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EXPRESSION OF THE RECEPTOR FOR TYPE I INSULIN-LIKE GROWTH FACTOR (IGF1R) IN GASTROINTESTINAL STROMAL TUMORS. AN IMMUNOHISTOCHEMICAL STUDY OF 1078 CASES WITH DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS

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Abstract

A majority of gastrointestinal stromal tumors (GISTs) carry gain-of-function KIT or PDGFRA mutations. However, no mutational activation of KIT or PDGFRA has been identified in pediatric gastric GISTs, neurofibromatosis-1 associated GISTs, and a small subset of sporadic GISTs in adults (so-called wild-type [WT] GISTs). Recently, pediatric gastric GISTs and some adult WT gastric GISTs have been found to have losses in the succinate dehydrogenase complex, a Krebs cycle/electron transport chain interface protein, as defined by immunohistochemical loss of SDHB expression. Also recently, expression of the receptor for type I insulin-like growth factor (IGF1R) has been detected in pediatric and WT GISTs, although only a small number of cases have been analyzed. In this study, IGF1R expression was examined immunohistochemically in 1078 well-characterized GISTs representing different clinico-genetic categories, and 103 non-GIST gastrointestinal tumors. IGF1R expression was detected in 71/80 of SDH-deficient GISTs (SDHB-negative GISTs), but only in 9/625 (1%) of the SDHB-positive gastric GISTs. The latter often carried KIT or PDGFRA mutations and generally occurred in older patients. None of the 373 intestinal GISTs were IGF1R-positive, while many primary intestinal sarcomas, including clear cell sarcomas, leiomyosarcomas, and undifferentiated sarcomas, were IGF1R-positive. The consistent lack of IGF1R expression in intestinal GISTs should be considered an additional immunohistochemical marker in the differential diagnosis between GISTs and non-GIST sarcomas. Because inhibition of IGF1R signaling might become a therapeutic target in GISTs, screening for IGF1R expression may become important in the near future.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the digestive tract. A great majority of these tumors is driven by KIT or platelet-derived growth factor receptor α (PDGFRA) gain-of-function mutations. However, some tumors show no evidence of such mutations and are often referred to as KIT/PDGFRA wild-type (WT) GISTs. [1–4]

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The best understood subset of KIT/PDGFRA wild-type GISTs are succinate dehydrogenase (SDH) deficient tumors marked by a loss of expression of succinate dehydrogenase subunit B (SDHB), a Krebs cycle and electron transport chain interface protein, whose loss leads to inactivation of the SDH-complex. [5–8] These GISTs occur exclusively in the stomach, and have predilection to children and young adults. Clinicopathologically they are characterized by a tendency to lymphovascular invasion, occurrence of lymph node metastases, and unpredictable behavior sometimes with a long latent periods between primary tumor and recurrence or metastases. [8] Carney-Stratakis syndrome is a rare disorder characterized by germline loss-of-function mutations in SDH genes and occurrence of paragangliomas, in addition to gastric GISTs. [9,10] Carney Triad is a sporadic syndrome defined by pulmonary chondromas and paragangliomas, in addition to gastric GISTs. [11,12] Neurofibromatosis 1-associated GISTs are also KIT/PDGFRA wild-type GISTs, and these occur predominantly in the small intestine. [13]

The receptor for type I insulin-like growth factor (IGF1R) is a transmembrane receptor tyrosine kinase, a member of insulin-like growth factor (IGF) signaling system. The IGF system consists of several circulating ligands, transmembrane receptor tyrosine kinases, circulating hormones and ligand-binding proteins. This system has been shown to play an important role in normal growth and development, and its pathological activation has been implicated in carcinogenesis related to both carcinomas and sarcomas. Inhibition of the IGF signaling system including IGF1R is considered a new targeted therapy approach in cancer treatment [14–18]

Recent studies, mostly based on small numbers of tumors have identified IGF1R expression in some GISTs. [19–24] However, the results have been variable. While some investigators reported IGF1R expression in pediatric GISTs and in a subset of WT GISTs [19,21,22,24], others found immunoreactivity with IGF1R antibodies also in GISTs carrying KIT and PDGFRA mutations. [20,23] In one study, IGF1R expression was detected in all 97 analyzed GISTs. [20]

This study systematically examined immunohistochemically expression of IGF1R in a large number of well-characterized GISTs, including different clinico-genetic categories, such as SDHB-positive and SDH-deficient GISTs.

