- Molecular classification of gastrointestinal stromal tumour (GIST)

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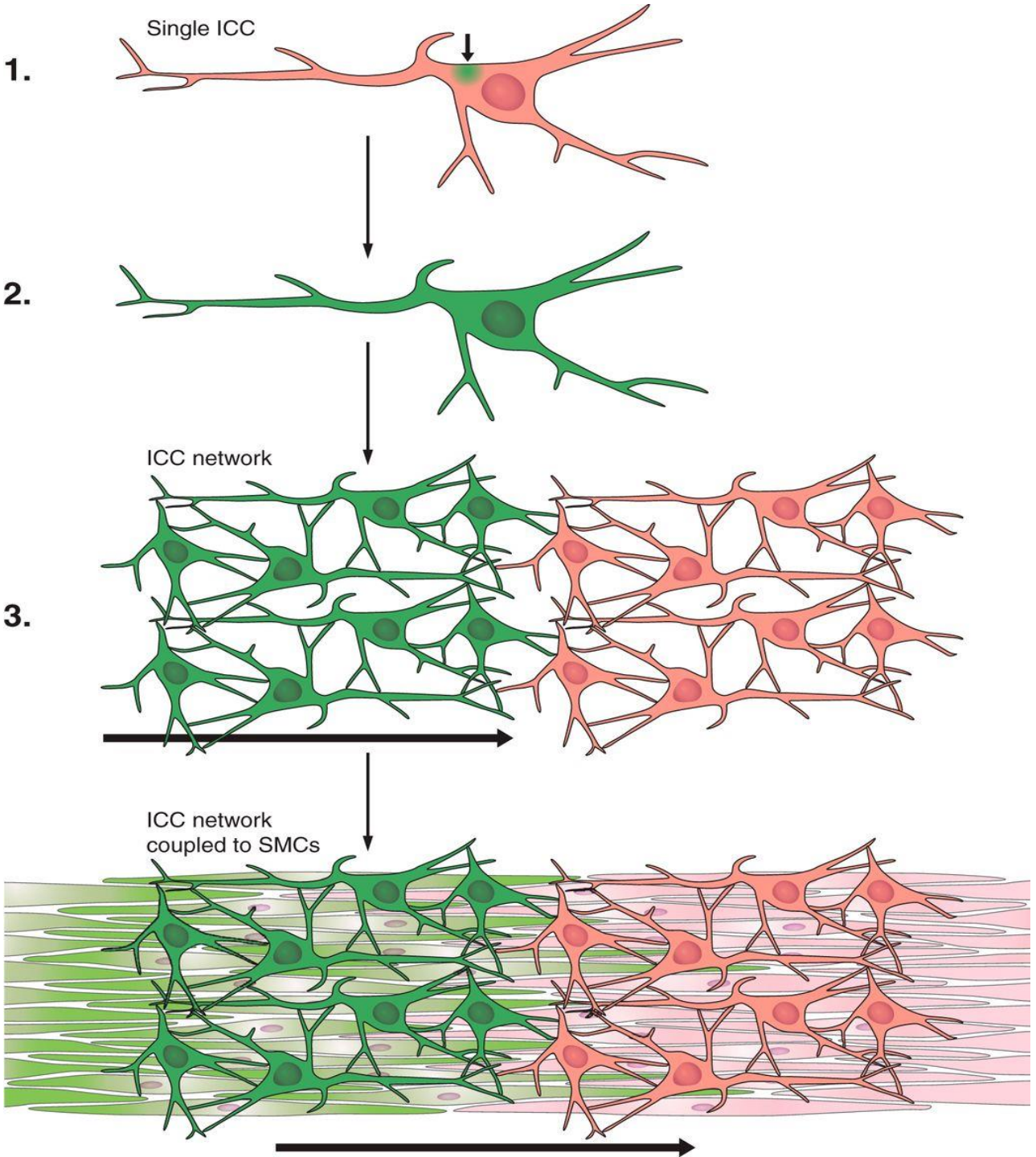
