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A nonrandom association of gastrointestinal stromal tumor (GIST) and desmoid tumor (deep fibromatosis): case series of 28 patients

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Background: Gastrointestinal stromal tumors (GISTs) and desmoid tumors (DTs) are two rare mesenchymal tumor. Anecdotal reports of individuals with both diseases led us to make the hypothesis that the association is a nonrandom event as the probability would be extremely low to observe such cases if they were independent events.
Patients and methods: We evaluated the existence of patients with GIST and DT in a large multicenter cohort at 10 institutions in the United States, Australia and Europe. Data on gender, age at diagnosis, *KIT*, *PDGFRA*, *CTNNB1* mutation status and follow-up time after diagnosis were collected.
Results: We identified 28 patients diagnosed with both tumors. DT was diagnosed after GIST in 75% of patients and concomitantly in 21%. In only one case (4%), GIST was diagnosed after DT. *KIT* or *PDGFRA* mutations were detected in 12 of 14 GIST, 9 in *KIT* exon 11, 2 in *KIT* exon 9 and 1 in *PDGFRA.*
Conclusion: A statistical analysis of these 28 cases suggests a nonrandom association between GIST and DT. Further studies may be able to elucidate the underlying biology responsible for this association.
Key words: beta-catenin, deep fibromatosis, desmoid tumor, GIST, imatinib, KIT

introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract but remains rare compared with gastrointestinal carcinomas. The term 'GIST' was introduced to indicate a distinctive subgroup of gastrointestinal sarcomas [1]. Subsequently, the interstitial cell of Cajal, or a cell in that lineage, was implicated as the precursor of these tumors, further distinguishing them from other sarcomas [2].

Gain-of-function mutations of *KIT* play a key role in the oncogenesis of these tumors [3]. Approximately 80% of patients with GIST have primary *KIT* mutations. Most *KIT* mutations involve the juxtamembrane domain, exon 11. Other exons harbor *KIT* mutations with varying frequencies include exons 9, 13 and 17 [4]. Of the GIST not harboring *KIT* mutations, ~30% have mutations in *PDGFR*A, which are mutually exclusive with *KIT* mutations [5]. A rare subset of GIST has been found to carry *BRAF* mutations in the absence of *KIT* or *PGDFRA* alterations [6]. Recently, mutations in the succinate dehydrogenase genes have been identified in tumors lacking a kinase gene mutation [7].

The standard treatment for patients with resectable GIST is surgery with the goal of achieving complete resection. For patients with metastatic or unresectable GIST, the introduction of molecularly targeted kinase inhibitors (e.g. imatinib, sunitinib) has significantly extended survival [8, 9]. The median time to disease progression is 18–24 months in patients with GIST who are receiving imatinib; however, imatinib has been

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shown to control disease for >6 years in a subset of individuals with GIST [10, 11].

As patients with GIST are living longer, their risk of developing other malignancies is now being evaluated and reported in the literature. Indeed, it is known that GIST can be associated with other neoplasms in conditions such as neurofibromatosis type 1, Carney's triad and Carney–Stratakis syndrome [12–15]. However, outside of these syndromes, the associations between GIST and other tumors remain unclear. Most reports describe single cases or very small series of patients from a single institution [16–20]. GIST has been reported to coexist with gastric, breast, prostate, renal, esophagus, colorectal, lung and pancreatic carcinomas; carcinoids; lymphomas and melanomas [21, 22]. Additionally, two case reports of a patient with desmoid tumors (DTs, also known as deep or aggressive fibromatosis) and GIST in the same anatomic location were recently reported [23, 24]. DT is very rare fibroblastic proliferations with a tendency for slow local infiltrative growth. Their cell of origin is not clearly defined, but recent evidence suggests that DT originate from mesenchymal progenitor cells [25]. DT occurs sporadically or in association with Gardner's Syndrome and Familial Adenomatous Polyposis (FAP) [26]. These do not metastasize but can cause significant morbidity through their locally destructive effects. Prior trauma, such as previous surgery, is known to increase the risk of sporadic and FAP-associated DT [27, 28]. Complete surgical resection with a wide margin and/or radiation therapy constitute the mainstay of resectable DT therapy, while chemotherapy, anti-inflammatory agents and tyrosine kinase inhibitors are all treatment options for locally advanced DT. The Wnt/β-catenin signaling pathway seems to play an important role in the development of DT, and nuclear expression of β-catenin has increasingly been used in the differential diagnosis of spindle cell neoplasms, particularly in the abdomen [29]. Mutations in the *CTNNB1* gene, which codes for β-catenin protein, have been found in the majority of DT patients, with most mutations occurring in exon 3 [30–32].

