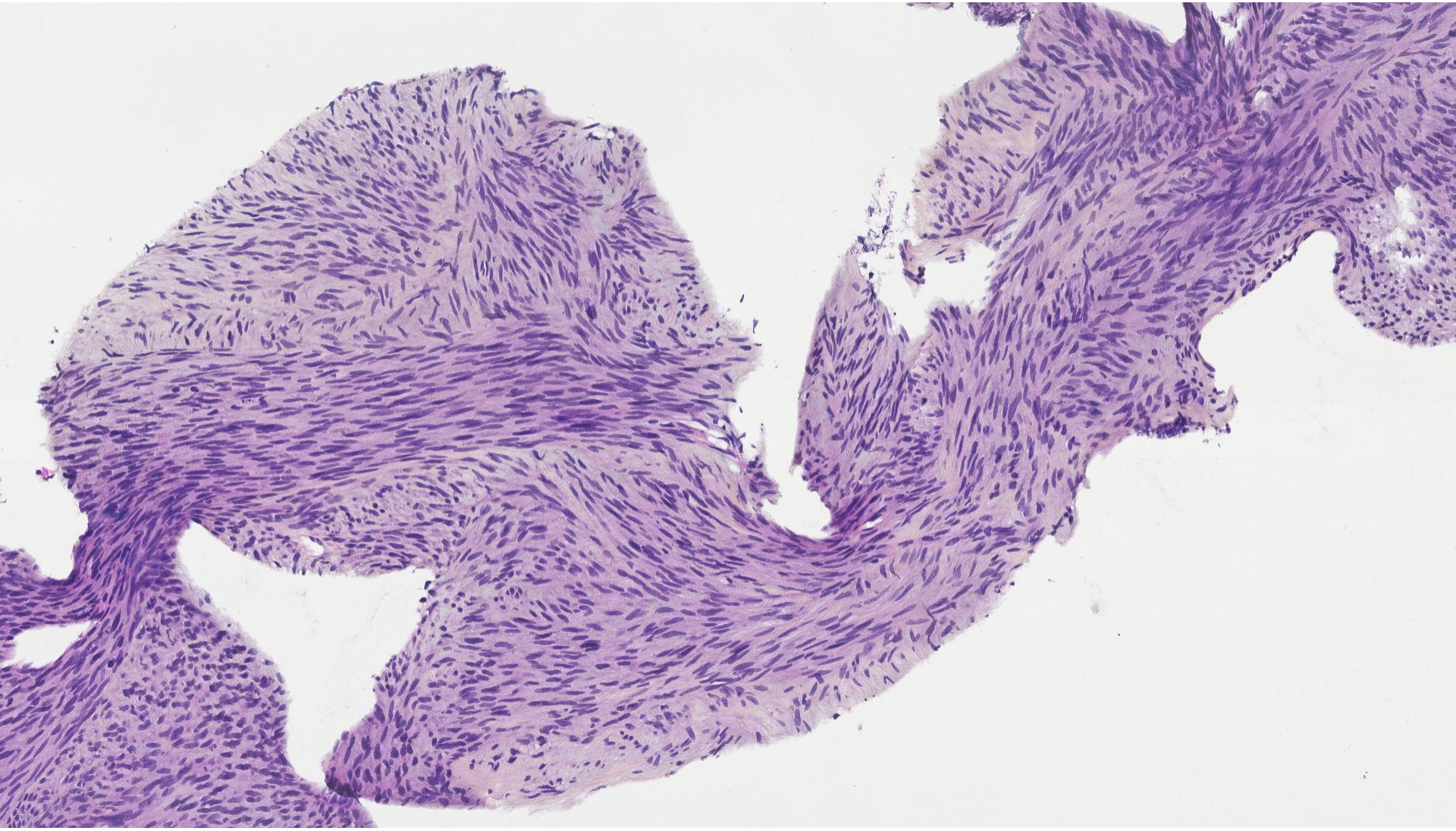
Gastroblastoma is a rare distinctive biphasic tumor of the stomach. The molecular biology of gastroblastoma has not been studied, and no affirmative diagnostic markers have been developed. We retrieved two gastroblastomas from the consultation practices of the authors and performed transcriptome sequencing on formalin-fixed paraffin-embedded tissue. Recurrent predicted fusion genes were validated at genomic and RNA levels. The presence of the fusion gene was confirmed on two additional paraffin-embedded cases of gastroblastoma. Control cases of histologic mimics (biphasic synovial sarcoma, leiomyoma, leiomyosarcoma, desmoid-type fibromatosis, *EWSR1–FLI1*-positive Ewing sarcoma, Wilms' tumor, gastrointestinal stromal tumor, plexiform fibromyxoma, Sonic hedgehog-type medulloblastomas, and normal gastric mucosa and muscularis propria were also analyzed. The gastroblastomas affected two males and two females aged 9–56 years. Transcriptome sequencing identified recurrent somatic *MALAT1–GLI1* fusion genes, which were predicted to retain the key domains of GLI1. The *MALAT1–GLI1* fusion gene was validated by break-apart and dual-fusion FISH and RT-PCR. The additional two gastroblastomas were also positive for the *MALAT1–GLI1* fusion gene. None of the other control cases harbored *MALAT1–GLI1*. Overexpression of *GLI1* in the cases of gastroblastomas was confirmed at RNA and protein levels. Pathway analysis revealed activation of the Sonic hedgehog pathway in gastroblastoma and gene expression profiling showed that gastroblastomas grouped together and were most similar to Sonic hedgehog-type medulloblastomas. In summary, we have identified an oncogenic *MALAT1–GLI1* fusion gene in all cases of gastroblastoma that may serve as a diagnostic biomarker. The fusion gene is predicted to encode a protein that includes the zinc finger domains of GLI1 and results in overexpression of GLI1 protein and activation of the Sonic hedgehog pathway.

