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Synchronous Presentation of GISTs and Other Primary Neoplasms: A Single Center Experience

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Abstract. *Background: Gastrointestinal stromal tumors (GISTs) are common mesenchymal neoplasms of the digestive tract and may occasionally arise within the abdomen without gastrointestinal tract connection. GISTs have recently attracted widespread interest because of the development of effective targeted molecular agents against it. While synchronous occurrence of a GIST with a tumor of different histogenesis was thought to be very rare, it is now apparent that they are more common than previously believed. Patients and Methods: We report our experience with GISTs and also six cases of GIST coexisting with other primary neoplasms. Using immunohistochemistry and mutational analysis, a possible correlation was investigated. A review of the literature was also conducted. Results: There were no significant differences in the immumohistochemical and molecular profile between single GISTs and GISTs coexisting with other tumors, nor was there any mutational correlation between GISTs and the coexistent tumors of different histogenesis regarding KIT and PDGFRA genes. Conclusion: Further molecular biology studies are required in order to investigate thoroughly the simultaneous development of tumors with different histotypes.*

Gastrointestinal stromal tumors (GISTs) comprise a recently defined entity of the most common mesenchymal tumors of the gastrointestinal (GI) tract. In the 1940s, Stout *et al*. first described stromal tumors arising from the smooth muscle of the GI tract regarding them as leiomyoma, leiomyosarcoma, leiomyoblastoma and bizarre leiomyoma (1). In the late 1960s, with the use of electron microscopy and in the early 1980s with the introduction of immunohistochemistry, the Schwannian differentiation was identified in some neoplasms of this kind (2). In 1983 this led Mazur and Clark to introduce the more generic term 'stromal tumor' (3).

It is believed that GISTs originate from the interstitial cells of Cajal (ICCs) or their precursors that regulate gut motility. This hypothesis is based on the observation that both GISTs and ICCs express the tyrosine kinase receptor KIT (4, 5).

In the era of targeted therapy GISTs are defined as KIT (CD117)-positive mesenchymal spindle, epithelioid or mixed-type cell neoplasms that may arise in the wall of all the portions of the GI tract from the esophagus to the anus and occasionally within the abdomen but without GI connection (6-8). GISTs strongly express (90-95%) the KIT (CD117) protein, a type III tyrosine kinase receptor encoded by c-KIT proto-oncogene. Approximately 70% of GISTs are positive for CD34, 30-40% are positive for smooth muscle actin (SMA), 10% for S-100 protein and <5% for desmin (2). As mesenchymal tumors, GISTs are typically strongly positive for vimentin, which is in accordance with their originating from the ICCs that present a KIT^+, $CD34^+$, Vim^+ immunophenotype (9, 10). They account for approximately 0.1%-3% of all primary GI neoplasms and for 5%-10% of all sarcomas (7, 11-13). GISTs typically occur in older individuals and the majority of them (60-70%) comprise primary neoplasms of the stomach, followed by small intestine (20-25%), colon and rectum (5%), and esophagus (<5%) (7-8, 11).

Benign tumors outnumber the malignant ones by far (7), however, at present every case of GIST is considered as potentially malignant (2, 14). High mitotic index and larger

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tumor size remain the most reliable predictors of increasing risk of malignancy (2). In population studies, the anatomic location did not have any prognostic value (15).

The coexistence of GISTs with other neoplasms of different histogenesis is a complex problem since the tumors can develop synchronously or asynchronously. Numerous cases of such coexistence have been reported in the literature (16-25). Most of these reports present only single cases. Of special interest are those cases in which one or more tumors were located within the same organ (16, 19-20).

The suggested and potentially curative treatment remains surgical with a wide local excision margin of the entire tumor. The patients' 5-year survival after surgical resection ranges from 48% to 80% (12). Metastatic or recurrent tumors are now treated with targeted therapy using imatinib molecule or sunitinib in imatinib resistant tumors (6, 18).

