Trakia Journal of Sciences, Vol. 10, Suppl. 2, 287-292, 2012

Available online at:
http://www.uni-sz.bg

ISSN 1313-7050 (print)
ISSN 1313-3551 (online)

MULTIPLE EXTRA-GASTROINTESTINAL TUMORS: A REPORT OF TWO CASES WITH CLINICO-PATHOLOGIC CONSIDERATION

V. Ivanova[1*], Iv. Taneva[2], Al. Vlahova[1], M. Karaivanov[3], P. Tonchev[4], P. Tokov[2], V. Dimitrova[2]

[1]Department of General and Clinical Pathology – Medical University, Sofia, Bulgaria
[2]Department of General and Operative Surgery – Medical University, Sofia, Bulgaria
[3]Department of General and Clinical Pathology – Medical University, Pleven, Bulgaria
[4]Department of Propaedeutics of Surgical Diseases – Medical University, Pleven, Bulgaria

ABSTRACT
Most gastrointestinal stromal tumors (GISTs), generally Kit-positive and Kit/PDGFRA mutation-driven mesenchymal tumors featuring Cajal cell-like differentiation, arise from the stomach or small intestine. Neoplasms with histology and immunohistochemistry similar to GISTs may occur outside the gastrointestinal tract most commonly in the omentum, mesentery, and retroperitoneum. These tumors are defined as extra-gastrointestinal (EGISTs) since they display no connection with gastric or intestinal wall. We present two patients with multiple EGISTs with retroperitoneum and mesentery site of origin correspondingly. Both cases were characterized with adverse prognostic factors: multiplicity, high mitotic rate, hypercellularity, and presence of necrosis. One of the patients died of massive pulmonary embolism soon after the operation. The other is still alive and in good health one year after operation and imatinib therapy onset. The aggressive surgical approach is the most effective one for EGISTs but in cases with non resectable or multiple tumors tyrosine kinase inhibitors give a new chance for treatment and prolonged life expectancy of these patients.

Key words: Extra-gastrointestinal stromal tumors, multiple, histological prognostic factors.

INTRODUCTION

Although GISTs are the most common primary mesenchymal malignancies of the gastro-intestinal tract (GIT), they are relatively rare neoplasms. Their annual incidence has been estimated as 11-15 per million (1). GISTs occur throughout the GIT from the lower esophagus to the anus: 60% arise from the stomach, 35% from the small intestine, less than 5% from the colorectum, and less than 1% have been reported to arise from the esophagus and appendix (1). Most frequently GISTs express a Kit protein, having a gain-of-function mutation in the regulatory juxtamembrane domein of the c-Kit gene. The Kit protein can be detected by immunohistochemical assay for the CD117 antigen. Some GISTs demonstrate an activating mutation in another class III receptor tyrosine kinase gene, the PDGFRA gene, which encodes the tyrosine kinase receptor alpha for members of the platelet-derived growth factor family. Extra-gastrointestinal stromal tumors (EGISTs) showing features of GISTs have been described at extra-gastrointestinal sites including the omentum, mesentery and retroperitoneal space. The clinical features and treatment of EGISTs are not well known since a relatively small number of such cases have been reported in the literature.

***Correspondence to**: *Vesela Ivanova, M.D., Ph. D. Department of General and Clinical Pathology - Medical University, Zdrave Str. 2, 1431 Sofia, Bulgaria, e-mail: veselaivanovamd@mail.bg, Tel: +359 2 9230 837, GSM; +359 885 162030*

