The histopathological differential diagnosis of gastrointestinal stromal tumours

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Abstract

Gastrointestinal stromal tumours (GISTs), initially presumed to be of "true" smooth muscle origin, encompass a heterogeneous, and as yet incompletely understood, group of mesenchymal tumours with respect to their origin, cellular differentiation, and prognosis. Cellular morphology ranges from predominantly spindle shaped to epithelioid in character, whereas differentiation pathways, as determined primarily by immunohistochemistry and ultrastructure, can vary from indeterminate to myoid and/or neural. Recent work has indicated that the interstitial cells of Cajal, a complex cellular network postulated to act as pacemaker cells of the gastrointestinal tract, which exhibit both myoid and neural features, could be candidates for tumour histogenesis. This would provide a plausible and attractive explanation for the variable differentiation pathways identified in the GIST category to date. Nevertheless, the occasional but undisputed location of GISTs outside the gastrointestinal tract (omentum, peritoneum, and retroperitoneum) might mitigate against such an origin, and their histogenesis remains open to debate. The c-kit proto-oncogene, encoding a growth factor receptor with tyrosine kinase activity, has been postulated to play an important role in tumorigenesis because "gain of function" mutations in this gene, localised to chromosome 4q11–21, are being increasingly identified in hereditary and sporadic cases. Monoclonal and polyclonal antibodies directed at the c-kit gene product expressed on the cell surface (CD117/c-kit) appear to be increasingly helpful in resolving the histopathological differential diagnosis between GISTs and true gastrointestinal smooth muscle neoplasms, schwannomas, and other far less frequently occurring mesenchymal tumours at this site. Although tumours with a clinically benign course appear to be more common than their malignant counterparts, no specific histological criteria have as yet been identified to enable an unambiguous prediction of biological behaviour. Increasing tumour size and mitotic activity favour aggressive tumour behaviour, whereas the prognostic value of germline and somatic mutations within the c-kit proto-oncogene remains to be elucidated further. It is the aim of this synopsis to highlight the relevant fundamental and diagnostic developments with respect to this complex group of neoplasms.

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In contrast to first impressions, it is now increasingly apparent that the category of mesenchymal tumours designated "gastrointestinal stromal tumours" (GISTs) encompasses a clinicopathologically distinctive but heterogeneous, and as yet poorly understood, group of neoplasms with respect to their origin, cellular differentiation, and prognosis.[1 2]

Most gastrointestinal mesenchymal tumours were initially presumed to be of smooth muscle origin, popularly labelled leiomyoma (benign) or leiomyosarcoma (malignant) when composed primarily of spindle shaped cells and benign or malignant leiomyoblastoma when composed primarily of cells with an epithelioid morphology.[3–5] However, further studies have demonstrated that within the GIST group there appears to be considerable variability in cellular differentiation at a morphological, immunohistochemical, and ultrastructural level. This phenotypic variability ranges from indeterminate ("uncommitted") to incompletely myoid and/or neural when compared with the characteristic features of true smooth muscle tumours occurring at this site and elsewhere in the body (table 1).[6–19] The above mentioned features, together with the increasing understanding of the (molecular) genetic changes identified within the GIST category, provide sufficient clinicopathological evidence to validate their distinction from "classic"/true gastrointestinal smooth muscle tumours.[6 20]

Furthermore, in contrast to typical smooth muscle tumours, it has become apparent that the variability in natural biological behaviour of these tumours is not predictable histopathologically using the generally accepted criteria associated with malignant potential. The numerous acronyms used for these neoplasms—which include STUMP (smooth muscle tumour of uncertain malignant potential), GIST (gastrointestinal stromal tumour), GANT (gastrointestinal autonomic nerve tumour), and most recently GIPACT (gastrointestinal pacemaker cell tumour)—clearly attest to the uncertainty and controversy concerning the histogenesis and clinical course of these tumours.[1 2 6 18]

Recent work is beginning to indicate that the interstitial cells of Cajal (ICC) (or more probably a precursor stem cell) of the gastrointestinal tract, which are believed to play an important function in the control of intestinal motility, might represent a possible histogenetic origin for the GIST category.[18 21 22] GISTs share numerous morphological, immunohistochemical, and ultrastructural features with the