The aim of this study was: i) to present the clinico-pathological, immunohistochemical and mutational analysis of our cases of GIST, ii) to assess the prevalence of other primary malignancies in patients with a GIST and iii) to compare the basic clinical data, selected histopathological parameters and mutational findings in patients with a GIST and concomitant neoplasms with those in patients with a single GIST.

Patients and Methods

A retrospective analysis was conducted of medical and pathological records of twenty patients diagnosed at our department between 1999-2008 as having leiomyosarcoma, epithelioid leiomyosarcoma, leiomyoma and as GIST. Preoperative evaluation was performed with endoscopic procedures, computed tomography (CT) scan and ultrasonography. The patients' medical records were retrieved from the respective clinics' archives and carefully re-examined to identify other coexistent disorders.

The numbers of slides available per tumor ranged from 2 to 28 (median 14) and all of them were histologically re-examined and re-evaluated by immunohistochemistry. Diagnosis of GIST was applied in those cases in which mesenchymal tumors of the GI tract showed morphological features of spindle cells, epithelioid cells, or mixed type as defined by Fletcher *et al*. (2) and also immunostained by antibodies against KIT (CD117) and/or CD34 antigens (2, 8, 14, 19).

The risk of tumor recurrence was defined using the tumor size and the mitotic rate. The risk levels of the tumors were classified into: very low[size <2 cm, mitoses<5/50 high power fields (HPF)], low (size 2-5 cm, mitoses <5/50 HPF), intermediate (size<5 cm, mitoses 6-10/50 HPF or size 5-10 cm, mitoses<5/50 HPF) and high risk (size >5 cm, mitosis>5/50 HPF or size >10 cm with any mitotic rate, or any size with mitotic count >10/50 HPF) as proposed by Fletcher *et al*. (2). Nuclear atypia or pleomorphism, tumor cell necrosis, mucosal invasion or ulceration, invasion to the adjacent organs or metastases to other organs were also taken into consideration (11, 26-28).

In all cases, tissues had been fixed in 10% neutral-buffered formalin, embedded in paraffin and stained with hematoxylin and eosin. All available slides were examined and immunohistochemical analysis was performed on at least one representative tissue block for each case. The primary antibody sources and dilutions were the following:CD117 [Clone p145 (c-kit); pre-treated at pH 9. 0, diluted 1:800], CD34 (clone QB-End-10; pre-treated at pH 9. 0, diluted 1:100), S-100 (Rabbit polyclonal; diluted 1:600); SMA(Clone HHF35; diluted 1:300) all DAKO (Carpinteria, USA), Ki67 [Clone SP6; pre-treated at pH6. 0, diluted1:200, Lab-Vision (Fremont, USA)], Vimentin [CloneV-9; diluted1:200, Thermo-Shandon (Pittsburg, USA)], Desmin [Clone D9; diluted 1:100, Euro-diagnostica (Arnhem, Netherlands)], glial fibrillary acidic protein (GFAP) [Clone GFP/6F2, diluted 1:100, Novocastra (Newcastle, UK)].

Table I. *Immunological characteristics of GIST patients.*

Case no.	CD117	CD34	VIM	SMA	DESM	S-100	GFAP	Ki-67
1	+++	+	–	+	–	–	–	20%
2	+++	–	+	+	–	–	–	6.8%
3	+	–	+	–	–	–	–	22%
4	++	+	+	–	–	–	–	6.5%
5	+	+	–	+++	–	–	–	28%
6	++	+++	++	–	–	–	–	18%
7	++	++	+	–	–	–	–	1.5%
8	+++	+++	++	–	–	–	–	1.7%
9	+++	+++	–	+	–	–	–	25%
10	+++	+	+	–	–	–	–	2%
11	+++	+++	+	+	–	–	–	2.5%
12	+	–	+	–	–	–	–	0%
13	++	+	+	–	–	–	–	1.5%
14	++	++	–	+/–	+/–	–	–	0%
15	++	+++	–	+	–	–	–	0.1%
16	++	++	+	+	–	–	–	0.1%
17	++	++	+	+	–	–	–	3.5%
18	++	++	+	+	+/–	–	–	2.3%
19	++	++	+	+	–	–	–	29%

The staining reaction (membranous or cytoplasmic) was graded from 0-3 depending on the percentage of immunoreactive tumor cells: 0 for tumors with fewer than 10% of positive tumor cells, 1+ for tumors with 10% to 50% of positive tumor cells, 2+ for tumors with 50% to 75% of positive tumor cells and 3+ for tumors with more than 75% of positive tumor cells (11).

