Minimally invasive experience for the treatment of gastrointestinal stromal tumours

Ann. Ital. Chir., 2015 86: 357-361
pii: S0003469X15023957

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Gastrointestinal stromal tumours are rare mesenchymal neoplasms, accounting less than 3% of all the gastrointestinal tumours, that may arise in all portions of the gastrointestinal tract but more frequently they involve stomach and small bowel. Generally are asymptomatic or slight symptomatic, although they may also cause acute clinical conditions. Histologically are characterised by a meshwork of spindle-like cells mixed with fibro-hyaline stroma. The immunohistochemical assessment, marked for a strong immunopositivity for CD117 antibodies, allows the differential diagnosis with others muscular, nervous and fibroblastic tumours.
Tumour size and mitotic rate are the most important prognostic indicators. Surgery represents the treatment for patients with primary non-metastatic disease, however a prolonged oncologic follow-up is always recommended.
Minimally invasive technique is increasingly adopted and preferred for its low morbidity and shorter in-hospital stay, and more and more reports confirm its safety, efficacy and feasibility.
We report a case series of three pauci-sympomatic patients, all hospitalised for severe anaemia related to a chronic gastrointestinal bleeding, successfully treated by laparoscopic approach for the removal of gastrointestinal stromal tumours, two located in the stomach and one in the jejunum.

KEY WORDS: Anaemia, Gastrointestinal stromal tumour (GIST), Laparoscopic approach, Jejunum, Stomach

Introduction

Gastrointestinal stromal tumours (GISTs) are rare neoplasms of mesenchymal origin, representing 0.1-3% of all the gastrointestinal malignancies [1-3]. These tumours usually occur in adults, older than 50 years, and rarely in children or in the second decade of age (<1%). Less than 5% of them are associated, in decreasing order of frequency, with one among the following genetic disorders: neurofibromatosis type 1, Carney triad, and familial GIST syndrome [1]. GISTs may arise anywhere in the submucosa of the gastrointestinal (GI) tract, from the oesophagus to the rectum [3]. The stomach is the site where these tumours occur in more than half of patients (50-70%); other common localisations are small bowel (20-35%), colon (5-10%) and oesophagus (5%) [1,3-7]. Only a small number of cases (approximately 5%) have been reported elsewhere in the abdominal cavity, such as omentum, mesentery and retroperitoneum. The clinical presentation of GIST is related to its size and localisation. Frequently they are asymptomatic and discovery

Pervenuto in Redazione Marzo 2015. Accettato per la pubblicazione Maggio 2015.
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is incidental. Acute abdominal pain, bowel occlusion, and gastrointestinal bleeding are possible related symptoms [1]. Open and laparoscopic approaches are described in worldwide literature.
We report a case series of three GISTs in patients admitted for anaemia and treated by laparoscopic technique.

Case Series

In six months, from November 2012 to April 2013, we observed three patients, who were admitted to the Regional Hospital of Orleans (France) for iron-deficient anaemia likely related to chronic bleeding. All patients were assessed with laboratory tests, endoscopy, ultrasounds and radiological investigations. Two patients were diagnosed a gastric neoplasm, in the third one the lesion was localised in the jejunum. Then, patients were hospitalised in the surgical ward for the tumour excision, that was carried out in all case in general anaesthesia, using a minimal invasive approach, and without abdominal drain placements. Blood loss was minimal in all cases. All specimens were processed by pathologists with routine hematoxylin-eosin stain and immunohistochemical analysis; both, microscopic appearances (spindle-shaped cell population mixed with fibro-hyaline stroma) and immonostaings (cytoplasmic immunoreactivity for CD-117 and CD-34) were consistent with the diagnosis of GISTs. There were no tumour rupture or spillage and no conversions in open surgery. No intra-operative mortality or complications occurred. The surgical margins were clear in all cases.
All tumours were classified according to Fletcher criteria, that distinguish the malignant potential risk in very low, low, intermediate and high in accordance with the number of mitoses and the tumour size. All patients, after surgery, were followed by oncologists for adjuvant monoclonal antibodies therapy and clinical surveillance.

