A Histopathological Review of Gastrointestinal Related Mesenchymal Tumors: The Hidden GIST

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Abstract

Background: The diagnosis of gastrointestinal stromal tumors is based on documentation of c-KIT and platelet-derived growth factor-alpha receptors or specific c-KIT mutations. Before the diagnosis of GIST was possible, all cases had been classified as sarcomas or benign tumors.

Objectives: To identify cases of GIST formerly diagnosed as abdominal or retroperitoneal mesenchymal tumors.

Methods: We reviewed the archive material on all surgical cases diagnosed as gastrointestinal related malignant mesenchymal tumors or GIST in our medical center during the last decade (1995–2004).

Results: Sixty-eight cases of retroperitoneal soft tissue sarcoma were identified. Thirty-eight were reconfirmed to be GIST, 19 were newly diagnosed as GIST (the hidden cases), 8 cases were re-diagnosed as mesenchymal tumors, and 3 cases of sarcoma remained sarcomas. Of all the GIST tumors, c-KIT-positive and PDGFRα-positive tumors were more characteristic of primary gastric tumors, while c-KIT-positive and PDGFRα-negative tumors were found in the colorectal area. The c-KIT-negative and PDGFRα-positive cases were of gastric origin.

Conclusions: Any c-KIT-negative malignant mesenchymal mass located near the proximal gastrointestinal tract should also be stained for PDGFRα to differentiate between GIST and other soft tissue sarcomas. Practically, formerly diagnosed abdominal or retroperitoneal soft tissue sarcomas should be reviewed to identify patients with misdiagnosed GIST and thereby avoid future unnecessary and ineffective chemotherapy.

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Gastrointestinal stromal tumors [1] are the most common mesenchymal tumor of the gastrointestinal tract, arising primarily from Cajal cells within the muscular wall of the stomach and small intestine. Malignant GIST is a type of sarcoma, comprising tumors of mesenchymal origin. In the visceral location, GIST, leiomyosarcoma and desmoid are the most common histologic types seen [2]. Most (70%) of the GISTs originate in the stomach and about 20–30% in the small intestine [3]. Approximately 95% of GISTs express the receptor tyrosine kinase KIT, which is essential for distinguishing these tumors from other sarcomas that develop in the abdomen. It has already been established that 75–80% of GISTs harbor mutations in the *KIT* gene, and that the resulting mutants of *KIT* play an important role in the development of these tumors [4]. Targeting of c-KIT by imatinib mesylate is the best approach towards advanced or unresectable GIST [5]. However, not all GISTs carry the c-KIT mutation. A subset of GISTs shows platelet-derived growth factor-alpha mutations. No differences in the activation of downstream signaling intermediates were observed between KIT-mutant and PDGFRα-mutant tumors, suggesting that mutant PDGFRα provides oncogenic signals that parallel those of mutant KIT, and that the two types of GISTs may be targeted by imatinib [6,7] .

Prior to the possibility of immunohistochemical identification of c-KIT and PDGFRα antigens, the diagnosis of GIST was rarely made. Most of the abdominal and retroperitoneal malignant mesenchymal tumors were diagnosed as soft tissue sarcomas and treated accordingly. Metastatic abdominal soft tissue sarcomas were treated by doxorubicin-based chemotherapy. While true soft tissue sarcomas may respond to doxorubicin-ifosfamide combination chemotherapy at a rate of 30%, GISTs showed a negligible response. Prior to the availability of tyrosine kinase inhibitors, there were no effective systemic therapies for advanced malignant GIST. However, since tyrosine kinase inhibitors have become easily available, the correct diagnosis of GIST and its differentiation from the other retroperitoneal mesenchymal tumors became more crucial. Today the diagnosis of GIST is based on documentation of c-KIT and/or PDGFRα antigens [8]. In this retrospective analysis we histopathologically reviewed all cases formerly diagnosed as abdominal or retroperitoneal mesenchymal tumors in order to find undiagnosed cases of GIST.