Mutational analysis of *KIT* and platelet-derived growth factor receptor alpha (*PDGFRA*) was performed in eighteen cases. DNA was extracted from formalin-fixed paraffin-embedded tumor samples (2-3 of 10 μm sections) using the Wizard Genomic DNA Purification kit (PROMEGA, Madison, USA) according to the manufacturer's instructions. Two μl of DNA underwent PCR amplification for *KIT* exons 9, 11, 13 and 17 and *PDGFRA* exons 12 and 18 using the previously described primers and PCR conditions (29). All PCR amplifications were performed in 50 μl reaction mixture, containing 10 mM Tris-HCl, 50 mM KCl, 1.25 mM $MgCl_2$, 0.2 mM of each dNTP, 2 units of Platinum Taq DNA polymerase (Invitrogen, Eugene, USA) and 0.5 μM of each primer. The amplification products were electrophoresed on 2% ethidium bromide gel to confirm the correct amplification. The PCR products were purified with NucleoSpin Extract II kit (Macherey-Nagel, Duren, Germany) and direct sequencing of the PCR products was performed using the same primers as for PCR amplification with the Big-Dye Terminator cycle sequencing kit on an ABI Prism 377 automated sequencer (Applied Biosystems, USA).

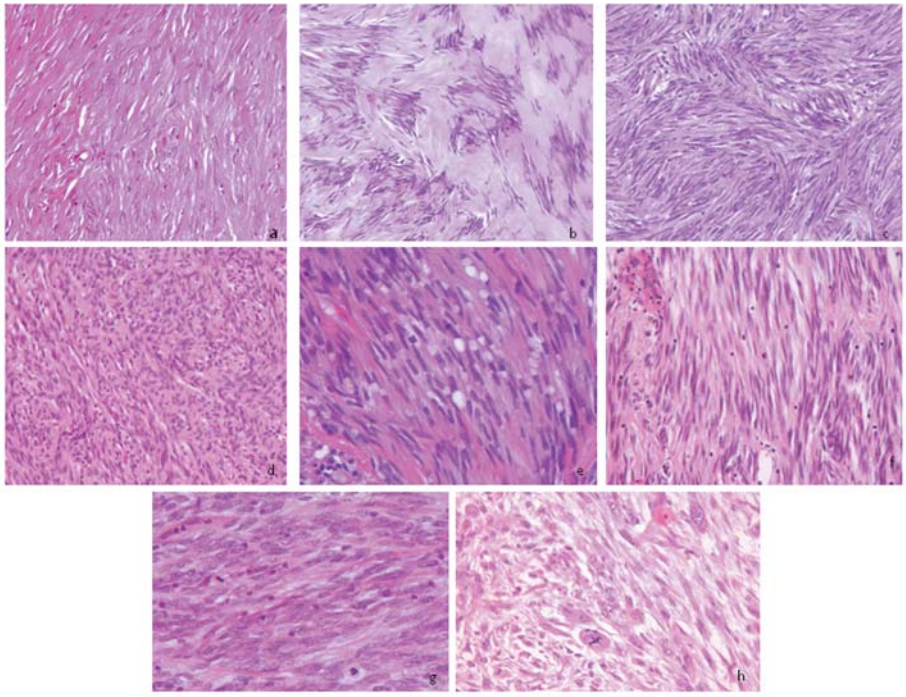

Figure 1. *Histological spectrum of spindle-cell GISTs (×100): a) Sclerosing subtype with extensive collagen deposition and relatively low cellularity. b) Spindle-cell subtype with skenoid bodies and no atypical cellular features. c, d) Hyper-cellular subtype with mild diffuse atypia. e) Spindle, palisading, vacuolated subtype with moderate cellularity and mild diffuse atypia. This subtype is virtually confined to gastric GISTs. f, g, h) Sarcomatoid GISTs, areas with mild, moderate and severe atypia.*