Modern Pathology (2017) **30,** 1443–1452; doi:10.1038/modpathol.2017.68; published online 21 July 2017

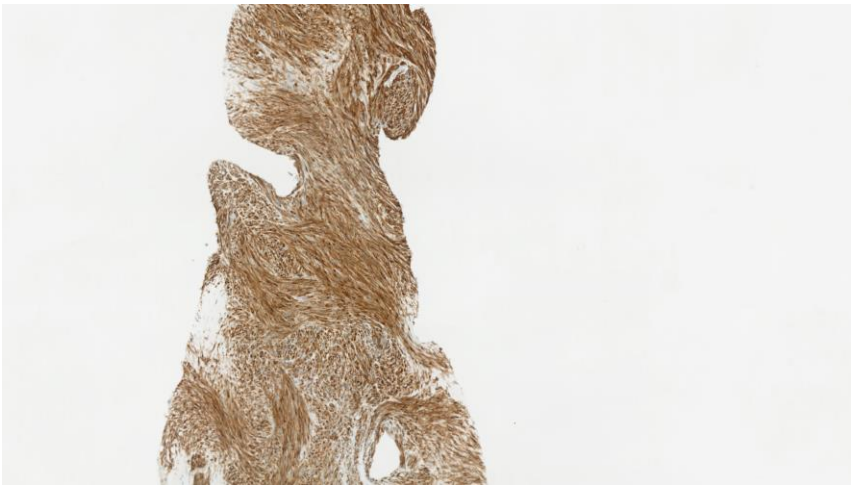




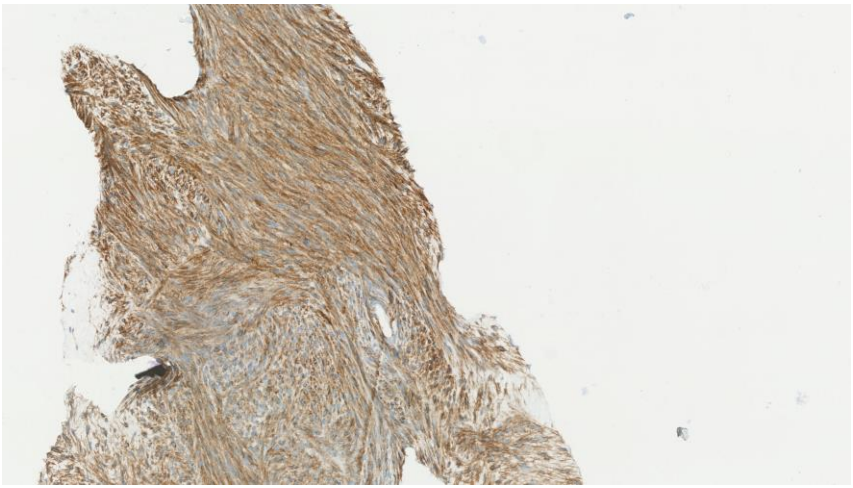
Gastrointestinal stromal tumour



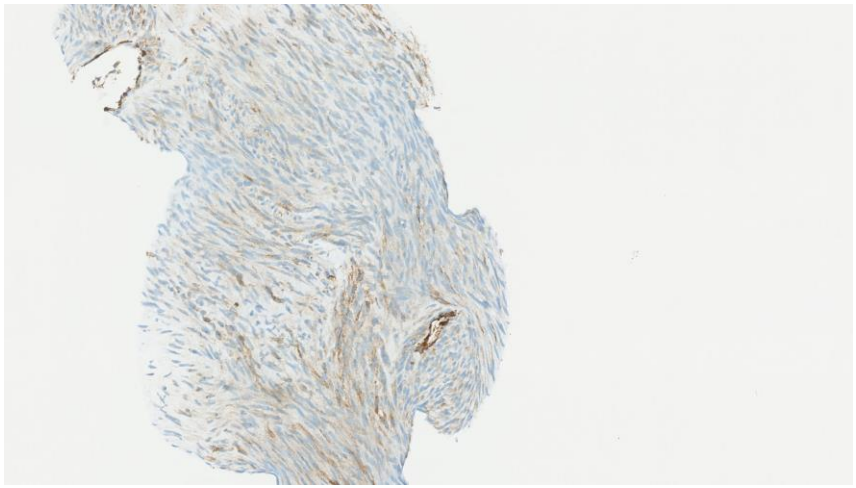
KIT (CD117)