Anecdotal reports of individuals with GIST and DT led us to evaluate a larger cohort of patients with both tumors, in order to gain insight into whether their simultaneous occurrence is a coincidental event. In this study, we have found 28 patients from 10 institutions with a history of both GIST and DT.

materials and methods

patients and tumor tissues

This retrospective analysis included 28 patients with both GIST and DT. Clinical characteristics and formalin-fixed paraffin-embedded GIST and DT specimens accrued between 1978 and 2008 were retrieved from the patient records and pathology sample collections of The University of Texas M. D. Anderson Cancer Center, Helsinki University Central Hospital, Fox Case Cancer Center, Oregon Health & Science University Knight Cancer Institute, Cleveland Clinic, Italian National Tumor Institute, Prince of Wales Hospital, H. Lee Moffit Cancer Center, the Armed Forces Institute of Pathology and Memorial Sloan-Kettering Cancer Center using a protocol approved by the respective Institutional Review Boards. Specimens were further screened and evaluated by experienced soft-tissue pathologists at M. D. Anderson, the Armed Forces Institute of Pathology or Fox Chase who confirmed DT and GIST histology. Demographic and clinical information, including treatment, histology and outcome-related variables were tabulated for analyses.

genomic DNA isolation

When tissues were available genomic DNA was extracted from 10-μm-thick formalin-fixed paraffin-embedded tissue sections cut from blocks with at least 80% tumor using the QIAamp DNA mini kit (Qiagen, Valencia, CA) or the Easy-DNA kit (Invitrogen, Carlsbad, CA).

analysis of KIT, PDGFRA and CTNNB1 mutations

PCR amplification of DNA for *KIT* exons 9, 11, 13 and 17; *PDGFRA* exons 12, 14 and 18 and *CTNNB1* (β-catenin) exon 3 was carried out. Each PCR amplification was carried out in a 50-μl volume containing 10 ng of genomic DNA, 15 μM concentrations of each primer, 0.2 mM deoxyribonucleotide triphosphate, 5 μl of 10× reaction buffer, 2.5 mM $MgCl_2$ and 1 U of AmpliTaq Gold DNA polymerase (Applied Biosystems, Foster City, CA). The *KIT* and *PDGFR*A primers were previously published [33, 34]. The PCR conditions were as follows: 30 s at 94°C; 30 s at 52°C and 1 min at 68°C for 36 cycles, followed by 10-min extension at 68°C. The primers for *CTNNB1* exon 3 primers were as follows: forward: 5′-TTTGATGGAGTTGGACATGG-3′ and reverse: 5′-CTGAGAAAATCCCTGTTCCC-3′. The PCR conditions for *CTNNB1* exon 3 were as follows: 30 s at 94°C; 30 s at 55°C and 1 min at 68°C for 36 cycles, followed by 10-min extension at 68°C. PCR products were analyzed in by gel electrophoresis and purified using a Qiaquick PCR purification kit (Qiagen). Direct sequencing was carried out from both directions using a BigDye Terminator v3.1 cycle sequencing kit on an ABI PRISM 3100 genetic analyzer (Applied Biosystems). The National Center for Biotechnology Information's Basic Local Alignment Search Tool was used to analyze both strands to identify mutations.

statistical analysis

A standardized incidence ratio (SIR) was used. This ratio is calculated by the number of events observed divided by the number of events expected. In this study, SIR was calculated to compare the incidence of DT in patients with GIST to the incidence of DT in the general USA population from 2000 to 2008 [35]. We calculated the 95% confidence intervals (CIs) of SIRs using the formula proposed by Vandenbroucke [36]. Overall survival was calculated as the time between the date the first neoplasm was diagnosed and the date of death or the last known date at which the patient was alive. Survival curves were estimated using the Kaplan and Meier method and the log-rank test.