CASE 1

A 63-year-old male was admitted to Surgical Clinic with symptoms of intense fatigue, heaviness in the abdominal area, nausea without vomiting, difficulty in miction and defecation, and body temperature in the afternoon up to 37.5°C. Despite his long-term obesity, in recent months the patient had lost about 20 kg, but the circumference of the abdomen had been continuing to grow. The physical examination

showed abdomen above the chest, respiratory mobile, with no palpable pain. Laboratory data: 119 g/l hemoglobin, hematocrit 0.36, leukocytes 17.109/l, ESR 84 mm/h; tumor markers – normal rates. Abdominal computed tomography (CT) scan demonstrated a soft tissue formation with heterogeneous structure, located under the diaphragm, between the stomach and spleen, leading to compression of organs mentioned above. There were extensive areas of necrosis (CT scan with contrast) and rich collateral network in the frontal surface of the formation. Pancreas – normal visible head, the rest was not displayed. At the operation, when the abdominal cavity was opened, a rounded tumor formation, attached to the diaphragm was found **(Figure 1)**. The tumor mass was localized behind the stomach and under the transverse colon, and lied on the mesentery of the small intestine, reaching the entrance to the pelvic floor. There was no communication with the guts. The total diameter of the tumor was 500 mm (the patient's weight was about 160 kg). The tumor was heterogeneous, composed of solid areas and cystic zones, filled with liquid **(Figure 2).** It was considered that the tumor was not removable by "en block" method and was extirpated as 10-12 kg fragmentized tumor masses. Multiple whitish round formations with diameter up to 20 mm were isolated in addition to the main tumor. The presumable clinical diagnosis was carcinoma of the pancreas. Microscopically, the tumors were characterized by interlacing bundles of elongated cells with spindle-shaped nuclei with a fibrillary collagenous background **(Figure 3)**. The nuclei of tumors cells in some areas showed a definite tendency to palisade and form anuclear zones reminiscent of neuropil. Mitotic rate varied from 2 to 50 mitotic figures (MF) per 50 high power fields (HPF) in slides from different tumor formations. Foci of hemorrhages and necrosis were present. Tumor cells reached to the peripancreatic fat tissue but did not infiltrate the pancreatic parenchyma. Immunohistochemical set of antibodies demostrated: the tumor cells were both CD117 **(Figure 4)** and CD34 strongly positive, Cytokeratin AE1/3, Smooth Muscle Actin, Desmin, and S-100 negative. A therapy with imatinib (Gleevec, Novartis) was initiated. The patient is still alive and in good health one year after operation.

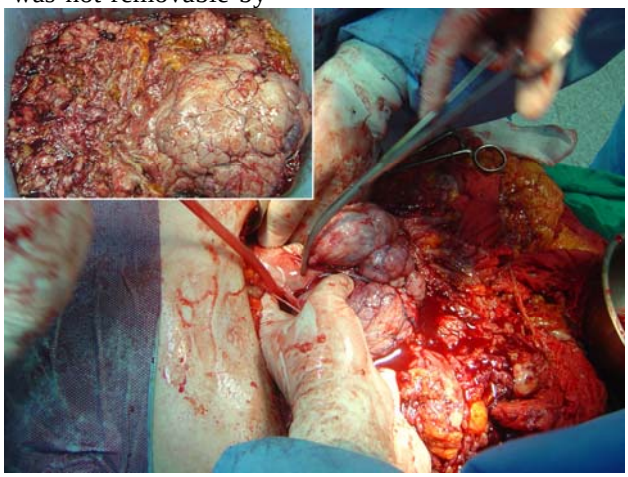

Figure 1. Case 1: intraoperative picture showing a huge tumor mass, attached to the diaphragm.

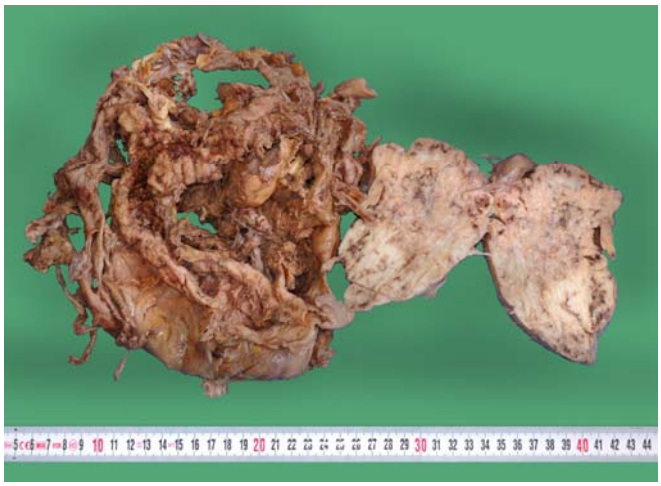

Figure 2. Case 1: gross appearance of the tumor formation, consisting of ruptured cystic and solid whitish firm areas.