ANO1 (DOG1)



alpha-actin



desmin

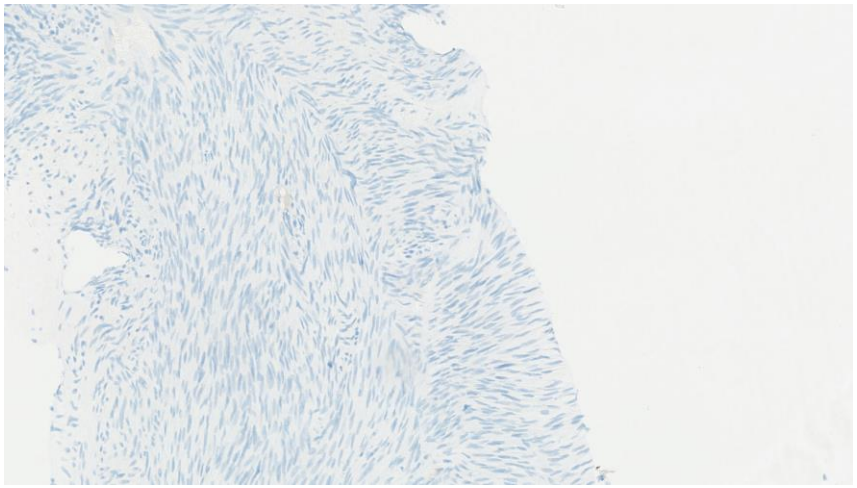


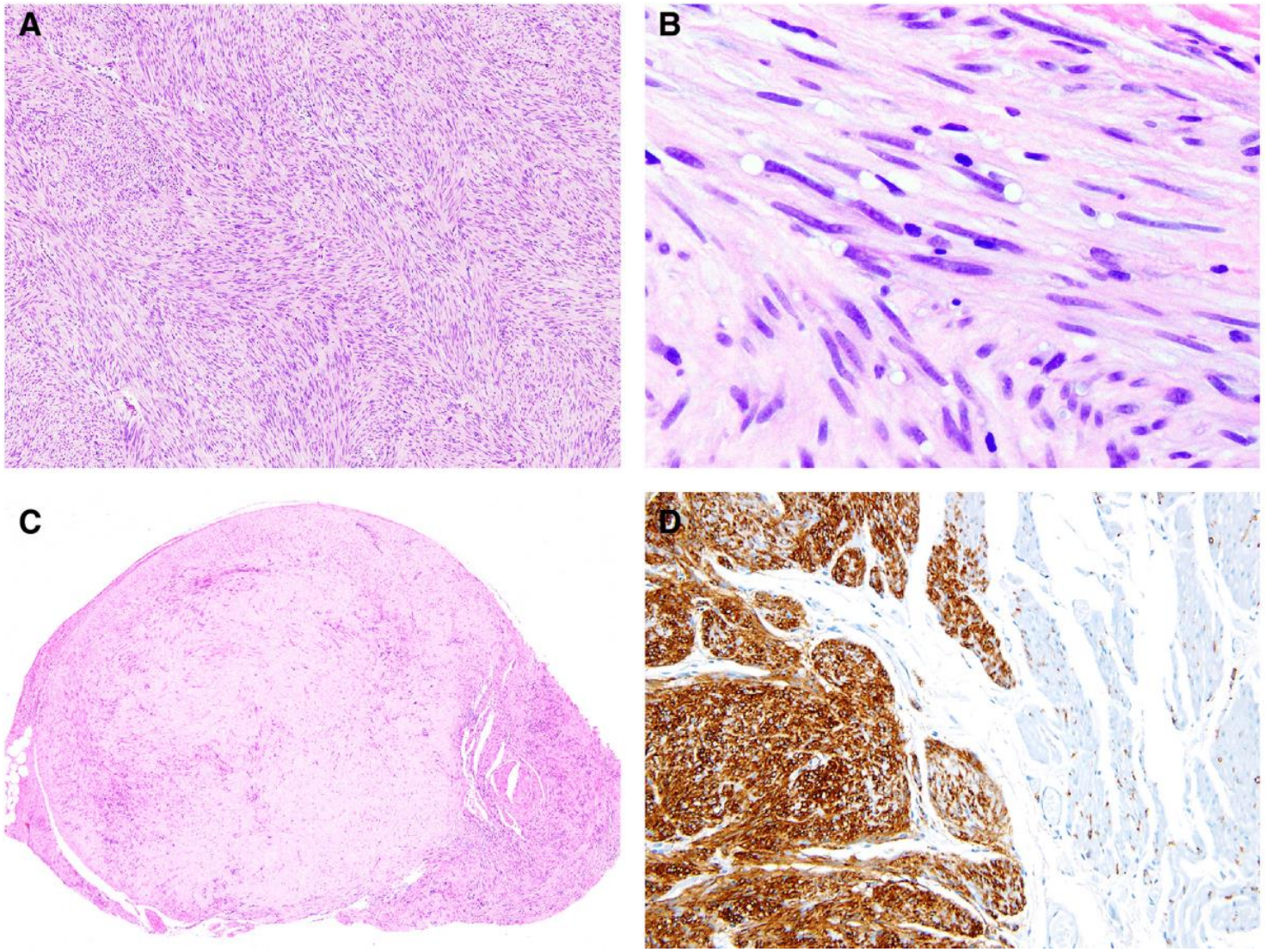
Table 1. Phenotype–genotype correlations for subtypes of gastrointestinal stromal tumour