Case 1

A 24-year-old woman presented for iron-deficient anaemia [Haemoglobin (Hb) 7 g/dl] and asthenia. The oesophagogastroduodenoscopy (EGD) showed a submucosal tumour on the lesser gastric curvature confirmed by an ultrasound scan and a contrast-enhanced abdominal computed tomography (CT) (Fig. 1). No distant metastases were observed. A three-trocar laparoscopic wedge resection was performed. Operative time was 46 minutes. Post-operative course was uneventful and patient was discharged at 4th post-operative day. Histology showed a well-capsulated tumour (37 x 35 mm) constituted by a spindle-like cell population meshwork presenting a low mitotic rate <5/50 High Power Fields (HPFs); immunohistochemistry showed an immunopositivity for CD117 and CD34 antibodies. Neoplasm was classified as "low risk of aggressive behaviour". Twenty-four months later, the patient was doing well and free of any clinical local recurrence or distant metastases.

Case 2

A 77-year-old woman was admitted for iron-deficient anaemia [Hb 6.9 g/dl] and slight abdominal pain. EGD showed a submucosal neoplasm on the greater gastric curvature. This lesion was further investigated by echo-endoscopy and contrast-enhanced CT, without detection

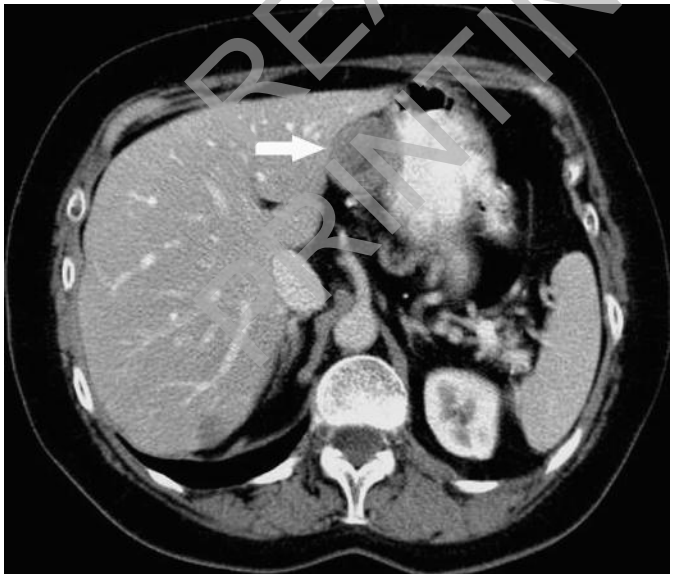

Fig. 1: Contrast-enhanced computed tomography (CT), axial plane, showing a GIST of the lesser gastric curvature. The white arrow is pointing out the tumour.

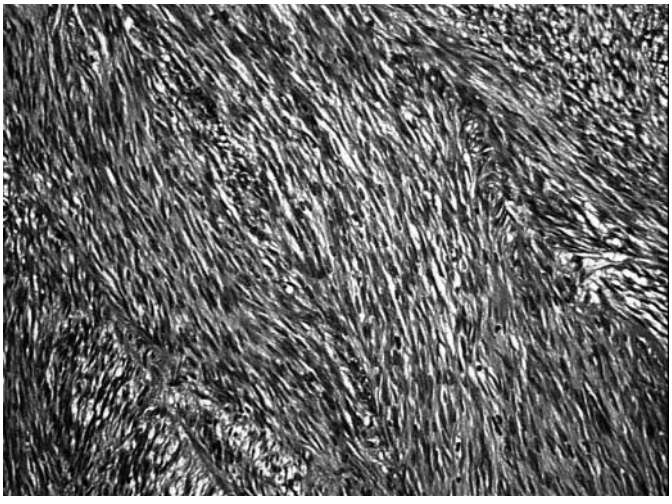

Fig. 2: Spindle-shaped cell population meshwork with a high mitotic rate in a gastric GIST (haematoxylin-eosin stain, original magnification x 100).

