



Coincident of Gastrointestinal Stromal Tumor and Two Other Primary Malignancies: A Case Report

Touraj Asvadi Kermani ¹, Farzad Kakaei ^{1,*} and Kowsar Tarvirdizade ²

¹Department of General and Vascular Surgery, Tabriz University of Medical Sciences, Tabriz, Iran

²Faculty of Medicine, Tabriz University of Medical Science, Tabriz, Iran

*Corresponding author: Department of General and Vascular Surgery, Imam Reza Hospital, Tabriz University of Medical Sciences, Golgasht Ave., Azadi Rd., Tabriz, Iran. Tel: +98-4133341317, Fax: +98-4115564857, Email: fkakaei@yahoo.com

Received 2019 February 04; Revised 2019 September 14; Accepted 2019 September 17.

Abstract

Introduction: Gastrointestinal Stromal Tumor (GIST) is an uncommon mesenchymal tumor of the gastrointestinal tract. It is rarely presented as Multiple Primary Malignancy Syndrome (MPMS) without an association with the familial syndromes.

Case Presentation: A 63-year-old Iranian Azeri man admitted to a government hospital, affiliated to the Tabriz University of Medical Sciences, Tabriz, Iran, in 2012. The illness presented with complicated gastrointestinal problems with the diagnosis of GIST of the stomach, treated with imatinib. They family history and the screening tests of malignancies were negative, but the patient diagnosed with Squamous Cell Carcinoma (SCC) of the lower lip, leading to 28 courses of radiotherapy, followed by the recurrence of gastrointestinal symptoms, the GIST and SCC of the esophagus, that was also detected accidentally.

Conclusions: Management of the multiple primary malignancy syndrome needs multidisciplinary teamwork. The study of MPMS, its etiology, and epidemiology can provide us proper ways of management.

Keywords: Carcinoma, Coincident, Esophagus, Gastrointestinal Stromal Tumor, Imatinib Mesylate, Lip, Multiple Primary, Neoplasms, Squamous Cell, Stomach

1. Introduction

Multiple Primary Malignancies (MPMs) include the presence of two or more distinctive primary malignancies, apart from metastases, in a single patient (1, 2). Because of the increasing number of cancer survivors, improved screening and diagnostic systems, and increased number of the older population, MPMs also have been on the rise (2, 3). According to the Surveillance, Epidemiology, and End Results Program (SEER) database, malignancies that are seen at the same time or with an interval of two months are synchronous and those seen at an interval of more than two months are metachronous. This interval is six months based on the International Association of Cancer Registries (IARC) (4). The incidence of MPMs is 0.7% to 11% in a cancerous population (5). The risk of new cancer in patients with primary cancer is 20% higher than the general population (6, 7). Some risk factors for MPMs include the presence of a past medical history of cancer or its familial history, exposure to carcinogens, immunologic and genetic disorders, radiotherapy and chemotherapy for primary malignancy, lifestyle (smoking, alcohol), squamous cell malignancies, and gender (4, 5, 8).

Gastrointestinal Stromal Tumors (GISTs) are mesenchymal tumors of the gastrointestinal tract and are uncommon with other malignancies (9, 10). These tumors are mostly seen as solitary malignancies but generally, familial GISTs can be recognized as tumors of MPMs that are related to some factors such as germinal mutations in c-KIT proto-oncogene, Platelet-Derived Growth Factor Receptor Alpha (PDGFRA), Neurofibromin 1 (NF1), and Succinate Dehydrogenase (SDH).

It is rarely seen as MPMs with tumors that have not associations with familial syndromes; however, there are some case reports in the literature that present this association (10).

The synchronous occurrence of GISTs with adenocarcinoma has been most reported. The coincidence of GISTs and lymphoma or carcinoid tumor has not been reported so far. The most frequent second malignancy is the epithelial tumor, especially related to the gastrointestinal tract, as observed in our patient.

These case reports have been about the co-existence of GIST and one other primary malignancy while this is a case report of GIST (as a sporadic tumor) with Squamous Cell

Carcinoma (SCC) of the lower lip and the SCC of the esophagus, representing GIST with two other malignancies. This case was reported based on the SCARE criteria (11).