Genotype	Sites and histology	Comments	Imatinib response
KIT-mutant			
Exon 11	All locations; usually spindle cell or mixed	Gastric tumours with exon 11 deletions more aggressive	Excellent
Exon 9	Small and large intestines; usually spindle cell or mixed		Respond better to higher dose
Exon 13	Usually small intestine; spindle cell	Uncommon	Some
Exon 17	Usually small intestine; spindle cell	Uncommon	Some
Exon 8	Small intestine; mixed	Very rare	Limited data
PDGFRA-mutant		Less aggressive than *KIT*-mutant tumours overall	
Exon 18	Stomach and omentum; epithelioid	D842V most common by far	Poor
Exon 12	Stomach; epithelioid	Uncommon	Variable
Exon 14	Stomach; epithelioid	Rare	Variable
SDH-deficient	Stomach; epithelioid or mixed	Approximately 50% have mutations in SDH subunit genes	Poor
SDHA-mutant	Stomach; epithelioid or mixed	Usually adults; most common; germline but low penetrance	Poor
SDHB/C/D-mutant	Stomach; epithelioid or mixed	Carney–Stratakis syndrome	Poor
BRAF-mutant (V600E)	Most often small intestine; usually spindle cell	Variable clinical behaviour; may respond to dabrafenib	Poor
NF1-associated	Usually small intestine; spindle cell	Multifocality common; ICC hyperplasia common; usually small with favourable outcome	Poor

ICC, Interstitial cells of Cajal; NF1, neurofibromatosis type I; SDH, succinate dehydrogenase.

Doyle LA, *Histopathology* 2014

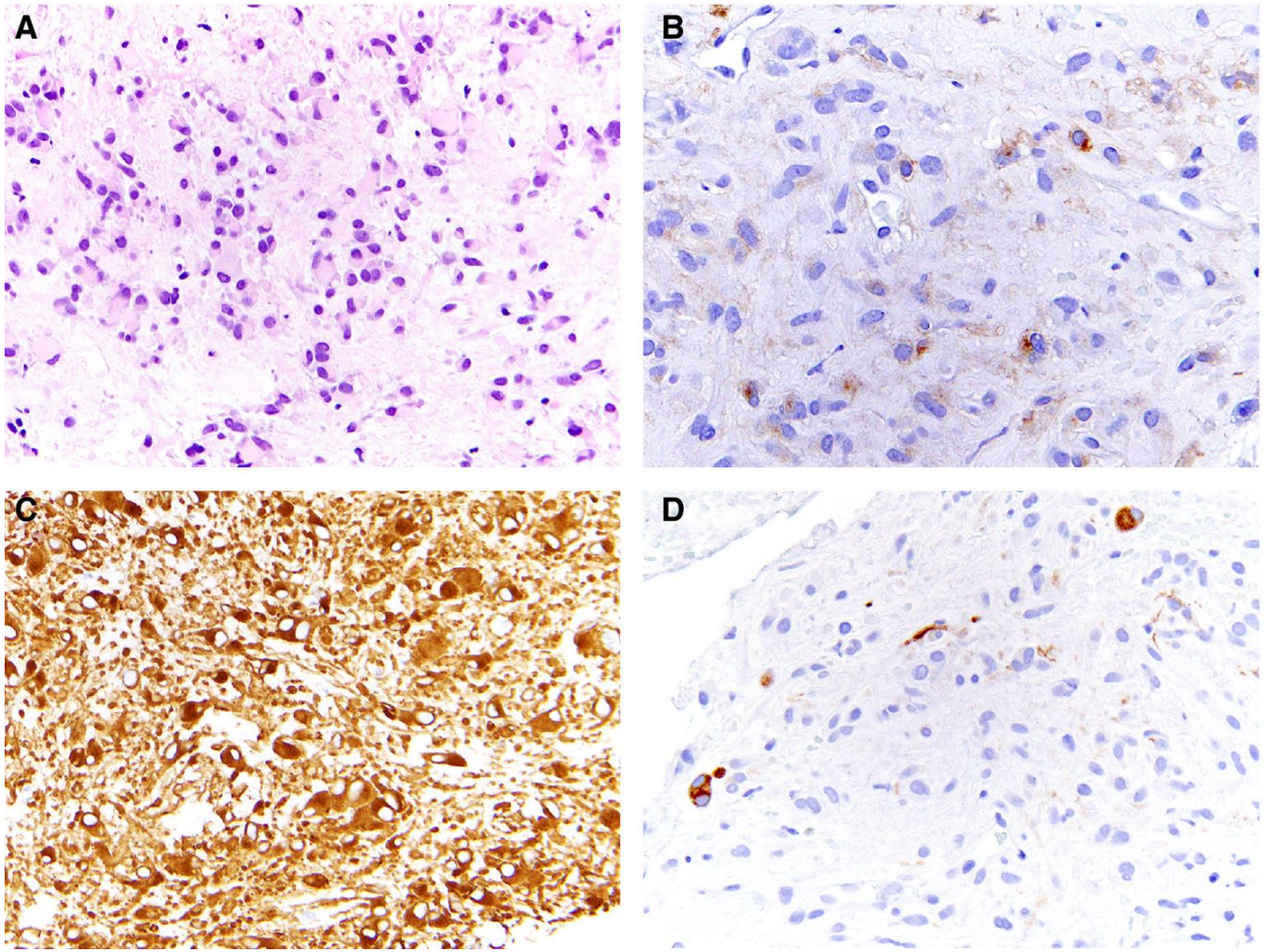
KIT-mutant gastrointestinal stromal tumour



