

GIST mimicking an hyperplastic polyp of descending colon



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Theodore G. Troupis^{*/**}, Stamatios Chatzikokolis^{**}, Adamantios Michalinos^{*}, Antonios Sarakinos^{*}, Panagiotis Kotsopoulos^{**}, Helen Patsea^{**}, Athanasios Kotsinas^{***}, Konstantinos Evangelou^{***}, Vassilis G. Gorgoulis^{***}

^{*}Department of Anatomy, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

^{**}Iaso General Hospital, Athens, Greece

^{***}Department of Histology and Embryology, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

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INTRODUCTION: *The authors describe a case of a patient who underwent resection of a colonic GIST mimicking a hyperplastic polyp of the descending colon.*

CASE REPORT: *We report the case of a colonic Gastrointestinal Stromal Tumor (GIST) of a 55 years old male patient who was admitted to us because of rectal bleeding and altered bowel habits. Patient was initially diagnosed for hyperplastic polyps of the descending colon and thus surgical treatment was proposed. Post operative histological examination of the polyps revealed a GIST that was classified as one of a very low malignancy based on NIH consensus risk stratification system. Patient is followed – up and until today presents no sign of disease.*

DISCUSSION: *Gastrointestinal stromal tumor (GIST) is a rare mesenchymal tumor commonly occurring in the gastrointestinal tract. It is usually found at the stomach and small bowel while colonic, rectal and esophageal GIST are rare. Diagnosis of GIST is based more on histological examination and less on clinical findings or radiological image since they are nonspecific. Complete surgical resection with negative margins remains the only effective treatment against GIST yet imatinib mesylate, a tyrosine kinase growth factor receptor inhibitor, is found to be effective against GIST and is currently used as treatment for metastatic, recurrent or non – operable GIST. Although the diagnosis is difficult, especially in the less common sites, the Authors suggest that GIST should be included in the differential diagnosis of colonic masses.*

KEY WORDS: Descending colon, Gastrointestinal stromal tumor, Hyperplastic polyp.

Introduction

Gastrointestinal Stromal Tumors (GIST) are rare tumors involving the gastrointestinal tract (GI tract) ^{1,2}. GIST account for less than 1% of all the tumors of the GI tract yet they represent the most common mesenchymal tumors corresponding up to 1/6 – 1/3 of all soft tissue

sarcomas, considering their small size and asymptomatic clinical features ¹⁻³. Annual prevalence of GIST is estimated between 10-20 per million per year, based on series of national studies ⁴⁻⁶. The most common GIST site is stomach (50-60%), followed by the small intestine (20-25%). GIST are rare on colon, presenting only 5% ^{4,7,8}. GIST present mutations at c-kit proto-oncogene and express CD117 antigen, a tyrosine kinase growth factor receptor, at 95% ^{1,3,9,10}. Some of CD117 (-) GISTs are found to express PDGFRA, another tyrosine kinase growth factor receptor. Another marker, DOG-1 a cell surface protein of unknown function identifies the vast majority of both c-Kit negative and PDGFRA mutated GIST cases that may still benefit from

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Correspondence to: Theodore Troupis, 75 Mikras Asias str, Goudi, Athens 11527, Greece (E-mail: ttroupis@med.uoa.gr).

imatinib mesylate (R). Surgical resection is the only effective treatment for GIST. Imatinib mesylate, a tyrosine kinase growth factor receptor inhibitor is found to be effective against GIST, and is currently used as treatment for metastatic, recurrent or non – operable GIST ^{2,10,13}. In this report the authors describe diagnostic procedure and treatment of a patient with a rare case of colonic GIST.

Case report

A 55 years old male patient, smoker (30 cigarettes/day for 30 years) was admitted to our hospital complaining of rectal bleeding and altered bowel habits. Patient had undergone appendectomy 30 years ago by a paramedial incision and also reconstruction of left inguinal hernia with the use of mesh, two years ago.

Clinical examination of the abdominal wall revealed deformity because of the previous appendectomy, normal bowel sounds and no sensitivity during palpation. A computer tomography (CT) scan of upper and lower abdomen was normal and the colonoscopy detected 4 polyps on the rectum and a big bleeding polyp on the descending – sigmoid colon at the antimesenteric border (Fig. 1). Biopsies of all polyps were performed and histological examination of the biopsy samples posed the provisional diagnosis of hyperplastic polyps.