MATERIAL AND METHODS

Study material

This study was based on 1078 GISTs. Different clinicopathologic subgroups, such as pediatric GISTs, SDH-deficient GISTs, and NF1- associated GISTs were included. 1037 GISTs from stomach (n=664), small intestine (n=337) and colon or rectum (n=36) were previously characterized. [4] In addition, 41 SDH-deficient KIT/PDGFRA wild-type GIST from National Cancer Institute GIST Clinic were evaluated. Also,103 gastrointestinal non-GIST mesenchymal neoplasms were studied for IGF1R expression.

Immunohistochemistry

The rabbit monoclonal antibody G11 recognizing the IGF1R beta subunit (Ventana Medical Systems, Tucson, AZ), was chosen to detect IGF1R for this study after evaluation of 3 commercially available IGF1R antibodies. The other two IGF1R antibodies were rabbit polyclonal antibodies, C-20 from Santa Cruz Biotechnology (Santa Cruz, CA) and antibody No. 3027 from Cell Signaling Technologies (Beverly, MA). Among these three antibodies G11 showed the best signal and specificity. Also, G11 antibody was recommended for IGF1R immunohistochemical studies by a recent investigation on lung cancer. That study

reported an excellent correlation between quantitative IGF1R mRNA expression and intensity of G11 immunoreactivity.[25]

Immunohistochemistry was performed on a Leica Bond-Max™ automated immunostainer (Leica Microsystem Inc., Bannockburn, IL). Heat-induced epitope retrieval and a high-pH buffer (Leica) were applied for 25 minutes prior to the primary antibody. G11 antibody was diluted in 1:100 and incubated for 15 min, followed by Leica polymer (15 min.). Diaminobenzidine was used as the chromogen with subsequent light hematoxylin counterstain. An IGF1R positive breast carcinoma was used as the positive control.

RESULTS

Eighty GISTs showed IGF1R expression. At least focal intense membrane and cytoplasmic immunoreactivity was seen in all cases considered positive (Fig. 1).

IGF1R in SDH-deficient GISTs

Great majority of IGF1R-positive cases were SDH-deficient gastric GISTs (71/80 [89%]) (Table 1). Also, 71/80 (89%) of all SDH-deficient gastric GISTs were IGF1R-positive. Most cases showed strong membrane positivity, and only 8 contained <50% of positive cells. The patient age range was 8–83 years (median, 30 years). Primary tumor size varied 1.8 – 15 cm (median, 5.8 cm). Mitotic rate was 0-52/50 HPFs (median, 5/50 HPFs). No KIT or PDGFRA mutations were found in the 53 analyzed tumors.

Only 9/80 SDH-deficient gastric GISTs were IGF1R-negative. Clinicopathologic features of these GISTs are summarized in Table 2. The patient age range was 15–61 years (median, 31 years). Primary tumor size varied 2.9–5 cm (median, 3.5 cm) and mitotic rate was 1–15/50 HPFs (median, 4/50 HPFs). None of the 6 analyzed tumors contained KIT or PDGFRA mutations.

IGF1R in SDHB-positive GISTs

Also, IGF1R was detected in a 9/625 gastric GISTs (1%) that retained SDHB expression. These GISTs occurred predominantly in older adults and 5/8 tumors examined had either a KIT or PDGFRA mutation. The IGF1R/SDHB- positive GISTs are further characterized in Table 3. None of the small intestinal sporadic or NF1-associated GISTs, or colorectal sporadic GISTs, showed immunohistochemically detectable IGF1R expression.

IGF1R in non-GISTs

IGF1R-positivity was commonly seen among various non-GIST malignant tumors (Table 4). Approximately half of leiomyosarcomas, undifferentiated sarcomas, and sarcomatoid carcinomas were positive. Both gastrointestinal clear cell sarcomas tested were also positive. The positivity typically appeared as moderate to strong cytoplasmic and variable membrane labeling (Fig. 2). None of the benign mesenchymal tumors: leiomyoma, schwannoma, inflammatory fibroid polyp, and plexiform fibromyxoma were positive (Table 4).