results

Patients with both GIST and DT were searched in a large cohort including 10 institutions. The total number of new patients per year in the USA institutions between 2000 and 2008 was 830 for GIST and 315 for DT. Twenty-eight patients harboring GIST associated with DT were identified as follows: M. D. Anderson Cancer Center (cases 1–4), Helsinki University Central Hospital (cases 5–6), Fox Case Cancer Center (cases 7–9), Oregon Health & Science University Knight Cancer Institute (case 10), Cleveland Clinic (case 11), Italian National Tumor Institute (case 12), Prince of Wales Hospital (case 13), H. Lee Moffit Cancer Center (cases 14–16), the Armed Forces Institute of Pathology (cases 17–23) and Memorial Sloan-Kettering Cancer Center (cases 24–28). Table 1 shows the clinical characteristics of this patient population, which included 19 men (68%) and 9 women (32%) whose ages ranged from 34 to 88 years. The majority of patients had sought medical advice because of vague symptoms such as epigastric pain, nausea or abdominal discomfort. Interestingly, no cases with a family history of FAP were observed.

Table 1. Patient and tumor properties, summary of the 28 patients who developed GIST and DT

Case no.	Age	Sex	Primary location of GIST	GIST size (cm)	*KIT* or *PDGFRA* mutation (GIST)	Imatinib	Site of DT	*CTNNB1* mutation (desmoid)	Interval of GIST with DT (months)	Length of follow-up (months)	Patient status
1	62	M	Gastric	20	KIT mutation exon 11: V560D	Yes	Perigastric/ peripancreatic	Exon 3: WT	39	58	NED
2	67	M	Gastric	10.5	KIT exon 11 mutation: deletion	Yes	Gastric	Exon 3: T41A	35	45	AWD
3	50	M	Gastric	0.5	ND	No	Retrogastric	ND	0	54	NED
4	45	F	Omentum	7	KIT mutation exon 11: D579del	Yes	Colon	Exon 3: WT	39	36	AWD
5	39	F	Jejunum	12.5	WT	Yes	Small bowel	Exon 3: WT	32	67	Died of GIST
6	62	F	Gastric	20	KIT exon 11mutation : del Lys 550-Glu556+ insLeu	Yes	Right rectus abdominis	Exon 3: WT	30	74	NED
7	59	F	Gastric	9.9	KIT exon 11mutation: W557-K558del	Yes	Small bowel	Exon 3: T41A	42	100	AWD
8	62	F	Jejunum	10	KIT exon 11 mutation: del 556-573	Yes	Small bowel	Exon 3: S45P	16	75	AWD
9	74	M	Gastric	7.5	ND	Yes	Omentum	Exon 3: T41A	25	54	NED
10	75	M	Gastric	10	PDGFRA exon 18 mutation: D842V	No	Peripancreatic	ND	0	68	NED
11	88	F	Small intestine	5	WT	No	Abdominal wall	Exon 3: WT	-7	118	NED
12	61	M	Gastric	30	ND	Yes	Abdominal wall	ND	28	72	Died of GIST
13	62	M	Gastroduodenal	15	KIT exon 11 mutation: deletion	Yes	Infrapyloric mesenteric	ND	36	95	Died of GIST
14	42	F	Jejunal	10.2	ND	Yes	Pelvic	ND	21	21	NED
15	71	F	Gastric	11.2	ND	Yes	Caudate lobe liver	ND	24	35	AWD
16	52	M	Pelvic	4	KIT exon 9 mutation	Yes	Mesenteric	ND	30	30	AWD
17	53	M	Gastric	ND	ND	No	Spleen	ND	33	ND	ND
18	75	M	Castric	16	ND	No	Mesenteric	ND	0	ND	ND
19	65	F	Gastric	1.8	ND	No	Mesenteric	ND	0	30	Died cause unknown
20	70	M	Gastric	6	ND	No	Thigh	ND	191	274	NED
21	66	M	Gastric	1.5	ND	No	Mesenteric	ND	0	212	NED
22	42	F	Small intestine	0.4	ND	No	Mesenteric	ND	0	307	NED
23	40	M	Small intestine	10	ND	No	Mesenteric	ND	12	12	No follow-up
24	34	M	Proximal jejunum	5.3	KIT exon 9 mutation: 502-3 AY duplication	No	Terminal ileum	ND	19	55	NED
25	58	M	Gastric	10.5	ND	Yes	Mesentery	ND	62	66	AWD
26	58	M	Gastric	5.4	KIT exon 11 mutation: Del (6aaDEL 552-7 MYEVQW)	Yes	Mesentery	ND	30	42	AWD
27	54	M	Gastric	6	KIT exon 11 mutation: Del (557-8 WK del)	Yes	Small bowel/ mesentery	ND	33	37	NED
28	68	M	Small intestine	30	ND	Yes	Proximal jejunum	ND	6	6	NED