Surgical resection of the “hyperplastic” polyp of the descending colon was scheduled after marking its borders with blue methylene and a metallic clip on the top of the tumor. A median subumbilical incision was performed to enter the abdominal cavity. Adhesions between abdominal wall, caecum and ascending colon were lysed

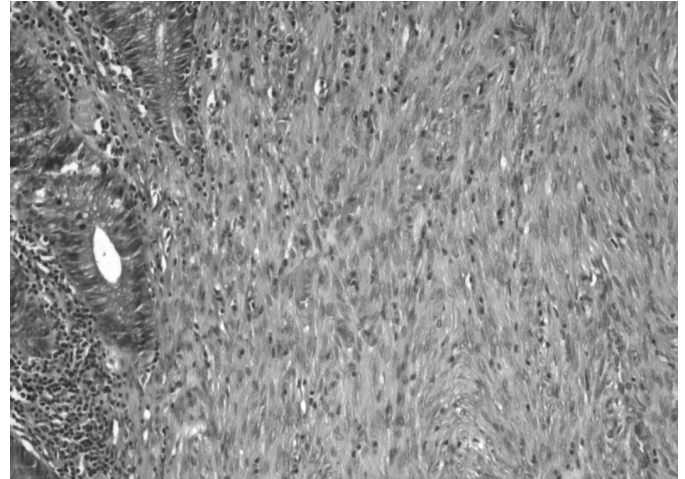


Fig. 2: Histological section of the tumor, showing spindle neoplastic cells with an eosinophilic cytoplasm arranged in a solid pattern. Nuclear atypia is mild. (H&E counterstain, magnification x200).

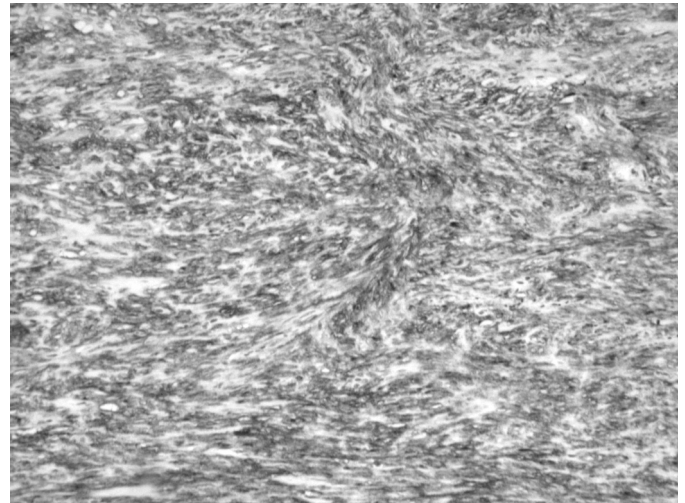


Fig. 3: The majority of neoplastic cells exhibit CD117 immunopositivity (magnification x200). DAB immunohistochemistry performed by an indirect streptavidin-biotin-peroxidase method on paraffin section counterstained with haematoxylin.

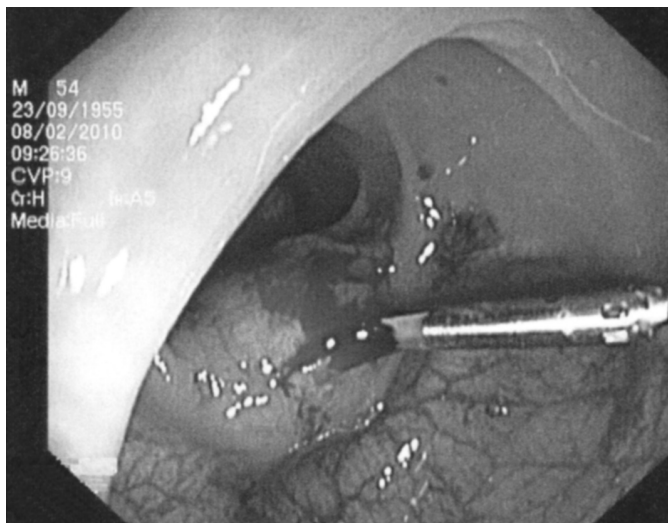


Fig. 1: “Hyperplastic polyp” of descending colon as shown in colonoscopy.