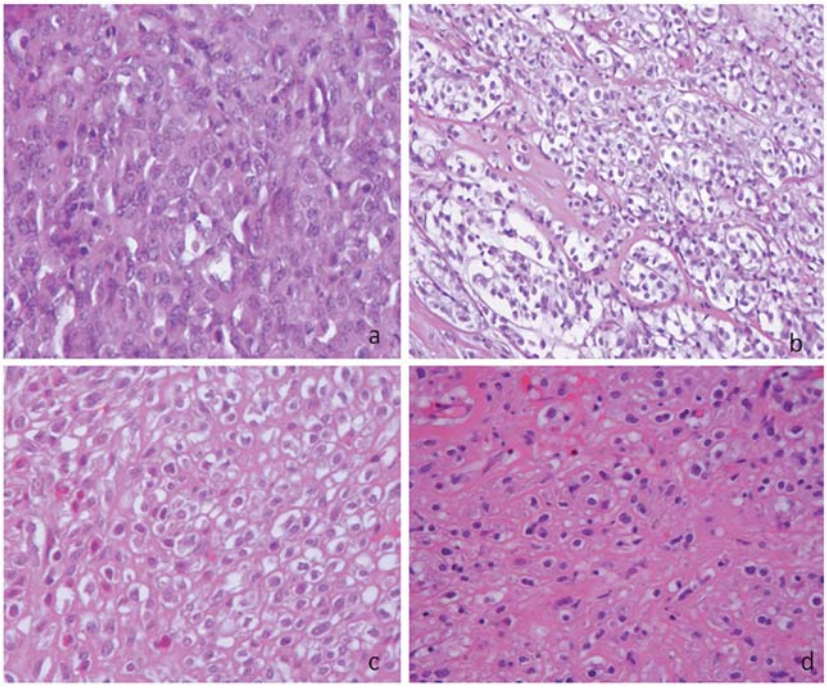

Figure 2. *Histologic spectrum of epithelioid GISTs (×200): a) Sarcomatous subtype. High cellularity with prominent atypia and mitotic figures. b) Discohesive subtype. Round cells with 'retracted' eosinophilic cytoplasm and nested architecture. c) Discohesive subtype with distinct cell membranes. d) Sclerotic subtype. Round cells in an eosinophilic intercellular matrix.*

Results

Among the 20 cases studied, four of the tumors with the previous diagnosis of leiomyosarcoma and epithelioid leiomyosarcoma were classified as GISTs using immunohistochemical staining for CD117, CD34 and vimentin, while the diagnosis of one case as leiomyoma did not change. Consequently, our study included 19 patients.

The male to female ratio was 8:11. The median patient age was 62.5 years (range 33-84 years). Twelve patients were older than 60 years, four patients were 40-60 years old and three patients were younger than 40 years. The median tumor size was 9 cm (range 1-20 cm). Three out of the 19 tumors were smaller than 2 cm, whereas six were 2-5 cm, five were greater than 5 cm and no larger than 10 cm, and five were greater than 10 cm.

GISTs involved the stomach in 10/19 of the cases, the small intestine in 7/19 (two were in the duodenum; and one of them in the ampulla of Vater) and the large intestine (sigmoid) in 1/19 of the cases. The omentum was the site of primary tumor in one case. Seven of the gastric GISTs were located in the corpus, two in the fundus and one in the antrum. It should be noted that one of these cases (case 5) occurred as a multifocal GIST, with a focus in the stomach (2 cm in diameter) and four foci in the jejunum (0.7-6.5 cm in diameter) at the same time.