Table 1 Morphological comparison of smooth muscle neoplasms and gastrointestinal stromal tumours (GISTs)

	Smooth muscle tumours	*GIST*
Mic	Variably spindled cells	Variable morphology
	Cigar shaped nuclei	**Often more spindly nuclei**
	Eosinophilic cytoplasm	Variably eosinophilic
	Bipolar, perinuclear location of cytoplasmic glycogen	Variable cytoplasmic glycogen
IHC	Vimentin positive	Vimentin positive
	SMA, MSA generally positive	**SMA, MSA patchy/absent**
	Desmin frequently positive (50–70% cases)	**Desmin usually negative**
	CD34 may be focally positive	**CD34 often positive (50–80% of cases)**
	CD117 negative	**CD117 generally positive (80–100% of cases)**
	All other markers negative	S100, NSE variably positive
EM	Invariable	**Variable: dependent on differentiation pathway**
	Prominant parallel arrays cytoplasmic microfilaments	Irregular/random arrays cytoplasmic intermediate filaments
	Regular and frequent fusiform dense bodies	Variably conspicuous/absence dense bodies
	Surface orientated pinocytotic vesicles	No/incomplete external basal lamina (many mitochondria)
	Plasmalemmal attachment plaques	Microtubules/dense core granules
	(Dis)continuous external basal lamina	Branching cytoplasmic processes

Relevant features are highlighted in bold.
EM, electron microscopy; IHC, immunohistochemistry; Mic, microscopy; MSA, muscle specific actin; NSE, neurone specific enolase; SMA, smooth muscle actin.

ICCs,[23–25] providing a plausible explanation for the variable differentiation identified in GISTs to date. Nevertheless, the non-gastrointestinal location (omentum, peritoneum, and retroperitoneum)[26] of a small proportion of cases indicates that the issue of histogenesis is still uncertain.

In this review we discuss the more recent and relevant fundamental and diagnostic developments with respect to this category of tumours.

Current definition and epidemiology

GISTs account for most mesenchymal tumours arising within the gastrointestinal tract.[1 2 6] Although this generally accepted and popular designation highlights the non-epithelial nature of gastrointestinal stromal tumours, it nevertheless represents a specific category of, as yet, incompletely characterised benign and malignant neoplasms with an incomplete myogenic and/or neural or "uncommitted" phenotype primarily at the immunohistochemical and ultrastructural level. Tumours of true smooth muscle, neural (schwannian), fibroblastic, and vascular origin are excluded.

The incidence of clinically malignant GISTs based on data from the Finish Cancer Registry is roughly four/million inhabitants in southern Finland,[2] although in our experience this is probably a conservative estimate; the ratio of benign/malignant GISTs remains difficult to measure because of the lack of unequivocal histopathological criteria for predicting tumour behaviour. GISTs arise most commonly within the wall of the stomach (65–70%) and small intestine (30–45%), and are seen far less frequently in the oesophagus, colon, and rectum, where true myogenic tumours predominate.[1 2] They generally present in adults with a peak incidence during the fifth and sixth decades, being infrequent before the age of 40, and no significant sex difference has been noted.[1 2] Aetiological factors have not been identified; a putative association with cellular Epstein-Barr virus infection has not been substantiated.[27–29] Clinical signs and symptoms (nausea, vomiting, abdominal pain, anaemia, and melaena) are non-specific and consequently not helpful for (differential) diagnostic purposes.

Histomorphology

Grossly, tumours vary greatly in size, ranging from 1–2 cm to more than 20 cm in diameter. The tumours are usually well circumscribed and generally unencapsulated, although a pseudocapsule may occasionally be seen. The lesions are either submucosal (with or without ulceration of the overlying mucosa), intramural, or subserosal. On sectioning, the cut surface varies in colour from grey/white to red/brown, depending on the degree of haemorrhage, and may be solid, partially cystic, or necrotic. Within the GIST category, cellular features demonstrate a broad morphological spectrum but there are two principal histological patterns: a spindle cell (60–70% of cases) (fig 1B) or epithelioid (30–40% of cases) (fig 1A) character, or a combination of both in variable proportions.