and a palpable mass was revealed on the descending colon. The descending colon was clamped proximal and distal to the lesion. The mass was removed by a longitudinal atraumatic incision on the antimesenteric border parallel to the colic taenia. The defect was sutured along its transverse axis. After meticulous haemostasis, the peritoneal cavity was inspected and the abdominal incision was closed. Patient recovered uneventfully and left the hospital free of symptoms and haemodynamically steady. Histological examination of the resected mass revealed a Gastro Intestinal Stromal Tumor (G.I.S.T) classified as one of a very low malignancy based on NIH consensus risk stratification system (1,2 cm m.d., 2-3 mitoses/HPF). Gross examination revealed the presence of a well circumscribed brownish tumor measuring 1.2 cm in the

descending colon. On sectioning, the tumor occupied the mucosa, submucosa and the entire muscular layer of the colonic wall with ulceration of the mucosa but no areas of hemorrhage or necrosis.

Microscopically, the tumor corresponded to a mesenchymal neoplasm consisting predominantly, of spindle shaped cells with eosinophilic cytoplasm and clear nuclei, arranged in a solid pattern (Fig. 2). There was mild nuclear atypia and the mitotic rate was 2-3 per 50 HPF (magnification X40).

Immunohistochemically, the tumor cells exhibited CD117 (Fig. 3), CD34 and vimentin immunopositivity, but no immunoreactivity for α -smooth muscle actin, desmin and S100 protein. The proliferation index assessed by Ki-67 immunohistochemistry was about 2%.

These morphological and immunohistochemical features revealed the diagnosis of a GIST with very low malignant potential.

Discussion

GIST are the commonest mesenchymal tumors of the GI tract, yet representing only for 1% of the total ^{2,3,5,6,14}. GIST express CD117, a tyrosine kinase growth factor receptor, as a result of a mutation at the c-kit protooncogene that defines their differential diagnosis between other mesenchymal tumors such as leiomyosarcomas, sarcomas etc. GIST constitute a target for a selective tyrosine kinase receptor inhibitor, Imatinib chemotherapeutic agent ^{1,2,8,10,15}. Complete surgical resection is the most effective treatment for GIST.

In 1941 Golden and Stout were the first to report tumors arising in the bowel wall and described them as leiomyblastoma, leiomyoma or leiomyosarcoma based on their morphologic characteristics ¹⁶. Major progress occurred in 1998 when Hirota et al discovered that GIST harbored c-Kit mutations and were positive for CD117 by immunohistochemistry ⁹. In 2001 the GIST workshop, held at the National Institutes of Health, defined certain elements on the diagnosis of GIST according to histological and immunohistochemical features ¹. In 2001 imatinib mesylate was found to be active against chemotherapy resistant GIST ¹³. Annual prevalence of GIST is estimated between 10-20 per million per year based on a series of national studies ^{3,5,6,2,17}. GIST are believed to have a slightly higher prevalence at men ^{5,6,8,13} though some evidence revealed even a ratio of 2/1. Most GIST tumors occur at 5th and 6th decade of life ^{2,10,17,18} with a median age of 63y³. Less than 20% of GIST occur before the age of 40 and they are extremely rare before 20⁵. Although not sufficiently evidenced, GIST are believed to be prominent at white-caucasian race. Most GIST occur sporadically even though familial GIST ^{2,8} and GIST Syndromic participation in Neurofibrotosis 1 and Carney – Stratakis syndrome ¹⁹ have also been described. GIST prevalence is increased at von Recklinghausen disease ⁵.

GIST account for 20-30% of all intrabdominal sarcomas ⁸. 80% of all GIST occur at GI tract. Of these, approximately 50-60% occur at stomach, 20-40% at jejunum and ileum, with a higher prevalence at jejunum, followed by 5-10% at colon and rectum and 5% at esophagus ^{4-6,8,17,18,14,20}. 10% of GIST occur outside the GI tract, on the omentum, mesentery and retroperitoneum and are collectively referred as Extra Gastrointestinal Stromal Tumors (EGIST) ^{5,10}. Sporadic cases have reported GIST in the pelvis minor, in the appendix, the gallbladder ²¹ and the urinary bladder ²². In 6% of the cases due to the progression of the disease and multifocal intraperitoneal dissemination it is impossible to determine the primary location of the tumor ⁵. It is to be noted that some studies indicated a much higher prevalence of small, asymptomatic GIST on the stomach ²³. In a study Hassan et al ²⁴ reported that 50% of all colonic GIST occur on the ascending colon, 25% on the transverse colon and 25% on the sigmoid colon, while Miettinen et al reported 23% on the caecum, 7.5% on the ascending colon, 26% on the transverse colon, 15% on the descending colon, 46% on the sigmoid colon whereas, 23% were of unspecified location ³.

