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Research Article

Cytomorphology of gastrointestinal stromal tumours: a comprehensive study

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ABSTRACT

Background: Gastrointestinal stromal tumours (GIST) are a heterogenous group of neoplasms. The main aim of the study is to review cases of spindle cell and epithelioid cell neoplasms of the GI tract and classify them as GIST and Non GIST morphologically.
Methods: The present study included 30 cases of 'gastrointestinal stromal tumours (GIST). GIST cases were reviewed based on morphology and were classified into "Risk of metastasis" categories based on the size and mitotic activity.
Results: The small intestine was the most commonly involved site (46.67%), followed by stomach (30%). Based on the size of the tumour and mitotic activity, the tumours were categorized as high risk (70%), intermediate risk (16.67%), low risk (6.67%), and very low risk (6.67%). High risk tumours predominated in all sites except the oesophagus. There was spindle cell predominance (76.8%) among all the cases. Epithelioid cells were seen in 36.7% of the cases.
Conclusions: Identifying mitotic figures and counting of GIST was associated with problems and were due to uneven distribution of the mitotic figures, variable thickness of the section and presence of inflammatory cells. Inspite of the difficulty mitoses is still considered as a good prognostic marker.

Keywords: Cytology, Gastrointestinal stromal tumours, Malignant tumours

INTRODUCTION

The ways in which spindle cell tumours and subsequently epithelioid cell tumours apparently arising from stromal and mesenchymal component of gastrointestinal (GI) tract have been perceived and classified over the past 50 to 60 years has been a subject of detailed review.

Following seminal description in 1940s by Stout and others, stromal tumours arising in GI tract were generally regarded as smooth muscle neoplasms (leiomyoma, leiomyosarcoma, leiomyoblastoma and bizarre leiomyomas) but relatively few of these neoplasms had convincing ultra-structural evidence of smooth muscle differentiation.

Use of immunohistochemistry (IHC) in early 1980s showed that many of these lesions lacked evidence of smooth muscle differentiation which led Mazur and Clark in 1983 to introduce generic designation "stromal tumours". It was observed that some stromal tumours of GI tract expressed neural crest antigens like S-100 protein and neuron specific enolase. Electron microscopically some cases showed schwannian or neuro axonal differentiation.[1]

A significant proportion of these lesions of both spindle cell and epithelioid type showed CD-34 positivity. This ubiquitous antigen was promulgated as reproducible marker of gastrointestinal stromal tumours (GISTs). It was evident over succeeding years that no more than 60% to 70% of GISTs are CD34 immunopositive. Schwann cell neoplasms and a proportion of smooth muscle tumours also showed CD34 positivity (Miettinen, Virolainen, Sarloma-Rikala, 1995).[2]

This led to a somewhat dichotomous approach. First approach was to pragmatically lump all mesenchymal tumours of GI tract under the heading GIST without regard to immunophenotypic differences or perhaps noting these differences in passing. The second approach was to strictly identify a group of mesenchymal tumours that excluded the leiomyomas and schwannomas under the rubric of GIST (Fletcher et al, 2002).[3]

Careful morphological examination and clinicopathological correlation remain essential for excluding mimics and for assessment of likely behaviour of this heterogenous group of neoplasms. So, the main aim of the study was to review cases of spindle cell and epithelioid cell neoplasms of the GI tract and also to categorise these neoplasms based on the "risk of metastasis" using the described criteria by Fletcher et al, 2002.[3]

METHODS

All the 30 cases reported at Hind Institute of Medical sciences, Lucknow as spindle cell neoplasms (leiomyoma, neurilemmoma, leiomyosarcoma and GISTs) of the GI tract, including those arising from the mesentery omentum and retroperitonium from July 2010 to December 2010, were included in this study.

The specimens consisted of resections and biopsies (Tru-Cut and Endoscopic). The specimens were fixed in 10% buffered formalin. The biopsies were entirely submitted. The gross features of the specimen were noted. The sampled tissue was routinely processed and paraffin embedded. Haematoxylin and eosin stained 5micron thick sections were studied under the light microscopy. Special Stains used were Masson trichrome stain and Periodic acid Schiff stain in this study.

The diagnosis of GIST is often suspected histologically because the majority of cases have remarkably uniform appearances falling into 1 of 3 categories. Spindle cell type (70%), epithelioid type (20%) or mixed type. Perhaps 5% of lesions show a variably prominent myxoid stroma, some cases (especially in small intestine) show a nested paraganglioma - like or carcinoid - like growth pattern. Only a small minority of cases (2% to 3%) show notable cytological pleomorphism. Criteria for distinguishing benign from malignant GISTs or at least to identify those lesions more likely to metastasize have been sought, analysed and disputed for many years. The morphological features that have gained greatest acceptance as being predictive of outcome are mitotic rate and tumour size. The following criteria were used in this study to define the malignant potential of GISTs.