Tumours composed primarily of spindle shaped cells are generally compact and highly cellular with a patternless, fascicular, whorled, storiform, or palisading architecture and minimal tumour stroma; epithelioid tumours may have a more fascicular or "nested" appearance, although all the other architectural patterns mentioned above may be identified. Within tumours composed primarily of spindle shaped cells, the cytoplasm may be either eosinophilic, basophilic, or amphophilic with a somewhat fibrillar appearance. Within the epithelioid group, the cytoplasm is more abundant, ranging from amphophilic to clear, and cellular borders are more clearly defined; a predominantly oncocytic cytoplasmic character has been described recently.[30] Cytoplasmic glycogen with a perinuclear distribution is regularly present. In general, the nuclear features of GISTs are highly variable, ranging from a monotonous predominantly oval/spindly appearance to obviously pleomorphic; they contain nucleoli of variable prominence and multinucleation may be seen but is not a prominent feature. Mitotic activity may be virtually absent or high. A variable inflammatory infiltrate composed mainly of lymphocytes and plasma cells may be seen. Haemorrhage and necrosis may be present. The prominence of a vascular network is variable.

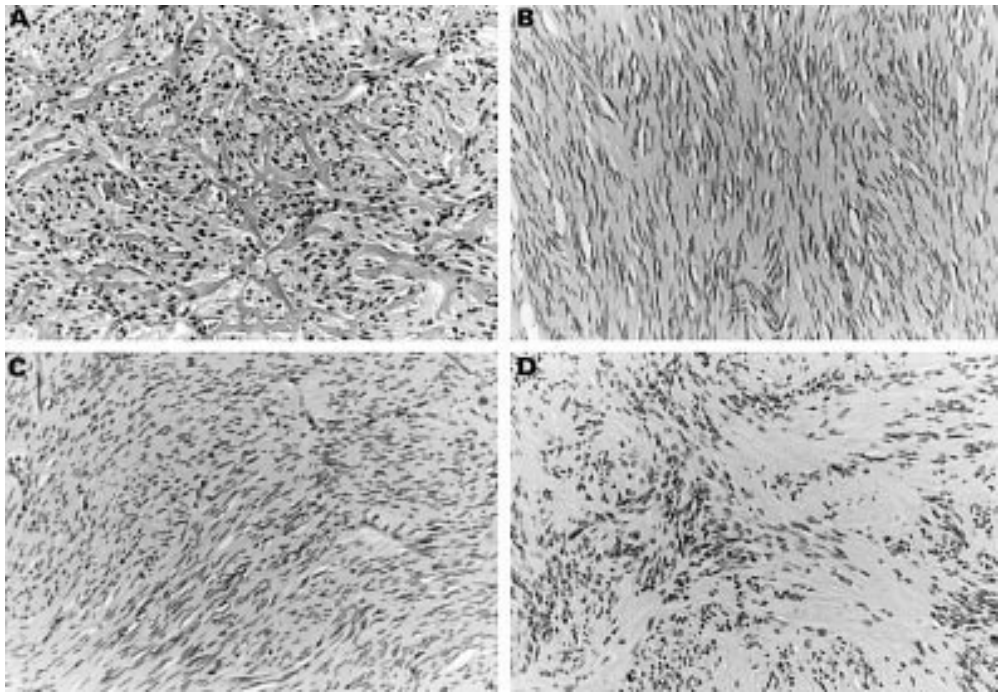

Figure 1 Medium power view (magnification, ×200; haematoxylin and eosin stain) illustrating the typical histological features of an (A) epithelioid and (B) spindle cell GIST, (C) a gastrointestinal leiomyoma (oesophagus), and (D) a schwannoma. It is evident that on morphological grounds alone this differential diagnosis may be extremely problematic, and the associated clinical implications may be considerable.

This broad histomorphological profile, together with the immunohistochemical and ultrastructural evidence, suggests a diversity of differentiation options detailed below (table 1).

