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Original Article PATHOLOGY

An entity that should be kept in mind: Synchronous gastrointestinal stromal tumor encountered in resection materials obtained for the detection of intra-abdominal malignancies

Selma Sengiz Erhan,[1] Gamze Kulduk,[1] Arzu Dobral,[1] Aytul Bugra[2]

[1]Department of Pathology, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkiye

[2]Division of Histopathology, Department of Morgue, Council of Forensic Medicine, Istanbul, Turkiye

ABSTRACT

OBJECTIVE: Gastrointestinal stromal tumors (GISTs), often sporadic, arise from interstitial Cajal cells of the gastrointestinal tract or their stem cell-like precursors. Apart from tumor-associated syndromes, it has been reported that GISTs are also associated with other tumors. There is no clear information about the etiology of these synchronous tumors. In this study, we wanted to present the clinicopathological features of 13 cases diagnosed as synchronous GIST with other tumors.

METHODS: Demographic characteristics of the cases, risk of progressive disease score, tumor localization, size, and the mitotic activity of tumors along with survival status were evaluated.

RESULTS: Thirteen of 101 cases diagnosed with GIST had a primary tumor synchronous with GIST. Synchronous GISTs were located in the stomach and small intestine. Most of the cases were detected incidentally in the intraoperative and post-operative periods. Risk scores for progressive disease were categorized as low (n=1), very low (n=1), and no risk (n=11). Non-GIST tumors were located in the stomach, transverse colon, left colon, rectum, gallbladder, kidney, and retroperitoneal space. Histological tumor types were adenocarcinoma, diffuse large B-cell lymphoma, mesothelioma, and neuroendocrine tumor. Life expectancy was found to be significantly lower in synchronous GISTs.

CONCLUSION: In cases operated for non-GIST tumors, the possibility of incidental detection of GIST should always be kept in mind.

Keywords: Adenocarcinoma; gastrointestinal stromal tumor; lymphoma, mesothelioma; neuroendocrine tumor; synchronous.

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Gastrointestinal stromal tumor (GIST) is a mesenchymal tumor originating from interstitial Cajal cells or their stem cell-like precursors, known as "pacemaker" cells of the gastrointestinal tract [1]. It develops as a result of activating mutations in the transmembrane growth factor receptor KIT or platelet-derived growth factor receptor alpha genes [2]. It is the most common mesenchymal tumor observed in the gastrointestinal system with incidence rates ranging between 0.1 and 3% [3].

It is more often seen in the stomach and second in the small intestine. It can also develop in the esophagus, colon, rectum, and even omentum and mesenteric fat tissue [1]. GISTs are mostly sporadic. However, other than hereditary GIST syndromes, GISTs coexisting with other tumor types have been reported at a rate of 4.5–33% [1, 2, 4]. To the best of our knowledge, in the English literature, they are generally cited in the form of case reports and less frequently as case

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Correspondence: Aytul BUGRA, MD. Adli Tip Kurumu, Morg Bolumu, Histopatoloji Birimi, Istanbul, Turkiye.
Tel: +90 212 415 54 00 - 1457 e-mail: aytulsargan@gmail.com

series [4–9]. We wanted to present our case series consisting of 13 cases with GIST coexisting synchronously with other tumors along with their clinicopathological findings.

MATERIALS AND METHODS

The ethics committee approval was obtained from the Clinical Research Ethics Committee of Prof. Dr. Cemil Tascioglu City Hospital (date: May 17, 2021, no: 206). The study was conducted in accordance with the Declaration of Helsinki.

Patient Selection

Among the cases diagnosed with GIST between 2007 and 2020, cases with GIST coexisting with other tumors were included in the study. Demographic characteristics (age, gender), localization, size, the mitotic activity of tumor, risk of progressive disease score, and survival rates of the cases were evaluated. The risk of progressive disease score was determined according to the Miettinen and Lasota-AFIP criteria [1].

Statistical Analysis

While evaluating the study data, frequency distribution (number, percentage) for categorical variables and descriptive statistics (mean, standard deviation) for numerical variables were determined. The difference between the two groups (if any) was examined with the independent sample t-test and the difference between more than two groups using a one-way analysis of variance (one-way ANOVA). As a result of the "one-way analysis of variance" (ANOVA), first, the Levene test for variance homogeneity, and then to determine the group or groups where the difference originated from the "multiple comparison test" (Bonferroni or Tamhane's T2) were performed. Bonferroni test was used to examine the difference between groups in variables that provide variance homogeneity, and Tamhane's T2 test was used to examine the difference between groups in variables that did not provide variance homogeneity. The Chi-square test was used to examine the relationship between two categorical variables.