KIT

Papke DJ, *Histopathology* 2021

PDGFRA-mutant gastrointestinal stromal tumour



KIT

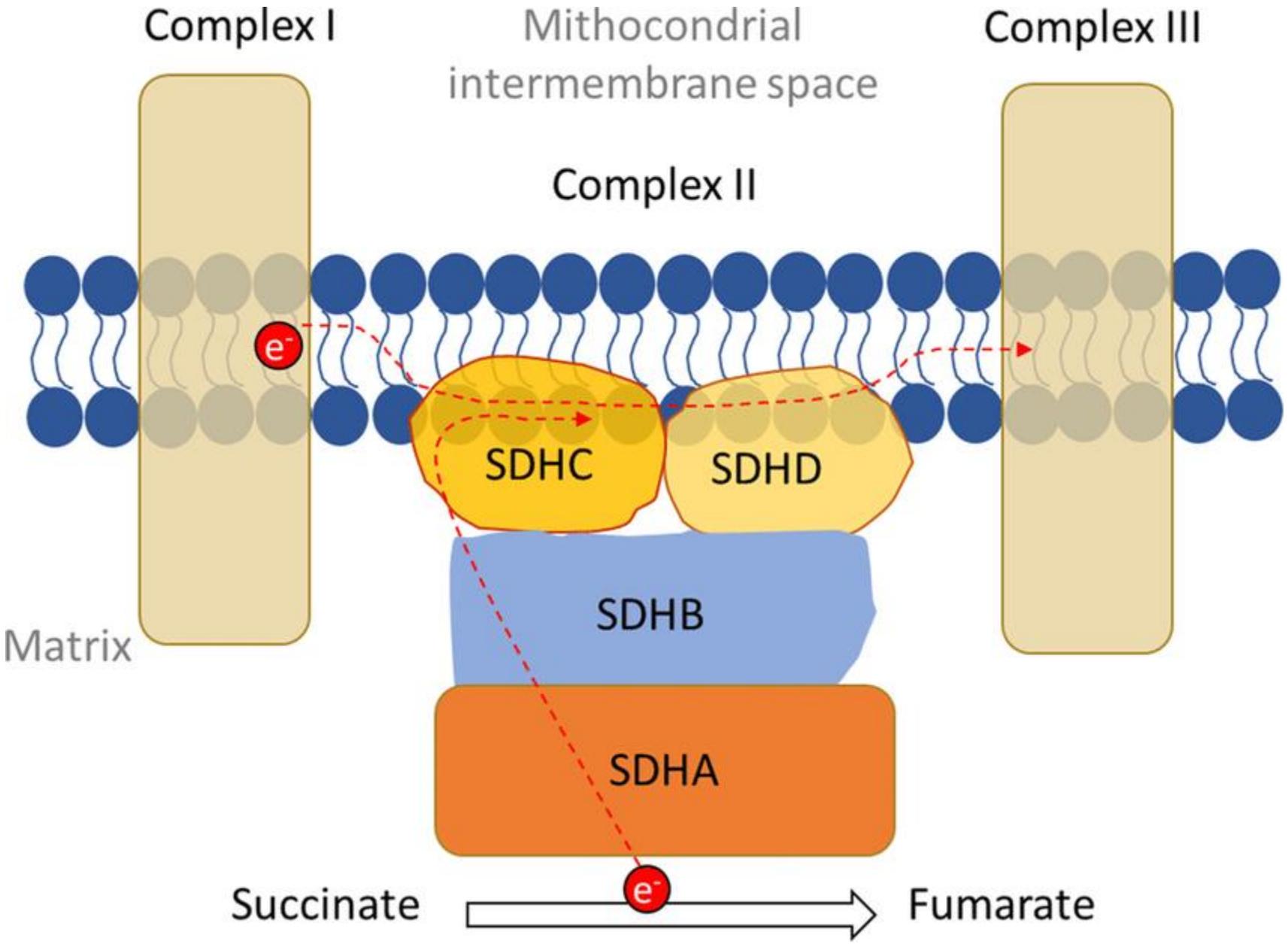
PDGFRA

Desmin

Papke DJ, *Histopathology* 2021

Succinate dehydrogenase (SDH)-deficient GIST

- Always occur in the gastric wall
- 10% of gastric GISTs
- Multinodular
- Plexiform
- Lymphovascular invasion in > 50%
- Lymph node metastases are common
- Slowly progressive, not dependent on mitotic rate
- Slow progression of lymph node, peritoneal and liver metastases
- Strongly positive for KIT and ANO1 (DOG1)


Complex I
Mithocondrial
intermembrane space
Complex III
Complex II
e-
SDHC
SDHD
SDHB
Matrix
SDHA
e-
Succinate
Fumarate

