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ORIGINAL PAPERS

Gastrointestinal stromal tumors (GISTs): role of CD 117 and PDGFRA Golgi-like staining pattern in the recognition of mutational status

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ABSTRACT

Aims: to determine whether potential correlations between CD117 and PDGFRA might serve as an indication for targeted therapies.

Material and methods: immunohistochemical expression of CD117 and PDGFRA was evaluated in 99 paraffin-embedded GISTs in conjunction with *KIT* and *PDGFRA* mutational status.

Results: CD117-positive staining was noted in 93 out of 99 cases. The predominant staining pattern was cytoplasmic, either with or without membrane accentuation; in 44.5% of cases, a clear Golgi-like pattern was evident. Correlations were found between *KIT* mutation and both CD117 expression (p = 0.006) and Golgi-like pattern (p = 0.026). Cytoplasmic PDGFRA-positive staining was detected in 87% of cases, both with and without membrane accentuation; in 8% cases an evident Golgi-like staining pattern was observed. A significant correlation was noted between *PDGFRA* mutations and Golgi-like staining pattern (p = 0.001). Moreover, 95% of PDGFRA-positive GISTs were also CD117-positive, suggesting that expression of the two markers is not mutually exclusive; most of these had mutations in *KIT* exon 11. *PDGFRA*-positive/CD117-negative tumors had mutations in *PDGFRA,* mainly in exon 18. PDGFRA-negative/CD117-negative staining was observed in 15% of cases, all of which displayed mutations in *KIT* exon 11. CD117-positive/PDGFRA-negative cases were characterized by mutations in *KIT,* mainly in exon 11.

Conclusions: CD117 and PDGFRA staining are not exclusive, and the presence of a Golgi-like staining pattern for either, whilst not pathognomonic, is highly suggestive of *KIT* and *PDGFRA* mutated GISTs, respectively, and may be used with some reservations as an alternative indication for prescribing targeted therapies.

Key words: Gastrointestinal stromal tumors. GISTs, CD117. PDGFRA. Mutational status. Golgi-like staining pattern.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors of the gastrointestinal tract that differentiate towards interstitial cells of Cajal or their precursors; they are generally KIT (CD117)-positive, and display *KIT* or *PDGFRA* gene mutations (1,2). More occasionally they may display mutations in others genes, including *BRAF* (3) and *SDHB* (4). These tumors have recently aroused particular interest due to their good response to new targeted therapies (5,6).

Immunohistochemical expression of CD117 has been considered one of the most sensitive markers for diagnosing both mutant and wild-type GISTs (2,7), but little is known regarding its role in predicting mutational status (8-10). PDGFRA staining, by contrast, is often held to be non-specific, ubiquitous and technically deficient, with no role in the diagnosis of GIST (7,9,11,12). However, recent studies have shown that a Golgi-like staining pattern for either CD117 or PDGFRA may be predictive of mutational status (7-9,11,12).

In this study, immunohistochemical expression of CD117 and PDGFRA was evaluated in 99 paraffin-embedded GISTs in conjunction with *KIT* and *PDGFRA* mutational status, in order to determine whether potential correlations between the two might serve as an indication for targeted therapies.

MATERIAL AND METHODS

Patient selection and clinical features

Representative samples were selected from a set of formalin-fixed, paraffin-embedded surgical specimens obtained

from 99 GISTs. Samples were from patients undergoing surgery at the Hospital Universitario Virgen Macarena (Seville) and Hospital Torrecárdenas (Almería) over a 20-year period (1989-2009). Tumor sample collection was approved by the Hospital Ethical Committees. Hematoxylin-eosin-stained slides were reviewed and the pathological diagnosis was confirmed by tumor location, morphology, immunostaining for CD117 and molecular analysis of *KIT/PDGFRA* status. Tissue microarrays (TMAs) were constructed using a TMADesigner® version 1.1 manual tissue arrayer (Alphelys, Plaisir, France); five 0.6 mm cores were taken from each paraffin-embedded sample.