GIST, gastrointestinal stromal tumor; DT, desmoid tumor; WT, wild type; ND, no data; NED, no evidence of disease; AWD, alive with disease.

In 21 cases (75%), GIST was diagnosed before DT. The average time between these diagnoses was 30 months (range, 6 months–16 years). In 6 cases (21%), both tumors presented synchronously and in 1 case (case 11; 4%), GIST was diagnosed after DT. The primary GIST tumor site was gastric in 17 cases (60%), small intestinal in 9 cases (32%) and pelvic or mesenteric in 1 case each (4%). DT involved the extremity in only one patient, who developed DT of the thigh 16 years after treatment for gastric GIST. In three patients (11%), DT developed in the surgical incision site and mimicked a recurrence of GIST. Imatinib was used for 17 patients (61%) and in 10 cases (36%) GIST developed before imatinib therapy was available. A strong family history of GIST (father, brother and aunts) was found in case 4, caused by a rare germ line mutation of *KIT* that was previously described [37]. Interestingly, there are reports in the literature investigating the use of imatinib for treating DT. In particular, in our series, patient number 2, a 67-year-old

man, received imatinib at 400 mg/day for gastric GIST and developed a DT on the posterior wall of the gastric antrum 35 months after the first diagnosis. His dose of imatinib was increased to 800 mg/day, resulting in a partial response in both tumors (Figure 1).

The frequency of mutations in *KIT* and *PDGFRA* in GIST was similar to that previously observed in large cohorts of patients with GIST [38]. *KIT* was mutated in 11 cases of 14 (79%), of which 9 cases (64%) were in exon 11 and 2 cases (14%) in exon 9. *PDGFRA* was mutated in one case (7%). Two cases (14%) lacked mutations in *KIT* or PDGFRA (wild type). β-catenin is commonly deregulated in DT indeed mutations in the *CTNNB1* gene have been identified with a prevalence of 85% in a large cohort of patients with DT [31]. In our samples available for genotyping, *CTNNB1* was mutated in 5 of 10 cases (50%) in exon 3 (4 type 41A and 1 type 45F; Table 1).

The annual incidence of GIST in the United States is estimated to be 10–15 cases/million [39], while the annual incidence of DT is 2–4 cases/million [40]. The expected number of DT events in patients with GIST was calculated by applying the DT rate for theoretical GIST population in the USA. To determine the statistical association between GIST and DT, the SIR was used. Analyses were restricted to cases from the USA from 2000 to 2008. In this case series, 13 patients were diagnosed with GIST and DT in the US between 2000 and 2008. This number was compared with 0.16, an estimated number of expected cases assuming the independence of events. The estimated risk of developing DT was significantly higher (SIR = 82; 95% CI 44–133) in GIST patients than in the general population. To assess the clinical outcomes of patients with GIST and DT, we displayed a Kaplan–Meier survival plots (Figure 2). The 5- and 10-year survival rates were 0.86 (95% CI 0.99–0.73) and 0.64 (95% CI 0.86–0.27), respectively.