GIST are thought to originate from Cajal cells, the GI tract pacemaker cells but it is also plausible that GIST arise from pluripotential stem cells that differentiate into a Cajal cell-like or smooth muscle cell-like phenotype. Macroscopically, GIST are white, solid, fleshy masses with a size from 1-35 mm and median size of 5 mm ⁶. Microscopically, they are classified either as spindle – shaped phenotype (70%), epithelioid (20%) or mixed (10%). Although the term GIST should apply only to neoplasms that are CD117 positive, rare exceptions were accepted during the 2001 Consensus conference. Immunohistochemically, GIST are positive for CD117 at 95% or more, for CD34 at 60-70%, at α smooth muscle at 30-40%. GIST are positive for S100 only at 5% and rarely for desmin, which helps their differential diagnosis from other tumors ^{1,3,5,6,17,18}. Concerning the colon, GIST are positive for CD117 at 95%, CD34 at 30% and negative for desmin and S100 ¹⁵. GIST are positive for c-kit mutations, usually at exon 11, or PDG-FRA mutations ^{9,11}.

Diagnosis of GIST is based on clinical symptoms, radiological findings and biopsy results including histological and immunohistochemical tests. 20-30% of the patients are asymptomatic and GIST are randomly discovered by radiological examination or during surgical procedure for other reason. Clinical features of GIST are not tumor specific for the nature of the lesion and depend on its size and position, including abdominal pain, rectal bleeding, nausea, vomiting, weight loss, anorexia, flatulence, early satiety, occlusive obstruction of the bowel, acute abdomen and anemia. On examination there may be a palpable abdominal mass ^{8,17,25}. Symptoms of GIST located on the colon, usually include abdominal pain and

altered bowel habits. Radiological image on CT includes an exophytic or intramural mass arising from gastrointestinal wall and protruding intraluminally or into the abdominal cavity²⁵. GIST can also be detected by endoscopic ultrasound (EUS) as submucosal, intramural or subserosal masses. Definite diagnosis of GIST can be established only by histological examination. Biopsy should be avoided in case of strong GIST suspicion because of possible cancer cell dissemination in peritoneal cavity. Thus for many GIST definite diagnosis is confirmed only postoperatively^{5,18}. Differential diagnosis of GIST includes true smooth muscle cells, desmoid tumors, inflammatory fibroid polyps, inflammatory myofibroblastic tumor, schwannomas, solitary fibrous tumors, uterine type leiomyosarcoma, metastatic melanoma, intestinal clear cell sarcoma, and angiosarcoma. Other CD117 positive tumors that enter differential diagnosis are the following: Metastatic malignant melanoma, malignant vascular tumor, metastatic pulmonary small cell carcinoma, Kaposi's sarcoma, and occasionally Ewing's sarcoma¹⁵.

Prognosis highly depends upon GIST's malignancy. It is to be noted that GIST cannot be clearly differentiated into benign or malignant because of the GIST potential to metastasize. For these reasons GIST are considered to have a malignant potential. A large number of classifications have been proposed to estimate the malignancy potential of GIST. The first and most widely used classification is that based on 2001 NIH consensus, which takes in consideration tumor size and mitotic rate. A modification was presented by Huang et al at 2007²⁶. Another classification system concerning the potential of malignancy, is the one proposed by the Armed Forces Institute of Pathology (AFIP)²⁷. Goh et al²⁸ recently presented a modification of the AFIP classification system. Secondary criteria are sometimes used without proven value. The prognostic importance of anatomic location is not yet defined. Some studies failed to prove its value⁷ while others accepted it as an important prognostic factor²⁹. Other histological secondary criteria are cellularity, mucosal ulceration, presence or absence of KIT +/- PDGFRA mutations, sclerotic lesions, nuclear palisadation, skeinoid fibers^{6,17}. Metastases and free rupture in the abdominal cavity have poor prognosis⁸. Our case was classified as a GIST very low malignant potential according to the criteria mentioned^{1,26}.