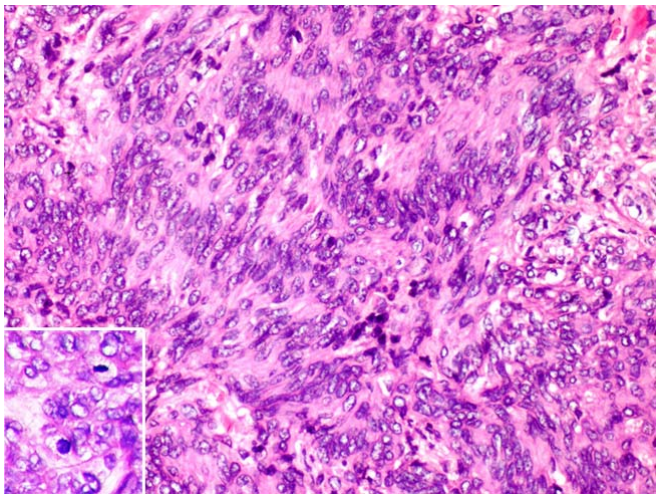

Figure 3. Case 1: Hematoxylin-Eosin stained histological slides revealing small intestinal GISTs-like morphology, consisting of palisade orientated spindle cells and anuclear zones; inset–high mitotic activity.

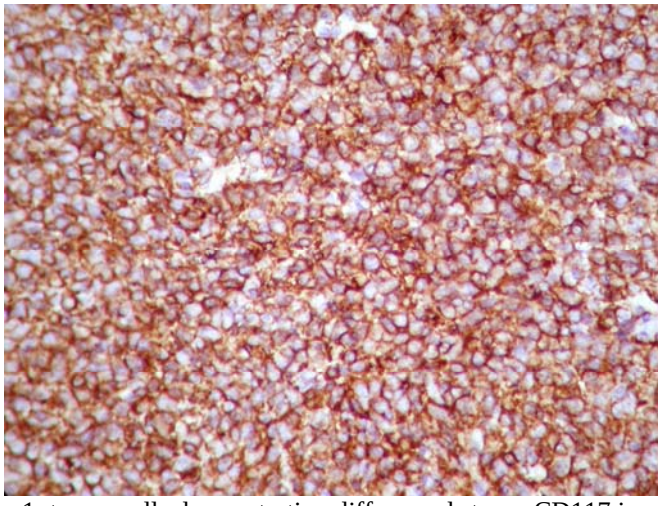

Figure 4. Case 1: tumor cells demonstrating diffuse and strong CD117 immunoreactivity

CASE 2

An 82-year-old male was hospitalized because of constipation and abdominal pain. Ultasonography revealed multiple round hypoechogenic formations in the abdomen. The intraoperative frozen section and biopsy report was "leiomyoma". One month later the patient was rehospitalized due to melaena and extirpation of some of the tumor masses with partial resection of the small intestine were performed. During the postoperative period the patient had local peritonitis and died of massive pulmonary embolism. At the autopsy examination multiple nodular formations (diameter up to 150 mm), attached to the mesenterium were found **(Figure 5)**. The tumor masses were grey-yellowish, firm, with foci of hemorrhages and necrosis **(Figure 6)**. Histologically, the tumors had the features of benign leiomyomatous proliferations with secondary changes (hyalinization and hemorrhages). There were new findings at the histology differing from the former described – these areas revealed hypercellularity, focal necrosis, high mitotic rate and atypical mitotic figures **(Figure 7)**. The mitotic rate reached to 75 MF/50 HPF. An ancillary immunohistochemical study was performed: the tumor cells were CD117 **(Figure 8)** strongly positive, Vimentin positive, and CD34, Smooth Muscle Actin, Desmin, S-100 protein, and CD68 negative.

