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Review

Inguinal GIST: A Systematic Literature Review of Primary and Metastatic Cases

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Abstract. *Background/Aim: Gastrointestinal stromal tumor (GIST) has a wide spectrum of clinical manifestations. Involvement of the groin region can cause interesting presentations but, as of 2020, has rarely been investigated. Our aim was to assess the clinicopathological and prognostic features of GIST appearing in this specific part of the body. Materials and Methods: We investigated the world literature dealing with primary or metastatic GIST appearing in the inguinal region (IGIST). A case of metastatic IGIST from our clinical records was also included. Results: We found only six cases of primary and nine of metastatic IGIST. All were of male gender, and most aged 60 years or more (10 cases). Inguinal hernia (11 cases) was the patient type most frequently affected. The association between metastatic IGIST and inguinal lymphadenopathy was statistically significant (p=0.049). Conclusion: IGIST is a rare entity with particular clinical manifestations. Inguinal hernia and inguinal lymphadenopathy should be carefully investigated in patients with a history of GIST.*

Gastrointestinal stromal tumors (GISTs) are the most frequent mesenchymal neoplasm in the gastrointestinal (GI) tract (80%) (1). Their estimated incidence is approximately 1/100,000 per year; male patients in their 60s represent the population most commonly affected (2). GISTs originate from stem cells differentiating toward interstitial cells of Cajal and expressing, in the vast majority of cases, specific receptors (tyrosine kinase receptor KIT or platelet-derived growth factor receptor alpha) and markers such as CD117 antigen (an epitope of the KIT receptor). However, dedifferentiation to a *de novo* or anaplastic KIT-negative phenotype post-imatinib mesylate treatment is possible (3, 4). GISTs usually arise from the GI tract (in descending order: stomach in 60-70%, small bowel in 20-30%, colorectum in 5%, esophagus in under 5%) but occasionally an extra-intestinal origin is observed (EGIST: omentum-mesentery-peritoneum in 5% and retroperitoneum in under 3%) (2, 5). Differential diagnosis from other mesenchymal tumors or subepithelial reactive processes can be challenging for pathologists and includes, inter alia, intra-abdominal fibromatosis, dedifferentiated liposarcoma, reactive nodular fibrous pseudotumor of the GI tract or mesentery and colonic ischemic pseudotumor (6-8). GISTs can run an asymptomatic course but can also manifest with pain, masses or bleeding involving the abdomen and GI system (9-11). The groin region represents a particular localization for GIST. At this level, in fact, the clinical scenario can be extremely variable, presenting as an inguinal bulge or lump, from soft to firm, reducible or non-tender, painless or complicated by local or systemic signs of inflammation (12-25). All of these manifestations can be the result of a primary or metastatic GIST located in the GI tract, lymph nodes (LNs) or soft tissues. Since, with the exception of a few anecdotal experiences and case reports, literature has rarely investigated inguinal GIST (IGIST), our aim was to offer a systematic review of this specific presentation assessing the main clinicopathological and prognostic features of IGIST.

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Key Words: Gastrointestinal stromal tumor, GIST, inguinal hernia, inguinal hernia sac, review.

Materials and Methods

We systematically reviewed world literature on IGIST. Investigation was carried out through eight popular search engines (PubMed, Science Direct, Scopus, Web of Science, Google Scholar, ResearchGate, Publons and Academia). Gastrointestinal stromal tumor, GIST, EGIST, inguinal GIST, inguinal hernia GIST, groin

Table I. *Literature review of primary cases of gastrointestinal stromal tumors manifesting in the groin region.*

Ref	Gender	Age, years	Site	Presentation	Duration of signs/symptoms	Metastasis	Treatment	Follow-up
12	M	76	Cecum	Incarcerated RIH + SBO	N.A.	No	IHR + RH	Alive after 1 month
13	M	80	Retroperitoneal EGIST	Irreducible RIH	6 Months	No	IHR + biopsy; imatinib	N.A.
14	M	59	Jejunum	Incarcerated LIH	10 Days	Pelvis, bladder	IHR; IR	NDF at 6 months
15	F	45	Ileum	Right inguinal mass	3 Years	No	Biopsy; IR + bladder cuff off; imatinib	DF after 1 year
16	M	74	Ileum	Incarcerated RIH + SBO	2 Days	No	IHR + LIR	Alive after 7 days
17	M	67	Peritoneal EGIST (LIH sac)/ hemorrhagic mass	Incarcerated LIH	Sudden inguinal pain	PC	IHR + mass SE; imatinib	N.A.

DF: Disease-free; EGIST: extra-intestinal-GIST; IHR: inguinal hernia repair; IR: intestinal resection; LIH: left inguinal hernia; LIR: laparoscopic IR; N.A.: not assessed; NDF: not disease-free; PC: peritoneal carcinomatosis; Ref: reference number; RH: right hemicolectomy; RIH: right inguinal hernia; SBO: small bowel obstruction.