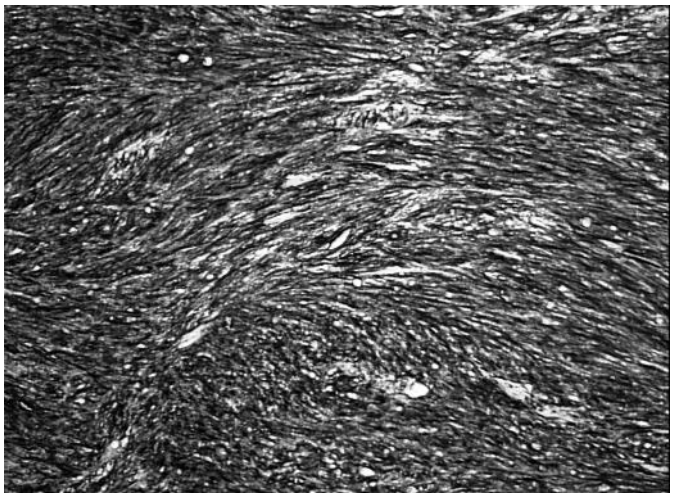

Fig. 3: Immuhistochemical positiviy for CD117 antibodies in a jejunal GIST (original magnification x 100).

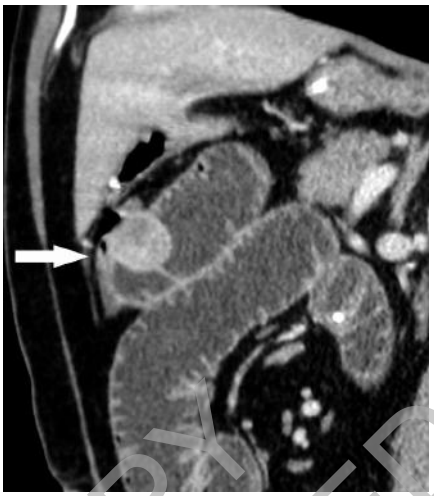

Fig. 4: Coronal image of contrast-enhanced CT showing a jejunal GIST. The white arrow is pointing out the tumour.

of synchronous distant metastases. A three-trocar laparoscopic wedge resection was performed along with the excision of a great epiploon lump suspect for malignancy. Operative time was 64 minutes. Post-operative course was marked for fever and patient was discharged at 9th post-operative day. Histology showed a capsulated tumour (58 x 41 mm) made up of spindle typical cells with a high mitotic rate (>10/50 HPFs) (Fig. 2); immunohistochemically, there was a strong positivity for anti-CD117 (Fig. 3) and anti-CD34 and a negativity for anti-α SMA (alpha-Smooth Muscle Actin) and anti-Protein S100 antibodies. Mesothelial hyperplasia without neoplastic features was found in the epiploon specimen. This tumour was classified as "high risk of aggressive behaviour". Twenty-one months later, the patient was still alive, and followed by oncologist for hepatic metastases.

Case 3

A 38-year-old man, presenting recurrent episodes of painless haematochezia with severe anaemia [Hb 6.4 g/dl], was hospitalised for obscure GI bleeding, since the conventional endoscopic investigations failed to detect the haemorrhage site. A contrast-enhanced CT showed a jejunal lesion without evidence of distant secondary localisations (Fig. 4). The patient underwent a four-trocar laparoscopic segmental resection of the jejunum. Operative time was 71 minutes. Post-operative course was uneventful and the patient was discharged on 5th post-operative day. Histology showed an ulcerated submucosal tumour (21 x 19 mm), with spindle-shaped cells and negligible mitotic activity (<5/50 HPFs) (Fig. 5). The specimen was immunopositive to CD117, CD34 and anti-α SMA. This tumour was classified as "low risk of aggressiveness". During the last follow-up visit, twenty-two months later, the patient was alive and doing well, without local recurrences or distant metastases.