2. Case Presentation

In 2012, a 63-year-old Iranian Azeri man from Tabriz, Iran, with a chief complaint of melena and epigastric pain was admitted to the Surgery Department of Imam Reza Government Hospital, affiliated to the Tabriz University of Medical Sciences, Tabriz, Iran. He had a history of type 2 diabetes, hypertension, and ischemic heart disease and was a candidate for Coronary Artery Bypass Graft (CABG). His serum hemoglobin level was 12 g/dL. In endoscopy, an ulcerated gastric mass was seen on the small curve (sized 4 × 4 cm) and a gastric polyp on the antrum of the stomach (sized 0.5 × 0.5 cm). A biopsy from the mass and polyp was done. The pathological study revealed a gastrointestinal stromal tumor for which staining was positive for CD-117, CD-34, and DOG-1 and negative for CD-45 and EMA. Since the patient was not satisfied with CABG and due to the high risk cardiovascular status for major gastrointestinal surgery, the operation was not done. Moreover, oncologist colleagues followed-up the patient with imatinib three times a day. In this follow-up period, studies for metastases were negative. Follow-up CTs showed that the size of the mass was decreasing, and partial remission was seen.

After four years in 2016, he had a lesion on the lower lip. A punch biopsy was done, and the pathology of the lesion was squamous cell carcinoma. Then, the patient underwent 28 courses of radiotherapy, and the lesion improved. Meanwhile, because of glaucoma, he lost his eyesight.

By the year 2017 in the follow-up endoscopy, the fundus and body of the stomach were atrophic and a submucosal mass (sized 7.0 by 8.0 cm) was seen on the lesser curve and two pedunculated polyps (1.0 cm and 1.2 cm) were found on the prepyloric area. The pathological study revealed GIST. Again, because of the high risk of surgery without CABG and dissatisfaction of the patient, the surgery was not done, and palliative therapy started.

However, after two months, the patient complicated with Gastric Outlet Obstruction (GOO). Therefore, emergent surgery of BILLROTH II with Roux-en-Y Gastrojejunostomy was done. Figure 1 shows CTs before and after surgery. As CTs showed, there was also a mass of esophagus, with the pathology of well-differentiated SCC of the esophagus. Due to his heart problem, a major surgery of esophagectomy and colon interposition could not be done. Despite the esophageal mass, he did not have dysphagia after BILLROTH II surgery and radiotherapy started.

After three months, he had dysphagia that revealed the probability of not responding to radiotherapy. A study

with barium swallow series showed dilation of the upper esophagus with stringing at the middle esophagus (Figure 2). In endoscopy, an infiltrative and ulcerative tumoral mass was seen that could not be passed; thus, a biopsy was done. The pathology of the mass was squamous cell carcinoma of the esophagus with IIb stage in CT (Figure 3). The patient was cachectic; so, he received Total Parenteral Nutrition (TPN). The esophagus was dilated with rigid esophagoscopy by a thoracic surgeon and gastroenterologist colleagues inserted a metal esophageal stent as palliative treatment (Figure 4). It is worth mentioning that all the used equipment was normal standard instruments. Radiotherapy continued until the patient passed away by heart failure in 2018. The main features of the patient are presented in Table 1.

3. Discussion

GISTs mostly originate from the stomach, followed by the intestine, colon, rectum, esophagus, and even from greater omentum and mesentery. MPMs including GISTs are commonly related to genetic and familial syndrome and rarely can be seen with separated tumors (10).

The incidence of MPMs is increasing; in patients with cancer, mere attention to the present disease can cause missing other malignancies. Therefore, having a systematic view of patients is necessary (8). In a study, it was estimated that the relative risk for second primary cancer every month increases by 1.11 folds for patients with primary malignancies (12). If these patients modify their lifestyles, they can decrease this relative risk even lower than the normal population. According to the European cancer registries, the incidence of MPMs is 6.3% (0.4% - 12.9%), and another study reported that it is 6.1% - 10.5% (6). The latest study reported it being between 2.4% and 17% (4). Bitorf et al. showed that 3.8% of patients with cancer had at least two primary cancers, and 2.8% of patients with two primary cancers had at least three primary cancers (1). In patients with cancer, the risk of the incidence of new primary cancer is 14%, as compared to 1% in the general population. Also, this risk is dependent on some factors such as the type of first cancer, age at first diagnosis, genetic and environmental factors, the way of treatment, etc. For example, the highest risk for developing new cancer is in patients that their first diagnosis of cancer was at the age of 0 to 7 years. Also, according to some studies, the cessation of smoking in patients with primary lung cancer can decrease the risk of new smoking-related malignancies (13).