Immunohistochemistry

Review of the literature with respect to the immunohistochemistry of GISTs yields a diverse and confusing array of data.[3–17 19 31–33] This lack of unanimity may be related to case selection. Because of the uncertainty about the histopathological criteria for categorising an intestinal mesenchymal tumour to the GIST group, and in particular their distinction from true smooth muscle tumours, it is probable that the different reported studies represent analyses of heterogeneous tumour populations. An increasingly frequent correlation of the cellular morphology with the immunohistochemical profile, ultrastructural features and, more recently, molecular genetic findings, and the subsequent removal of tumours with complete smooth muscle differentiation from the GIST category (leiomyoma/leiomyosarcoma), has sharpened the immunohistochemical picture of GISTs to some extent. An additional reason for the reported diversity could be related to the wide choice of monoclonal and polyclonal antibodies available (with their varying specificities), as well as differences in the technical parameters used and variable interpretation of the staining results by the individual pathologists involved.

However, despite these possible variables, the antibodies most commonly used in the various studies to characterise GISTs are those directed against vimentin, desmin, muscle specific actin (MSA/HHF-35), smooth muscle actin (SMA), S100 protein, neurofilament (NF), neurone specific enolase (NSE), PGP9.5, CD34, and CD117 (c-kit).

With respect to the controversy surrounding a myogenic origin, the myoid markers MSA and SMA are variably expressed, whereas desmin is almost never present. Furthermore, MSA and SMA are generally only focally present or completely absent, indicating that at most smooth muscle differentiation is probably incomplete (table 1).[1 2 6]

A possible schwannian/neural differentiation (S100 protein, PGP9.5, and NSE positivity) may be present in a proportion of SMA and MSA negative tumours; a small proportion of tumours express both myogenic and schwannian/neural differentiation, whereas a small number of GISTs are positive for vimentin only and exhibit no detectable differentiation at an immunohistochemical level. Nevertheless, as is evident from the above data, the nature of this diversity remains a controversial area requiring further study.

Antibodies to CD34 and CD117 in particular, although not tumour specific, are generally used in the differential diagnosis of GISTs from smooth muscle and other intestinal mesenchymal tumours because they appear to be expressed in most GISTs.[1–18 31–37]

CD34 (MY10, QBEND10) is a 110 kDa transmembrane glycoprotein present on human haematopoietic progenitor cells and vascular endothelium.[38] CD34 is expressed by a wide variety of tumours (table 2) and is detectable in 50–80% of GISTs (table 3). However, because CD34 may also be expressed by true smooth muscle cells, it is not a particularly helpful marker on its own. Nevertheless, in combination with CD117 and

Table 2 CD34 positive tumours

Gastrointestinal tumours
- Gastrointestinal stromal tumours

Tumours occurring primarily outside the gastrointestinal tract
- Non-gastrointestinal smooth muscle tumours
- Solitary fibrous tumour
- Dermatofibrosarcoma protuberans
- Kaposi's sarcoma
- Lipoma/angioliopma/spindle cell lipoma/atypical lipoma
- Neurofibroma
- Vascular tumours
- Epithelioid sarcoma

Although CD34 positivity, as part of an appropriate immunohistochemical panel, is diagnostically useful in the context of gastrointestinal spindle cell tumours, it is important to realise that it is a ubiquitous antigen present in many different tumours.

Table 3 Immunohistochemical positivity for CD34 and CD117 in gastrointestinal stromal tumours (GISTs)

CD117	*CD34*	*Ref*
100% (78/78)	72% (56/78)	18
94% (46/49)	82% (42/49)	39
88% (28/32)	69% (22/32)	18
81% (69/85)	56% (48/85)	34

CD117 is the more sensitive marker and CD117 might not be positive in all GISTs.

S100 it can still be useful in differentiating between GIST and other mesenchymal tumours encountered in the intestinal tract.[18 34 39]

Far more useful than CD34 is CD117/c-kit, discussed in more detail later. Once again, although not cell or tumour specific (tables 4 and 5), CD117 is expressed in 80–100% of GISTs (table 3), irrespective of tumour cytomorphology. Furthermore, CD117 is not expressed in smooth muscle or neural tumours and is consequently a powerful aid in the differential diagnosis between GISTs and other gastrointestinal mesenchymal tumours.[18 34 39] A recent clinicopathological study of GISTs primary in the omentum, peritoneum, and retroperitoneum has reinforced the importance of CD117 in making the distinction between GISTs at unusual locations and morphologically comparable mesenchymal tumours at these sites, facilitating a correct diagnosis and appropriate clinical follow up.[26]

