

A rare case of Wild-Type GIST of descending colon with GANT characteristics

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Cite this article as: Kalliouris DN, Nikou E, Zaravinos S, Manesis K, Oikonomou C, Lingria A, et al. A rare case of Wild-Type GIST of descending colon with GANT characteristics. *Turk J Gastroenterol* 2018; 10.5152/tjg.2018.18561.

Dear Editor,

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract. They constitute a distinct group of mesenchymal tumors, presenting different histological aspects in comparison to other types, such as tumors of neural origin (schwannoma and paraganglioma), smooth muscle cell origin (leiomyoma and leiomyosarcoma), fibroblastic tumors, and vascular tumors (angiosarcoma), among others. Gastrointestinal autonomic nerve tumors (GANTs) are rare tumors, probably developing from the myenteric plexus of Auerbach. They are considered as a subgroup of GISTs with specific ultrastructural appearance. Although cytological, immunohistochemical, and ultrastructural characteristics of GIST and GANT appear to be relatively heterogeneous, similarities in pathology may complicate the diagnosis (1).

We present a rare case of a 55-year-old patient with difficulty in the differential diagnosis between GIST and GANT. The patient presented to our emergency department with a complaint of deep vague abdominal pain in the left upper quadrant during the last 3 weeks. The patient received an antibiotic for suspected urinary infection. On clinical examination, abdominal pain with tenderness in the suprapubic area and in the left hypochondrium was observed. Blood tests revealed mild leukocytosis (white blood cell 11,800/ μ L and neutrophil 78.2%) and increased C-reactive protein (15.6 mg/dL) and erythrocyte sedimentation rate (120 mm/h). Computed tomography (CT) scan demonstrated a prestenotic distension of the splenic flexure of the colon with thickening of the bowel

wall and an intraluminal multilobular formation (Figure 1). On endoscopic examination of the colon, a pedunculated mass partially obliterating the lumen of the descending colon was detected (Figure 2). The patient underwent left hemicolectomy. On histological examination of the removed specimen, two firm pedunculated formations with mucinous characteristics with elastic–friable composition were revealed. Microscopically, the two polyp-like lesions were attributed to GIST with spindle cell development and high mitotic index. Immunohistochemical examination was positive toward S100 antibodies (Figure 3), vimentin (Figure 4), and platelet-derived growth factor receptor alpha (PDGFRA) and negative toward CD34, CD117, smooth muscle antibody, DOG-1, and desmine. Ki-67 index was found to be positive in 80% of the neoplastic nuclei (G2). The edges of



Figure 1. Computed tomography scan demonstrated a prestenotic distension of the splenic flexure of the colon with thickening of the bowel wall and an intraluminal multilobular formation

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Received: July 15, 2018 Accepted: September 2, 2018 Available online date: November 20, 2018

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DOI: 10.5152/tjg.2018.18561

the specimen were free of tumor infiltration. Mutational analysis for c-kit (cd117) and PDGFRA was not detected, and there was also no mutation found on the BRAF gene. The above-mentioned findings indicate a wild-type GIST (WT-GIST) neoplasm with a high probability of GANT deviation (S100 positivity) of T3 No Mx-stage IIIb highly

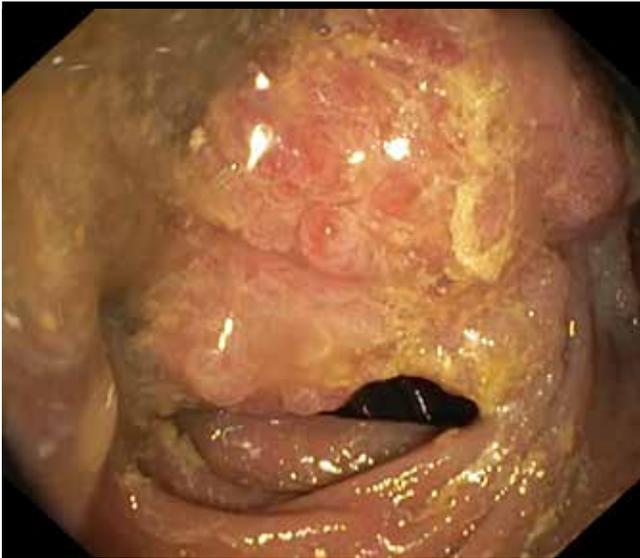


Figure 2. On endoscopic examination of the colon, a pedunculated mass partially obliterating the lumen of the descending colon was detected