In 2017, Danila et al. from Italy reported a case of synchronous GISTs with prostatic cancer and non-small cell lung cancer (10). In analyzing GIST patients in 2014 in Germany, 5 out of 37 patients (13.5%) suffered from more than

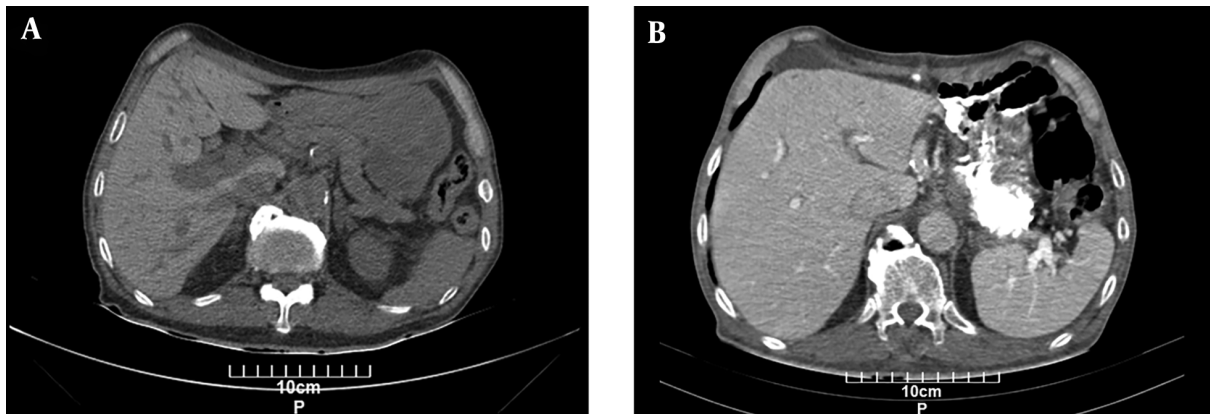


Figure 1. A, preoperative CT without contrast showing a mass of distal part of the stomach; B, postoperative CT with intravenous (IV) and oral contrast showing remained stomach

Table 1. Main Features of the Patient

Year	First Signs	Finding	Pathology	Treatment
2012	Melena and Epigastric pain	A gastric ulcerated mass on the small curve of the stomach (4 × 4 cm) and a gastric polyp on the antrum of the stomach (0.5 × 0.5 cm)	Gastrointestinal stromal tumor (GIST); CD-117 (+); CD-34 (+); DOG-1 (+); CD-45 (-); EMA (-)	Imatinib
2016	Lower lip ulceration	Lower lip lesion (1.0 × 1.5 cm)	Squamous Cell Carcinoma (SCC)	28 courses of radiotherapy
2017	No sign, found incidentally	Esophageal mass	Well-differentiated esophageal; Squamous Cell Carcinoma (SCC)	Total parenteral nutrition, esophageal dilation, insertion of metal esophageal stent and radiotherapy



Figure 2. Study with barium swallow series showing dilation of the upper esophagus with stringing at the middle esophagus

two other malignancies in addition to GIST (14). In 2010, studying the survival ratio of 783 GIST patients showed that 24 of them (3.1%) had had more than two other primary malignancies (15).

The present case also had gastrointestinal problems

with the diagnosis of GIST of the stomach, treated with imatinib. After a while, the patient complicated with SCC of the lower lip, leading to 28 courses of radiotherapy, followed by the recurrence of gastrointestinal symptoms; the SCC of the esophagus was also detected accidentally.



Figure 3. Stage IIb tumor of the esophagus (CT with IV and oral contrast)