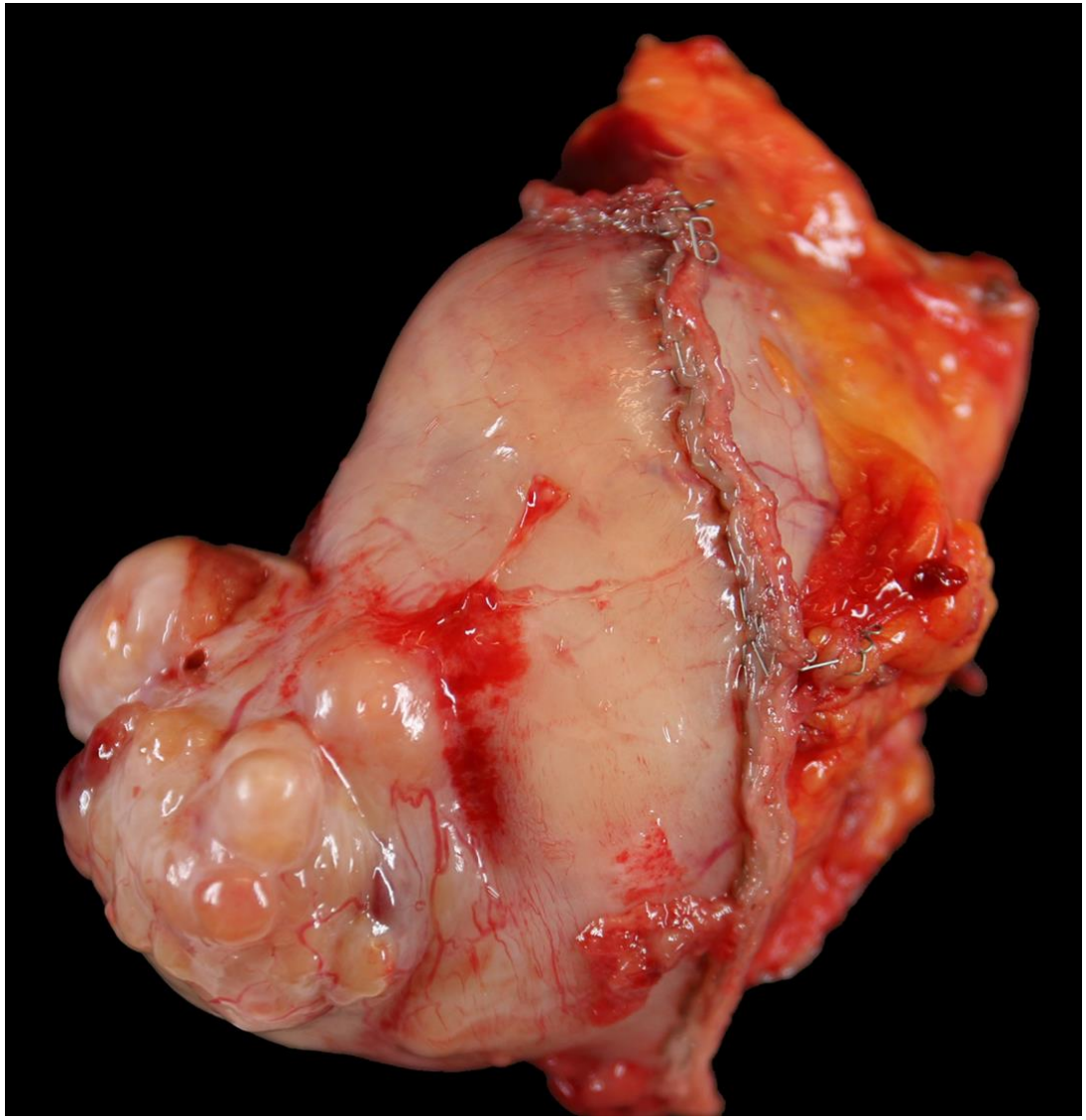
SDH-deficient GIST

- SDHB immunohistochemistry can be used to screen for SDH deficiency in general
- When *SDHA*, *SDHB*, *SDHC* or *SDHD* mutations are present: germline mutation in 80%
- Sometimes associated with Carney-Stratakis syndrome (gastric GIST + paraganglioma)
- Point mutations or deletions in *SDHA*: GIST at older age (35 years) than other SDH-deficient GISTs (20 years)

SDH-deficient GIST

- 35% point mutations or deletions of *SDHA*
- 30% mutations of *SDHB*, *SDHC* or *SDHD*
- 35% hypermethylation of *SDHC* promoter (characteristic of Carney triad: gastric GIST + paraganglioma + pulmonary chondroma)

SDH-deficient GIST



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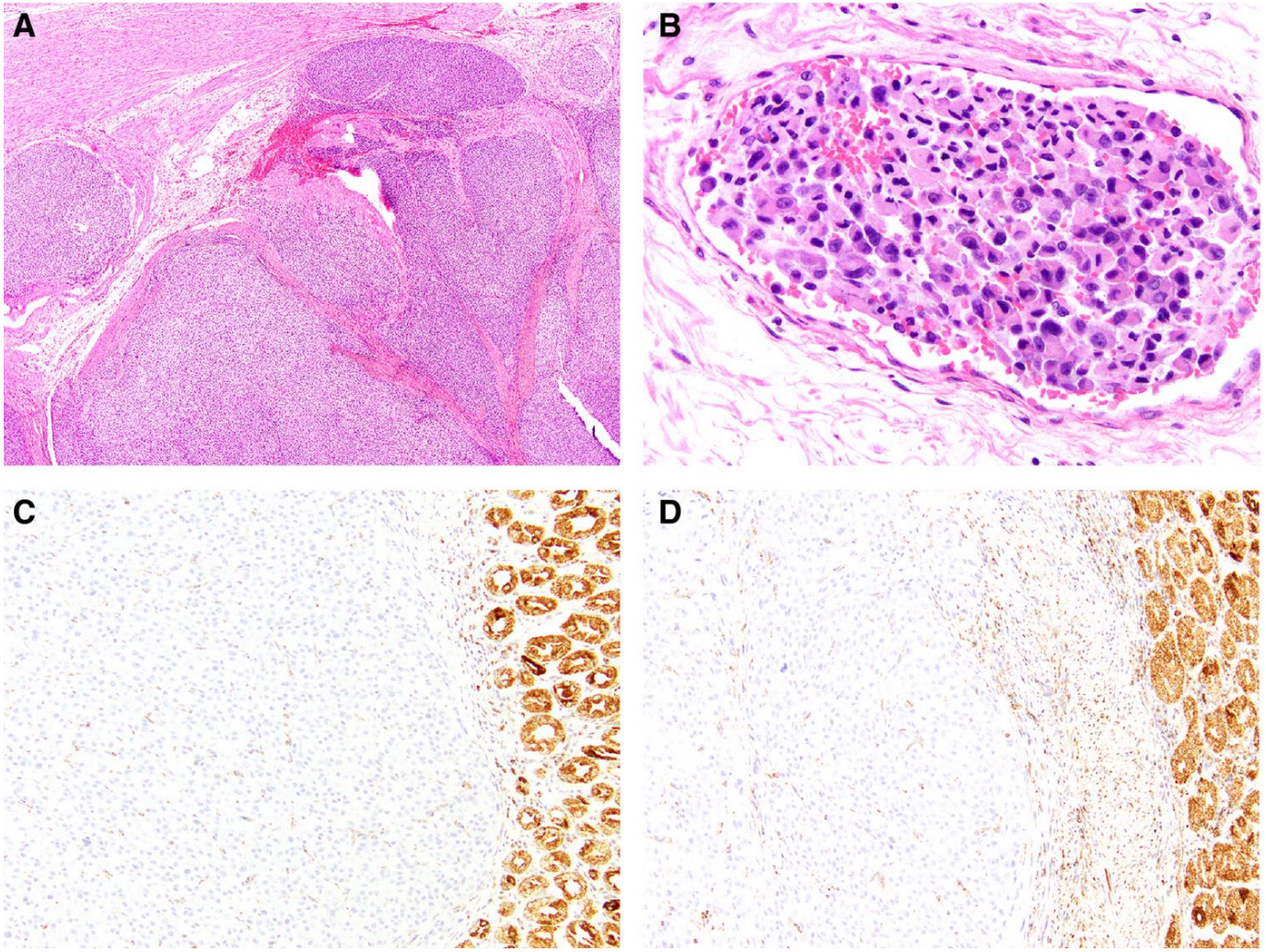
SDH-deficient GIST