malignant. The patient did not receive chemotherapy and still remains free of disease 19 months postoperatively.

Gastrointestinal stromal tumors are the most common mesenchymal tumors of the GI tract and account for 0.1% to 3% of all gastrointestinal tumors. The stomach and small intestine are the two most frequent primary sites, accounting for 85%. GISTs may mostly represent sporadic cases, but they could also be part of familiar syndromes, such as the Carney triad, Carney–Stratakis syndrome, and neurofibromatosis type 1 (2). Surgical treatment remains the cornerstone of management for localized GIST, with curative results >50% of the cases. For locally advanced or metastatic GISTs, which are refractory to conventional radio- and chemotherapy, the discovery of the gain mutations regarding the KIT and PDGFRA genes has led to the use of adjuvant imatinib therapy. In cases of imatinib resistance, second-line treatment with sunitinib and regorafenib has been approved. Immunohistochemistry has showed the presence of GIST, without KIT/PDGFR mutations, called WT-GIST, which is imatinib resistant, due to the alternative pathways of mutations or due to the acquisition of secondary mutations in KIT/PDGFR. As a result of all these alternative mutational pathways, the clear cut-off point of the adjuvant therapy in high-risk WT-GIST or the best systemic treatment remains unknown (3).

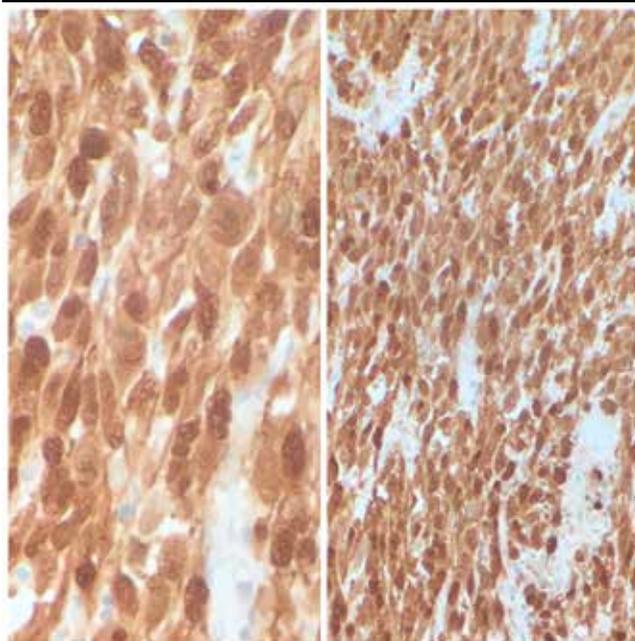


Figure 3. Immunohistochemical examination was positive toward S100 antibodies

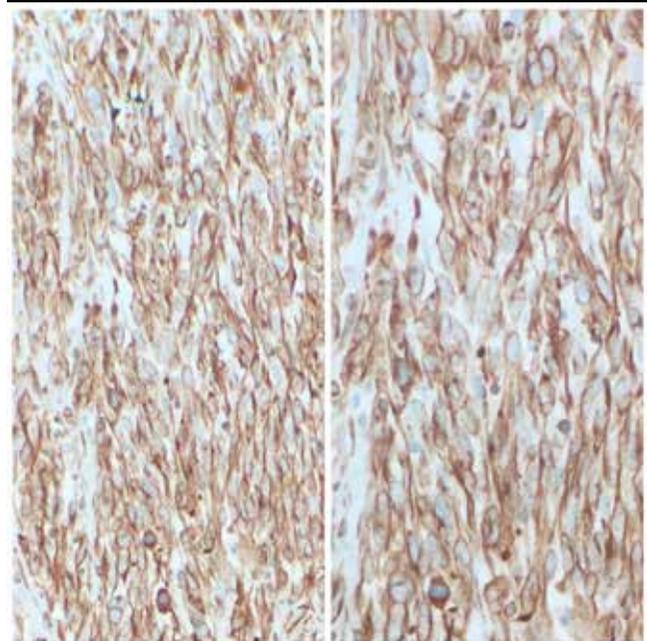


Figure 4. Immunohistochemical examination was positive toward vimentin

A schematic approach is being attempted in order to shed light on the various forms of GISTs.

c-kit-mutated GIST. Almost 75% of all GISTs present gain-of-function mutations in the KIT gene in exons 11, 9, 13, and 17, which activate downstream pathways (RAS/RAF/MAPK, JAK/STAT3, and PI3K/AKT/mTOR), increasing proliferation or evading apoptosis. The c-kit mutation is a clinically important therapeutic target (imatinib). They tend not to metastasize to lymph nodes, and there is no difference when compared with sporadic GISTs in terms of medical or surgical treatment.

Platelet-derived growth factor receptor alpha-mutated GIST. Mutations in this gene are less frequent (approximately 15%). They are also gain-of-function mutations, which activate the same transduction pathways as the c-kit. This is the reason why c-kit and PDGFRA mutations are mutually exclusive. GISTs that do not present any mutation of these two genes are called WT-GISTs.