discussion

The development of tyrosine kinase inhibitors has lead to dramatic improvements in long-term survival of patients with GIST. The primary objective of this study was to determine the existence of the association between GIST and DT. Our analysis resulted in the identification of 28 cases. On a previous study, on a single institution-based tumor registry, we found that ∼20% of the GIST patients developed at least one additional tumor [20]. The occurrence of other malignancies appeared higher than that was expected in the general population. However, to our knowledge, the present study is the first report of a series of patients with coexisting GIST and DT. This relationship raises the questions about a potential link

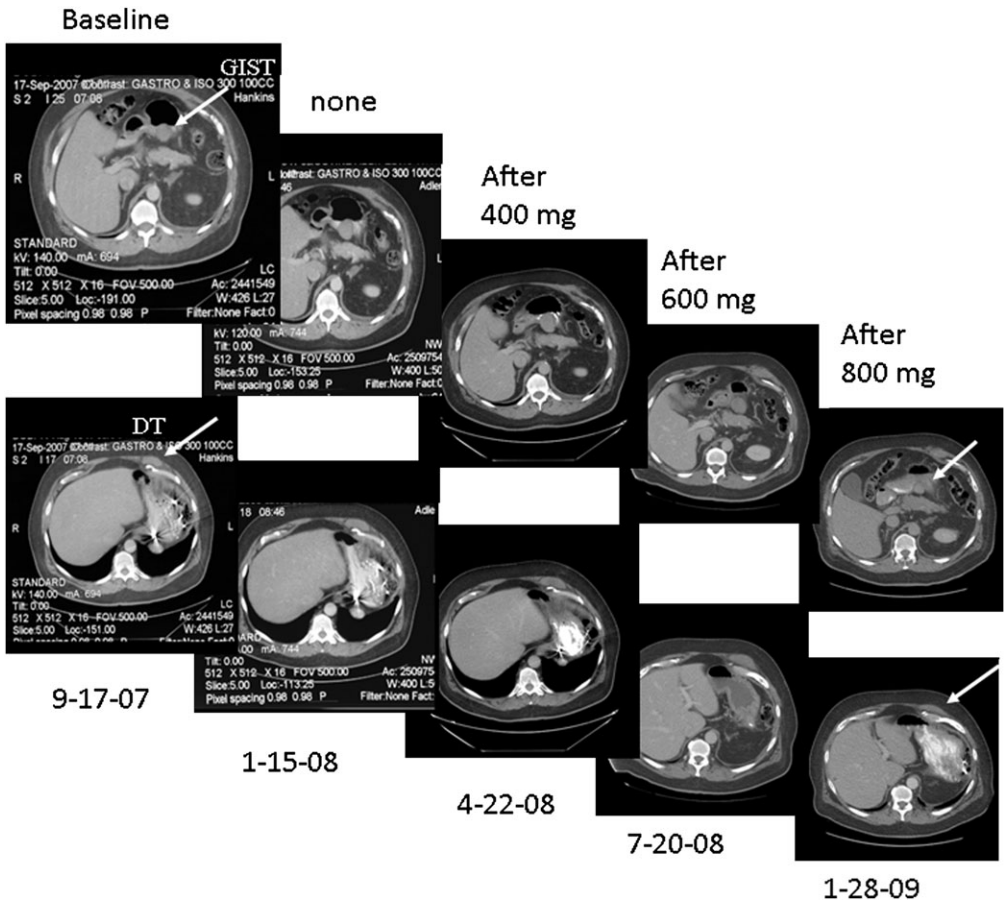

Figure 1. Computed tomography of patient #2 shows that imatinib at 800 mg/day may induce a partial response in gastrointestinal stromal tumor (GIST) and desmoid tumor (DT). Arrows indicate tumor localization.