DISCUSSION

In this study we examined the immunohistochemical expression of the receptor for type I insulin-like growth factor (IGF1R) in a large number of gastrointestinal stromal tumors (GISTs). Activation of this growth factor receptor has been implicated as an oncogenetic factor in common carcinomas, such as those of breast, colon, lung, prostate, and squamous cell carcinomas of the head and neck. [17,26–29] Also, many sarcomas, especially pediatric

tumors, Ewing, osteo- and rhabdomyosarcomas express IFG1R and have therefore been recognized as potential targets for inhibition of the IGF-signaling system. [14–16,30]

Recently, a subset of GISTs has been identified with IGF1R activation, and therefore inhibitor treatment might be a therapeutic consideration. This especially applies to pediatric GISTs and KIT/PDGFRA wild-type GISTs of younger patients. Studies employing western blot analysis, gene expression arrays and immunohistochemistry have reported high IGF1R expression in pediatric and young adult GISTs and some adult WT GISTs, although only a small number of cases have been studied. Also, the association between high IGF1R expression and SDH-deficient status was not evaluated. [19,21,22,24]

In this study, we found immunohistochemical IGF1R expression in 8% of GISTs. IGF1R was detected only in gastric GISTs. It was essentially restricted to succinate dehydrogenase (SDH) deficient GISTs, of which 89% were IGF1R-positive. SDH-deficient GISTs form a clinicopathologically distinctive group of KIT/PDGFRA-wild type gastric GISTs that has been recently delineated. [5–8] These GISTs can be identified by immunohistochemical loss of SDHB. Nearly all pediatric gastric GISTs, a substantial percentage of gastric GISTs in younger patients (<40 years), and a few sporadic GISTs in older adults belong to this category. [8] Based on our findings, IFG1R-positivity may also be a useful surrogate marker to identify SDH-deficient GISTs, as IGF1R positivity largely coincides with this group.

The molecular basis of IGF1R expression in GISTs is unknown. Low copy number gene amplifications, reported in one study, [24] have not been confirmed by two other investigations[21,22], although a relatively small number of tumors was analyzed. Also, no gain-of-function mutations were identified in IGF1R juxtamembrane and tyrosine kinase domains.[24] Other, yet unknown, genetic and epigenetic mechanisms most likely enhance IGF1R expression in GISTs. Recently, several molecular mechanisms altering IGF signaling system have been identified in different type of sarcomas. These include autocrine IgF1 stimulation in Ewing sarcoma and activation of IGF1R signaling by the SS18-SSX sarcoma fusion protein in synovial sarcoma.[18]

The results obtained in two previously published studies are at variance with our observations. One of these studies identified IGF1R expression in all analyzed 94 GISTs [20], while another found 22/96 (23%) adult GISTs as IGF1R-positive. [23] These studies utilized two different rabbit polyclonal IGF1R antibodies: one from Santa Cruz Biotechnology and another from Cell Signaling Technologies. Based on our evaluation, rabbit monoclonal antibody G11 to IGF1R (Ventana Medical Systems) was more specific than either one of those for immunohistochemical studies on formalin fixed paraffin embedded tissues.

Only 1% (9/625) non-SDH deficient GISTs were IGF1R-positive in this study. These tumors occurred in older patients and were often KIT/PDGFRA mutation-positive. We could not identify distinct clinicopathologic features in this small group of cases. This subgroup should be further analyzed to determine whether IFG1R is an oncogenic force in these tumors.

None of sporadic intestinal GISTs showed IGF1R expression. Also, neurofibromatosis-1 associated GISTs, a distinct subgroup of KIT/PDGFRA wild-type GISTs that typically occur in the small intestine were found to be consistently IGF1R negative. This suggests that IGF1R is not likely related to their pathogenesis or progression.

In contrast to intestinal GISTs, many intestinal non-GIST sarcomas, including leiomyosarcomas, undifferentiated sarcomas, and gastrointestinal clear cell sarcomas showed strong IGF1R expression similar to that seen in SDH-deficient GISTs. Therefore, these tumors could also be future candidates for IGF1R inhibitor treatment.

Consistent lack of IGF1R expression in intestinal GISTs and its presence in other GI sarcomas could be considered a potential new immunohistochemical marker in the differential diagnosis of intestinal GISTs, which can be at times difficult. IGF1R-positivity in intestinal mesenchymal tumors, in addition to negativity for KIT and Ano-1/DOG1 would favor non-GIST sarcoma, as opposed to GIST.

