Colon Adenocarcinoma Associated with Synchronous Extramural Gastrointestinal Stromal Tumor (GIST) of the Ileum

Paschalis Gavriilidis
Anastasia Nikolaidou

1 Department of Surgical Oncology, Theageneio Anticancer Hospital, Thessaloniki, Greece
2 Department of Pathology, Theageneio Anticancer Hospital, Thessaloniki, Greece

Patient: Female, 68
Final Diagnosis: Gastrointestinal stromal tumour and colon adenocarcinoma
Symptoms: Fatigue
Medication: —
Clinical Procedure: Right Hemicolecctiony and enterectomy
Specialty: Surgery

Objective: Rare disease

Background: GISTs are mesenchymal tumors representing approximately 1% of all gastrointestinal neoplasia. Their concurrence with colorectal cancers is rare.

Case Report: We present a case of coexistence of colon adenocarcinoma and GIST of the ileum in a 68-year-old white woman.

Conclusions: The coexistence of mesenchymal and epithelial neoplasia is very challenging; further research is needed to clarify the role of oncogenic mutations and signalling pathways in carcinogenesis of neoplasia of various histogenic origins.

MeSH Keywords: Colectomy • Colonic Neoplasms • Gastrointestinal Stromal Tumors

Abbreviations: GIST – gastrointestinal stromal tumor; GI – gastrointestinal tract

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Background

GISTs are the most common mesenchymal tumors of the GI tract and can appear from the oesophagus to the anus. They arise from the interstitial cells of Cajal [1]. The coexistence of GIST and colorectal adenocarcinomas is rare. Most cases of associated GIST and adenocarcinomas have been described in the stomach. In most cases GIST was discovered incidentally during an operation for primary gastrointestinal adenocarcinoma [1,2]. Studies based on the expression of the c-kit proto-oncogene support the hypothesis of common carcinogenic etiology. However, the few published cases cannot rule out a possible incidental occurrence of GIST and adenocarcinoma [3].

Case Report

A 68-year-old white woman was admitted with the endoscopic and pathologic diagnosis of adenocarcinoma of the ascending colon. Apart from low hemoglobin (Hb10.3), her past medical history was unremarkable. The preoperative CT scan revealed a colonic tumor of the ascending colon but did not detect any associated tumour elsewhere in the gastrointestinal tract. She underwent a right hemicolectomy and during the abdominal exploration an extramural tumor of the ileum (5.5×5.8×4.5 cm) was found (Figure 1). Subsequently, an enterectomy was performed and both specimens were sent to pathology. Pathology reported well-circumscribed GIST spindle cells infiltrating the submucosa, muscularis propria, and subserosal layers of the small bowel. There was neither mucosa invasion nor serosal breach. Mitotic activity was inconspicuous. Upon immunostaining, the tumor cells demonstrated strong diffuse positivity with CD117, BC22, SMA, and CD34. Focal positivity was seen with S 100. The tumor cells were negative for desmin and MNF116. On the basis of the sample received, according to Miettinen criteria for risk stratification, this tumor has a moderate risk (24%) of progressive disease (localized in the ileum, less than 5 mitoses in 5 mm², >5 cm, and <10 cm in size). The patient recovered uneventfully and was discharged on the 5th postoperative day. She is scheduled for follow-up visits every 3 months in colorectal outpatient clinics.

Discussion

The term GIST was coined for the first time in 1983 to define neoplasms with complete lack of myogenic or neural component [4]. Somatic mutations trigger the process of carcinogenesis in most GISTs by activating the KIT signalling pathway [5]. Activated KIT subsequently phosphorylates JAK, STAT, MAP kinase, and PI3 kinases, which in turn activate signalling cascades that play vital roles in differentiation and mitogenesis of GIST neoplasms [5].

Mutations of KIT protein can be detected in 80% of benign and in 90% of metastatic GISTs [6]. PDGFR-a and BRAF mutations are alternative molecular pathways in GIST tumorigenesis, in particular BRAF mutations are related with benign intestinal GIST of low malignancy potential [7,8]. Studies on p16 tumor suppressor protein showed that patients with p16 loss have a dismal prognosis [9,10]. GISTs occur most often in the stomach (60%); intestine (30%); colon (<5%); mesentery, omentum, and retroperitoneum (<5%); anorectum (<5%); and oesophagus (3%) [11]. Most GISTs appear sporadically and are occasionally identified in rare syndromes such as neurofibromatosis type I, as well as in Carney triad and Carney-Stratakis syndromes [12,13]. Recently, many centers report epidemiological data demonstrating high occurrence of GISTs with other malignant neoplasms [13–15]. The most frequently associated are gastric and colorectal neoplasms [16,17]. The reported frequency ranges from 2.95 to 33% [17]. Most of these associated GISTs are asymptomatic and found during intraoperative examination of the abdomen [18]. The prognosis of a GIST is based on tumor location, size, and mitotic activity [9–11]. In case of coexistence, accurate staging of both malignancies is very important because the dominant malignancy determines the outcome. The invention of imatinib mesylate opened new perspectives in the treatment of GISTs; especially, its neoadjuvant use helps to downstage inoperable cases and to achieve negative margins resections [19]. To date, researchers have not been able to determine if the association between GIST and colonic tumors is a simple coincidental coexistence or whether the 2 neoplasias are connected by a causal relationship. Attempts have been made to explain the coexistence and simultaneous development of GIST tumor with other gastrointestinal malignancies by studying the c-kit expression in both tumors. It is well known that kit protein can be detected in 80% of benign and 90% of metastatic GIST; it is also believed that mutations of the kit proto-oncogene are the cause of GIST tumors [6,20,21]. There are reports that show 30% c-kit expression in colorectal...
malignancies [21]. Moreover, it is reported that the c-kit activation in colorectal cancers promotes their invasiveness and metastatic potential [22]. However, there are other reports that contradict the hypothesis of common carcinogenic etiology by showing that the c-kit expression is very rare in colon cancer cell lines [2]. Researchers tried to explain the concurrence of GIST and colorectal cancer by studying the role of metallothionein (MT) in oncogenesis. MTs are coded by 10 genes and play a crucial role in angiogenesis, apoptosis, and cell survival, and are overexpressed in lung, ovarian, breast, uterus, pancreas, and skin cancers. However, they are down-regulated in colorectal, hepatic, and gastric cancers [23,24]. MT is over-expressed in all GISTs [25,26]. From all the above findings, genetic pathways seem to be different in these 2 neoplasias.

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It is obvious that further data are required to support the hypothesis of common carcinogenic etiology.

Conclusions

Accurate staging is essential because the dominant neoplasia usually determines the outcome. Further research is needed to clarify the role of oncogenic mutations and signalling pathways in carcinogenesis of neoplasia of different histiogenic origins.

Conflict of interest

None.