The following clinical and pathological data were accessed: patient age and gender, tumor location (gastric, small and large bowel, extragastrointestinal), tumor size, histological type (spindle, epithelioid, mixed), and mitotic index in 50HPF.

Immunohistochemical analysis

For immunohistochemical analysis, 5 µm serial sections were stained with a panel of antibodies: CD117 (Diagnostic Biosystem, CA; prediluited), PDGFRA (Santa Cruz Biotechnology, USA; dilution 1:100) using the streptavidin-biotin-peroxidase complex technique. Negative (primary antibody replaced by normal horse serum) and positive controls (sections of a human breast cancer) were included in each slide run. All controls yielded satisfactory results. Specimens with diffuse or focal immunostaining were considered positive. Tumors with ≤ 5% of positive cells were considered negative. Staining for individual antibodies was classed as either positive or negative.

DNA isolation and molecular analysis

One selected paraffin block was chosen for molecular analysis; DNA was isolated using a QIAmp DNA FFPE Tissue kit according to manufacturer's instructions (Quiagen, Hilden, Germany). *KIT* exons 9, 11, 13 and 17 and *PDGFRA* exons 12 and 18 were amplified by polymerase chain reaction (PCR). The PCR reaction was carried out using a Taq PCR Master Mix (Quiagen, Hilden, Germany) including 0.1-1 µg of extracted DNA and 0.2 µM forward and reverse primers to a total volume of 30 µL. Primers and experimental conditions are shown in table I. PCR products were examined using a QuiAXcel DNA High Resolution kit (Quiagen, Hilden, Germany) and sequencing was carried out with an automated analyzer (ABI PRISM 3130xl Genetic Analyzer, Applied Biosystem, USA). *KIT* and *PDGFRA* sequencing results were compared with gene sequences in the NCBI genebank.

Statistical analysis

Clinical and immunohistochemical data were analyzed using the SPSS for Windows, version 17.0 software package (SPSS Inc., Chicago, IL, USA). Chi-square tests were used to analyze associations between variables. A p-value of less than 0.05 was considered statistically significant.

Table I. Primers are presented in 5′ to 3′ orientation with the coding strand labeled (+) and the noncoding strand labeled (-). Tm and cycle number correspond to the linear part of the amplification

	Primers	*Strand*	*Condition (Tm; cycle nº)*
KIT exon 9	TCCTAGAGTAGTAAGCCAGGGCTT TGGTAGACAGAGCCTAAACATCC	+ -	56 ºC, x40
KIT exon 11	CCAGAGTGCTCTATAGACTG AGCCCCTGTTTCATACTGAC	+ -	56 ºC, x40
KIT exon 13	GACATCAGTTTGTCAGTTG GCAAGAGAGAACAACAG	+ -	56 ºC, x40
KIT exon 17	GTGAACATCATTCAAGGCG TTACATTATGAAAGTCACAGG	+ -	56 ºC, x40
PDGFRA exon 12	TCCAGTCACTGTCCTGCTTC GCAAGGGAAAAGGGAGTCTT	+ -	56 ºC, x40
PDGFR exon 18	ACCATGGATCAGCCAGTCTT TGAAGGAGGATGAGCCTGACC	+ -	56 ºC, x40

RESULTS

Clinical features and mutational status

All tumors displayed clinical/pathological features consistent with GIST, and expressed CD117 and/or harbored *KIT/PDGFRA* mutations. The median age was 64 years (range: 13-87), and samples were from 51 (51.5%) males and 48 (48.5%) females. Forty-eight (48.5%) tumors originated in the stomach, 36 (36.1%) in the small bowel, 7 (7.2%) in the large bowel and 8 (8.2%) in extragastrointestinal locations in the mesentery and omentum. Mean tumor diameter was 7.65 cm (range 1.0-25 cm). Tumor diameter was less than 2 cm in 60 (60. 6%) cases, between 2 and 5 cm in 31 cases (30. 9%) (31. 3%), between 5 and 10 cm in 6 cases (6.1%) and over 10 cm in 2 cases (2.1%). Histologically, 78 (79.2%) neoplasms were of spindle type, 15 (15.1%) of epithelioid type and 5 (5.1%) showed mixed cytomorphology. Mitotic counts ranged from 1 to 60 in 50 high power fields (50HPF): 54 samples (55%) displayed < 2 mitotic counts; 17 (17%) between 2 and 5; and 28 (28%) > 5.