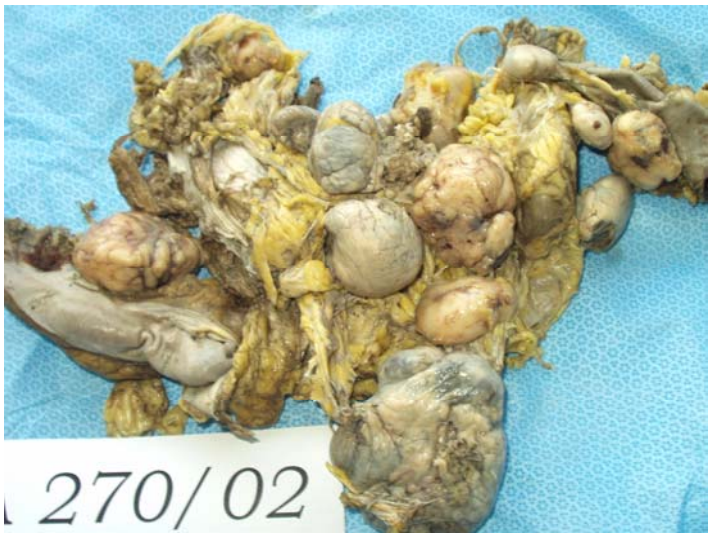

Figure 5. Case 2: autopsy material showing multiple tumor formations, attached to the mesenterium, not reaching the intestinal lumen.

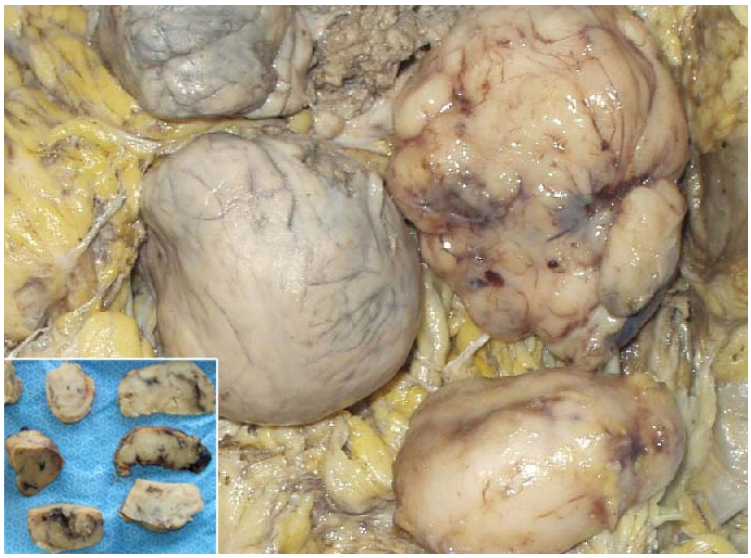

Figure 6. Case 2: autopsy material demonstrating numerous grey-yellowish firm tumors; inset–cut surface with foci of hemorrhages and necrosis.

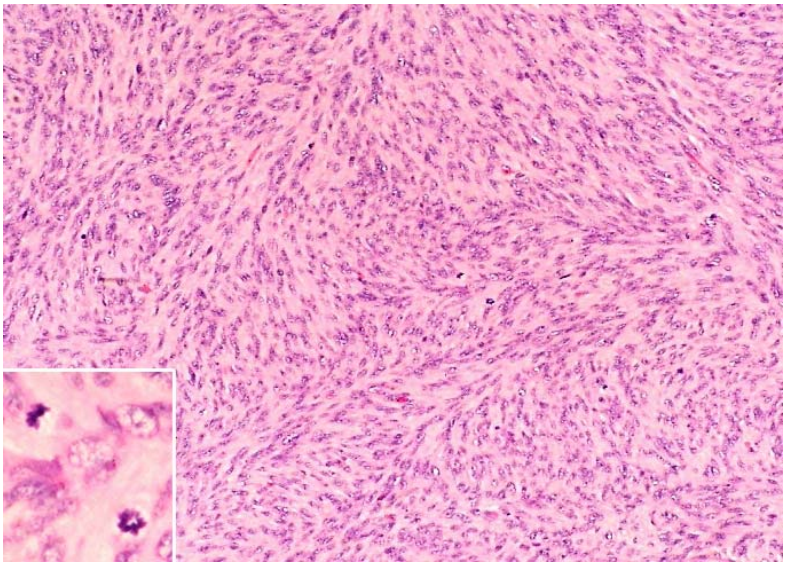

Figure 7. Case 2: Hematoxylin-Eosin stained histological slides revealing spindle cells with high mitotic rate, arranged in interlacing fascicles; inset–high mitotic activity.