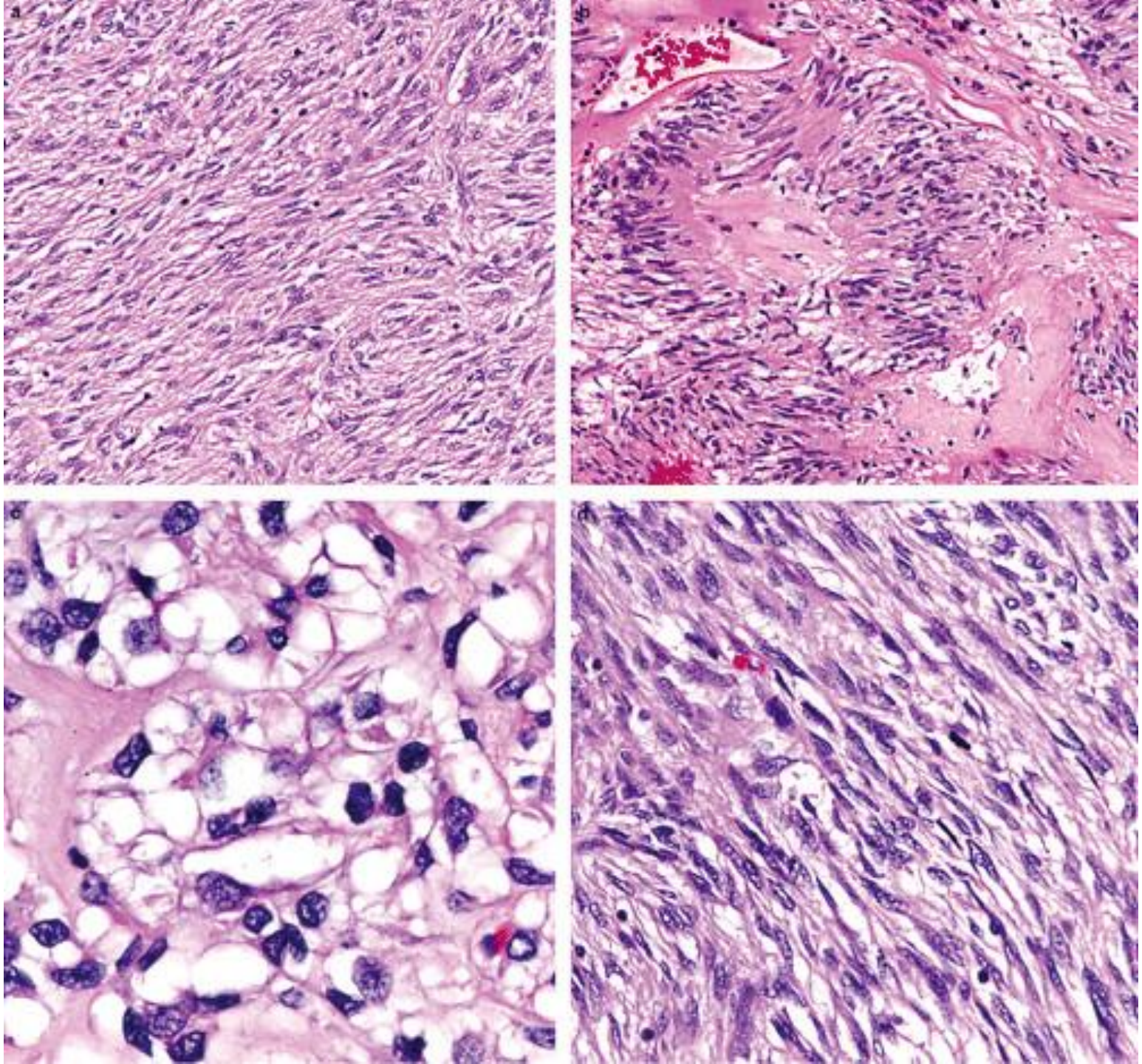
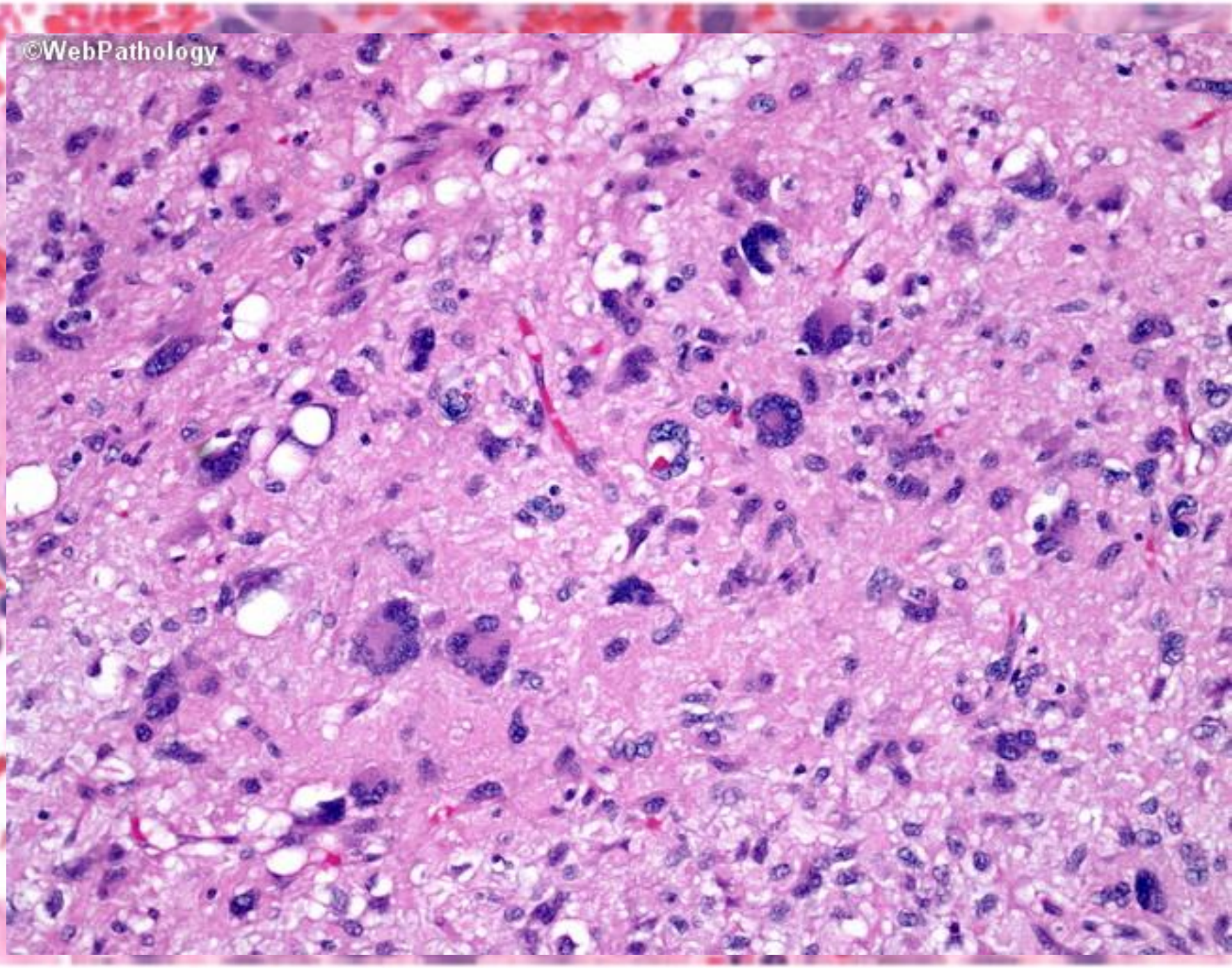