Molecular analysis revealed *KIT* mutation in 68/99 (69%) cases, *PDGFRA* mutation in 11/99 (11%) and wild

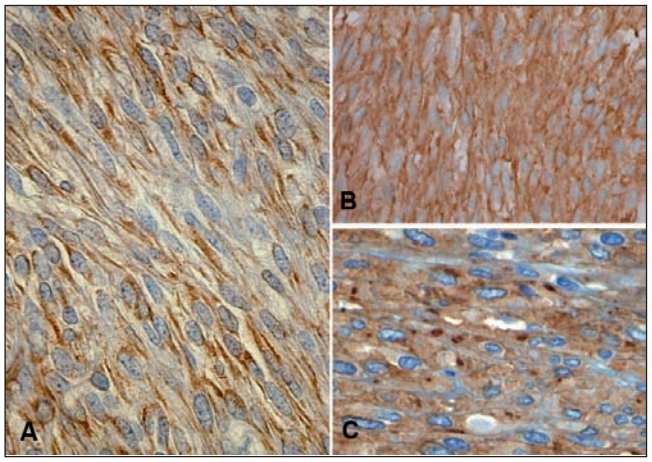

Fig. 1. GIST. CD117 staining pattern. A. Cytoplasmic staining. B. Cytoplasmic with membrane accentuation. C. Cytoplasmic and paranuclear Golgi-like staining.

type (wt) *KIT/PDGFRA* in 20/99 (20%). Among cases with *KIT* mutation, 64/68 (94%) had exon 11 mutations and 4/68 (6%) exon 9 mutations. There were no cases of exon 13 or exon 17 mutation. Among cases with *PDGFRA* mutation, 9/11 (82%) had mutations of exon 18 and 2/11 (18%) of exon 12. All CD117-negative cases had *KIT* (3, exon 11) or *PDGFRA* (2, exon 18; 1, exon 12) mutations.

Immunohistochemical analysis of CD117 and PDGFRA

A total of 93 of the 99 cases studied (94%) stained positive for CD117. Distribution was as follows: stomach, 43/48 (89.6%), small bowel, 35/36 (97.2%), large bowel 7/7 (100%), extragastrointestinal 8/8 (100%). Staining was mostly diffuse, but occasional cases displayed focal staining. The staining pattern was predominantly cytoplasmic, either with or without membrane accentuation; in 49/99 (49.5%) cases, a remarkable cytoplasmic dot-like or Golgi-like pattern was evident (Fig. 1). CD117-staining patterns as a function of mutational status are shown in table II. A clear correlation was noted between *KIT* mutation and both CD117 expression ($p = 0.006$) and Golgi-like pattern ($p = 0.026$) (Table II; Fig. 2A). Although most tumors with a Golgi-like pattern had mutations in exon 11, three cases had mutations in exon 9 (Table II). Of the six cases staining negative for CD117 (Fig. 2), 3 had mutations in *KIT* and the other 3 in *PDGFRA* (Table II).

Eighty-six of 99 cases (87%) stained positive for PDGFRA, with the following distribution: stomach 42/48 (87.5%), small bowel 30/36 (83%), large bowel 7/7 (100%) and extragastrointestinal 7/8 (87.5%). Staining was mostly diffuse and cytoplasmic, either with or without membrane accentuation; in 7/86 (8%) cases a notable Golgi-like staining pattern was observed (Fig. 3). Although no significant correlation was found between diffuse cytoplasmic staining and mutational status, there was a significant correlation between *PDGFRA* mutations and the Golgi-like staining pattern ($p = 0.001$) (Table III). No PDGFRA-negative cases had *PDGFRA* mutations.