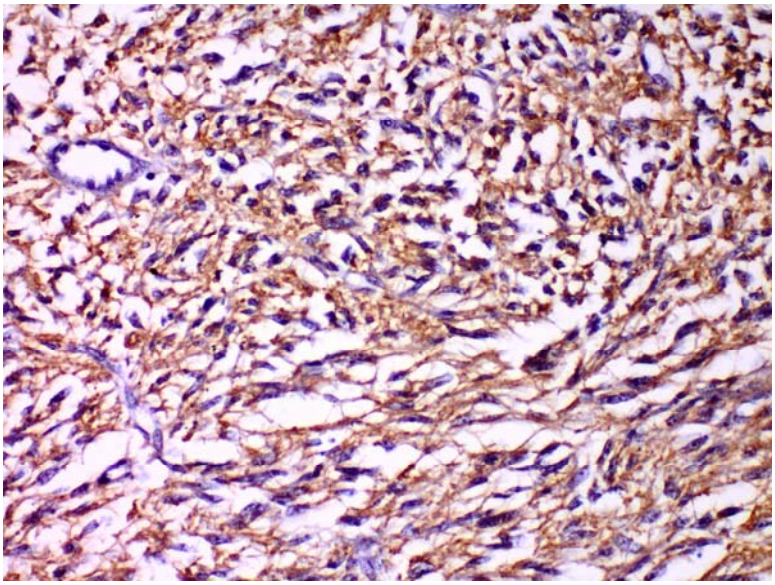

Figure 8. Case 2: tumor cells demonstrating diffuse and strong CD117 immunoreactivity.

DUSCUSSION

Most GISTs, generally Kit-positive and Kit/PDGFRA mutation-driven mesenchymal neoplasms featuring Cajal cell-like differentiation, arise from the stomach or small intestine. EGISTs are rare sromal tumors that occur outside the GIT and comprise about 5-7% of all GISTs (2). EGISTs, located in the omentum, mesentery, retroperitoneum, and undefinate abdominal sites, display no connection (however tenuous) to the wall or serosal surface of the viscera. The cell origin of EGISTs remains controversial. These tumors could represent apparent GISTs that have arisen from the outermost muscle coat of the bowel, but have lost their contact to the point of origin due to an extensive extramural growth pattern (3).

The clinical, pathological and prognostic features of GISTs are widely known, while data about EGISTs are few. Histologically, EGISTs can be of spindle cell, epithelioid or mixed type. The spindle cell type, as presented in our cases, is similar to small intestinal GISTs morphology. In a large study, Reith et al. (4) noted that EGISTs expressed CD117 (100%), CD34 (50%), Neuron-Specific Enolase (44%), Smooth Muscle Actin (26%), Desmin (4%), and S-100 protein (4%).

The behavior of stromal tumors differs according to location, with a trend toward increasingly aggressive behavior as they proceed distally along the GIT. The majority of GISTs located in the stomach have a good prognosis, whereas those in the small intestine have a significantly worse prognosis. In this regard, EGISTs are similar to stromal tumors arising in the distal GIT (4, 5). A study of a small number of omental (9 cases) and mesenteric (7 cases) EGISTs seemed to show a better prognosis for the omental ones (6).

In contrast to GISTs, all authors have pointed out that no association between a tumor size and outcome of EGISTs (4, 5). Most of these tumors are large (more than 10 cm) was first detective because they seldom produce clinical symptoms compromised the bowel lumen (ulcer, obstruction or hemorrhage). Therefore, tumor size, which is commonly used in GISTs as a prognostic factor, may not be applicable to EGISTs.