Patients and Methods

We revised the archive material on all surgical cases diagnosed as gastrointestinal related malignant mesenchymal tumors or GIST in our medical center during the last decade (1995–2004). The histopathological revision was performed according to the consensus approach for the diagnosis of GIST [9] based on histology and immunohistochemical findings. This review was carried out by a dedicated pathologist (J.I.), and included light microscopy study of the available archive slides, and new immunohistochemical staining for all the pertinent GIST and sarcoma tumor antigens. All samples were stained for c-KIT, PDGFRα, CD34, vimentin, smooth muscle antigen, desmin, S100 and creatine kinase. The recent consensus meeting for the management of GISTs suggested that molecular biology techniques may be applied for the diagnosis of GIST [8]. However, since molecular biology techniques are expensive tools, and not always available and feasible, we decided to check reactivity to

GIST = gastrointestinal stromal tumors
PDGFRα = platelet-derived growth factor-alpha

c-KIT and PDGFRα with immunohistochemistry. Only specimens that were stained positively for c-KIT or PDGFRα were diagnosed as GIST, regardless of the status of the other antigens. On the other hand, c-KIT-negative and PDGFRα-negative tumors were diagnosed as soft tissue sarcomas (non-GIST mesenchymal tumors) of various types, based on the microscopic appearance and immunohistochemical staining.

Results

Sixty-eight cases (32 males and 36 females) of gastrointestinal related mesenchymal tumors were identified and histopathologically revised. Patients' age ranged from 27 to 91 years (median 69 years). The site of the primary tumor was the colon in 2 patients, the duodenum in 2, the gastro-esophageal junction in 3, the mesentery in 1, the rectum in 3, the retroperitoneum in 3, the small bowel in 12, and the stomach in 42. Tumor size ranged from 0.8 to 26 cm (median 6.5 cm).

Fifty-seven of the tumors were finally diagnosed as GIST. Their histological type was epithelial in 21 cases, spindle in 21, mixed in 14, and pleomorphic in 1. Malignant GIST was defined in 47 cases, and benign in 10. GIST size ranged from 0.8 to 26 cm (median 6 cm). Table 1 presents the distribution of diagnoses of GIST versus non-GIST mesenchymal tumors. GISTs in this series more commonly originated in the stomach, followed by the large bowel (colon + rectum).

Of the 68 cases with primary diagnosis of gastrointestinal related mesenchymal tumor, 38 cases were confirmed to be correctly diagnosed as GIST, 19 cases were newly diagnosed as GIST ("hidden cases"), 8 cases were re-diagnosed as mesenchymal tumors, and 3 cases of sarcoma remained sarcomas. Most of the lost cases of GIST were formerly diagnosed as leiomyosarcoma of the stomach or retroperitoneal soft tissue sarcoma. The distribution of diagnoses, the original and second-look diagnosis are detailed in Table 2.

Of all the GIST tumors, the combination of c-KIT-positive and PDGFRα-positive was more characteristic of primary gastric tumors (57.5%), while c-KIT-positive and PDGFRα-negative was found in colorectal primary tumors. The c-KIT-negative and PDGFRα-positive cases were related to gastric origin. Therefore, gastric GISTs may be divided into two groups: c-KIT-positive (75%) or c-KIT-negative (25%). Only rarely in this series were c-KIT-negative PDGFRα-positive tumors found distally to the stomach. The status of c-KIT and PDGFRα staining according to the GIST origin is shown in Table 3.

CD34 did not add to the diagnosis of GIST when either c-KIT or PDGFRα was positive. CD34 was negative in 34/57 cases (60%), and positive in only 40%. Of the 11 cases with both c-KIT-negative and PDGFRα-negative staining, only one showed CD34 positivity, but the favored diagnosis based on microscopic appearance was de-differentiated liposarcoma. All cases of GIST were negatively stained for actin and desmin.

No correlation was found between the histological types of GIST, i.e., epithelial, spindle or mixed, and the staining for c-KIT, PDGFRα or CD34. Also, there was no correlation between the grade of malignancy (benign, low, intermediate or high) and these antigens. All the cases with metastases at the time of diagnosis were of high grade biology.

Table 1. The distribution of tumor diagnosis according to site

Site	Final diagnosis	No. of cases
Duodenum	GIST	1
	Leiomyosarcoma	1
Gastro-esophageal junction	GIST	3
Large bowel	GIST	2
Mesentery	Desmoid	1
Rectum	GIST	3
Retroperitoneum	De-differentiated liposarcoma	1
	Leiomyosarcoma	2
Small bowel	Desmoid	1
	GIST	11
Stomach	GIST	37
	Leiomyosarcoma	5
All sites	GIST	57