Interestingly, 95% of PDGFRA-positive GISTs were also CD117-positive (82/86), indicating that expression of the two markers is not mutually exclusive (Table IV). Most CD117-positive/PDGFRA-positive cases had mutations in *KIT* exon 11 (54/82, 66%), although the correlation was not statistically significant. Half of the PDGFRA-positive/CD117-negative tumors (4/86) had mutations in *PDGFRA,* mainly in exon 18 (2/4). All PDGFRA-negative/CD117-negative (2/2) tumors had *KIT* exon 11 mutations. Finally, CD117-positive/PDGFRA-negative had *KIT* mutations (8/11), mainly involving exon 11 (64%) (Table IV).

Table II. Mutational status and CD117 expression patterns

CD117	*KIT*	*PDGFRA*	*WT KIT/PDGFRA*
Cytoplasmic/Membrane	29/68 (43%)	5/11 (45%)	10/20 (50%)
Golgi pattern	36/68 (53%)	3/11 (27.5%)	10/20 (50%)
Negative	3/68 (4%)	3/11 (27.5%)	0/20 (0%)

CD117	*KIT Exon 11*	*KIT Exon 9*	*PDGFRA Exon 18*	*PDGFRA Exon 12*
Cytoplasmic/ Membrane	28/64 (43.7%)	1/4 (25%)	4/9 (44.5%)	1/2 (50%)
Golgi pattern	33/64 (51.6%)	3/4 (75%)	3/9 (33.3%)	0/2 (0%)
Negative	3/64 (4.7%)	0/4 (0%)	2/9 (22.2%)	1/2 (50%)

DISCUSSION

The term "stromal tumors" was coined by Clark and Mazur in 1983 (13), to designate a subgroup of gastric mesenchymal tumors that lacked both smooth muscle and Schwannian differentiation; the term was subsequently extended to include other, similar, digestive-tract tumors, and the acronym GIST started to become widely used (14). Current interest in these tumors largely reflects their good response to kinase-inhibitor therapy (15). Although the clinical response to imatinib is known to depend on mutational status (6,16-19), GISTs are routinely diagnosed by conventional histology in conjunction with immunohistochemical demonstration of KIT receptor (CD117) expression (2), since other unrelated neoplasms have similar phenotypes or genotypes (20,21). In normal gastrointestinal-tract wall, positive staining for CD117 is only observed in the interstitial cells of Cajal or, more occasionally, in mast cells scattered throughout the thickness of the wall (2). In GISTs, positive staining may be diffuse, patchy or focal, and CD117-negative staining rates range between 2.2 and 8% depending on the characteristics of the tumors stud-

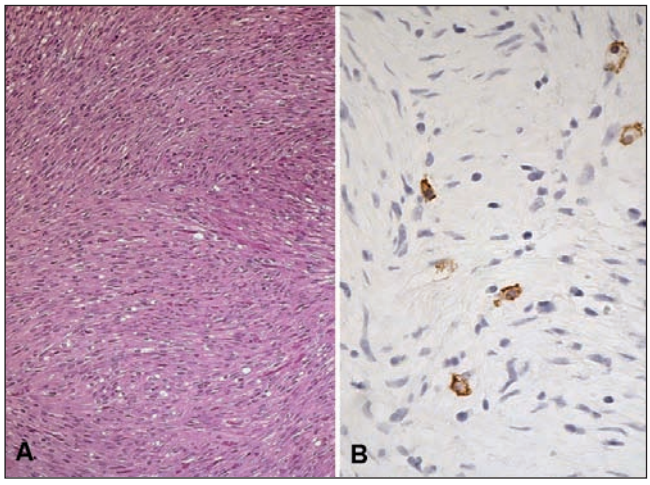

Fig. 2. GIST. CD117-negative. A. Spindle cell neoplasm. B. Negative staining in tumor cell with internal positive control in mast cells.