Table 1: The proposed approach for defining risk of aggressive behaviour in GISTs (Fletcher et al, 2002)[3].

Risk category	Size	Mitotic count
Very low risk	< 2 cm	< 5 / 50 HPF
Low risk	2-5 cm	< 5 / 50 HPF
Intermediate risk	<5 cm 5 – 10 cm	6-10/50 HPF < 5 – 10 cm
High risk	> 5cm > 10 cm Any size	> 5/ 50 HPF any Mitoses >10/50HPF

The values are expressed in numbers and percentage (%)

RESULTS

Table 2: Age distribution.

Age Group	Total	%
21-30	3	10
31-40	3	10
41-50	9	30
51-60	5	16.67
61-70	5	16.67
71-80	4	13.33
81-90	1	3.33
Total	30	100

Table 3: Clinical features of patients.

Clinical Symptoms	No. of cases	Percentage
Mass abdomen & pain abdomen	21	70
Gastrointestinal bleeding	7	23.3
Intestinal obstruction	4	13.3
Bowel disturbance	5	16.6
Dyspepsia	3	10
Dysphagia	3	10
Anaemia/Fever/Loss of weight/Loss of appetite	11	36.6
Bladder incontinence	1	3.3
Recurrent disease	2	6.6
Metastatic disease	6	20

The present study consisted of 30 cases of GISTs. The age of the patients ranged from 28 to 87 years with a mean of 54.6 years. Majority of cases were located in the age group of 41-50 years (30%). Most of the patients (80%) were more than 40 years of age (Table 2). There was a female preponderance with male to female ratio being 1:2.3.There was a female predominance in all age groups.

Table 4: Categorisation of GISTs based on risk of metastasis.

Risk Grade	Criteria	No. of Cases	%
High Risk	Tumour size >5cm, Mitoses >5/50 HPF Tumour size >10cm, any Mitoses Any size >10 Mitoses/50HPF	21	70
Intermediate Risk	Tumour size <5cm, Mitoses 6-10/50 HPF Tumour size 5-10cm, Mitoses <5/50HPF	5	16.67
Low Risk	Tumour size 2-5 cm Mitoses <5/50 HPF	2	6.67
Very low risk (Leiomyoma)	Tumour size <2 cm Mitoses <5/50 HPF	2	6.67

HPF: high power field

Table 5: Cell types in GISTs at all sites.

Site	Spindle cell N (%)	Epithelioid cell (pure) N (%)	Epithelioid cell (Mixed/focal) N (%)
Oesophagus	2 (6.7)	-	-
Stomach	5 (16.7)	1 (3.3)	5 (16.7)
Intestine	14 (46.7)	1 (3.3)	2 (6.7)
EG	2 (6.7)		2 (6.7)
Total %	76.8	6.6	30.1

EG: extragastrointesinal

Clinically, mass abdomen and pain abdomen were the most common symptoms (21 cases), systemic symptoms like anaemia, fever, loss of weight and loss of appetite were the next common features, seen in 11 cases followed by gastrointestinal bleeding (upper or lower) in 7 cases. Bowel disturbances in the form of constipation and alternating constipation with diarrhoea were present in 5 cases. Metastatic disease was present in 6 cases, among which two were associated with recurrent tumour (Table 3). Among the other 4 cases, 1 was a retroperitoneal tumour with metastasis in the pubic bone, one was an ileoceacal tumour with multiple metastatic peritoneal nodules, and another was a jejunal tumour with metastatic peritoneal nodules. Yet another case of gastric GIST diagnosed on biopsy had evidence of metastasis in the lung, liver and bone on radiological examination.

There was a preponderance of high risk GISTs with 21 cases (70%), followed by intermediate risk, 5 cases (16.67%), low risk, 2 cases (6.67%) and very low risk 2 cases (6.67%) (Table 4).

The commonest site of involvement was small intestine constituting 46.67% of the cases. The next was stomach comprising of 30% of cases (9). The less frequently involved sites were large intestine 1 case (3.33%), retroperitonium 2 cases (6.67%), and mesentery and omentum 1 case (3.33%) each. There was a preponderance of high risk cases in all sites except oesophagus.

Among 21 high risk cases, 17 showed high cellularity. However, only 7 showed high grade nuclear atypia and majority exhibited moderate degree of nuclear atypia. There were four cases of high risk GISTs with moderate cellularity and moderate atypia and were categorised so due to their clinical behaviour and presence of metastasis.

All cases of intermediate risk GISTs had moderate cellularity and mild to moderate atypia. The two cases which showed necrosis was due to intussusception. The two cases of low risk GISTs had moderate cellularity and minimal atypia. One of these had necrosis due to intussusception. Both the cases of very low risk had low cellularity and showed no mitoses, atypia or necrosis.