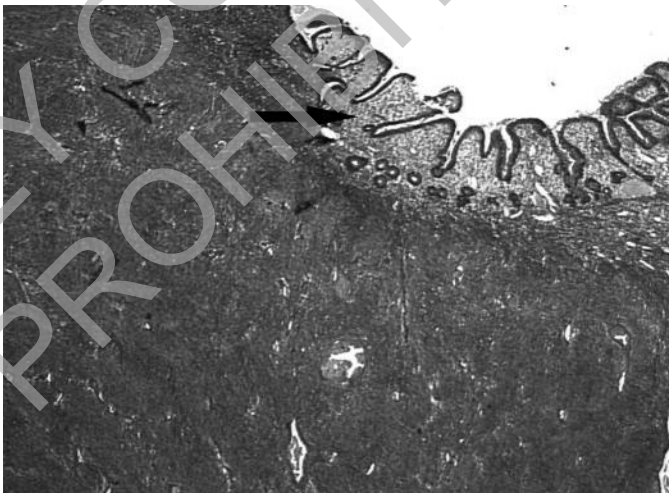

Fig. 5: Ulcerated jejunal GIST. The black arrow is pointing out the erosion of the mucosa. (haematoxylin-eosin stain, original magnification x 40).

Discussion

GIST are the most frequent mesenchymal tumour of the GI tract [1]. These neoplasms are believed to originate from the interstitial cells of Cajal or their stem cell-like precursors, pluripotential intestinal pacemakers which are located in the submucosal and myenteric plexus of the GI tract [1].

Stomach is the most frequent site of GIST development (50-70%), followed by the small bowel (20-35%) [3-8]. Generally, these stromal neoplasms are asymptomatic or may present symptoms which may be vague abdominal pain, asthenia, anaemia, GI bleeding or weight loss; they may also begin as bowel obstruction, acute bleeding or symptoms resulting from compression of nearby organs [9]. Whereas asymptomatic GISTs are discovered incidentally, symptomatic ones may be diagnosed by endoscopic procedures, contrast-enhanced CT, and echo-

endoscopy; sometimes, an abdominal exploration, by laparoscopic or open approach, is required as well [5].
Pre-operative biopsy is strongly recommended in a restricted number of patients with locally advanced disease [8].
Metachronous metastases commonly develop, also after a long period from the primary surgery, in the abdomen, mainly involving liver and peritoneum; therefore a long follow-up is mandatory in all patients in order to ensure that local and distant recurrences be early detected [1,9].
In addition, approximately 20% of patients with GIST develop other synchronous malignancies, and the occurrence of two or more other cancers in these patients appears to be a negative prognostic factor [8].
A differential diagnosis with other smooth muscle tumours (e.g. leiomyoma, leiomyosarcoma), nerve sheath tumours (e.g. schwannoma), and fibroblastic tumours (e.g. undifferentiated sarcoma, inflammatory myofibroblastic tumour, desmoids) should be performed [1,3,9]
The mutations within the KIT (c-kit receptor tyrosine-kinase) and PDGFRA (Platelet-Derived Growth Factor Receptor Alpha) genes, with constitutive activation of KIT and PDGFRA oncoproteins, characterise the GISTs pathogenesis and represent a crucial therapeutic target [6]. Such activation determines the increase of cellular proliferation and the decrease of apoptosis, ultimately leading into neoplasia, and probably into further unknown genetic events [1]. GISTs show a variable malignant potential, therefore even some low-risk lesions, might either remain stable or rapidly progress to widely metastatic disease (20-30%) [2,8,10]. The most concrete prognostic indicators remain tumour size and mitotic rate [1-3,10]. Macroscopically these neoplasms present as well-capsulated solid (subserosal, intramural, or polypoid) masses. Histological aspects include a population of spindle-shaped cells, sometimes with epithelioid or pleomorphic elements, mixed with fibro-hyaline stroma, and a variable mitotic rate. The immunopositivity for the CD117 (70-95%) represents a key feature of GIST. The CD34 positivity, present in 60-70%, may be helpful to reach the diagnosis [1,3,6]. As previously described by Fletcher *et al.*, GISTs were subdivided in four class of risk of aggressiveness considering tumour size (expressed in cm) and mitotic rate (expressed as number of mitoses per 50 HPFs) as follows: a) very low malignant potential (< 2 cm with < 5 mitoses); b) low malignant potential (2-5 cm with < 5 mitoses); c) intermediate risk (< 5 cm with 6-10 mitoses, and 5-10 cm with < 5 mitoses); d) high risk (> 5 cm with > 5 mitoses, and > 10 cm with any mitotic rate, and any size with > 10 mitoses) [3,10]. Subsequently, a review on 1684 patients, suggested that these parameters should be applied differently in gastric and small intestinal GISTs, in consideration of the higher malignant potential of the latters [1]. Other predictors of more aggressive biologic behaviour include high cellular density, high nuclear ratio, mucosal infiltration, presence of peritoneal nodules, invasion of peritoneal fat and involvement of nearby organs [1,10].