In addition, Kaplan–Meier analysis was used to determine the average life expectancy. The data were completed by transferring them to the IBM SPSS Statistics 23 (USA) program.

Highlight key points

- The possibility of incidental detection of GIST should always be kept in mind.
- Synchronous GIST survival time was shorter.
- GISTs coexisting with other tumors were located in the stomach and small intestine.

Table 1. Clinicopathologic findings of cases with GIST (n=101)

	%
Sex	
Male	55.4
Female	44.6
Tumor localization	
Stomach	58.4
Small intestine	29.7
Colon	5
Others	6.9
Tumor size	
<2 cm	19.8
2–5 cm	27.7
5–10 cm	27.7
>10 cm	24.8
Mitosis	
≤5	78.2
>5	21.8
Risk score	
No risk	17.8
Very low risk	12.9
Low risk	20.8
Intermediate risk	19.8
High risk	28.7
Ki-67 proliferative index	
<5	53.5
≥5	46.5
Presence of another tumor	12.9

RESULTS

Clinicopathological Findings of the Cases

There were 101 cases diagnosed with GIST. The cases consisted of 55.4% (n=56) of male and 44.6% (n=45) of female patients. The median age of the patients was 61.1 (ranging from 27–83) years. Tumors were localized in the stomach, small intestine, and colon (sigmoid colon and rectum) with rates of 58.4% (n=60), 29.7% (n=29),

TABLE 2. Clinicopathologic findings of cases with GISTs coexisting with other tumor types

		GIST			Other tumor(s)			
Age	Sex	Localization	Size (cm)	Risk scores	Histologic type	Localization	Size (cm)	TD
77	F	Stomach	0.6	No risk	AdenoCa	Stomach	6	Post
83	M	Stomach	1.5	No risk	AdenoCa	Stomach	5	Intra
40	M	Stomach	0.5	No risk	AdenoCa	Stomach	6	Post
56	F	Stomach	0.7	No risk	AdenoCa	Stomach	2.5	Post
54	M	Stomach	0.6	No risk	AdenoCa	Stomach	4	Post
66	M	Stomach	1	No risk	AdenoCa	Stomach	10.5	Post
73	M	Stomach	0.6	No risk	AdenoCa	Transverse colon	11	Post
54	M	Small intestine	1.8	Very low	RCC	Kidney	16	Intra
83	M	Small intestine	0.6	No risk	AdenoCa	Rectum	1.5	Intra
62	F	Small intestine	3.5	Low	DLBCL	Retroperitoneum	WSI	Pre
80	F	Small intestine	1.5	None	Mesothelioma	Gallbladder	1.5	Intra
59	F	Small intestine	0.4	None	NET	Stomach	2.6	Intra
78	M	Small intestine	1.5	None	AdenoCa	Left colon	3	Intra

GIST: Gastrointestinal stromal tumor; TD: Time of diagnosis; F: Female; M: Male; AdenoCa: Adenocarcinoma; RCC: Renal cell carcinoma; DLBCL: Diffuse large B-cell lymphoma; NET: Neuroendocrine tumor; WSI: Widespread involvement; Post: Post-operative; Intra: Intraoperative; Pre: Pre-operative.

and 5% (n=5), respectively. Other categories included 6.9% (n=7) of tumors that were located in the abdomen and retroperitoneal space. According to the risk scoring for progressive disease, the high, intermediate, low, very low, and no risk categories were observed at the rates of 28.7%, 19.8%, 20.8%, 12.9%, and 17.8%, respectively (Table 1).

In the statistical analysis, no statistically significant difference was found between the genders in terms of mean age (p=0.095), and between tumor locations (p=0.100).

Clinicopathological Findings of Cases with GIST Coexisting with Other Tumors

In 12.9% (n=13) of the cases, there was a second primary tumor other than GIST. Males consisted 61.5% (n=8) of the cases in this group and 38.5% (n=5) of them were female. The mean age of the patients was 66.54±13.31 years (age range 40–83).