Wild-type GIST. Approximately 10% of GISTs do not harbor detectable mutations in KIT or PDGFRA. These are called WT-GISTs. Generally, these types are less sensitive to tyrosine kinase inhibitors. The molecular biology of these GISTs has become more complex due to the discovery of different subgroups, which harbor mutations in the succinate dehydrogenase (SDH) complex, NF-1 gene (neurofibromatosis), and BRAF or KRAS genes. With reference to KITwt/PDGFRAWt GISTs, they can be divided into two groups based on the immunohistochemical status of SDH subunit B. Quadruplewt GIST is a term that indicates the absence of mutation in all known genes (KITwt/PDGFRAWt/SDHwt/RAS-Pwt) (4).

Gastrointestinal autonomic nerve tumors are rare stromal tumors, accounting for 1% of all malignant GI tumors. Their histological features are similar to GIST, but their ultrastructural characteristics suggest that they originate from the myenteric plexus of Auerbach. Histologically, GANTs may have spindle and large epithelioid cells arranged in sheets, fascicles, or nests, but as already mentioned, these are also characteristics shared by GISTs. The cells show intense staining for vimentin, S100 protein, neuron-specific enolase, chromogranin, and synaptophysin. Immunohistochemically, GIST and GANT are

two entities difficult to differentiate due to many similarities in their clinical and immunological profiles. WT-GIST and GANT have a common feature of low response to tyrosine kinase inhibitor. Recent studies identified new molecular groups and new mutations in BRAF and SDH as well as the acquisition of secondary mutations in KIT and PDGFRA, fact that requires the implication of new therapeutic strategies and the conduct of new studies regarding treatment (5).

There is still an ongoing debate regarding the possible role of adjuvant therapy in high-risk WT-GIST and GANT. The fact that the genotype of each GIST influences the treatment response, drug resistance, and prognosis, accurate diagnosis is essential for adequate and prompt treatment.

Informed Consent: Informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - D.K., E.N.; Design - D.K., K.M.; Supervision - D.K., S.Z., E.N.; Resource - D.K.; Materials - D.K., A.L.; Data Collection and/or Processing - D.K., E.N.; Analysis and/or Interpretation - D.K., A.L., A.K.; Literature Search - D.K., C.O.; Writing Manuscript - D.K.; Critical Reviews - D.K., D.F., P.S., G.A.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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