SDHB

SDHA

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Other genetic drivers in GIST

- Each accounting for < 1% of gastric GISTs
- *BRAF* V600E-mutant GIST
  - Small intestine and stomach
- GIST with *FGFR1* rearrangement
  - Small intestine and stomach
- *EGFR*-mutant GIST
  - Small intestine and stomach
- *ALK* and *NTRK* fusions
  - Small intestine and rectum

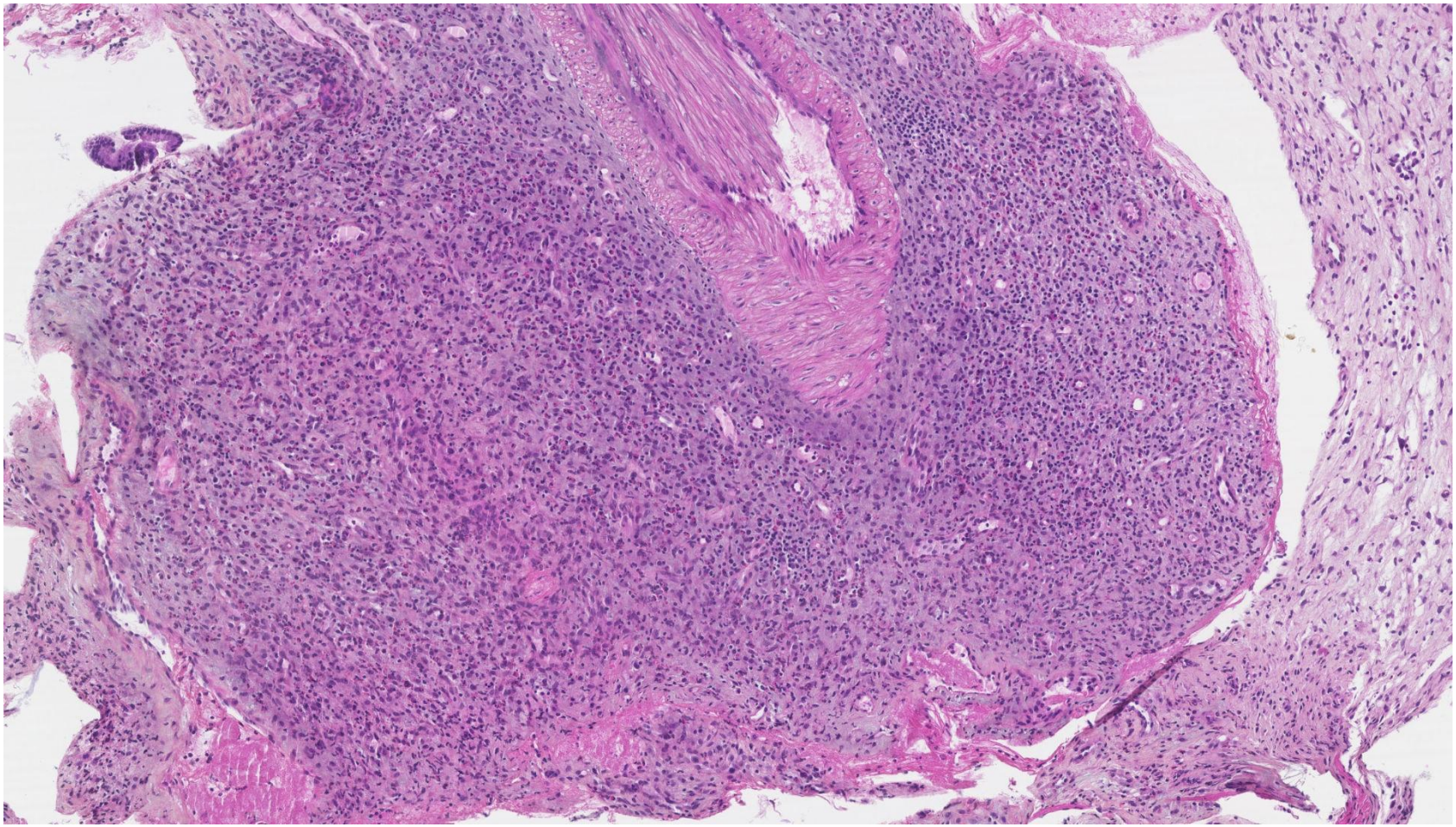
Inflammatory fibroid polyp

- Stomac (antrum) > ileum > elsewhere in the GI tract
- Usually centred in the submucosa
- Sessile or polypoid, often incidental findings