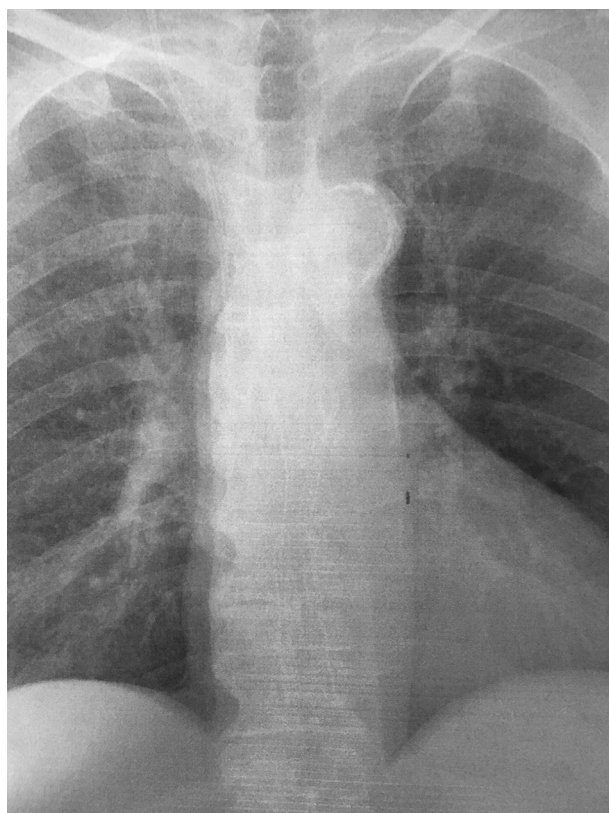


Figure 4. Chest X-ray showing a metal esophageal stent

The management of such patients needs multidisciplinary teams and their discussion because there is no universal protocol for this issue (1, 4). Moreover, differentiation between second primary cancer and metastases

is very important because of their different management ways; for example, for second primary cancer, surgery can be a good option but for metastatic tumors, systemic chemotherapy is a better option (12). Therefore, the study of MPMs, its etiology, and epidemiology can provide doctors with better ways of management (3). GISTs with other malignancies presenting as MPMs and differentiation of this condition from the familial syndrome or metastases need more studies for giving better ways of management because this is a rare condition and is reported in special literature (9).

Acknowledgments

We thank the Pathology and Oncology Departments of Tabriz University of Medical Sciences.

Footnotes

Conflict of Interests: There is no conflict of interest for this study.

Funding/Support: Vice Chancellor of Research of Tabriz University of Medical Sciences funded the study.

Patient Consent: Written informed consent was obtained from the patient for the publication of this case report and images.

References

- Williamson CW, Paravati A, Ghassemi M, Lethert K, Hua P, Hartman P, et al. Five simultaneous primary tumors in a single patient: A case report and review of the literature. *Case Rep Oncol.* 2015;**8**(3):432–8. doi: [10.1159/000440799](https://doi.org/10.1159/000440799). [PubMed: [26600775](https://pubmed.ncbi.nlm.nih.gov/26600775/)]. [PubMed Central: [PMC4649736](https://pubmed.ncbi.nlm.nih.gov/PMC4649736/)].
- Demirci U, Coskun U, Gocun PU, Gurlek B, Saka B, Ozturk B, et al. Four different malignancies in one patient: A case report. *Cases J.* 2010;**3**:53. doi: [10.1186/1757-1626-3-53](https://doi.org/10.1186/1757-1626-3-53). [PubMed: [20205852](https://pubmed.ncbi.nlm.nih.gov/20205852/)]. [PubMed Central: [PMC2825507](https://pubmed.ncbi.nlm.nih.gov/PMC2825507/)].
- Sakellakis M, Peroukides S, Iconomou G, Boumpoucheropoulos S, Kalofonos H. Multiple primary malignancies: A report of two cases. *Chin J Canc Res.* 2014;**26**(2):215.
- Vogt A, Schmid S, Heinimann K, Frick H, Herrmann C, Cerny T, et al. Multiple primary tumours: Challenges and approaches, a review. *ESMO Open.* 2017;**2**(2). e000172. doi: [10.1136/esmoopen-2017-000172](https://doi.org/10.1136/esmoopen-2017-000172). [PubMed: [28761745](https://pubmed.ncbi.nlm.nih.gov/28761745/)]. [PubMed Central: [PMC5519797](https://pubmed.ncbi.nlm.nih.gov/PMC5519797/)].
- Gokyer A, Kostek O, Hacıoglu MB, Erdogan B, Kodaz H, Turkmen E, et al. Clinical features of the patient with multiple primary tumors: Single center experience. *North Clin Istanbul.* 2017;**4**(1):43–51. doi: [10.14744/nci.2017.67044](https://doi.org/10.14744/nci.2017.67044). [PubMed: [28752142](https://pubmed.ncbi.nlm.nih.gov/28752142/)]. [PubMed Central: [PMC5530157](https://pubmed.ncbi.nlm.nih.gov/PMC5530157/)].
- Utada M, Ohno Y, Hori M, Soda M. Incidence of multiple primary cancers and interval between first and second primary cancers. *Cancer Sci.* 2014;**105**(7):890–6. doi: [10.1111/cas.12433](https://doi.org/10.1111/cas.12433). [PubMed: [24814518](https://pubmed.ncbi.nlm.nih.gov/24814518/)]. [PubMed Central: [PMC4317925](https://pubmed.ncbi.nlm.nih.gov/PMC4317925/)].