The spindle cell predominated in 76.8% of the cases. Epithelioid cells were seen in all sites either mixed or focal (36.7%) except oesophagus, but were more frequently seen in the stomach (20%) (Table 5).

DISCUSSION

The tumours of the GI tract which are now designated as GIST based on c-KIT and more recently on PDGFR∝ mutations were described in most of the published series in the past as “Smooth Muscle Neoplasms”. Only a few recent articles are titled as “GIST”. This study is mainly based on morphology. Risk categorisation as high risk, intermediate risk, low risk and very low risk is based on the size and mitotic activity (Fletcher et al).[3] The corresponding categories in the older literature are leiomyosarcoma (high risk), indeterminate or smooth muscle tumour of uncertain malignant potential (intermediate and probably low risk) and the category of very low risk probably represents those tumours which were diagnosed as leiomyomas but metastasized.

According to recent literature true smooth muscle tumours of the GI tract are extremely rare and about 90% of spindle cell tumours are now categorized as GIST supported by the immunomarkers and, c-KIT and PDGFR∝ mutations. GISTs however, variably express smooth muscle markers and true smooth muscle tumours are c-KIT negative.[4]

Evans (1985) in his study of 56 cases of smooth muscle tumors of the GI tract found that majority of the patients (80%) were above the age of 40 years with maximum number of cases in the age group of 50 to 59 years.[5] Similarly, in the present study 80% of the patients were more than 40 years, but most were located in a younger age group (41 to 50 years).

The commonest presentation was mass and pain abdomen (70%) followed by anaemia/fever/loss of weight/loss of appetite (36.6%) and GI bleeding (23.3%) in the present study. Similarly, the main clinical features were abdominal pain, GI bleeding, weight loss and a palpable abdominal mass in 72% of gastric and 50% of small intestinal tumours in the above mentioned previous study.[5]

Table 6: Histologic grading of small intestinal stromal tumours based on tumour size and mitotic count.

Author	No. of cases	Benign	Borderline	Malignant
		Size(cm) Mitoses	Size (cm) Mitoses	Size (cm) Mitoses
Goldblum and Appelman, 1995 [16]	20 (Duodenal)	< 4.5 HPF <2/50	- -	≥ 4.5 ≥ 2/50 HPF
Franquemont and Frierson, 1992 [7]	16	< 5.0 HPF <2/10	≥ 5.0 HPF or 2/10	≥ 5.0 HPF and ≥2/10
Ma et al, 1997 [17]	22	< 5.0 HPF <5/50	≥ 5.0 <5/50 HPF	Any ≥ 5/50 HPF
Brainard and Goldblum, 1997 [15]	39 (Jejunal and ileal)	Non–adverse outcome		Adverse outcome
		<5.0 <5/50 HPF		> 5.0 ≥ 5/50 HPF
Present Study	14 (Jejunal and ileal)	Low risk	Intermediate risk	High risk
		< 5.0 > 2.0 HPF <5/50	< 5.0 HPF >6-10/50 5 – 10 <5/50 HPF	> 5.0 HPF >5/50 > 10.0 mitoses Any Any size ≥ 10/50HPF

The size of the tumours ranged from 0.75cms to 43cms in our study with a mean size 12.1cms. Our study included retroperitoneal tumours. In a study of 30 cases of GISTs by Nada et al which did not include retroperitoneal tumours the size ranged from 2.5 to 20cms.[6] The mean size for all tumours was 6.5cms (range 0.5-37) in series by Franquemont and Frierson.[7]

In the present study mitotic rate (MR) was expressed per 50 HPFs after counting 200 HPFs. It is difficult to make a meaningful comparison between the MR expressed in the present study and those in the past. Most of the earlier studies have expressed MR/10HPFs as originally described by Ranchod and Kempson.[8] They advocated examination of 5 sets of 10 HPFs and the set with highest mitotic count was used as the final rate. This method allows for regional variation in MR that is typical of GIST. Haque and Dean stressed the regional variability of MR in GIST and they chose to count 200 HPFs and express the final rate as the number of mitoses/50 HPFs. They further discuss that a mitotic rate of 5/50 HPFs appears much lower than 5/10HPFs but a rate of 5/50HPF may not be equivalent to 1/10HPF.[9] Counting mitoses in 10HPF of a mitotically active area would probably yield a higher rate than counting 200 fields, because in many GISTs the additional 190 fields would contain no mitoses at all. Regional variability of MR was observed in the present study.