GISTs were located in the stomach in 53.8% (n=7) of the cases and the small intestine in 46.2% (n=6) of them. While the rate of the cases that were detected pre-operatively was 7.8% (n=1), 46.1% (n=6) were detected intraoperatively, and 46.1% (n=6) were detected during the macroscopic examination of the resection materials. Tumor diameters varied between 0.4 and 3.5 cm, and in 53.8% (n=7) of the cases, it was 1 cm or less.

In the histopathological examination, spindle cell morphology was observed in 92.2% (n=12), and spindle+epitheloid cell morphology was observed in 7.8% (n=1) of the cases. Based on these findings, leiomyosarcoma, schwannoma, and peripheral nerve sheath tumors were considered in the differential diagnosis. In the immunohistochemical study, CD117 was positive in all of the cases and CD34 in 69% (n=9) of the cases. While focal staining with actin was observed in 23% (n=3) of the cases, no staining with desmin and S-100 was noted.

In the progressive disease risk scoring, 85.6% (n=11) of small bowel tumors were in "no risk" category, whereas 7.2% (n=1) were in "very low risk" and 7.2% (n=1) were in the "low risk" category. Other tumors were primarily located in the stomach, followed by the transverse colon, left colon, rectum, gallbladder, kidney, and retroperitoneal space. In 46.1% (n=6) of the cases, GIST and the coexistent tumor were localized in the gastric tissue. In 53.8% (n=7) of the cases, synchronous tumors were localized in different tissues (Table 2). The most common histological tumor type was adenocarcinoma (n=9). These cases were in pathological stages of pT1b (n=1), pT3 (n=7), and pT4a (n=1). The case diagnosed as a neuroendocrine tumor (NET) was in the pathological stage of pT3 and the case diagnosed as renal cell carcinoma (RCC) was in the pathological stage of pT3b. Cases

Table 3. Localizations of GISTs and distribution of other tumors according to risk scores

	Risk scores					Test/p
	No risk	Very low risk	Low	Intermediate	High	
Small intestine						
n	4	1	6	7	12	
%	22.2	7.7	28.6	35.0	41.4	
Stomach						
n	13	12[a]	12	12	10[b]	16.707/0.033*[3]
%	72.2	92.3	57.1	60.0	34.5	
Other						
n	1	0	3	1	7	
%	5.6	0.0	14.3	5.0	24.1	
Other tumor (s)-						
n	7[b]	12[a]	20[a]	20[a]	29[a]	
%	38.9	92.3	95.2	100.0	100.0	
Other tumor(s)+						46.132/0.000*[3]
n	11[a]	1[b]	1[b]	0[b]	0[b]	
%	61.1	7.7	4.8	0.0	0.0	

GIST: Gastrointestinal stromal tumor; a, b: Represents the difference between group percentages (a=maximum percentage); 3: Chi-square test; *: P<0.05.

diagnosed as mesothelioma and diffuse large B-cell lymphoma (DLBCL) had a higher pathological grade.

A statistically significant correlation was found in terms of the risk scores and localization of GIST and the presence of other tumors (p=0.033). Accordingly, the rates of being in the "very low" and "no risk" categories in GISTs localized in the stomach were significantly higher in GISTs coexisting with other tumors (p=0.000) (Table 3). The average survival time for all cases was 106.3 months. During the follow-up, 35.2% (n=31) of the cases diagnosed with GIST and 53.8% (n=7) of the cases diagnosed with synchronous GIST were deceased. While there was no difference between the localization and the mean survival rates among patients with primary GISTs, (p>0.05), a statistically significant difference was found between average survival rates when GIST was accompanied by other tumors. Accordingly, the average life expectancy in cases with synchronous GISTs was significantly lower than in cases without (p=0.007).

DISCUSSION

Genetic instability, gene mutations, immunodeficiency, field cancerization, aging, and persistent environmental carcinogens may trigger the development of multiple primary tumors (MPTs). These tumors have an incidence rate changing between 0.7 and 11.7% [10, 11]. The reported frequency of coexistence of GIST and other tumors ranged between 4.5 and 33% [1, 6]. Recently, it has been reported that the frequency of detection of synchronous tumors has increased with increased awareness and advanced imaging methods [4–6, 12]. In our study, the coexistence rate of GIST with other tumors was consistent with the literature data.

