Gastrointestinal stromal tumors: The histology report

Angelo P. Dei Tos a,*, Licia Laurino a, Italo Bearzi b, Luca Messerini c, Fabio Farinati d

On behalf of the “Gruppo Italiano Patologi Apparato Digerente (GIPAD)” and of the “Società Italiana di Anatomia Patologica e Citopatologia Diagnostica”/International Academy of Pathology, Italian division (SIAPEC/IAP)

*Department of Pathology, General Hospital of Treviso, Treviso, Italy
bDepartment of Pathology, University of Ancona School of Medicine, Ancona, Italy
cDepartment of Pathology, University of Florence School of Medicine, Florence, Italy
dDepartment of Surgery and Gastroenterology, University of Padua School of Medicine, Padua, Italy

Abstract

Gastrointestinal stromal tumors (GISTs) represent a mesenchymal neoplasm occurring primarily in the gastrointestinal tract, and showing differentiation toward the interstitial cell of Cajal. Its incidence is approximately 15 case/100,000/year. Stomach and small bowel are the most frequently affected anatomic sites. GIST represents a morphological, immunophenotypical and molecular distinct entity, the recognition of which has profound therapeutic implications. In fact, they have shown an exquisite sensitivity to treatment with the tyrosine kinase inhibitor imatinib.

Diagnosis relies upon morphology along with immunodetection of KIT and/or DOG1. When dealing with KIT negative cases, molecular analysis of KIT/PDGFRA genes may help in confirming diagnosis. Molecular evaluation of both genes are in any case recommended as mutational status provides key predictive information. Pathologists also play a key role in providing an estimation of the risk of biological aggressiveness, which is currently based on anatomic location of the tumor, size, and mitotic activity.

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1. Introduction

Gastrointestinal stromal tumors (GISTs) represent a mesenchymal neoplasm of the gastrointestinal tract showing differentiation along the line of interstitial cell of Cajal [1] (Level 2). The majority of GISTs express KIT and/or DOG1 and harbour activating mutations of the KIT or PDGFRA genes. GISTs occur sporadically in the vast majority of cases whereas a smaller fraction occurs in the context of genetic syndromes [2] (Level 3). Rare familiar forms have also been reported. Interestingly, a higher incidence of GIST is observed in patients affected by the NF1 syndrome [3]. In the Carney triad GISTs are associated with extra-adrenal paragangliomas, and pulmonary chondromas [4], whereas in the Carney and Stratakis syndrome only GIST and paraganglioma are seen which are inherited as an autosomal dominant disorder [5]. Pediatric GISTs represent a distinctive subset, in which tumors tend to occur mostly in females, to be KIT/PDGFRa wild type, and generally pursue a clinically indolent course.

The pathology report plays a key role in the therapeutic planning of patients affected by GIST: Critical issues are represented by:

- Accurate morphologic diagnosis implemented by relevant immunohistochemical stains

* Address for correspondence: Angelo P. Dei Tos, MD, Department of Pathology, General Hospital of Treviso, Piazza Ospedale 1, 31100 Treviso, Italy.
E-mail address: apdeitos@ulss.tv.it (A.P. Dei Tos).
• Assessment of the risk of progression
• Analysis of the mutational status of KIT and PDGFRA genes

2. Epidemiology

Gastrointestinal stromal tumors (GISTs) are rare tumors, with an estimated incidence of 1.5/100,000/year [6] (Level 3). This only refers to clinically relevant GIST, since likely a much higher number of microscopic lesions could be found pathologically, if looked for. Whenever so-called microGISTs are carefully searched for both in surgical specimens of resected segments of GI tract or at autopsy, an incidence approaching 20% has been indicated by several studies [7] (Level 2). GISTs are more frequent in the stomach (approximately 60%) and in the small bowel (30%). Esophagus, large bowel and rectum are comparatively much rarer anatomic locations accounting for approximately (10%). Rarely GIST can occur in the mesentry (so-called extra gastrointestinal GIST).

3. Diagnostic approach and tissue handling

The diagnostic approach to GIST depends upon size and anatomic location. A firm diagnosis obviously only relies upon histopathologic examination, however, the decision whether to obtain tissue material or not is not univocal.

3.1. Lesion smaller than 2 cm

When small esophageal, gastric or duodenal nodules less than <2 cm in size are detected, endoscopic biopsy may be difficult, and therefore laparoscopic or laparotomic excision may be the only way to achieve a histologic diagnosis. Many of these GISTs will be low-risk. Therefore, the standard approach to these patients is endoscopic ultrasound assessment and then follow-up, reserving excision for patients whose tumor increases in size or becomes symptomatic. In those cases which have been histologically proven to be GIST, standard treatment is excision, unless major morbidity is expected.