Miettinen et al in their review article have stated that most mitoses in GISTs are regular. In their experience atypical mitoses with tripolar and quadripolar shapes were very uncommon in GISTs, in contrast to true leiomyosarcomas and undifferentiated non GIST sarcomas.[10] In the present study some high grade tumours showed the presence of atypical mitoses and these probably represent leiomyosarcoma or undifferentiated non GIST sarcomas.

Size and mitoses were the two criteria used in this study to classify the tumours into risk categories. Miettinen et al in their article on evaluation of malignancy and prognosis of GIST have concluded that the clinical behaviour of a GIST can be predicted with relative accuracy based on the combination of tumour size and mitotic activity.[10] Both the criteria should be applied together although some small tumours, <5cms with mitotic activity <5/50HPFs do metastasize. Significance of size is site dependent, specifically gastric tumours tend to be less aggressive than intestinal tumours, even those >5 cms. in size, provided that their mitotic activity is no more than 5/50 HPFs. They have also stated that GISTs

<2cms have negligible mitotic activity (usually <5 / 50 HPF). Such tumours are largely benign at all sites when completely removed. Evans has stated that malignant gastrointestinal smooth muscle tumours had diameters as small as 1 cm. and maximal mitotic rates as low as one mitotic figure per ten high power fields, thus suggesting that these parameters cannot be relied upon in the differential diagnosis.[5]

Franquemont and Frierson have also concluded that cellularity was significantly associated with clinical outcome, in spindle and epithelioid GISTs from all the sites.[7] However, Roy and Sommers found no association between metastatic risk and cellularity. In the present study though majority of the tumours belonging to the high risk group showed high cellularity, there were 4 tumours that were moderately cellular but aggressive at clinical presentation.[11,17] Berman and O' Leary have commented that although high cellularity is more prevalent in high risk tumours and pauci-cellularity more common in low risk tumours, the consensus was that cellularity is not valuable independent prognostic indicator.[12]

In the present study most of the high risk GISTs (66.66%) showed moderate degree of nuclear atypia. All the tumours which showed grade 3 nuclear atypia belonged to the high risk category. Similarly, Ranchod and Kempson observed that marked cytologic atypia was not a frequent finding in leiomyosarcomas but when present, was found only in malignant tumours and was associated with abundant mitoses.[13] Most leiomyomas in their study showed mild or no atypia, a feature shared by very low risk and low risk tumours in the present study. Also in the study by Evans both low and high grade leiomyosarcomas showed mostly moderate degree of nuclear atypia.[5] Miettinen et al in their review article describe that nuclear atypia is generally not prominent in GISTs and its significance is unclear.[10] Fletcher et al have commented that only a minority of cases (<2%-3%) show notable cytologic atypia.[3] They describe this feature as often suggestive of a true smooth-muscle neoplasm, which would often tend to have brightly eosinophilic cytoplasm.

In the present study among the 9 high risk small intestinal GISTs, 5 showed less frequent (<5 & <2) mitoses per 50 HPFs when compared to gastric high risk GIST (>5/50 HPFs). A diagnosis of high risk GIST was based on other morphological parameters like high cellularity, tumour cell necrosis, mucosal invasion and severe atypia. In one case the patient had metastatic disease at presentation. Akwari et al in their study of 108 cases of intestinal leiomyosarcoma comment that 1 mitotic figure/10HPFs if found consistently in a cellular tumour should be taken as evidence of malignancy.[14] Comparison between the previous studies of histologic grading of GISTs and the present study have been displayed in Table 6**.**

Spindle cells predominated in GISTs at all sites in the present study (60%) with a pure epithelioid cell pattern in 6.6% and tumours with mixed/focal epithelioid cells constituted 30% of the cases. Fletcher et al have described spindle cell type as the most common in GISTs (70%) with epithelioid cell type or mixed type consisting of 20 to 30% of the cases similar to our study.[3] Epithelioid cells were seen more frequently seen in the gastric tumours. A similar observation is made in the study by Franquemont and Frierson.[7] In the older literature the presence of epithelioid cells was correlated with benign behaviour. However, in the present study all the tumours with epithelioid cells belonged to the high risk category. Since the present study did not include follow-up it is difficult to correlate morphology with clinical behaviour.

CONCLUSION

Gastrointestinal stromal tumours are a heterogenous group of neoplasms. With the recent advent of targeted therapies using Sprycel and Tasigna the responsibility of the pathologists has increased to give a specific diagnosis. It is also important to suggest the prognosis based on the pathological findings.

Identifying mitotic figures and counting them was associated with problems and were due to uneven distribution of the mitotic figures, variable thickness of the section and presence of inflammatory cells. Inspite of the difficulty mitoses is still considered as a good prognostic marker. The other features which were useful in risk categorisation were cellularity, nuclear atypia, tumour cell necrosis and mucosal invasion. Since this study did not include follow-up, the significance and outcome of such a risk categorisation could not be determined.

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