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CLINICAL STUDY

Simultaneous occurrence of synchronous and metachronous tumors with gastrointestinal stromal tumors

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Abstract: *Objective:* To examine the frequency and clinicopathological features of synchronous and metachronous tumors which occur simultaneously with gastrointestinal stromal tumors (GIST).
Methods: Clinical and pathologic records of 78 patients diagnosed with primary GIST and treated at our institution between 1997 and 2009 were reviewed.
Results: GIST occurred simultaneously with other primary GI malignancies in 16.1 % (n=13) of all patients with GIST. Of the simultaneous secondary tumors, 69.2 % (n=9) were gastrointestinal tumors, and the remaining were biliary system and breast tumors. GIST most frequently had gastric localization (n=6, 46.1 %).
Conclusion: Although GIST are uncommon neoplasms, their synchronous and metachronous coexistence with other tumors is rather frequent, mostly as incidental tumors accompanying a gastrointestinal neoplasm. Therefore, during surgery on cases with gastrointestinal neoplasms, the surgeon needs to be careful about a synchronous GIST. At the same time, more detailed studies are needed about the carcinogenesis of dual tumors coexisting with GIST *(Tab. 1, Ref. 14)*. Full Text in free PDF *www.bmj.sk.*
Key words: gastrointestinal stromal tumor, synchronous tumor, metachronous tumor.

Gastrointestinal stromal tumors (GIST) were first defined by Mazur and Clark as a group of mesenchymal tumors distinct from other GIS sarcoma. Later studies showed them to be the most common mesenchymal tumors of the gastrointestinal tract (1–4).

Two or more tumors appearing simultaneously or consecutively in several organs or systems are known as synchronous tumors while those appearing at different times are called metachronous tumors (5). To date, synchronous and metachronous tumor cases stemming from both the gastrointestinal system and other organs and systems have been reported to coexist with GISTs. These rather rare occurrences require further studies.

Previously, GISTs have been reported to coexist with gastrointestinal and prostatic adenocarcinomas, esophageal squamous cell carcinomas, periampullary neuroendocrine carcinomas, ileal neuroendocrine tumors, gastrointestinal lymphoma, thyroid follicular carcinomas, hepatocellular carcinomas and oral malignant melanoma; however, there are no studies on the carcinogenesis of these tumors (6–14).

We thus aimed to reconsider the simultaneous occurrence of synchronous tumors in our GIST cases and present our findings in light of the literature.

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Methods

Clinical and pathologic records of 78 patients diagnosed with GIST at Uludag University Medical School's Pathology Department between 1997 and 2009 were reviewed. These GIST cases had been classified as having very low, low, moderate or high malignancy potential after Fletcher. Eleven of these GIST cases had gastrointestinal neoplasms, and 2 had extragastrointestinal neoplasms, one synchronous and the other one metachronous. The characteristics of cases are summarized in Table 1.

At the time of diagnosis, all of these 13 GIST cases had undergone detailed immunohistochemical examination for both diagnostic and prognostic reasons, and all were C-kit (CD117) positive. In 7 (53.9 %) of these 13 cases, GISTs adjacent to the primary tumor or in a close localization had been detected incidentally by resection materials from the malignant epithelial tumor, and had low or very low potential for malignant behavior (cases 1, 3, 7, 9, 10, 11, 13). In a further 2 cases (15.4 %), the primary tumors were jejunal GISTs with high malignancy potential. These patients had presented to the hospital due to tumor-related complaints, and their endoscopic examination incidentally revealed other tumors in different localizations (cases 2 and 6). In 2 (15.4 %) of the remaining 4 cases, both tumors were detected during the initial examination and excised in the same session (cases 4 and 12). One of the remaining cases had a breast tumor excised due to different complaints within the same year, and the other one had a kidney tumor excised.

Discussion

The role of mutations in proto-oncogenes and tumor sup-

Tab. 1. Clinicopathological characteristics of cases that had secondary tumors coexisting with GISTs.

Case number	Age	Sex	Risk category for malignant behavior	2nd tumor diagnosis	GIST localisation	2nd tumor localisation	S or M?
1	67	F	VL	adenocarcinoma	small bowell	choledoc	S
2	55	F	H	tubular adenoma	small bowell	colon	S
3	73	M	VL	adenocarcinoma	stomach	stomach	S
4	72	M	L	tubulovillous adenoma with moderate-high grade dysplasia	rectum	rectum	S
5	41	F	L	phillodes tumor	stomach	breast	S
6	53	M	H	tubular adenoma	small bowell	colon	S
7	64	M	L	adenocarcinoma	stomach	stomach	S
8	42	M	H	Rcc (2 years ago)	small bowell	kidney	M
9	65	M	VL	adenocarcinoma	stomach	stomach	S
10	57	F	VL	adenocarcinoma	stomach	stomach	S
11	75	M	L	adenocarcinoma	small bowell	gall bladder	S
12	62	M	M	adenocarcinoma	stomach	rectum	S
13	60	M	L	adenocarcinoma	colon	colon	S

S – synchronous, M – metachronous; VL – very low, L – low, M – moderate, H – high

pressor genes, among other systems, is well-known in the formation of a benign or malignant tumor in the organism. These stages in tumoral formation are collectively known as carcinogenesis. It is known that more than one tumor may form simultaneously or at different times in some people. Those that form simultaneously or within 4 months – 1 year of each other are known as synchronous tumors, whereas those that form over a longer period are known as metachronous tumors (5).

GISTs are uncommon neoplasms. The literature includes few cases of synchronous and metachronous tumors coexisting with GISTs. However, the majority of these publications are case reports or small-scale case series, thus failing to inform the reader about incidence (6–14). Agaimy et al. gathered these publications in the literature and made the statistics of malignancies and solid tumors accompanying sporadic GIST cases other than Neurofibromatosis 1 and Carney triad-associated tumors (14). Based on these data, there were 518 cancers in 486 GIST patients among 4,813 cases with informative data. The overall frequency of second tumors in different series varied from 4.5 % to 33 % (mean, 13 %). GISTs of gastric location were most commonly involved with other neoplasms, reflecting their overall high frequency (60 %) of all GISTs. The major types of GIST-associated cancers were gastrointestinal carcinomas (n=228; 47 %), lymphoma/leukemia, (n=36; 7 %), and carcinomas of prostate (n=43; 9 %), breast (n=34; 7 %), kidney (n=27; 6 %), lung (n=26; 5 %), female genital tract (n=25; 5 %), and carcinoid tumors (n=13; 3 %). Other cancers included soft tissue and bone sarcomas (n=15; 3 %), malignant melanoma (n=12; 2 %), and seminoma (n=6; 1 %). In our series, the frequency of second tumors coexisting with GISTs was 16.6 % (13 cases out of 78). Second tumors mostly occur with gastric GISTs (n=6, 46.1 %), followed by small bowel (n=5, 38.5 %) and colorectal GISTs (n=2, 15.4 %). These findings parallel those of Agaimy et al.

With respect to the type and localization of second tumors, gastrointestinal malignancy and tumors (adenomas) were number one in our series too (n=9, 69.2 %). In both case reports and small-scale series cited in the literature, the simultaneous occurrence of GISTs with gastrointestinal malignancies has been stressed and it has been hypothesized that both tumors may have similar carcinogenesis. Although c-kit overexpression has been identified in some colorectal cancers, the role of c-kit mutation in colorectal carcinogenesis has not been clarified.

In summary, the carcinogenesis of secondary tumors coexisting with GISTs deserves to be studied for both the prognosis and treatment of patients, and genetic based studies in larger series are particularly needed.

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