Five cases of the tumors were transmural with a polypoid protrusion into the lumen and four of them exhibited mucosal ulceration. Eight cases were intramural, limited to the muscularis propria. One case was transmural with mucosal ulceration and with invasion of the mesentery and part of the wall of the large intestine. One case was transmural limited to the muscularis propria and invading the mesentery. One case appeared as a nodular subserosal small tumor and two other cases were limited to the submucosa.

The large tumors were irregular and lobulated with frequent hemorrhage, necrosis and cystic degeneration. Small tumors were usually well demarcated, nodular and predominantly solid with focal haemorrhage and variable cystic changes. The cut surface of the tumors varied from tan-pink to yellowish and grey-white often molted by hemorrhagic discoloration.

Histologically, fourteen tumors had a predominantly spindle-cell pattern of growth. Sclerosing areas with extracellular collagen and low cellularity, skenoid features, nuclear palisading, suggesting the presence of neurogenic tumors, hyper-cellular or vacuolated-cell areas and sarcomatous features, as defined by Miettinen *et al*. (26), were also observed (Figure 1). The epithelioid pattern was dominant in three cases. The epithelioid cells were round with eosinophilic or clear 'retracted-like' cytoplasm and distinct cell membranes and were disposed in sheets or in clusters. Sclerotic, sarcomatous and hyper-cellular patterns were also observed (Figure 2). A mixed, spindle and epithelioid pattern was seen in two cases. Atypia, multinucleation, coagulative and liquefactive necrosis, myxoid areas and telangiectatic vessels with fibrinoid change and calcifications were some of the histological features observed. The mitotic activity varied, ranging from less than 1 to 55 mitotic figures per 50 HPFs. Epithelioid or spindle-cell GISTs with diffuse atypia, or large GISTs usually had more than 10 mitoses per 50 HPFs.

CD117 positivity was documented in all spindle, epithelioid and mixed types of tumors (100%, 19/19 cases) with the following staining grades: 1+ (3 cases), 2+ (10 cases) and 3+ (6 cases). CD34 positivity was detected in sixteen out of the 19 cases (84.2%) with the following staining grades: 0 (3 cases), 1+ (5 cases), 2+ (6 cases), 3+ (5 cases). Both CD117 and CD34 were also positive in metastatic sites. All the immunohistochemistry results are summarized in Table I.

All mutations detected, whether involving base pair (bp) substitutions or deletions, preserved the open reading frame. Overall KIT exon 9, 11, 13 and 17 mutations were detected in 15 of the 18 GIST samples. Three patients had no detectable mutations with the methods used. Twelve patients had mutations within *KIT* exon 11. Two patients had mutations within *KIT* exon 9 and one patient had mutations within exon 13. No mutations were found in *KIT* exons 17 and *PDGFRA* exons 12 and 18. The detected mutations within *KIT* exon 11 were heterogeneous and consisted of 7 simple deletions and 2 point mutations and one insertion. No mutations were found in the concomitant tumors. Our results concerning the types and distribution of *KIT* and *PDGFRA* gene mutations among GISTs are summarized in (Table II).

Out of 19 patients suffering from GIST we found six cases with synchronous or metachronous occurrence of GIST and other malignancies (Table III).

Patients follow-up results by risk category for malignant behaviour of tumors and *KIT* and *PDGFRA* gene mutations among GISTs did not reveal any correlation with overall survival.

Discussion

The coexistence of GISTs with other neoplasms is rare but more common than was previously considered. Maiorana *et al*. (19) estimated that 11.5% of gastric GISTs occur synchronously with other gastric malignancies, while reports of two other series, studying the synchronous occurrence of GISTs with other neoplasms, give the respective percentage at 14%, 27% and 33.3% respectively (15, 21, 27). In our report, this percentage is 31.5%.