However, for rectal nodules the standard approach is biopsy/excision after ultrasound assessment regardless of tumor size, because the risk of a GIST at this site is higher.

3.2. Lesion larger than 2 cm

The standard approach to nodules >2 cm in size is biopsy/excision. In presence of an abdominal nodule not amenable to endoscopic assessment, laparoscopic/laparotomic excision is the standard approach. In case of a larger mass, especially if surgery is likely to be a multivisceral resection, multiple core needle biopsies represent the standard approach. They should be obtained preferably through endoscopic ultrasound guidance, or otherwise through an ultrasound/CT-guided percutaneous approach. Accurate recognition of the histotype is obviously crucial.

Immediate laparoscopic/laparotomic excision is an alternative on an individualized basis, especially if surgery is limited. If a patient presents with obvious metastatic disease, then a biopsy of the metastatic focus is sufficient and the patient usually does not require a laparotomy for diagnostic purposes.

3.3. Tissue handling

The tumor sample should be fixed in 10% buffered formalin (Bouin fixation should be banned, since it prevents proper molecular analysis). Large specimens should be sectioned in order to allow proper fixation and consequent optimal morphological as well as immunohistochemical evaluation. Frozen tissue collection is encouraged.

The surgical specimen should be sectioned by the pathologist. Margins should be inked in order to allow the most accurate assessment of their status.

4. Pathologic diagnosis

Pathologically, the diagnosis of GIST relies on the variable combination of morphology, immunohistochemistry (CD117 and/or DOG1) and, in selected cases, on molecular analysis (Level 3).

Morphologically GISTs are subdivided in spindle cell, epithelioid cell, and mixed types, however, such subclassification has no clinical relevance. GISTs most often present as a cytologically bland spindle cell or epithelioid cell proliferation, set in richly vascularized stroma (Fig. 1A, B). Mitotic activity is generally low, however, approximately 25% of cases exhibits more than 10 mitoses/50 HPF. Coagulative necrosis is seen in less than 20% of cases. Overt cytologic atypia represents a rare finding, as is the presence of dedifferentiation. Both features should in principle lead to consider a diagnostic alternative.

Most GIST (>90%) exhibit cytoplasmic immunoreactivity for KIT (CD117). A proportion of GIST (in the 5% range overall) is CD117-negative [8] however, approximately one third of these cases will stain with DOG1, an equally sensitive and specific GIST marker [9] (Fig. 1C, D). GIST shows variable expression of many other immunophenotypic markers such as CD34, smooth muscle actin and h-caldesmon, however, none of them are specific. Desmin is seen in less than 20% of cases and rare cases may show the expression of epithelial markers or S-100 protein. PDGFRA strong immunopositivity is often observed in PDGFRA mutated cases, however this finding needs further validation.

The morphologic assessment also plays a key role in the estimation of the risk of progression (see below). The pathology report must therefore always include the size, the mitotic count, the anatomic location, and the status of margins (R0, R1 or R2). Mitotic count should be expressed as number of mitoses per 50 HPF (or alternatively a total area of 10 mm² should be analyzed).
5. Stage classification and risk assessment

The risk of relapse is estimated on the basis of mitotic rate, tumor size, tumor site, surgical margins and whether tumor rupture has occurred (Level 2). Tumor size and mitotic count are considered by the 2002 Consensus risk classification (Table 1) [10].

This was correlated with prognosis in an epidemiological study, showing that the “high risk” category has a much worse prognosis than the others. “Very low risk” and “low risk” categories have a very favorable prognosis. In most of the population-based series, the “intermediate risk” category of the Consensus classification did not discriminate patients with an unfavorable prognosis.

A more recently proposed risk classification incorporates primary tumor site in addition to the mitotic count and tumor size. In particular, it reflects the fact that gastric GISTs have a better prognosis than small bowel or rectal GIST (Table 2) [11].

The risk estimate for subgroups is based on a single retrospective analysis. However, this classification better distinguishes across different risk levels.

Table 1
NIH2002 risk assessment scheme

<table>
<thead>
<tr>
<th>Size (cm)</th>
<th>Mitoses (50 HPF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Low risk</td>
<td>2–5</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>≤5</td>
</tr>
<tr>
<td>High risk</td>
<td>6–10</td>
</tr>
<tr>
<td>&gt;5</td>
<td>&gt;5</td>
</tr>
<tr>
<td>&gt;10</td>
<td>Any MR</td>
</tr>
</tbody>
</table>

Table 2
Risk assessment scheme (by Miettinen and Lasota [11])