Table 2. The distribution of diagnoses: original and histopathological review

First diagnosis	Histopathological review	No. of cases
GIST	GIST	38
GIST	Desmoid	2
GIST	Leiomyosarcoma	5
GIST	HG STS	1
Leiomyosarcoma	GIST	**12**
MPNST	GIST	**1**
Soft tissue sarcoma	GIST	**6**
High grade soft tissue sarcoma	Dedifferentiated liposarcoma	1
Soft tissue sarcoma	Leiomyosarcoma	2
Non-GIST mesenchymal tumor	"The hidden" GISTs"	**19** of 57 cases

Table 3. Status of c-KIT and PDGFRα according to the GIST origin

Site of origin	c-KIT positive	c-KIT negative	
Stomach & gastro-esophageal junction	23 7	10 –	PDGFRá+ PDGFRα-
Small bowel & duodenum	6 5	1	PDGFRá+ PDGFRα-
Colon & rectum	0 5	0	PDGFRá+ PDGFRα-

Discussion

Our results point to the need for revision of histopathological diagnoses of abdominal and gastrointestinal related mesenchymal tumors in order to reveal hidden or lost cases of GIST. It is especially true in this era of increasing knowledge of signal transduction pathways in malignant tumors, and the targeting of specific proteins essential for tumor development.

We re-diagnosed 19 cases of GIST that had been formerly diagnosed as soft tissue sarcomas. Whereas abdominal soft tissue sarcoma responds poorly to chemotherapy and carries a gloomy prognosis, GISTs do respond to targeted therapy with imatinib or newer agents such as sunitinib, and are associated with a more favorable prognosis and long-term survival in selected cases.

We preferred to define the 19 cases of GIST as hidden cases and not as misdiagnosed. The incidence of the "hidden GIST phenomenon" was 33% of abdominal soft tissue sarcomas in the current study and 20% in another series [10]. The growing experience using c-KIT staining yielded more cases of c-KIT-positive GIST from among the abdominal mesenchymal tumors, while the addition of PDGFRα immunohistochemistry to the diagnostic panel of GIST yielded the option of defining a c-KIT-negative PDGFRα-positive GIST. Therefore, it is conceivable that as the diagnostic methods improve, more cases of GISTs are found.

The most important aspect in the diagnosis of GIST is of course the histological picture. The three histological types already mentioned are spindle, epitheloid and mixed. For the confirmation of the suspected diagnosis of GIST, and for possible targeting by tyrosine kinase inhibitor, c-KIT assessment should be carried out. In case the c-KIT is negative a panel of immunostains is usually performed, including CD34, cytokeratin, smooth muscle antigen, S100 and desmin. It is known that CD34 can be positive in 60–70% of GISTs, Smooth muscle antigen is positive in 30%, and S100 and desmin in 2–5%. As none of these antigens is specific for GIST, molecular biology tools are applied for identification of KIT and PDGFRα mutations.

In the current study we found that the classic combination of c-KIT-positive PDGFRα-negative GISTs originated in any part of the gastrointestinal tract, whereas c-KIT-negative PDGFRα-positive GISTs were found only in the proximal portions of the tract. Also, the combination of c-KIT-positive and PDGFRα-positive GISTs were more typical of the proximal parts.

The discovery that some c-KIT-negative GISTs show oncogenic mutations in PDGFRα has introduced a new level of complexity with respect to both the diagnosis and therapy of GISTs. PDGFRα-mutant GISTs are similar to KIT-mutant GISTs in several characteristics, such as mutations in homologous domains, activation of downstream signaling pathways, and cytogenetic aberrations that correlate with progression [11,12]. Clinically, more than 95% of PDGFRα-mutant GISTs arise in the stomach, mesentery or omentum [13,14], whereas GISTs harboring mutations in KIT exon 9 are almost exclusive to the small intestine [15,16]. The majority of PDGFRα-mutant GISTs have an epithelioid morphology, while spindle cells dominate most KIT-mutant tumors. PDGFRα mutations (exons 11 and 17) were found only in GISTs and not in other tumors [17].

Based on our study, any malignant mesenchymal mass located along or near the proximal gastrointestinal tract and found to be c-KIT negative should be stained also for PDGFRα in order to differentiate between GIST and other soft tissue sarcomas. On the other hand, any c-KIT-positive mesenchymal tumor does not necessarily require further staining for PDGFRα. It has been reported that more than one-third of GISTs with PDGFRα mutations may respond to imatinib and that mutation screening may be helpful in the management of these tumors [1,10].

In practical terms, it is suggested that formerly diagnosed abdominal or retroperitoneal soft tissue sarcomas be reviewed in order to identify patients with misdiagnosed GIST and thereby avoid future unnecessary and ineffective chemotherapy for this disease.

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