CASE REPORT – OPEN ACCESS

International Journal of Surgery Case Reports 9 (2015) 98–100

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

Unique case of sporadic multiple gastro intestinal stromal tumour

Luigina Graziosi[a,*], Elisabetta Marino[a], Vienna Ludovini[b], Alberto Rebonato[c], Verena De Angelis[b], Annibale Donini[a]

[a] General and Emergency Surgery, Santa Maria della Misericordia Hospital, University of Perugia, Via dottori, 06134 Perugia, Italy
[b] Clinical Oncology, Santa Maria della Misericordia Hospital, University of Perugia, Via dottori, 06134 Perugia, Italy
[c] Radiology Unit, Santa Maria della Misericordia Hospital, University of Perugia, Via dottori, 06134 Perugia, Italy

ARTICLE INFO

Article history:
Received 24 October 2014
Received in revised form 13 January 2015
Accepted 13 January 2015
Available online 15 January 2015

Keywords:
Gastrointestinal stromal tumour
Multiple gist
V559A/1676 T > C

ABSTRACT

INTRODUCTION: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract and they derived from transformed neoplastic precursors of Cajal's interstitial cell (ICC).
PRESENTATION OF THE CASE: We are presenting a sporadic and exemplary case of 42 multiple GISTs in a young female patient. Our patient showed anemia for the gastric GIST bleeding and only after other tumors were instrumentally and intra-surgery discovered. The patient showed genetic mutation V559A/1676 T > C of the juxtamembrane domain of the exon 11 causing the replacement of Valine with Alanine in the 559 codon.
DISCUSSION: GISTS estimated annual incidence is 12–14 per million. Multiple GISTs associated with familiarity or hereditary syndromes are described only in few case reports and sporadic mGISTs have not been studied yet. Literature review has been done.
CONCLUSION: We are presenting a sporadic and exemplary case of 42 multiple GISTs in a young female patient localized trough out all the gastrointestinal tract. This is the only case of sporadic multiple GISTs reported in literature.

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract and they derived from transformed neoplastic precursors of Cajal's interstitial cell (ICC).

Their estimated annual incidence is 12–14 per million [1].

Stomach and small intestine are the most commonly affected organs. Rare cases of primary GISTs originating outside the gastrointestinal tract have also been reported, although the actual existence of extra gastrointestinal GISTs is still debated.

GISTs can exhibit a wide spectrum of clinical behaviors that could go from indolent and curable disorders to highly malignant diseases that could metastasize and become lethal.

KIT and PDGFR-α activation seems to be a central tumorigenic event in the development of GISTs. KIT mutations are identified in 60–90% of cases [2]. KIT mutations in sporadic GISTs have been found in 4 different regions: extracellular domain (exon 9), juxtamembrane domain (exon 11), tyrosine kinase I domain (exon 13), and tyrosine kinase II domain (exon 17) [3].

Most GISTs occur sporadically in patients between 50 and 60 years.

GISTs are generally considered solitary tumors and the occurrence as multiple primary tumors is an exceptional event, usually restricted to familial GISTs or distinct pediatrics syndromes such as neurofibromatosis type 1 (NF1) or Carney's syndrome.

Multiple GISTs (MPGs) can be divided into 4 subtypes: (1) familial multiple GISTs with germline mutations of KIT or PDGFR-α genes, (2) multiple GISTs associated with NF-1 without mutations of KIT or PDGFR-α, (3) multiple GISTs associated with Carney's triad without mutations of KIT and PDGFR-α and finally (4) sporadic multiple GISTs [4].

Multiple GISTs associated with familiarity or hereditary syndromes are described only in few case reports and sporadic mGISTs have not been studied yet.

We are presenting a sporadic and exemplary case of 42 multiple GISTs in a young female patient.

In addition a literature review was made.