In conclusion, we show that rabbit monoclonal antibody G11 identifies a subset of GISTs as IGF1R-positive, and these were essentially restricted to SDH-deficient gastric GISTs regardless of age, while all small intestinal GISTs are negative. The IGF1R positive cases may be candidates for new targeted therapies employing IGF1R inhibition, and therefore screening for IGF1R expression may become therapeutically important. In addition, IGF1R immunoreactivity is a marker for non-GIST intestinal sarcomas, and this may be helpful in the differential diagnosis of intestinal GISTs and non-GIST sarcomas. Also, IGF1R may be a therapeutic target for some intestinal non-GIST sarcomas.

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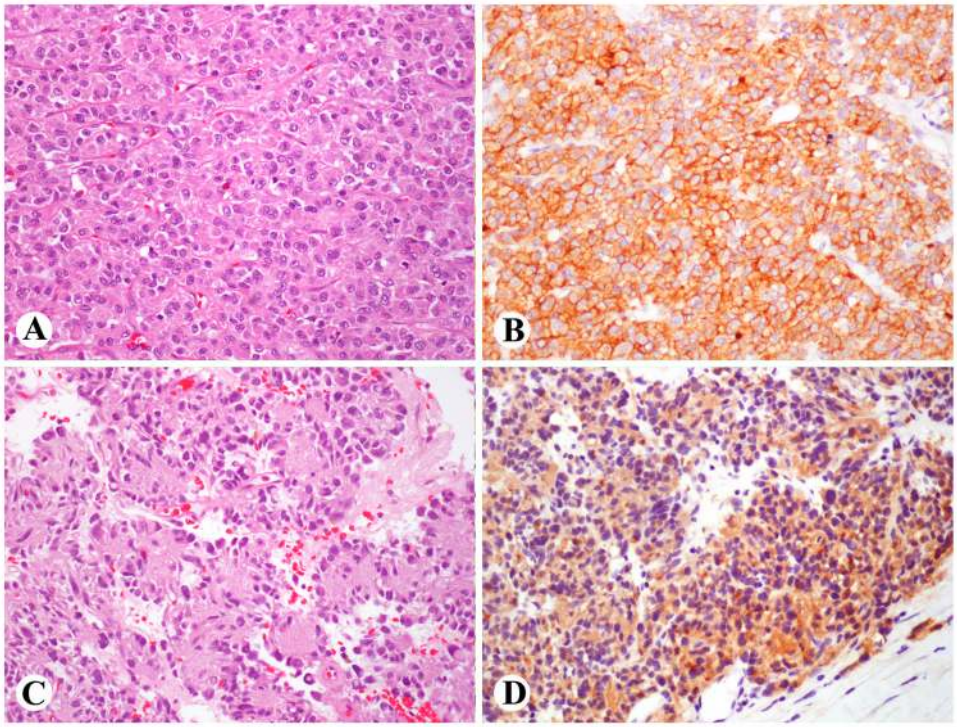

Fig. 1.

Two examples of IGF-IR-positive, SDH-deficient GISTs with matching histological stains. A,B. An epithelioid GIST with strong membranous positivity. C,D. An epithelioid GIST with pseudorosette pattern with weaker but focally strong IGF-IR-positivity.

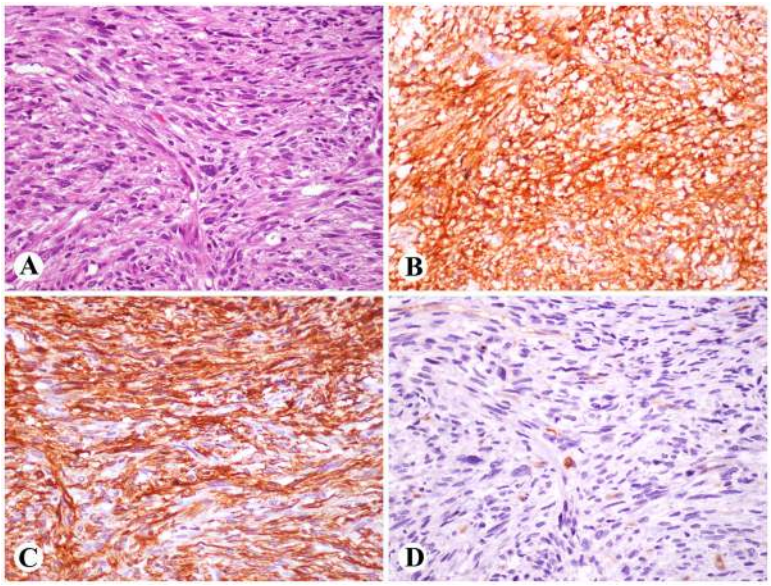

Fig. 2.