Ultrastructural features

Electron microscopy has provided some degree of clarification of the range of cellular differentiation in the GIST group.[1 2 6 14 16 18 19 31 40] In contrast to the ultrastructural features of true smooth muscle cells, there is clearly a wide spectrum of cellular differentiation within and between GISTs (table 1). Well developed myofilaments are not often present, as is the case for well developed focal densities and attachment plaques. Nevertheless, focal bundles of actin myofilaments and inconspicuous dense bodies are seen in as many as 40% of cases and correlate with the immunohistochemical evidence of incomplete myoid differentiation.[2 14] In addition, complex cytoplasmic extensions and neurite-like processes, microtubules, synapse-like structures, and dense core granules indicative of variable neural differentiation, which correlate with the immunohistochemically observed nerve sheath/neural phenotype, are seen independently in a proportion of cases and in combination with the above mentioned myoid features.[1 2 6 14] Skeinoid fibres, representing extracellular amorphous eosinophilic arrays of interwoven modified collagen, may occasionally be seen and are an additional feature indicative of neural differentiation.[14] In contrast to the above mentioned subgroups, a small proportion of cases exhibit no diagnostic features and are referred to as being of uncommitted type.[14] Considering the immunohistochemical expression of CD34 and CD117 in most GIST subgroups, including the uncommitted group, together with the broad spectrum of ultrastructural features seen in these tumours, the increasingly accepted hypothesis is that the GIST group might represent a variable differentiation spectrum arising from a common precursor cell—discussed below—and that a distinction between the various subtypes is probably artificial.[1]

Table 4 Normal tissues expressing CD117/c-kit (adapted from Chan[1])

Gastrointestinal tract	*Sites outside gastrointestinal tract*
Interstitial cells of Cajal	A subset of CD34 positive haemopoietic stem cells
Mast cells	Melanocytes
	Basal cells epidermis
	Immature Langerhans cells in the epidermis
	Variety of epithelial cells (breast/salivary gland/sweat gland/renal tubule)
	Cells present in the reproductive system
	A subset of glial cells
	Osteoclast precursor

Tabulation of the diverse cell types that might express CD117/c-kit. Consequently, although CD117 is a diagnostically useful antigen expressed by the interstitial cells of Cajal (and in most gastrointestinal stromal tumours), it is important to be aware of the expression of this antigen in a variety of other cells.

Table 5 CD117/c-kit positive tumours (adapted from Chan[1])

Gastrointestinal tumours
- Gastrointestinal stromal tumours

Tumours occurring primarily outside the gastrointestinal tract
- Melanoma (loss in vertical growth phase and metastases)
- Clear cell sarcoma of tendons and aponeuroses
- Endometrial carcinoma
- Anaplastic small cell carcinoma of the lung
- Ewing's sarcoma group
- Anaplastic large cell lymphoma
- Reed-Sternberg cell in Hodgkin's lymphoma
- Mastocytosis
- Acute myeloid leukaemia
- Glioma
- Germinoma

CD117/c-kit positivity, in the setting of an appropriate immunohistochemical panel, is very useful in resolving the differential diagnosis of gastrointestinal spindle cell tumours. Nevertheless, it is important to remember that this antigen is present in a variety of different tumours, particularly in the context of metastatic disease.

Molecular biology

The c-kit proto-oncogene has been mapped to chromosome 4q11–21 (W locus) and encodes a type III tyrosine kinase growth factor receptor belonging to the immunoglobulin supergene family.[35 41 42] The c-kit molecule has a molecular weight of 135 kDa and consists of 976 amino acids, incorporating an extracellular domain composed of five immunoglobulin-like regions, a transmembrane domain, and an intracellular domain responsible for the kinase activity. Stem cell factor (kit-ligand/steel factor/mast cell growth factor) serves as the extracellular receptor ligand and is believed to play a role in cellular survival, proliferation, and differentiation.[43] The c-kit gene product (c-kit/

Table 6 Comparison of criteria reported in the literature to predict biological tumour behaviour