Reith et al. (4) examined 48 EGISTs arising in the abdominal cavity and the retroperitoneum. They reported that high cellularity, mitotic activity (>2MF/50HPF), and presence of necrosis were significantly associated with an adverse outcome in univariate analyses. Only 5% of patients with less than two of the above three histologic features experienced death or tumor metastasis, while 92% of patients having two or more of the features had an adverse outcome. The nuclear atypia, growth pattern (spindled, epithelioid, or mixed), and size had not a predictive value. In Yamamoto et al.'s study (2), a high mitotic rate (> 5 MF/50 HPF) and a high MIB-1 proliferating index (>10%) were each significantly associated with an adverse outcome.

Miettinen et al. (5) comparing 51 cases of solitary and 39 of multiple omental GISTs reached a conclusion that multiple omental GISTs had a poor prognosis: the median survival was only 8 months, and there were no long-term survivors. The authors suggested that these tumors are advanced, metastatic GISTs dislodged or extending into the omentum from an inconspicuous GI attachment. Thus, multiplicity indicates malignant tumor behavior, and further prognostication by histologic parameters seems to have limited if any relevance in these cases.

The current best modality of treatment for GISTs, including EGISTs, is surgical resection, with postoperative recurrence seen in 50% of cases of GISTs treated with surgery alone (7). During the intervention it is important to achieve a complete removal of the mass and regional lymph nodes, even if prognostic value of lymphatic involvement of these tumors is still unclear. GISTs are resistant to conventional chemotherapy and radiotherapy. The recent availability of the Kit/PDGFRA tyrosine kinase inhibitor imatinib has revolutionized the treatment of GISTs and the survival of the patients with metastatic and inoperable tumors has improved dramatically. Mutation analysis is important in identifying those GISTs that are not sensitive to imatinib or benefit from a higher dosage because of lesser imatinib sensitivity.

IN CONCLUSION, we present two patients with multiple EGISTs with retroperitoneum and mesentery site of origin correspondingly. Both cases were characterized with adverse prognostic factors: multiplicity, high mitotic rate, hypercellularity, and presence of necrosis. One of the patients died of massive pulmonary embolism soon after the operation. The other is still alive and in good health one year after operation and imatinib therapy onset. The aggressive surgical approach is the most effective one for EGISTs but in cases with non resectable or multiple tumors tyrosine kinase inhibitors give a new chance for treatment and prolonged life expectancy of these patients.

REFERENCES

1. Miettinen, M. and Lasota, J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Path Lab Med, 130: 1466-1478, 2006.
2. Yamamoto, H., Oda, Y., Kawaguchi, K., et al. C-kit and PDGFRA mutations in extragastrointestinal stromal tumor (gastrointestinal stromal tumor of the soft tissue). Am J Surg Path, 28: 479-488, 2004.
3. Agaimy, A. and Wunsch, P.H. Gastrointestinal stromal tumors: a regular origin in the muscularis propria, but an extremely diverse gross presentation: a review of 200 cases to critically re-evaluate the concept of so-called extra-gastrointestinal stromal tumors. Langenbecks Arch Surg, 319 (4): 322-329, 2006.
4. Reith, J.D, Goldblum, J.R., Lyles, R.H., et al. Extragastrointestinal (soft tissue) stromal tumors: an analysis of 48 cases with emphasis on histologic predictors of outcome. Mod Pathol, 13: 577-585, 2000.
5. Miettinen, M., Sobin, L.H., Lasota, J. Gastrointestinal stromal tumors presenting as omental masses – a clinicopathologic analysis of 95 cases. Am J Surg Path, 33: 1267-1275, 2009.
6. Miettinen, M., Monihan, J.M., Sarlomo-Rikala, M., et al. Gastrointestinal stromal tumors/smooth muscle tumors (GISTs) primary in the omentum and mesentery: clinicopathologic and immunohistochemical study of 26 cases. Am J Surg Path, 23: 1109-1118, 1999.
7. De Mateo, R.P., Lewis, J.J., Leung, D., et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg, 231: 51-58, 2000.