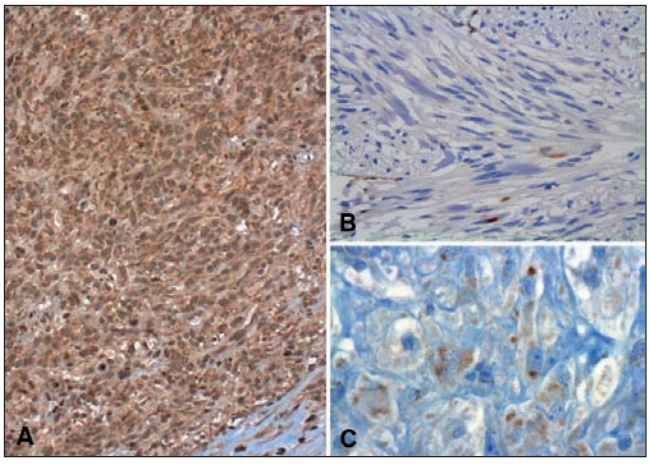

Fig. 3. GIST. PDGFRA staining pattern. A. Cytoplasmic and membrane staining in tumor with epithelioid phenotype. B and C. Cytoplasmic and paranuclear Golgi-like staining in an epithelioid tumor.

ied (11,12,22-24). Staining for CD117 is generally easy to evaluate. Positivity typically appears as diffuse cytoplasmic staining, sometimes with a varying degree of membrane accentuation; in some cases, however, focal Golgi-like staining may be observed (20). This Golgi-like staining pattern has aroused interest over recent years, because it has been linked to mutated KIT molecules accumulation (11,25); for that reason, it has been proposed as a possible marker for *KIT* mutations, and therefore as an indicator for imatinib therapy (9-11). Here, 94% of tumors (93/99) were CD117-positive, and a Golgi-like staining pattern was observed in 49.5% (49/99). Although most of these tumors (73%) had *KIT* mutations (36/49), the Golgi-like pattern was also observed in wt *KIT/PDGFRA* tumors (10/49) and in *PDGFRA*-mutated tumors (3/49), indicating that expression of the markers is not mutually exclusive, as asserted by Miselli et al. (9). Emile et al. (8) reported a significant association of this pattern with exon 11 mutations and with homozygosis status, but these findings have not been confirmed (8,9). In the present series, a statistically-significant association was observed between the Golgi-like pattern and *KIT* mutations, affecting not only exon 11 but also –in three cases– *KIT* exon 9.

The existence of tumors with morphological and clinical features similar to those of GISTs but staining negative for CD117 highlights the limitations of this antibody as a universal marker for GISTs. Although negative staining may be attributable to focal expression (e.g. in small biopsies) or to technical constraints (deficient fixation, prolonged storage, technical error), molecular biology techniques have shown that staining may be negative even in tumors with KIT or PDGFRA either *ab initio* or in the course of tumor progression (26). Moreover, congenital GISTs, which are morphologically indistinguishable from adult GISTs, are typically CD117-negative (27,28); this

Table III. Mutational status and PDGFRA expression pattern

PDGFRA	*KIT*	*PDGFRA*	*wt KIT/PDGFRA*
Cytoplasmic/Membrane	57/68 (84%)	7/11 (64%)	15/20 (75%)
Golgi pattern	1/68 (1.5%)	4/11 (36%)	2/20 (10%)
Negative	10/68 (15.5%)	0/11 (0%)	3/20 (15%)

PDGFRA	*KIT Exon 11*	*KIT Exon 9*	*PDGFRA Exon 18*	*PDGFRA Exon 12*
Cytoplasmic/ Membrane	54/64 (84%)	3/4 (75%)	6/9 (67%)	1/2 (50%)
Golgi pattern	1/64 (2%)	0/4 (0%)	3/9 (33%)	1/2 (50%)
Negative	9/64 (14%)	1/4 (25%)	0/9 (0%)	0/2 (0%)