1.
Single ICC
2.
3.
ICC network
ICC network
coupled to SMCs

Box 1 Molecular classification of gastrointestinal stromal tumour (GIST)

A. I. *KIT and*
   II. Platelet-derived growth factor receptor α *(PDGFRα)* mutated type (80%–90% of GISTs)
B. KIT/PDGFRα (double) wild-type (10%–15%)
   I. Succinate dehydrogenase (SDH)-deficient or negative GISTs/type II (20%–40%)
   II. *RAS-P (RAS/BRAF)* mutant type (15%)
C. KIT/PDGFRα/SDH (triple) wild-type/type I (1%–2%)
   I. *NF-1* mutated
   II. Sporadic
D. KIT/PDGFRA/SDH/RAS-P (quadruple) wild-type (5%)

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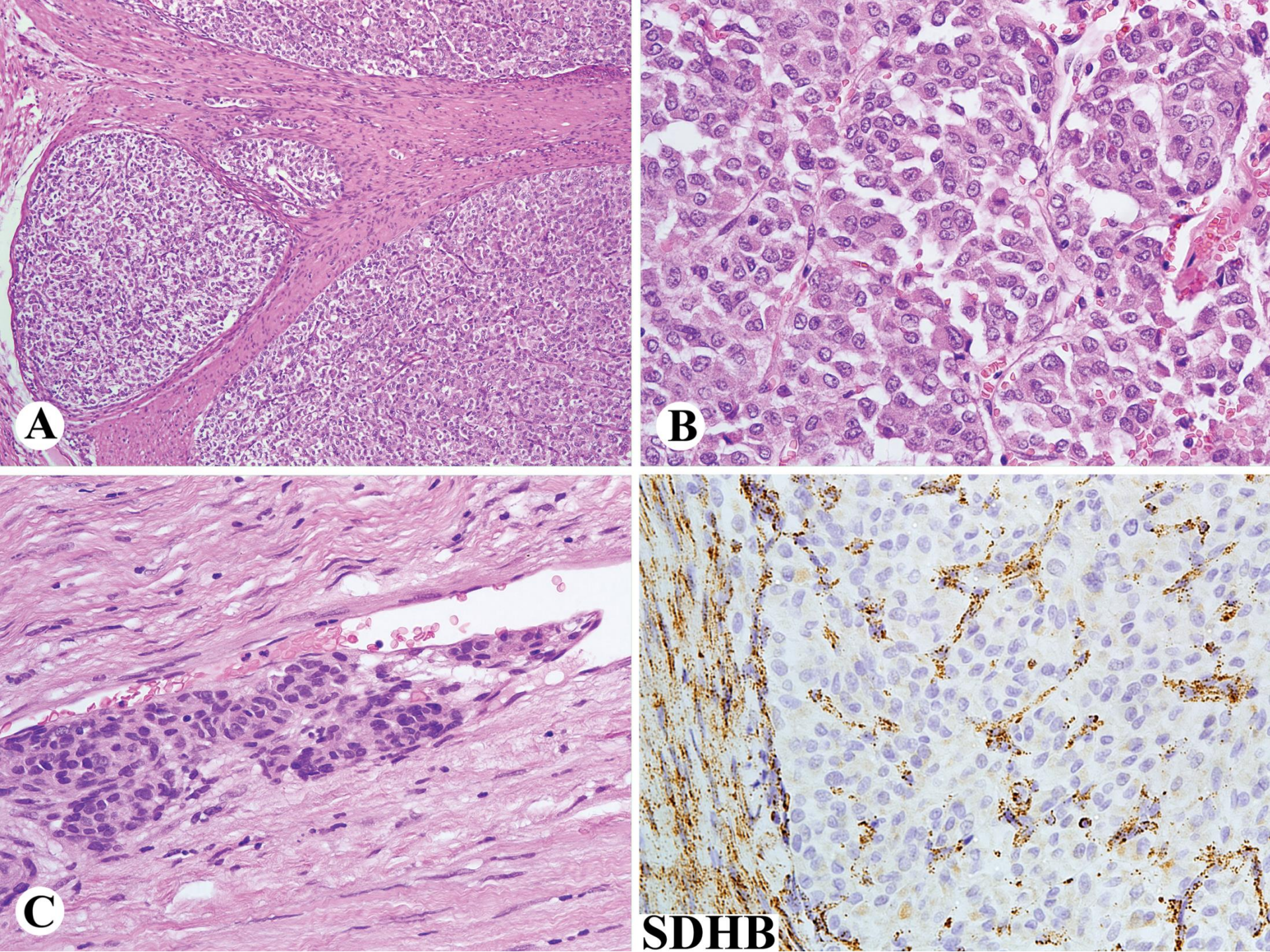

A
B
C
SDHB

- There are clinical characteristics that typify SDH-deficient GISTs. They occur in children, usually a female predilection with an age range 18–30 years, in the stomach (antrum/distal), have an indolent course despite resistance to imatinib.