Surgical en bloc removal with pseudocapsule to yield an adequately free resection margins is the only definite treatment for operable GIST². Small GIST (<2cm) of the upper GI tract, showing no high risk malignant EUS features do not require surgical excision. For these lesions endoscopic surveillance is recommended within 6-12 month intervals according to NCCN Clinical practice Guidelines in oncology³⁰. Tumor free resection margins are yet to be defined. When possible, GIST can be laparoscopically removed. GIST very rarely give metastases to lymph nodes and thus lymphadenectomy is not necessary.

Classic chemotherapeutic agents are not effective against GIST, probably due to elevated levels of p glycoprotein and MDR⁸. Imatinib, a tyrosine kinase receptor inhibitor is effective against GIST. Imatinib at a daily dose of 400-800mg is of proven value at inoperable GIST, metastatic GIST and recurrent GIST^{2,10}. The use of Imatinib as adjuvant or neoadjuvant therapy or in cases of incomplete surgical resection, remains obscure^{19,31}.

Conclusion

GIST often escape differential diagnosis, especially if they occur in anatomical positions where they are not expected, such as colon, due to their relative infrequency, the absence of specific clinical or imaging findings and the necessity of histological, immunohistological and molecular tests for confirmation of the diagnosis. Still, because of the possible malignant potential of all GIST, a high level of clinical vigilance is necessary in order to avoid consequences of late diagnosis or treatment. It is not to be neglected that some studies so a much higher prevalence than the one calculated and thus continuous updating of knowledge and clinical suspicion is necessary for all specialists.

Riassunto

I GIST (Gastro Intestinal Stromal Tumors) sono tumori rari che traggono origine dalle cellule di Cajal, che rappresentano il pacemaker del tratto gastrointestinale. La loro incidenza è calcolata tra i 10 e 120 milioni per anno, si incontrano alla 5^a ed alla 6^a decade di vita ed hanno una lieve prevalenza per gli uomini.

Rappresentano il 20-30% di tutti i sarcomi intra-addominali, per la maggior parte nel tratto gastrointestinale (GI). La sede più comune è lo stomaco mentre la sede colica è rara.

Macroscopicamente si presentano come masse solide, biancastre, carnose e istologicamente sono classificati come fusiformi, epitelioidi o misti. Presentano reattività immunoistochimica per CD 117 nel 95% e raramente per CD34. L'analisi molecolare dimostra mutazione al c-kit proto oncogene ed al PDGFRA.

Il loro aspetto clinico non è specifico e dipende grandemente dalla grandezza del tumore e dalla sua posizione anatomica. I sintomi più abituali sono il dolore addominale, la rettorragia, la nausea, il vomito. Anche le loro immagini radiologiche sono aspecifiche e comprendono masse esofitiche o intramurali. Solo l'aspetto istologico fa fare la diagnosi precisa di GIST, ma la biopsia è spesso evitata perché può provocare una disseminazione cellulare. Spesso la diagnosi di GIST è posta postoperatoriamente. Il calcolo della prognosi di un GIST si basa sul Consensus NIH del 2001 che ha proposto un sistema

di classificazione basato sulla grandezza del tumore e sul numero delle mitosi. Talvolta vengono usati criteri istologici e clinici secondari. È stata proposta una modifica di questo sistema.

L'asportazione in blocco insieme alla pseudo capsula è il solo metodo efficace per il trattamento dei GIST, possibilmente per via laparoscopica. L'Imatinib mesilato, un inibitore tirosino-kinasi del recettore è efficace contro i GIST ed è usato per il trattamento adiuvante o neoadiuvante, oppure in caso di escissione chirurgica incompleta.

Questo articolo tratta l'iter diagnostico e terapeutico di un GIST del colon simulante un tumore iperplastico dei colori discendente. Vengono descritti gli esami clinici, radiologici ed istologici insieme a considerazioni diagnostiche ed i processi di trattamento. Gli Autori ritengono che, in relazione al fatto che talvolta i GIST sfuggono alla diagnosi differenziale, il loro possibile potenziale maligno e la possibilità di una prevalenza molto maggiore di quella attualmente calcolata, in relazione a certe relazioni, è necessaria una grande attenzione clinica al fine di ottenere una buona cura dei pazienti.

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