	Benign	*"Borderline"*	*Malignant*
de Saint Aubain Somerhausen and Fletcher[44]			
MI	0–2/30HPF	3–4/30HPF	>4/30HPF
	(spindle cell lesion, no atypia)	(spindle cell lesion, no atypia)	(spindle cell lesion, no atypia)
		2–3/30HPF	>2/30HPF
		(spindle cell lesion, mild atypia)	(spindle cell lesion, frank atypia)
	0/30HPF	1/30HPF	>1/30HPF
	(epithelioid lesion)	(epithelioid lesion)	(epithelioid lesion)
Miettinen and colleagues[2]			
MI	0–1/10HPF	2–5/10HPF	>5/10HPF
	(gastric lesion)	(gastric lesion)	(gastric lesion)
	Criteria concerning mitotic activity for tumours at other sites is less informative		
Size	<5 cm	5–10 cm	>10 cm
	(gastric lesion)	(gastric lesion)	(gastric lesion)
	Criteria for size is less well established		
Kindblom and colleagues[18]			
MI	0/10HPF		1 or more/10HPF
Other	Bland cytology	Some but not all of the features of malignancy	Frank cellular/nuclear atypia
	No necrosis		Necrosis
	No mucosal infiltration		Mucosal infiltration
			Haemorrhage

Comparison of the criteria used in attempts to predict biological tumour behaviour. The data highlight the current variability in parameters used as reported in the literature. Although mitotic activity defined in mm^2 or field diameter would be preferable, the designation "high power fields (HPF)" is used in the cited literature.
MI, mitotic index.

CD117) is expressed in a wide variety of normal tissues, including the ICCs of the gastrointestinal tract (table 6),[43 45] and increasingly germline and sporadic gain of function mutations within c-kit are being detected in GISTs, although their specific role in tumorigenesis remains elusive.[20 39 46–48] Furthermore, partial DNA losses of chromosome 14q (possibly suggesting loci for additional tumour suppressor genes involved in GIST tumorigenesis) have been identified in both clinically benign and malignant GISTs, whereas they have not been identified in leiomyomas or leiomyosarcomas, and might be potential markers for this tumour group.[49–51]

The nature and prognostic relevance of c-kit mutations is very topical and receiving increasing attention in the literature. The identification of germline mutations in families with GISTs suggests an association between genetic aberrations at the c-kit gene locus and the development of GIST. Furthermore, with the increasing identification and clinicopathological documentation of c-kit mutations at multiple sites within the gene, possible associations with prognosis are beginning to be analysed. Although data are still very limited, several recent papers have reported contradictory findings with respect to a possible association between mutation positive GISTs and prognosis.[48 52 53]

Histogenesis

For a variety of sarcomas, such as synovial sarcoma and epithelioid sarcoma, no benign counterpart has been identified to date, and a histogenetic source remains to be determined. Similarly, the broad morphological spectrum exhibited by GISTs at a light microscopic and ultrastructural level has generated much debate and controversy concerning tumour histogenesis. Although this will probably remain for the foreseeable future, Kindblom *et al*,[18] and more recently Sircar *et al*,[22] have elegantly provided considerable support for a possible histogenetic origin from the ICCs encountered in the gastrointestinal tract, which are thought to play a role in coordinating intestinal motility[21 54] (summarised by Chan[1]). The ICCs appear to be modified smooth muscle cells occurring at various intramural sites within the intestinal tract, primarily in the muscularis propria and in association with the myenteric plexus. In depth analysis and comparison of these cells with the cellular component of GISTs identified many important similarities: ICCs demonstrate an incomplete myogenic and neural differentiation at an immunohistochemical and ultrastructural level (providing an attractive explanation for the variable differentiation noted in the GIST spectrum, including the GANTs), and exhibit features that can be identified in all the tumour types currently ascribed to the GIST group. In particular, immunohistochemical expression of CD34 and CD117, although not tumour or tissue specific (tables 1–3 and 6), appears to be an important unifying parameter in GISTs. Furthermore, regional variation in the distribution of ICCs in the gastrointestinal tract (being more common in the stomach and the small intestine and least frequent in the oesophagus and rectum) correlates well with the observed prevalence of GISTs at the various anatomical sites.[1 2] Their convincing arguments that tumour morphology could be accounted for by variable degrees of differentiation (by mechanisms as yet unknown) in an ICC precursor cell is worth investigating further to elucidate the histogenesis of these interesting but complex neoplasms. Nevertheless, the occasional location of GISTs outside the gastrointestinal tract[26] (omentum, peritoneum, and retroperitoneum), where the ICCs are not known to be present, indicates that the issue of histogenesis is by no means resolved.