7. Testori A, Cioffi U, De Simone M, Bini F, Vaghi A, Lemos AA, et al. Multiple primary synchronous malignant tumors. *BMC Res Notes*. 2015;**8**:730. doi: [10.1186/s13104-015-1724-5](https://doi.org/10.1186/s13104-015-1724-5). [PubMed: [26613933](https://pubmed.ncbi.nlm.nih.gov/26613933/)]. [PubMed Central: [PMC4662827](https://pubmed.ncbi.nlm.nih.gov/PMC4662827/)].
8. Jena A, Patnayak R, Lakshmi AY, Manilal B, Reddy MK. Multiple primary cancers: An enigma. *South Asian J Cancer*. 2016;**5**(1):29–32. doi: [10.4103/2278-330X.179698](https://doi.org/10.4103/2278-330X.179698). [PubMed: [27169120](https://pubmed.ncbi.nlm.nih.gov/27169120/)]. [PubMed Central: [PMC4845605](https://pubmed.ncbi.nlm.nih.gov/PMC4845605/)].
9. Rebegea LF, Patrascu A, Miron D, Dumitru ME, Firescu D. Metachronous gastrointestinal stromal tumor associated with other neoplasia - case presentation. *Rom J Morphol Embryol*. 2016;**57**(4):1429–35. [PubMed: [28174815](https://pubmed.ncbi.nlm.nih.gov/28174815/)].
10. Comandini D, Damiani A, Pastorino A. Synchronous GISTs associated with multiple sporadic tumors: A case report. *Drugs Context*. 2017;**6**:212307. doi: [10.7573/dic.212307](https://doi.org/10.7573/dic.212307). [PubMed: [29167690](https://pubmed.ncbi.nlm.nih.gov/29167690/)]. [PubMed Central: [PMC5699020](https://pubmed.ncbi.nlm.nih.gov/PMC5699020/)].
11. Agha RA, Fowler AJ, Saeta A, Barai I, Rajmohan S, Orgill DP, et al. The SCARE Statement: Consensus-based surgical case report guidelines. *Int J Surg*. 2016;**34**:180–6. doi: [10.1016/j.ijvsu.2016.08.014](https://doi.org/10.1016/j.ijvsu.2016.08.014). [PubMed: [27613565](https://pubmed.ncbi.nlm.nih.gov/27613565/)].
12. Karthikeyan VS, Sistla SC, Srinivasan R, Basu D, Panicker LC, Ali SM, et al. Metachronous multiple primary malignant neoplasms of the stomach and the breast: Report of two cases with review of literature. *Int Surg*. 2014;**99**(1):52–5. doi: [10.9738/INTSURG-D-13-00056.1](https://doi.org/10.9738/INTSURG-D-13-00056.1). [PubMed: [24444270](https://pubmed.ncbi.nlm.nih.gov/24444270/)]. [PubMed Central: [PMC3897342](https://pubmed.ncbi.nlm.nih.gov/PMC3897342/)].
13. American Cancer Society. *Cancer facts & figures 2009*. Atlanta: American Cancer Society; 2009. Report No.: Special section, multiple primary cancers. 24 p.
14. Vassos N, Agaimy A, Hohenberger W, Croner RS. Coexistence of gastrointestinal stromal tumours (GIST) and malignant neoplasms of different origin: Prognostic implications. *Int J Surg*. 2014;**12**(5):371–7. doi: [10.1016/j.ijvsu.2014.03.004](https://doi.org/10.1016/j.ijvsu.2014.03.004). [PubMed: [24632413](https://pubmed.ncbi.nlm.nih.gov/24632413/)].
15. Pandurengan RK, Dumont AG, Araujo DM, Ludwig JA, Ravi V, Patel S, et al. Survival of patients with multiple primary malignancies: A study of 783 patients with gastrointestinal stromal tumor. *Ann Oncol*. 2010;**21**(10):2107–11. doi: [10.1093/annonc/mdq078](https://doi.org/10.1093/annonc/mdq078). [PubMed: [20348145](https://pubmed.ncbi.nlm.nih.gov/20348145/)]. [PubMed Central: [PMC2946863](https://pubmed.ncbi.nlm.nih.gov/PMC2946863/)].