An example of an IGF1R-positive intestinal non-GIST sarcoma. A. Intersecting spindle cell fascicles and focal pleomorphism in an intestinal leiomyosarcoma. B. Strong IGF-IR-positivity with a membranous and cytoplasmic pattern. C. The tumor is also positive for alpha smooth muscle actin. D. Tumor cells are negative for KIT, and only mast cells and some neovascular endothelia are positive.

Table 1

Immunoreactivity for type 1 insulin-like growth factor receptor (IGF-IR) in different subgroups of GISTs.

			Patients with IGF1R positive tumor	
GIST category	**IGF-IR (% positive)**	**Median % of positive cells**	**Age range (median), years**	**KIT/PDGFRA mutants**
SDH-deficient gastric GISTs	71/80 (89)	100	8–83(30)	0/61
SDHB-positive gastric GISTs	9/625 (1)	60	33–88 (63)	5/8
Small intestinal, sporadic GISTs	0/324			
Small intestinal, NF-1 associated GISTs	0/13			
Colorectal sporadic GISTs	0/36			
Total	80/1078 (8)			

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Table 2

Clinicopathologic features of SDH-deficient gastric GISTs, which lacked type I insulin-like growth factor receptor (IGF1R) expression.

No	Age	Sex	Tumor size (cm)	Histology	Mitoses/50HPF	Prognostic Group	Follow-up (months)	KIT/PDGFRA Mutation status
1	31	F	2.9	Sp	1	2	ANED (354)	ND
2	39	F	3	Sp/Ep	5	2	NA	WT
3	15	F	3.5	Sp/Ep	6	5	NA	ND
4	18	F	3.5	Ep/Sp	3	2	NA	WT
5	25	F	4	Sp	5	2	NA	ND
6	22	F	5*	Sp/Ep	15	6a	NA	WT
7	61	M	Liver metastases	Sp/Ep	ND	ND	DUNK (26)	WT
8	39	M	UNK	Ep	3	ND	NA	WT
9	48	M	UNK	Ep	1	ND	NA	WT

Ep = epithelioid cell, Sp = spindle cell, ANED = alive no evidence of disease, DUNK = died of unknown causes, NA = not available,

*multiple small adjacent nodules.

Table 3

Clinicopathologic features of SDHB-positive gastric GISTs with type I insulin-like growth factor receptor (IGF1R) expression.

No	Age	Sex	Tumor size (cm)	Histology	IGF-IR (%)	Mitoses/50HPF	Prognostic Group	Follow-up (months)	KIT/PDGFRA Mutation status
1	33	M	2	Ep	60	25	4	DUNK (60)	WT
2	47	F	6	Ep	60	2	3a	NA	WT
3	61	M	6	Ep	60	5	3a	NA	NA
4	76	M	8.5	Ep	100	12	6a	DUNK (89)	WT
5	88	M	9	Sp	50	0	3a	DUNK (8)	KIT exon 11 V559A
6	63	M	10	Sp	60	4	3a	NA	KIT exon 11 557_558delinsC
7	69	M	10.5	Ep	20	1	3b	NA	PDGFRA exon 18 843_847delinsT
8	36	F	11	Ep	50	9	6b	NA	PDGFRA exon 18 D842V
9	70	F	11.5	Sp	50	1	3b	NA	KIT exon 11 V560G

Ep = epithelioid morphology, Sp = spindle cell morphology, DUNK = died of unknown causes, NA = not available.

Table 4

Immunoreactivity for type I insulin-like growth factor receptor (IGF1R) in gastrointestinal neoplasms other than GISTs.

Tumor type	IGF-IR (% positive)
GI-Clear cell sarcoma	2/2 (100)
Inflammatory fibroid polyp	0/19
Inflammatory myofibroblastic tumor	0/6
Leiomyoma	0/21
Leiomyosarcoma	4/8 (50)
Plexiform fibromyxoma	0/4
Sarcomatoid carcinoma	3/6 (50)
Schwannoma	0/8
Undifferentiated/unclassified sarcoma (non-GIST)	14/29 (48)
Total	24/103 (23)