GIST, GIST sac, primary GIST and metastatic IGIST were the key words utilized for searching. English and non-English articles were considered. All other kinds of malignancies involving the inguinal canal were excluded from the review. We also included one case of metastatic IGIST present in our clinical records. The patient, an 89-year-old man who underwent resection of a stomach GIST 6 years earlier, experienced acute abdominal pain of 4 days' duration. On examination, a painful, irreducible and non-pulsatile mass was palpated in his left groin and an incarcerated inguinal hernia was suspected. At surgery, after opening the hernia sac, multiple bleeding congested nodules were observed encumbering an intestinal loop. Intraoperative histology revealed metastatic IGIST. Hemostasis was achieved using electrocautery and the inguinal defect repaired with Lichtenstein tension-free mesh technique. Three days after surgery, the patient died of acute kidney failure and cardiac arrest.

Statistics. Statistical analysis of the reviewed data was performed using MedCalc® Statistical Software version 19.6 (Ostend, Belgium; https://www.medcalc.org; 2020). Categorical and continuous variables were compared with the chi-square test and the Student's *t*-test, respectively. Univariate analysis was conducted through one-way and two-way analysis of variance. Multivariate analysis was assessed with Cox proportional hazards model. A value of $p \leq 0.05$ was considered statistically significant.

Results

As of 2020, after examining the relevant literature, we found only 14 articles describing 14 patients with an inguinal manifestation of GIST: interestingly, all were case reports (12-25). Six tumors were primary GIST (12-17) (Table I) while the others were metastatic IGISTs (18-25) (Table II). To the latter list, we also added the case of metastatic IGIST taken from our clinical records. The vast majority of cases involved male sex (M/F: 14/1), age 60 years and over (11 patients, 78.6%), irreducible inguinal hernia (10 cases) and a GIST with GI origin (eight cases). Seven out of the 10 interventions for inguinal hernia repair were accomplished with or followed by surgical excision of the main mass. Interestingly, the finding of an inguinal lymph node (iLN) as a manifestation of metastatic IGIST was statistically significant ($p=0.049$) at univariate analysis. Correlation of metastatic IGIST with iLN plus duration of clinical scenario ≥10 days was borderline significant ($p=0.08$). All the other results from univariate and multivariate analyses of the reviewed primary and metastatic IGISTs did not achieve statistical significance. Regarding survival, there were two deaths in the group with metastatic IGIST, one due to tumor progression, the other following postoperative renal and cardiac complications (Table II).

Discussion

In keeping with the pertinent literature, the reviewed patient population were mainly composed of men in their 60s having a concomitant or previous primary GIST arising from the GI tract (2, 4). Currently, several clinicopathologicaI features of GIST have been well documented and associated with high risk of malignant potential, recurrence and poor prognosis, such as high proliferative index, tumor dimension larger than 5-10 cm, extra-gastric localization, rupture, GI hemorrhage, lack or mutation of a specific receptor helpful for targeted therapy, development of a *de novo* or post-imatinib anaplastic dedifferentiation and presence of lymph node or distant metastases (4, 26-30). A clinical manifestation starting in the groin may represent a further risk factor of dismal prognosis in GIST. Our review of world literature showed that IGIST has rarely been studied and most

Table II. *Review of cases of metastatic gastrointestinal stromal tumor (mIGIST) manifesting in the groin region.*

Ref	Gender	Age, years	pGIST Presence/site	Site/appearance	Presentation	Duration of signs/symptoms	Other mGIST	Treatment	Follow-up
18	M	60	No/DG+LM 3 years earlier	Inguinal LN/ whitish nodule	RIM	5 Months	No	SE+imatinib	DF at 29 months
19	M	76	Ileum	Inguinal LN/N.A.	RIM	Sudden melena	No	SE+imatinib	NDF death at 30 months
20	M	82	Cecum	Inguinal LN/N.A.	Irreducible RIH	4 Months	Lungs	LN SE+IHR+ imatinib	N.A.
21	M	45	Retroperitoneal EGIST	Inguinal LN/ irregular shape	LIN	1 Month	No	SE+imatinib	DF at 15 months
22	M	72	SB	Hematoma in RIH sac	Irreducible RIH	10 Days	No	IHR; SE	N.A.
23	M	82	No/jejunal GIST resected 2 years earlier	RIH sac/ ovoid whitish mass	Irreducible RIH	Sudden inguinal pain	PC, PL	SE+IHR+ imatinib	DF at 2 years
24	M	53	Retroperitoneal EGIST involving SB and LB	RIH sac/nodule	Reducible RIH	Sudden inguinal pain	Liver, LNs	IHR+nodule SE; imatinib; sunitinib; mass SE+LM; regorafenib	N.A.
25	M	67	Retroperitoneal EGIST	LIH sac/necrotic hemorrhagic mass	Irreducible LIH	Sudden PC, IM inguinal pain	IHR+SE; imatinib	N.A.	
Our case	M	89	No/DG 6 years earlier	Ileum/multiple hemorrhagic nodules	Irreducible LIH	4 Days	No	IHR+biopsy	Death at 3 PO days (MI)