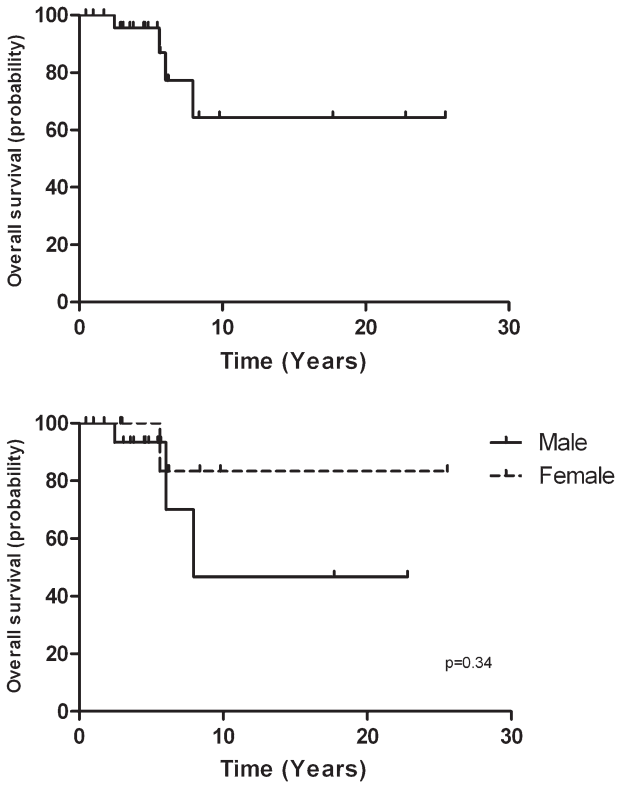

Figure 2. Overall survival analysis by the Kaplan–Meier method.

between these two neoplasms and the possibility of a cancer predisposition syndrome.

There were more men than women (19 versus 9) in our population of patients who developed both tumors. Accepting the possibility of a selection bias in this population, this gender distribution differs from that reported in previous DT studies, where female predilection is suggested; female to male ratios commonly ranged between 1.4 and 1.8 [41, 42]. In addition, a Kaplan–Meier survival analysis revealed a no significant difference in survival between men and women (Figure 2). Furthermore, the peak incidence of DT has been reported as 25–35 years; however, in our case series, DT occurred at an average of 59 (range 34–88 years) [40, 42]. Because these tumors are rare, the size of this series and the SIR suggest a nonrandom association between these histopathologically distinct tumors. At this stage, we can only speculate about this association.

Patients with GIST may be predisposed to developing DT or patients with DT might be prone to GIST. These possibilities should be considered when the patient has an occurrence of either of these tumors. Although there are no data to support a genetic predisposition syndrome, a germ line mutation might underlie predisposition for these two tumors. The possibility that activated KIT pathway is involved in the development of DT must also be considered. However, gain-of-function mutations of *KIT* were not found in DT tissues samples in our series. Most of the patients had abdominal surgery to remove their GIST and then developed a DT. Surgical trauma has been shown to induce desmoid growth, but this implication seems insufficient to explain all the cases of GIST and DT in the current series. Additionally, no history of FAP was observed in our patients that could explain the increase of risk for developing a post-operative desmoid. However, this series cannot conclude that GIST patients who undergo surgery are at higher risk for DT than other patients who undergo abdominal surgery. Furthermore, treatment with imatinib does not appear to play a role in the development of DT because 11 cases in our series were not treated with imatinib. Interestingly, there are reports in the literature investigating the use of imatinib for treating DT. Case reports have described responses to imatinib, and a series of 19 patients with DT showed a partial response in three patients [43–45]. Another possibility is that GIST patients under physical and radiological surveillance are more likely to have DT detected compared with 'normal' population. Finally, it is interesting to speculate that circulating stem cell factor (KIT ligand) or platelet-derived growth factor in patients with GIST could stimulate the growth of DT. Indeed, cross talk between the KIT and Wnt signaling pathways was recently described in mast cell leukemia. In this model, nuclear accumulation of β-catenin was increased by a gain-of-function mutation of *KIT* [46]. Recent clinical data regarding the effectiveness of sorafenib in both GIST and desmoid tumors highlight a possible therapeutic option when medical treatment of both conditions is necessary [47].

We show in the present study statistical evidences for a nonrandom relationship between the concomitant development of GIST and DT. Excluding a recurrence of GIST is fundamental for the clinical management of a patient that could potentially still benefit from targeted therapy, such as imatinib. Further investigation is needed to establish the link between these tumors and to evaluate possible risk factors for their association.

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disclosure

The authors have declared no conflicts of interest.

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