Biological behaviour

Predicting the potential biological behaviour of these tumours remains difficult and an analysis of the literature to resolve this issue provides many conflicting data.[1 2 13 54–70] Mitotic activity[1 2 6 13 54 56–58 61 66 69–72] tumour size,[57 63 66 69–72] tumour necrosis,[54 57] histological type/pattern,[67]

immunohistochemical profile, staining for proliferation antigens, and ploidy status,[13 56 57 60–63 65 68] among others, have all been extensively evaluated in this context without any consensus being established.[22 54] An analysis of GISTs at each anatomical site[1 2 6 54 58 59 66 69–72] in an attempt to identify possible site specific prognostic factors has not appreciably facilitated matters, although oesophageal tumours as a group have the most favourable long term survival and small intestinal tumours have the worst.[55] Although no unequivocal data are as yet available, current efforts are being focused on attempting to establish whether the presence/absence of c-kit mutations, and/or the nature of the mutation, have a bearing on prognosis.

Current data indicate that increasing mitotic activity[54 57 63 66] and increasing tumour size[54 57–59 63 66] may be of some use in predicting biological behaviour, and various cut off values for mitotic activity and tumour size have been proposed (table 6).[1 2 22] Nevertheless, no individual factor is of unequivocal independent prognostic use, and a constellation of parameters is used to provide some indication of a probable clinical course. As a consequence of the general confusion regarding the natural behaviour of this group of tumours, it is our practice to be extremely cautious with any form of prediction (for example, in histologically bland tumours of large size) and to emphasise the need for stringent longer term clinical follow up.

Aggressive disease, despite surgery with appropriate free resection margins, is characterised by local recurrence, omental and peritoneal seeding,[73] and metastatic disease to the liver; pulmonary and osseous metastases occur less frequently and primarily in more advanced disease. The value of adjuvant radiotherapy and chemotherapy remains to be determined unequivocally.[2]

Differential diagnostic considerations

GISTs, gastrointestinal leiomyoma or leiomyosarcoma, schwannoma, local extension by a primary retroperitoneal dedifferentiated liposarcoma, benign and malignant vascular tumours, intra-abdominal fibromatosis (desmoid tumour), carcinoid with a spindle cell morphology, and metastatic disease (spindle cell melanoma/spindle cell carcinoma) are the predominant tumours that may need to be considered in the differential diagnosis. Most of these tumours can be characterised accurately on the basis of precise clinical data and diligent microscopy, supplemented by appropriate immunohistochemical, ultrastructural, and molecular biological analyses (table 1). Separating GISTs from true smooth muscle tumours, clinically relevant because of differences in biological behaviour, can sometimes be difficult. Although immunohistochemical (CD117 positivity in GISTs) and ultrastructural examination (at most incomplete smooth muscle differentiation in GISTs) should facilitate the distinction from true smooth muscle tumours, it is possible that the rare CD117 (c-kit) negative GIST exhibiting extreme myoid differentiation might not be identifiable with current techniques. The clinically relevant distinction between an S100 positive, CD117/CD34 negative GIST with a predominantly epithelioid morphology and metastatic melanoma, in the absence of a known primary, could in rare circumstances be potentially problematic; the nature of the S100 positivity, diffuse in melanoma and at most patchy in GIST, should facilitate this distinction.

Conclusion

GISTs are the most common mesenchymal neoplasms of the stomach and small intestine and are relatively less frequent at other gastrointestinal sites. A lack of awareness of their broad morphological spectrum can complicate diagnosis. Nevertheless, an increasing awareness of their immunophenotypic, ultrastructural, and genotypic features coupled with an evolving understanding of their histogenesis is facilitating our ability to identify these tumours. Consequently, it should now become increasingly possible (and important) to study selected tumour populations (or subgroups), retrospectively and prospectively, in an attempt to highlight the parameters influencing their biological behaviour.

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