DF: Disease-free; DG: distal gastrectomy for gastric GIST; EGIST: extra-intestinal-GIST; IHR: inguinal hernia repair; IM: intraperitoneal metastases; LB: large bowel; LIN: Left inguinal nodule; LM: liver metastasectomy; LN: lymph node; mGIST: metastatic GIST; MI: myocardial infarction; N.A.: not assessed; NDF: not disease-free; PC: peritoneal carcinomatosis; pGIST: primary GIST; PL: pelvic lymphadenopathy; PO: postoperative; Ref: reference number; RIH: right inguinal hernia; RIM: right inguinal mass; SB: small bowel; SE: surgical excision.

knowledge comes from single case reports; despite this, we found several clinical associations and prognostic similarities between IGIST and GIST presenting the aforementioned traditional predictors of poor survival (12-25). Age ≥60 years appears a very common characteristic in the IGIST population (11 out of 14 patients considering both primary and metastatic cases). Although no statistical association between age and IGIST was found by our analysis, some authors formerly demonstrated that overall and disease-specific-survival of patients with GIST older than 50 years were significantly lower than young patients and this was confirmed at least for the group with metastatic IGIST (for patients >60 years, two deaths, one with tumor progression) (19, 31). Female gender seems a protective feature in GIST and this may also be true for IGIST (in fact, 93% of patients with IGIST were men) (31). A silent or irreducible hernia was the most frequent clinical manifestation affecting the groin region (11/14 cases). Regarding primary cases, the protruding tumors arose from the small bowel in three, large bowel in one and retroperitoneum in two cases (Table I); concerning metastatic IGISTs, deposits in the inguinal canal were derived from the small bowel in two, large bowel in one and retroperitoneum in two cases (Table II). Characteristically, all these sites are associated with a malignant potential higher than that of gastric origin (28-31). Interestingly, metastatic IGIST significantly correlated with the presence of inguinal lymphadenopathy (p=0.049): therefore, the appearance of an iLN in a patient with previous or concomitant history of GIST should always be suspected as a metastasis from primary tumor and investigated before surgical excision. GI bleeding comprises a traditional feature of malignancy for GIST: in the group with metastatic IGIST, three patients presented with hemorrhagic complications of the groin (22, 25). Metastatic IGIST also presented in the inguinal regional in the shape of a nodule (two cases) or mass (two cases).

Etiopathogenesis of IGIST presenting with inguinal hernia is rather interesting and varies depending on the phase of disease. An intrabdominal (intestinal, colonic, peritoneal or retroperitoneal) primary GIST can drop into the inguinal canal, causing a silent or incarcerated inguinal hernia (12-14, 16, 17). Inguinal hernia can also be the clinical manifestation of a metastatic IGIST; since the lymphatic route is improbable for GIST, some authors have hypothesized that neoplastic cells might be released from the primary tumor spontaneously (due to enlargement of the tumor mass with subsequent

hypovascularization, hypoxia, necrosis and crevice of the most peripheral areas), or following surgical maneuvers executed during a former intervention for GIST, then be exfoliated into the peritoneal cavity and become trapped by the narrow neck of a pre-existing inguinal hernial sac (21). Concerning inguinal hernia, some authors have also suggested that a long-standing silent hernia which becomes acutely incarcerated has a higher risk of containing a cancer: One patient with primary and another with metastatic IGIST having a silent longstanding inguinal hernia became symptomatic after 6 and 4 months, respectively (13, 20, 32, 33).

Conclusion

IGIST comprises a particular clinical presentation for GIST/EGIST and its prognostic features should be further addressed by future studies. The groin region can be affected by IGIST in several ways. A clinical suspicion of inguinal metastasis should always be considered when managing patients with a previous medical history of GIST. In this category of patients with inguinal hernia or iLN, preoperative investigation and exploration of the hernia sac should always be mandatory.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

All the authors agreed with the content of the article. Dr. Virgilio conceived the research idea. Dr. Virgilio wrote the article. Dr. Annicchiarico and Dr. Pagliai reviewed the literature. Dr. Montali selected patients amenable to inclusion or exclusion. Dr. Morini prepared the tables. Dr. Costi supervised the entire project.

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