Envoi SPECIALIST PATHOLOGISTS *inside insights*

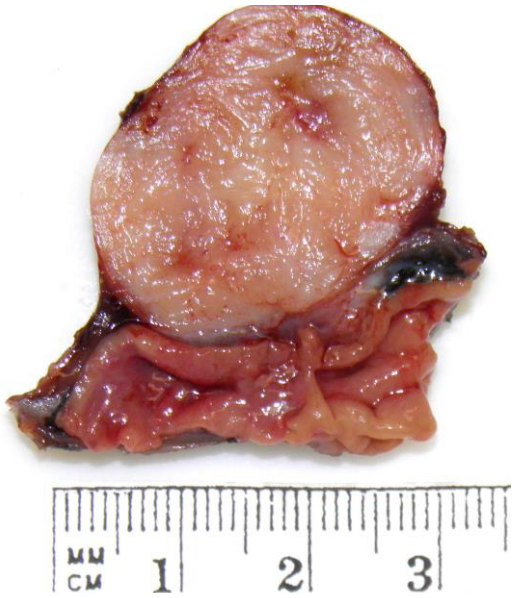
Update No.3 - 2017 *Dr Greg Miller*

Gastrointestinal stromal tumour

Definition: A mesenchymal tumour of the gastrointestinal tract thought to arise from the interstitial cells of Cajal, pacemaker cells present in the muscle layers of the GIT.

Clinical features: GISTS are usually found in older individuals (median age 60-65) of both sexes. Most GISTS occur in the stomach (60% of macroscopic GISTS) or the small intestine (25%). They are also known to arise from the oesophagus, colon, rectum, omentum and mesentery (accounting for the remaining 15% of cases). Macroscopic GISTS are rare, accounting for 2% of gastric malignancies, but microscopic GISTS are thought to occur in 10-30% of the population.

Fig. 1 Macroscopic appearance

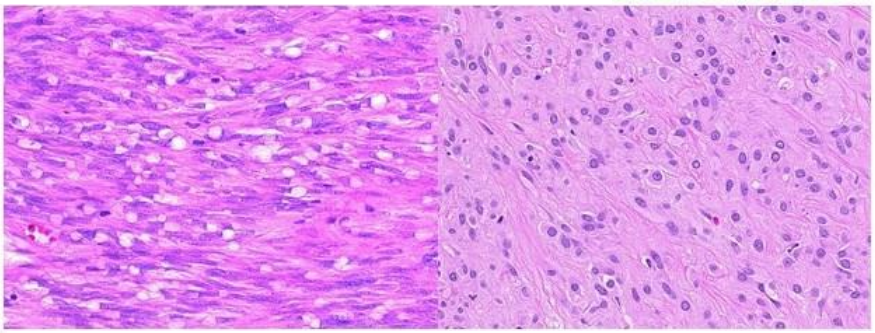


Morphology: GISTS are usually well circumscribed fleshy tumours with haemorrhage, necrosis or cystic degeneration of the cut surface (Fig. 1). They generally do not involve the mucosal surface until larger when they may cause ulceration.

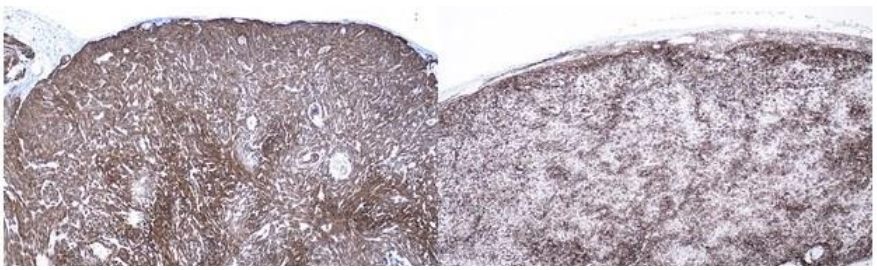
The microscopic features range from bland spindle cells to highly cellular epithelioid morphology (Fig. 2). Variable degrees of atypia can be present, which is of no significance. Spindle cell GISTs tend to have a mutation in KIT exons 9 or 11 while epithelioid GISTs have a much more varied mutation profile

Immunohistochemistry: The most commonly used immunohistochemical stain to diagnose GISTs is c-kit (CD117), which is positive in 95% of cases. Another specific marker is DOG-1, which stains a similar percentage of GISTS but also stains PDGFR mutant GISTS (which are c-kit negative). Many GISTS will also stain with CD34 and SMA.

Fig. 2 GIST with spindled (left) and epithelioid (right) morphology.



c-KIT positive staining DOG-1 positive staining



Prognosis: Eighty percent of GISTS are localized (confined to a single organ) at time of diagnosis. Because GISTS are not epithelial tumours (such as colonic tubular adenomas/colonic adenocarcinomas) they cannot be classified as benign or malignant. Instead, prognostic indices have been developed based on the chance the lesion will go on to develop recurrent/metastatic disease. This is expressed as a "percentage risk of progressive disease", based on large series of cases (Table 1.). Up to 50% of GISTS will go onto develop progressive disease. Importantly, tumour rupture, either before or during surgery, is also a negative prognostic indicator.

Risk of progressive disease is currently determined by the following criteria:

- location of the primary tumour
- size
- proliferative activity (number of mitoses per $5mm^2$).

Table 1. WHO Prognostic groups for GIST

Prognostic group	Mitotic count (/5mm2)	Size (cm)	% patients with progressive disease during follow up	
			Gastric	Small intestine
1	≤ 5	≤ 2	0	0
2		>2 ≤ 5	1.9	4.3
3a		>5 ≤ 10	3.6	24
3b		>10	12	52
4	> 5	≤ 2	0	50
5		>2 ≤ 5	16	73
6a		>5 ≤ 10	55	85
6b		>10	86	90

For all parameters, the risk of progressive disease is higher for small bowel over gastric GISTs.

Differential diagnosis: This can also be considered based on the site of the lesion and includes schwannoma and inflammatory fibroid polyp in the stomach, leiomyoma in oesophagus and large bowel, and desmoid fibromatosis for lesions located in the mesentery.

Molecular features of GISTS: Most GISTS have mutations in **KIT** (75%) or **PDGFR alpha** (10%) that cause constitutional activation of the MAP kinase pathway. Although not yet used for prognostic stratification or treatment decisions, the location and type of mutation in KIT is important. Higher concentrations of Imatinib are required for GISTS with a KIT mutation involving an insertion in exon 11 (AY502-503).

The remaining 15% of GISTS without KIT or PDGFRA mutations are described as 'wild type' tumours'. Recently, mutations in other genes have been shown to account for many of these cases. **BRAF V600E** mutations are found in 2%. GISTs with BRAF mutations usually present in the small intestine and do not respond to Imatinib. Mutations in the **succinate dehydrogenase subunits A, B, C and D** account for 6% and **neurofibromatosis (NF1)** approximately 1%. SDH mutations are seen in paediatric GISTs and in some adult gastric antral GISTS (as part of Carney-Stratakis syndrome and Carney triad). They show a plexiform growth pattern and epithelioid morphology. Clinically they have an indolent course even with lymph node metastases and do not respond to Imatinib.

Further Reading

Am J Surg Pathol 2015; 39:9 22-930.
Seminars in Diagnostic Pathology 2015; 32: 392-399.
Surgical Pathology 2015; 8: 515-524.
Modern Pathology 2014; 27: S1–S16
Arch Pathol Lab Med 2006; 130: 1466-1478