- SDH is a heterotetrameric enzyme complex situated in the inner mitochondrial membrane and is entirely encoded by chromosomal DNA. The SDH complex participates in the Krebs' cycle.

- Germline mutations have been identified in SDH-deficient GISTs in the genes for four of the five protein subunits that comprise the SDH complex: SDHA, SDHB, SDHC, and SDHD
- single somatic SDHA mutation has been identified.
- Based on the limited data available, it is not possible to determine the overall frequency of these mutations at this time

- MicroGISTs, less than 1 cm in diameter, are quite common. Autopsy studies have identified microGISTs, known variably as GIST tumorlets or GISTlets in up to 22.5% of patients.5 However, the vast majority of microGISTs do not progress to clinically important lesions that require medical attention.

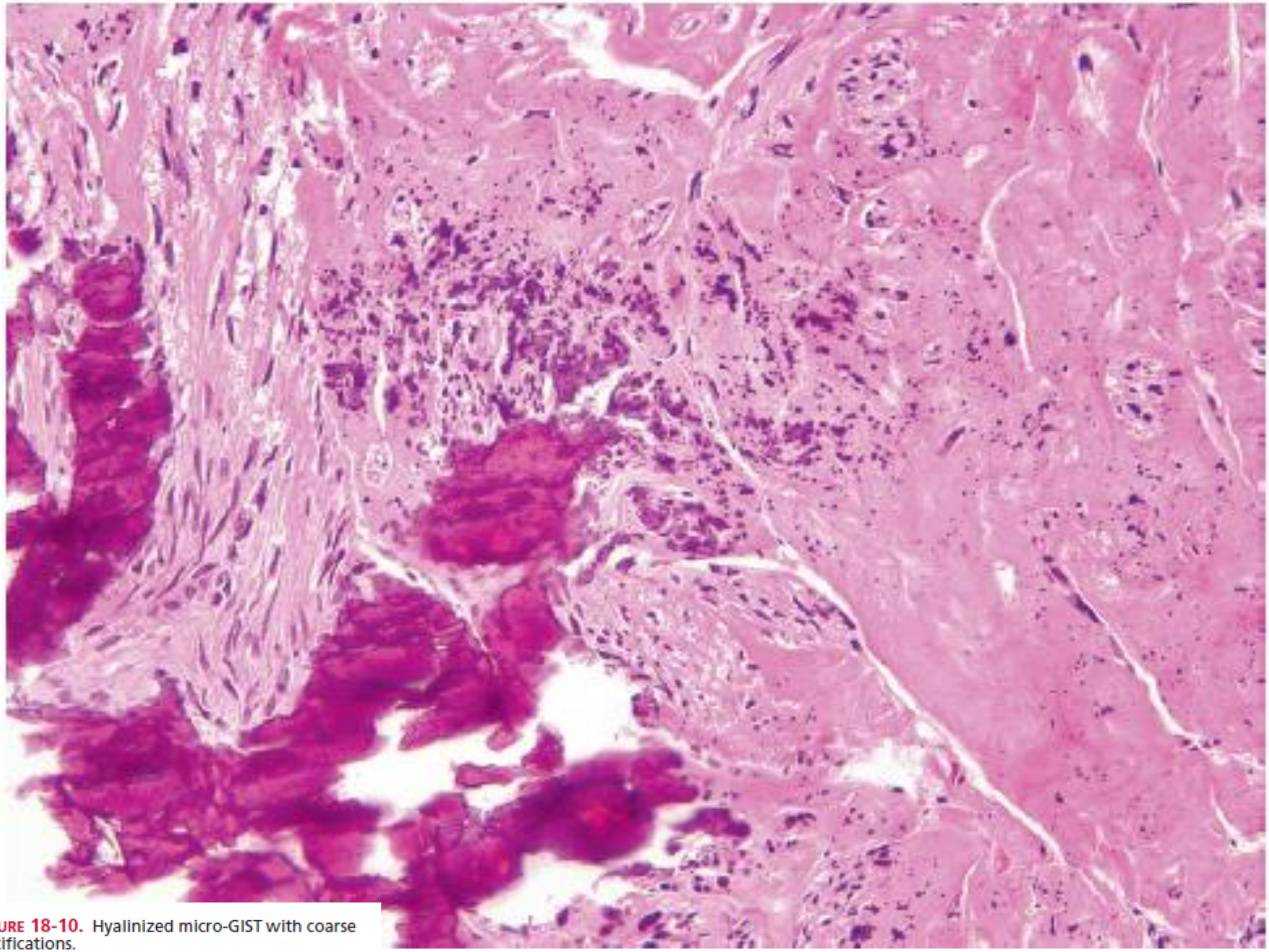
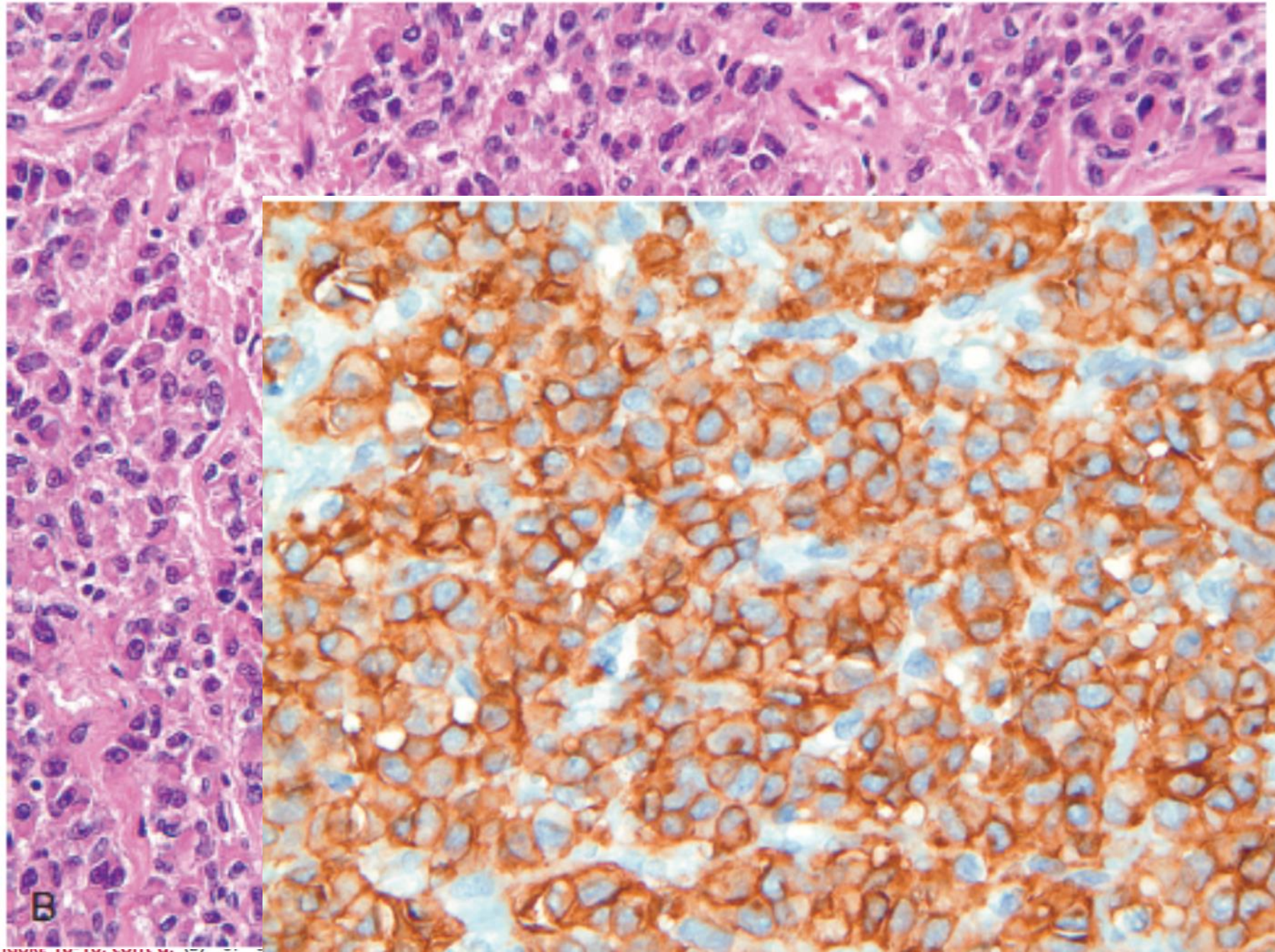