- Abdominal pain, bleeding, obstruction, intussusception
- Middle-aged adults (> females)
- *PDGFRA* activating mutations (exon 18 mainly in gastric, exon 12 mainly in ileal cases)
- Rare cases are familial

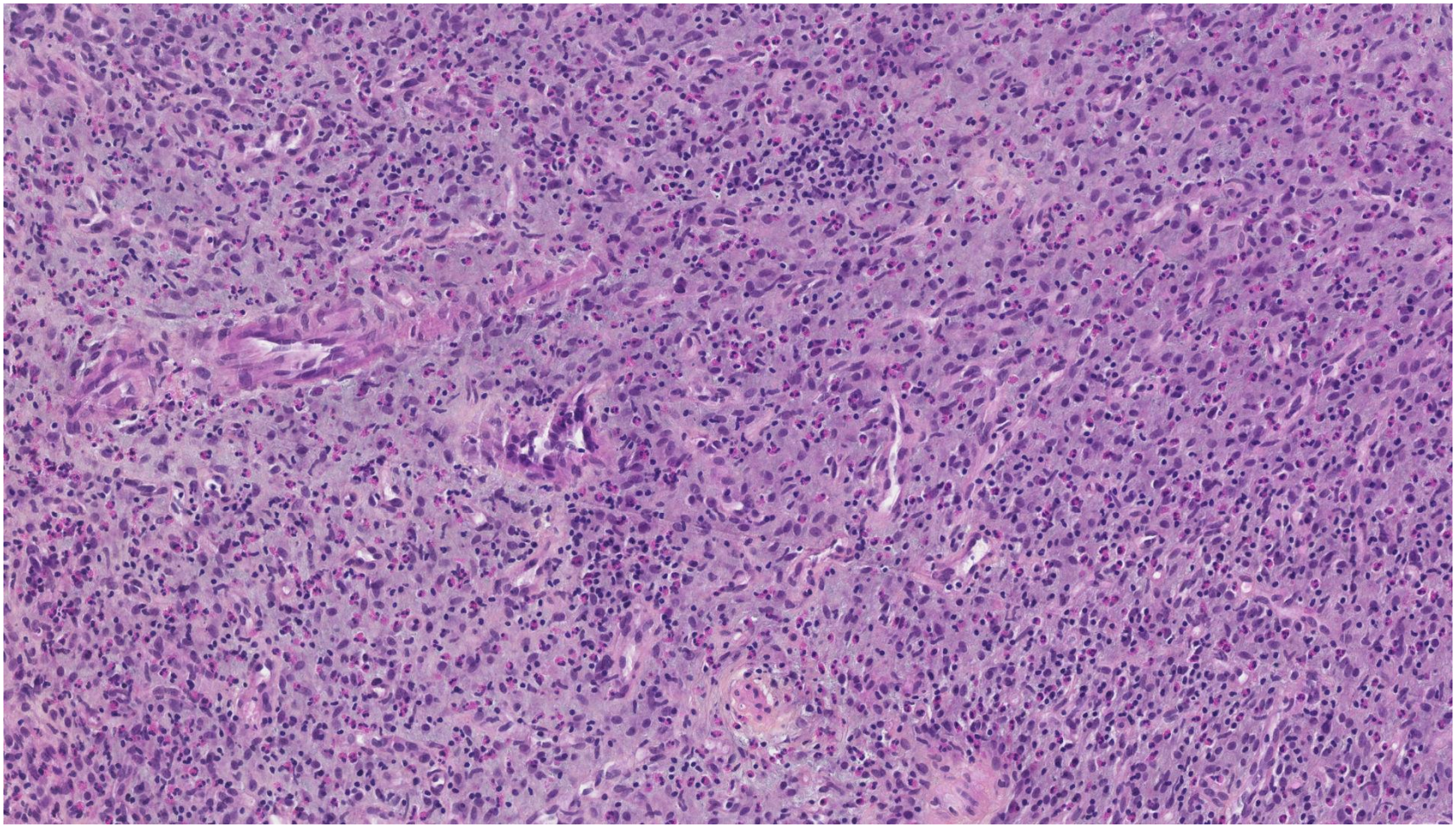
Inflammatory fibroid polyp

- Short spindle cells, stellate cells, inflammatory cells (> eosinophils)
- Stroma often oedematous, sometimes myxoid or collagenous

Inflammatory fibroid polyp



Inflammatory fibroid polyp



Inflammatory fibroid polyp

positive

- CD34
- PDGFRA
- (SMA)

negative

- KIT
- ANO1
- Desmin
- S-100 protein
- SOX10
- Keratins