<table>
<thead>
<tr>
<th>Size</th>
<th>Mitotic rate</th>
<th>Stomach</th>
<th>Duodenum</th>
<th>Jejunum/ileum</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>&gt;2 ≤5</td>
<td>very low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>&gt;5 ≤10</td>
<td>low</td>
<td>intermediate</td>
<td>no data</td>
<td>no data</td>
<td>high</td>
</tr>
<tr>
<td>&gt;10</td>
<td>intermediate</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>≤2</td>
<td>none</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>&gt;2 ≤5</td>
<td>intermediate</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>&gt;5 ≤10</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>&gt;10</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>Any size</td>
<td>&gt;10</td>
<td>Any MR</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>

Fig. 1. A. Gastrointestinal stromal tumor, spindle cell type (H&E, 20×). B. Gastrointestinal stromal tumor, epithelioid cell type (H&E, 20×). C. KIT (CD117) positive immunostain (40×). D. DOG1 positive immunostain in a KIT negative GIST(40×).
Table 3
Risk assessment scheme (by Joensuu [12])

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Tumor size (cm)</th>
<th>Mitotic index (50 HPF)</th>
<th>Anatomic site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>&lt;2.0</td>
<td>&lt;5</td>
<td>Any</td>
</tr>
<tr>
<td>Low</td>
<td>2.1–5</td>
<td>&lt;5</td>
<td>Any</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2.1–5</td>
<td>&gt;5</td>
<td>Gastric</td>
</tr>
<tr>
<td></td>
<td>&lt;5.0</td>
<td>6–10</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>5.1–10</td>
<td>&gt;5</td>
<td>Gastric</td>
</tr>
<tr>
<td>High</td>
<td>Any</td>
<td>Any</td>
<td>Tumor rupture</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>Any &gt;10</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>&gt;5.0</td>
<td>&gt;5</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>2.1–5.0</td>
<td>&gt;5</td>
<td>Non gastric</td>
</tr>
<tr>
<td></td>
<td>5.1–10</td>
<td>&gt;5</td>
<td>Non gastric</td>
</tr>
</tbody>
</table>

Tumor rupture, whether spontaneous or at the time of surgical resection, should be recorded, because it denotes a high risk independent of any other prognostic factor (Table 3) [12].

The recent introduction of nomograms may represent an alternative, more practical approach to facilitate clinical decision making [13] (Level 1).

6. Differential diagnosis

Even if GISTs represent the commonest mesenchymal neoplasm at the gastrointestinal location a broad differential diagnosis must be taken into consideration. Accurate recognition of GIST is obviously crucial as the treatment varies according to histologic subtype. Immunohistochemistry plays a major role as all the possible mimics of GIST (with the notable exception of malignant melanoma and seminoma) are KIT/DOG1 negative. Smooth muscle tumors (leiomyoma and leiomyosarcoma) and neural tumors, most often cellular schwannoma (CSCHW) represent the commonest alternative to GIST. Other rarer histotypes are represented by intra-abdominal desmoid fibromatosis, synovial sarcoma (SS), follicular dendritic cell sarcoma (FDACS), and PEComas.

The evaluation of appropriate immunophenotypic markers in context with morphology in most cases allows an accurate classification (Table 4).

In general GISTs are by far the most likely option in both the stomach and the small bowel, whereas smooth muscle tumors are comparatively more frequent in the colon-rectum and in the esophagus.

7. Role of mutational analysis

Mutational analysis of the KIT (exons 11, 9, 13, 17) and PDGFRA (exons 12, 14, and 18) genes can be helpful in confirming the diagnosis of GIST, if doubtful (particularly in CD117/DOG1-negative spindle cell suspect cases).

Mutational analysis also has predictive value for sensitivity to molecular-targeted therapy (including dosage) and prognostic value, so that it must be included in the diagnostic work-up of all GISTs [14]. As an example, mutations occurring in exon 11 of the KIT gene are associated with sensitivity to imatinib, whereas mutations occurring in the exon 18 of the PDGFRA gene (D842V) are associated with primary resistance both in vivo and in vitro.

Recent data indicate that a small fraction of GIST wild type for both KIT and PDGFRA genes may carry mutations of the bRAF gene [15]. It has also been shown that GIST occurring in the contest of Carney and Stratakis Syndrome (an autosomal dominant condition in which GISTs are associated with paragangliomas) mutations of the succinate-dehydrogenase genes are detected [5].

Centralization of mutational analysis in a laboratory enrolled in an external quality assurance program and with specific expertise in the disease should be considered.

8. Treatment

Multidisciplinary treatment planning is needed (involving pathologists, radiologists, surgeons and medical oncologists).

As pathologic diagnosis has a major impact on treatment it seems useful to summarize herein also guidelines for treatment.

9. Limited disease

Standard treatment of localized GIST is complete surgical excision, without dissection of clinically negative lymph nodes aiming at R0 resection. In case R0 surgery is not feasible, it either might be achieved through less mutilating surgery, or if the surgical conduct is safer after cytoreduction, imatinib pretreatment is recommended. Surgery is performed following maximal tumor response, generally after 6–12 months.