FIGURE 18-10. Hyalinized micro-GIST with coarse calcifications.



GIST. KIT immunohistochemical
abrupt loss of staining in the
component (upper right).

TABLE 18-3 Genetics of Gastrointestinal Stromal Tumors

GENETIC TYPE	RELATIVE FREQUENCY
KIT mutation (relative frequency 75% to 80%)	
Exon 8	Rare
Exon 9 insertion AY502-503	10%
Exon 11 (deletions, single nucleotide substitutions and insertions)	67%
Exon 13 K642E	1%
Exon 17 D820Y, N822K, and Y823D	1%
PDGFRA mutation (relative frequency 5% to 8%)	
Exon 12 (such as V561D)	1%
Exon 14 N659K	less than 1%
Exon 18 D842V	5%
Exon 18 (such as deletion of amino acids IMHD 842-846)	1%
KIT and *PDGFRA* wild-type (relative frequency 12% to 15%)	
BRAF V600E	3%
SDHA, *SDHB*, *SDHC*, and *SDHD* mutations	3%
Sporadic pediatric GISTs	~1%
GISTs as part of the Carney triad	~1%
NF1-related	Rare

Are GISTs derived from ICCs?

Interstitial cells of Cajal (ICC) form the interface between the autonomic innervation of the bowel wall and the smooth muscle itself.

The KIT RTK plays essential roles in the development and maintenance of normal ICCs .

It is postulated that GISTs originate from CD34 positive stem cells within the wall of the gut and differentiate toward the pacemaker cell phenotype (ICC)

Malignant GISTs may represent dedifferentiated ICCs that maintain a CD34-positive stem cell phenotype

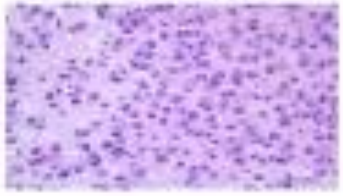
Attractive hypothesis but still open to question

- Approximately 5% of GISTs are negative for KIT by immu- nohistochemistry.
- Most of these GISTs turn out to be PDGFRA mutant GISTs
- DOG1 is strongly expressed in ICC and is very sensitive and specific for the diagnosis of GIST.
- DOG1 is strongly expressed in over 99% of GIST.
- It is important to note that it is positive in most KIT-negative GISTs

- GISTs are occasionally positive:
- S-100 (5%),
- desmin (2%),
- cytokeratins (2%), which is helpful in distinguishing GIST from schwannoma (KIT negative, diffusely S-100 positive),
- smooth muscle tumors (KIT negative, desmin positive),
- metaplastic (sarcomatoid) carcinoma (KIT negative, keratin positive). S-100, desmin, and cytokeratins, when positive, are usually only focally positive in GIST

- It is also important to remember that melanoma, which occasionally metastasizes to the bowel, is both S-100 and KIT-positive, although the degree of KIT immunoreactivity is typically less than that seen in GIST. For the differential diagnosis of GIST, the most useful immunohistochemical panel is KIT, DOG1

Molecular-Morphologic types GIST

KIT mutated	*PDGFR* mutated	SDH deficient	*RAS-P* mutated	Quadruple wild type
Spindle/mixed	Epithelioid	Epithelioid	Spindle	N/A
				
c-KIT/DOG1 +ve	DOG1 +ve	SDHB -ve	SDHB +ve	SDHB +ve
				

Thank you for all your attention!