Table IV. Mutational status and CD117/PDGFRA expression

	Exon 11 KIT	*Exon 9 KIT*	*Exon 18 PDGFRA*	*Exon 12 PDGFRA*	*wt KIT/ PDGFRA*	*Total*
CD117/ PDGFRA	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*	
+/+	54/82 (66%)	3/82 (4%)	7/82 (8.5%)	1/82 (1%)	17/82 (20.5%)	82/86 (96%)
+/-	7/11 (63%)	1/11 (10%)	0/11 (0%)	0/11 (0%)	3/11 (27%)	11/13 (80%)
-/+	1/4 (25%)	0/4 (0%)	2/4 (50%)	1/4 (25%)	0/4 (0%)	4/86 (5%)
-/-	2/2 (100%)	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/2 (0%)	2/13 (15%)

contrasts with findings reported for pediatric GISTs, which are mostly CD117-positive (3). Molecular analysis of apparently CD117-negative GISTs is therefore recommended. An early study of CD117-negative GISTs (29) found that most originated in the stomach, mesentery or epiploon, had epithelioid cell morphology and displayed the following molecular profile: 72% had *PDGFRA* mutations, 16% had *KIT* mutations and 8% were wt *KIT/PDGFRA*. Later reports from less-selective studies note a significant increase in the number of CD117-negative tumors harboring *KIT* mutations (17,30). In the present study, 50% of CD117-negative tumors had *KIT* mutations, and the other 50% *PDGFRA* mutations; almost all of them (5/6) originated in the stomach.

In the normal gastrointestinal tract, PDGFRA staining is found in colocalization with S100 in ganglion bodies, nerve fibers and Schwann cells (11). In GISTs, the PDGFRA staining pattern is variable; it may be either cytoplasmic, with or without membrane accentuation, or paranuclear (Golgi-like pattern), or a combination of the two. However, results reported in the literature indicate some disagreement: Rossi et al. (12) found that PDGFRA and KIT expression were mutually exclusive, and were indicative of mutations in these genes, whilst Pauls et al. (11), Peterson et al. (31) and Miselli et al. (9) reported that PDGFRA was ubiquitously expressed, though with certain variations. According to Pauls et al. (11), the Golgi-like staining pattern is found both in mutant (*KIT* or *PDGFRA*) and wild-type GISTs, but is more common in *PDGFRA*-mutated tumors, whilst the cytoplasmic/membrane staining pattern is ubiquitous, irrespective of mutational status. Misselli et al. (9), however, report that the Golgi-like pattern is found only in tumors with *PDGFRA* mutations, whereas only the cytoplasmic/membrane pattern is observed in *KIT*-mutated and wild-type tumors; they also note that PDGFRA staining is less intense in *KIT*-mutated than in *PDGFRA*-mutated tumors (21 *vs*. 92%), whilst CD117 positivity is more intense in *KIT*-mutated GISTs (78 *vs*. 12%); however, the tendency to express both markers is more marked in the latter. In the present series, both markers tended to be expressed in *KIT*-mutated tumors. The Golgi-like staining pattern was not exclusive to *PDGFRA*-mutated tumors, as suggested by Miselli et al. (9), although a statistically-significant association with them was observed; the results obtained here thus lend support to the findings reported by Pauls et al. (11).

In conclusion, expression of CD177 and PDGFRA is not mutually exclusive, while the presence of a Golgi-like staining pattern either for CD117 or for PDGFRA , though not exclusive, is significantly associated with mutations in the respective genes, and may therefore be considered highly suggestive of mutational changes. Caution must be exercised when using these findings as an indicator for therapy, since it is now known that certain *KIT* and *PDGFRA* mutations do not respond to imatinib therapy (*PDGFRA* Exon 18, Asp846Val; *KIT* exon 17, Asn822Lys) or do so only at higher doses (*KIT,* exon 9) (19).

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