Surgical resection represents the treatment of choice for patients with primary non-metastatic disease, yet routinely lymph node dissections can be avoided [10-13]. Current evidences revealed that laparoscopic technique is safe, effective and feasible, higher increasing for its minimally invasive benefits, such as minimal blood loss, less pain and shorter hospital-stay [6,13-16]. Laparoscopy approach is also recommended, regardless of the tumour size and site, when performed by trained surgeons working in high-volume centre [7]. The intra-operative ultrasounds and the hand-assisted technique are helpful for tumours greater than 5 cm in diameters and in case of metastases suspect [5]. Nevertheless, for large GISTs located in particular anatomic sites it may still be necessary an open approach [10]. The conversion rate, laparoscopy *vs* open surgery, varies from 0 to 31% [15]. Open approach has a role for the palliative treatment of metastatic GISTs, with significant improvement of tumour-related symptoms. In addiction, surgical debulking may prolong survival of patients with tumour drug-responsive [2]. Survival in poor performance status patient and with not clear surgical edges is significantly affected, showing a survival rate ranging from 35% to 65% [8, 12]. According to the National Comprehensive Cancer Network guidelines, contrast-enhanced abdominal and pelvic CT is the appropriate technique for staging and follow-up [13].

Acknowledgement

For the accurate revision of the manuscript, We wish to thank Mr Sam Palella, a native speaker, with an extensive experience in the correction of scientific papers.

Riassunto

I tumori gastrointestinal stromali sono rare neoplasie mesenchimali, che rappresentano meno del 3% di tutti i tumori gastroenterici; tali tumori possono originare in tutte le porzioni del tratto gastrointestinale ma più frequentemente coinvolgono stomaco ed intestino tenue. Generalmente, sono asintomatici o responsabili di una lieve sintomatologia, tuttavia possono anche dare origine a condizioni cliniche acute. Microscopicamente sono caratterizzati da un reticolo di cellule fusiformi frammisto ad uno stroma fibroialino. L'immunoistochimica, con una marcata immunopositività per gli anticorpi anti CD117, permette la diagnosi differenziale con altri tumori muscolari, nervosa o fibroblastici. La dimensione tumorale e l'indice mitotico sono i più rilevanti fattori prognostici. La chirurgia rappresenta il trattamento per la malattia primitiva non metastatica, ma un prolungato follow-up oncologico è sempre raccomandato. La tecnica mini-invasiva è sempre più adottata e preferita per la bassa morbilità e la breve durata del ricovero, e sem-

pre più autori ne confermano la sicurezza, l'efficacia e la fattibilità.
Noi riportiamo una serie di casi relativa a tre pazienti paucisintomatici, tutti ricoverati per grave stato anemico da sanguinamento intestinale cronico, trattati con successo con approccio laparoscopico per la rimozione di tumori gastrointestinali stromali, due a sede gastrica ed uno digiunale.

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