GISTs are generally sporadic. GISTs can be associated with hereditary diseases such as the Carney triad, and Leigh syndrome and familial GISTs have been observed to a lesser extent [1]. There is very little information about the genetic basis of sporadic GISTs that may play a role in their synchronous existence with other tumors [7, 8]. It is not clear yet whether this coexistence is merely a simple incidental or a causal relationship. It is emphasized in studies that unknown potential carcinogens stimulate the proliferation of both epithelial and stromal cells. In several studies, it has been mentioned that the c-kit mutation may play a role in the development of epithelial tumors as well as GIST [13, 14]. In our study, mutation analysis was not performed on patients diagnosed with GIST. Therefore, we could not comment on whether there is a relationship between the presence of mutations and the synchronous development of other tumors.

GISTs are generally difficult to recognize in the pre-operative period since some of them are small in size and some are interpreted as metastatic lymph nodes [15]. In this respect, intraoperative consultation can be a method that can be used to rule out the possibility of metastatic tumors for establishing the correct diagnosis [16]. Tumors of this size can be detected mostly as a result of the surgery performed for other tumors. These data also emphasize the importance of the roles of the surgeon and the pathologist. The findings we observed in our study also supported this data. Only 7.8% (n=1) of the cases were detected in the pre-operative period. While 46.1% (n=6) of the other cases were detected and examined by the surgeon during the operation, 46.1% (n=6) were detected by the pathologist during the macroscopic examination of the material. Tumors <1 cm in size described as MicroGIST are defined as the pre-clinical form of GIST [17]. In autopsy studies, it is detected in 20–30% of the cases with GIST. Ten cases diagnosed with GIST in our study were in this category. In seven of these cases, tumors were localized in the stomach and colorectal regions.

The most common localizations for synchronous GISTs are the gastrointestinal tract (GIT), urogenital system, and female genital system [5, 7, 18]. Among these, tumors originating from GIT are observed more frequently and they are especially detected as synchronous tumors [5, 7]. Among GIT tumors, tumors of the stomach and esophagus are observed more frequently. Other tumors that may accompany GISTs in the group of MPTs include lymphoma, prostate, kidney, lung carcinomas, NET, and less frequently melanoma, soft tissue, and bone sarcomas [4, 6, 9, 12, 19, 20]. In our study, while GISTs were more frequently localized in the stomach and small intestine, other tumors were localized in the stomach, transverse colon, left colon, rectum, gallbladder, kidney, and retroperitoneal space. Adenocarcinoma was the most commonly coexistent histological type. In addition, RCC, mesothelioma, DLBCL, and NET were the other detected tumor types.

Based on histopathological criteria determining the possibility of local recurrence and distant metastasis, approximately 30% of GISTs are malignant and/or carry malignant potential [1]. However, in many studies, it is observed that the risk of progressive disease is in low and very low categories in most of the synchronous GISTs [18]. Possible reasons for this concomitancy include the operation of the cases for other tumors and the fact that these tumors can be detected in smaller sizes in careful examinations during and after the operation. In our study, our findings were similar to the literature, and the risk of progressive disease was in the "low" category in one (7.2%) of two cases localized in the small intestine and the "very low" category in the other (7.2%), while 11 (85.6%) cases were in the "no risk" category.

GISTs have a better prognosis than other GIT tumors. However, studies have reported that patients with MPTs and especially synchronous tumors had a shorter survival time, and MPTs including GISTs showed a poor prognosis [11, 21, 22]. We also reached the same conclusion in our study, and the survival time was shorter in synchronous GIST cases. However, this issue may be related to the aggressive course of malignancies observed in other malignancies. In a study, it has been suggested that the tumor group that determines survival is tumors of other systems diagnosed synchronously with GISTs [8]. Additional mutations caused by as-yet-unknown potential carcinogens may also have an impact on survival. Further studies are needed on this subject.

Limitation

The limitation of our study is the lack of molecular studies for the c-kit mutation in the cases we included in the study.

Conclusion

In our study, cases of GIST coexisting with other tumors were located in the stomach and small intestine. While there was no risk of progressive disease in more than half of the cases, it was observed that synchronous GIST survival time was shorter. Most of the cases were detected incidentally in the intraoperative and post-operative periods. While this fact highlights the importance of the role of the surgeon and pathologist, it also shows that these tumors may be more common than thought.

Ethics Committee Approval: The Prof. Dr. Cemil Tascioglu City Hospital Clinical Research Ethics Committee granted approval for this study (date: 17.05.2021, number: 206).

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