An important role for the pathologist is to evaluate the
mutational status as it may help to exclude less sensitive mutational status (e.g., PDGFRA D842V mutations) from therapy with imatinib.

Evaluation of the margins also represents a key step. In fact, if an R1 excision has been made, re-excision may be a choice, provided the original site of the lesion can be found and major functional sequelae are not foreseen.

A randomized trial demonstrated that imatinib for 1 year is able to prolong early relapse-free survival in >3 cm localized GISTs with a macroscopically complete resection [16]. At the moment, there is no global consensus in the medical community [17]. Adjuvant imatinib is an option for those patients with a substantial risk of relapse.

Again a major role for pathologists is foreseen, as in addition to the risk assessment (wherein mitotic count needs to be the most accurate), mutational analysis may again guide the selection of those patients who are more likely to benefit from the treatment. Tumor rupture at the time of surgery puts the patient at a very high risk of peritoneal relapse and, therefore, these patients should be considered for imatinib therapy.

10. Extensive disease

In locally advanced inoperable patients and metastatic patients, imatinib is standard treatment [18–20]. This applies also to metastatic patients who have been completely relieved of all lesions surgically. Standard dose of imatinib is 400 mg daily. Treatment should be continued indefinitely, since treatment interruption is generally followed by relatively rapid tumor progression in virtually all cases, even when lesions have been previously surgically excised [21].

The efficacy of surgery of metastatic responding patients is under investigation [22].

The standard approach in the case of tumor progression on 400 mg is to increase the imatinib dose to 800 mg daily, with the possible exception of insensitive mutations.

In case of progression or intolerance on imatinib, second-line standard treatment is sunitinib [23]. After failing on sunitinib, the patient with metastatic GIST should be considered for participation in a clinical trial of new therapies or new combinations.

11. Response evaluation

Antitumor activity translates into tumor shrinkage in the majority of patients, but some patients may show only changes in tumor density [24,25]. These changes in tumor radiological appearance should be considered as tumor response. Likewise, some increase in tumor density within tumor lesions may be indicative of tumor progression.

Pathologically, post imatinib GISTs exhibit variable degrees of myxohyaline degeneration. Coagulative necrosis is usually not observed and complete responses are only very rarely encountered.

12. Follow-up

Recurrences most often involve the peritoneum and/or the liver. Again the pathologists play a key role in assessing the risk of relapse. As already mentioned, risk assessment is based on mitotic count, tumor size and tumor site. Such parameters may help also in determining the routine follow-up policy. High-risk patients generally relapse within 2–3 years, while low-risk patients may relapse later, although less frequently.

13. Conclusions

GIST is a distinctive clinico-pathological entity the accurate recognition of which represents the prerequisite for a correct therapeutic planning. Pathologists need to be aware of their role as the data they provide impacts on the choice of treatment as well as on estimation of its efficacy. The main tasks are as follows:

1. To establish a firm diagnosis of GIST by integrating morphologic, immunophenotypic (KIT and DOG1 expression) and molecular (when applicable) data.

2. To determine the risk of tumor progression by evaluating size, mitotic activity and anatomic location.

3. To analyze the mutational status of the KIT and PDGFRA genes.

14. Pathology report

Relevant clinical information

– Sex, age

– Anatomic site of origin
  (a) Esophagus
  (b) Stomach
  (c) Ileum
  (d) Duodenum
  (e) Jejunum
  (f) Colon
  (g) Rectum
  (h) Peritoneum
  (i) Other

– Number of lesions

– Primary versus metastatic

– If metastatic:
  (a) Liver
  (b) Peritoneum
  (c) Other

– Associated syndromes
  (a) Neurofibromatosis type 1
  (b) Carney’s triad
  (c) Carney and Stratakis’ diad

Gross description

– Size
Microscopic description
- Cell Type
  (a) Spindle
  (b) Epithelioid
  (c) Mixed
- Mitotic count
  (a) Expressed as number of mitosis/50 HPF or number of mitoses/10 mm²
  (b) Epithelioid
  (c) Mixed
- Mitotic count
  (d) Expressed as number of mitosis/50 HPF or number of mitoses/10 mm²
- Necrosis
- Presence of pleomorphism
- Status of margins

Risk assessment
- According to one of the available schemes. Miettinen’s scheme is currently preferred.

Immunophenotype
- KIT (CD117)
- DOG1

Mutational status
- KIT gene
  (a) Exons, 11, 9, 13, 17
- PDGFRA gene
  (a) Exons 12, 14, 18

Conflict of interest
The authors have no conflict of interest to report.

References