Despite the major advances in the recent years in understanding the molecular biology of GISTs, little is known so far about their rare synchronous occurrence with tumors of different histogenesis. The development of GISTs synchronously with other neoplasms may indicate at least one common factor which may be involved in the

Table II. *Types and distribution of KIT and PDGFRA gene mutations among GISTs.*

Case no.	Tumor site	*KIT*				*PDGFRA*	
		Exon 9	Exon 11	Exon 13	Exon 17	Exon 12	Exon 18
1	OM	Wt	PK558_V560/del6	Wt	Wt		
2	A: SI	Wt	PI563_P585/del6	Wt	Wt		
	B: Metastatic (M)	Wt	PI563-P585/del6	Wt	Wt		
3	SI	Wt	Wt	pN655K/T>C	Wt		
4	S	pF467_H485/del48	Wt	Wt	Wt		
5	A: Jejunum	Wt	Wt	Wt	Wt		
	B: Stomach	Wt	pW557R/T>A	Wt	Wt		
6	A: SI	Wt	Wt	Wt	Wt	Wt	Wt
	B: OM	Wt	Wt	Wt	Wt	Wt	Wt
7	A: GIST (S)	Wt	Wt	Wt	Wt	Wt	Wt
	B: Leiomyosarcoma	Wt	Wt	Wt	Wt	Wt	Wt
8	A: GIST (sigmoid)	Wt	pQ556_W557/del6	Wt	Wt		
	B: Caecal adenoCa	Wt	Wt	Wt	Wt		
9	S	Wt	pQ556_V560/del12	Wt	Wt		
10	AV	Wt	pQ549_E554/del15	Wt	Wt		
11	S	Wt	pW557R/T>C	Wt	Wt		
12	S	Not done					
13	A: GIST (S)	Wt	Wt	Wt	Wt	Wt	Wt
	B: Pancreatic adenoCa	Wt	Wt	Wt	Wt	Wt	Wt
14	A: GIST (S)	Wt	pL594P/T>C	Wt	Wt		
	B: Pancreatic adenoCa	Wt	Wt	Wt	Wt		
15	S	Wt	pV559_S590/del90	Wt	Wt		
16	A: GIST (rectum)	Wt	PQ556-W557/del6	Wt	Wt		
	B: Thyroid	Wt	Wt	Wt	Wt		
17	Duodenum	T500-S501/in6	Wt	Wt	Wt		
18	S		W557R/T>A				
19	SI		K558/ins3	Wt	Wt		

SI: Small intestine; S: stomach; OM: omentum; AV: ampulla of Vater; Wt: wild-type; adenoCa: adenocarcinoma.

Table III. *Pathologic features of the synchronous/metachronous GISTs and other primary gastrointestinal or non-gastrointestinal neoplasms.*

Case no.	*GIST*		Synchronous gastrointestinal malignancy		
	Location	Size (cm)	Type	Location	Size (cm)
8	Sigmoid	2.8	Adenocarcinoma (Dukes' stage B)	Caecum	5
12	Gastric wall (corpus)	1.5	Adenocarcinoma (Lauren diffuse type); Polymyalgia rheumatica	Anterior & posterior gastric wall	7
13	Greater curvature	3.2	Adenocarcinoma, well-differentiated	Head of the pancreas	8.5
14	Stomach (fundus)	1	Adenocarcinoma, moderately differentiated	Head of the pancreas	2.5
			Metachronous non-gastrointestinal malignancy		
7	Lesser curvature	2.5	Epithelioid leiomyosarcoma	Corpus of the uterus	22
16	Rectum	1.7	Papillary thyroid carcinoma, Hashimoto disease	Left lobule	1.9

pathogenesis of these neoplasms. Various hypotheses have been made; it has been suggested that gene mutations or a single carcinogenic agent might interact with adjacent tissues, inducing the development of tumors of different histotypes in the same organ while pure coincidence could not be excluded (19). The presence of a mutation or deregulated *KIT* expression is also observed in chronic myeloid leukaemia, germ cell tumors, small cell carcinoma of the lung, neuroblastoma, melanoma, ovarian, breast and colorectal carcinoma (15).

GISTs harbor mutations in the *KIT* proto-oncogene in 85% to 90% of tumors regardless of size. *KIT* contains a total of 21 exons. Exon 11 mutations are the most common involving approximately 60% to 70% of GISTs. Exon 9 mutations are found in at least 10% of cases and are more common in small intestinal GISTs. Exon 13 and 17 mutations are rare, accounts for approximately 1% or less than 1% of all GISTs (5, 6, 28). Approximately 5% to 10% of GISTs have mutations within *PDGFRA*, which is a member of the same family of receptor tyrosine kinases as *KIT*. The mutations that are found within *PDGFRA* involve exons 12, 14 and 18 which are homologous to *KIT* exons 11, 13 and 17 (6, 30). A subset of approximately 5-10% of GISTs are wild-type and negative for both *KIT* and *PDGFRA* mutations (6, 28, 29).

Our findings regarding age, sex, size, location, clinical presentation, histological and immunohistochemical features in terms of GIST presentation are consistent with the literature (2, 8, 9, 11, 14, 19, 26). In addition, our results concerning the types and distribution of *KIT* and *PDGFRA* gene mutations among GISTs are indicated in Table II. Five GISTs cases studied, despite the presence or not of mutations in the *KIT* or *PDGFRA* gene, coexisted with other primary tumors (totally six GIST cases coexisted with other primary malignant neoplasms) (Table III). Three of the five GISTs studied presented KIT mutations (exon 11) while in neither of these three cases mutations were detected in the concomitant tumor.

GISTs that occur simultaneously with other neoplasms in our study (Table III) were usually smaller and of low or very low risk of malignancy compared to a single GIST and this finding is in accordance with the literature (15). This probably reflects the fact that in the first group GISTs are discovered at a very early stage, before becoming symptomatic and during the preoperative evaluation for a different malignancy.

To date, few cases of GISTs and pancreatic adenocarcinoma have been reported (15, 25). We add to the literature another two cases of this type of concurrence. There is only one report of a coexistence of GIST and thyroid carcinoma and one with uterine sarcoma (15). We add our one case respectively. To our knowledge there is no other report of synchronous gastric GIST and gastric adenocarcinoma in patients with polymyalgia rheumatica. In addition, this is the first report of coexistence between a sigmoid GIST and a caecal adenocarcinoma.

The problem of the coexistence of GISTs with other neoplasms is important from an oncological, surgical and histopathological point of view. As many GISTs are clinically silent and detected incidentally during surgery for a different reason, it is essential that a thorough surgical intra-abdominal examination be performed. Another problem arising from the incidental discovery of GISTs is that they can be mistaken for a metastasis of the coexistent primary tumor, thus precluding its staging (15). A peculiar situation could arise in the liver where a focal lesion could be a GIST metastasis or a concurrent primary tumor (22).

In conclusion, we found six cases of GISTs coexisting with other neoplasms: a) one gastric GIST and gastric adenocarcinoma in a patient with a background of polymyalgia rheumatica, b) two cases of gastric GISTs concurring with pancreatic adenocarcinomas c) one gastric GIST concurring with a uterine sarcoma, d) one sigmoid GIST with a caecal adenocarcinoma, probably the first case of such a concurrence in the literature and e) one rectal GIST with a thyroid papillary adenocarcinoma arising in background of a Hashimoto disease. GISTs with concomitant tumors were of low or very low malignant behaviour and such tumors are more often incidentally discovered in comparison with single GISTs. We did not observe any significant differences in the immumohistochemical and molecular profile between single GISTs and GISTs coexisting with other tumors. The rate of association of GISTs with other tumors was consistent with that reported in the literature (29).

In our restricted material, there was no mutational correlation between the GISTs and the coexistent tumors of different histogenesis regarding the *KIT* and *PDGFRA* genes, however, further molecular biology studies are required in order to investigate the simultaneous development of tumors with different histotypes thoroughly.

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