2. Case presentation

A 51-year-old female with a negative familial history for cancer was admitted to our General and Emergency Department for melena and anemia (hemoglobin value: 5.5 g/dl) without any signs

* Corresponding author at: University of Perugia, Santa Maria della Misericordia Hospital, Via Dottori, 06132 Perugia, Italy. Tel.: +39 755786445; fax: +39 755786445.
E-mail address: luiginagraziosi@yahoo.it (L. Graziosi).

http://dx.doi.org/10.1016/j.ijscr.2015.01.025

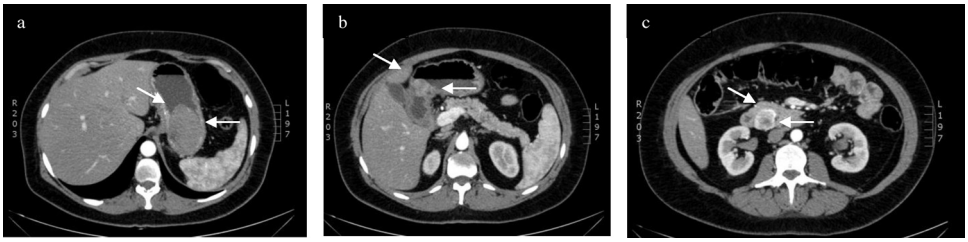

Fig. 1. (a) Gastric GIST; (b and c) duodenal GIST.

of hemodynamic instability. Transfusions of red packed cells were started immediately. A first attempt to perform an upper gastrointestinal endoscopy was poorly diagnostic due to the presence of undigested material. The exam revealed a yellowish tumor covered with smooth mucosa just below the cardia. A second endoscopy revealed 3 polypoid tumors: a 3 cm lesion just below the cardia with recent signs of bleeding, a 0.8 cm lesion in the gastric body and 1,5 cm lesion in the antrum. Multiple biopsies were taken during this procedure. In order to investigate the lesions' origin an endoscopy ultrasonography was done and it showed that all of them seem to originate from the submucosal layers. Biopsies of these gastric lesions were inconclusive. Tumor markers CEA, CA 19-9, CA 15-3, CA 125 and αFP were within normal ranges.

A staging CT revealed a greater diameter of the lesion below the cardia (71 × 48 mm); it also showed two other tumors located in the second duodenal portion (31 mm in diameter) and in the first jejunal loop (30 mm in diameter), respectively (Fig. 1). No metastatic localizations nor in liver or lungs were detectable and neither peritoneal dissemination nor lymphnodal spreading were revealed.

An abdominal MRI highlighted multiple polypoid masses arising in the small bowel and in the cecum, those lesions appeared hyper-intense and in homogeneous due to necrosis and recent bleeding. The radiological findings were compatible with multiple mesenchymal tumors without metastatic spreading.

A surgery procedure was scheduled. Antibiotic (Cefazolin 2 g + Metronidazole 500 mg i.v.) and antithrombotic (Clexane 4000 I.U. s.c.) prophylaxis was administered thirty minutes before surgery. A median laparotomy with complete abdominal exploration was performed to rule out metastatic spreading. In consideration of the location and size of the gastric tumor a total gastrectomy with perigastric lymphnodal clearance was indicated. An end to side, circular, Roux-en-Y esophago-jejunostomy was created.

Local surgical resection was performed for duodenal GISTs.

Enucleation of the jejunal and ileal lesions was performed. Distal ileum and proximal colon were resected and intestinal tract was restored by means of side-to-side anastomosis between the ileum and the ascending colon. Two drains were positioned close to the esophagojejunostomy, while another drain was positioned in the Douglas pouch. A nasojejunal tube was left in place.

The postoperative course was uneventful. Full bowel movement with stool passage was recovered in the third post-operative day. The patient underwent a water-soluble swallow test on the fifth post-operative day, which did not show anastomotic leak or obstruction. Oral intake was resumed in the same day and drains were removed. Medication of the median incision took place every 48–72 h according with dressing status. Patient was discharge in good general conditions on the ninth post-operative day.

Pathologic report revealed 42 neoplasms arising from the submucosal, intramuscular or subserosal layer of the gastrointestinal tract with surface ulceration. At gross examination the lesions were well circumscribed although a true capsule was not present. At cut the surface was gray to pink in color with concomitant areas of cystic degeneration, infarction, hemorrhage and necrosis. Main microscopic features recorded were spindle or epithelioid cells patterns. Immunohistochemistry revealed a strong positivity for CD-117 and DOG-1, confirming the diagnosis of multiple sporadic GISTs.

The median lesion size was 19.15 mm with a standard deviation of 15.67 (range 6–65). The patient underwent adjuvant chemotherapy with glivec and both CT and pet-CT after 12 months from the surgery were negative for disease progression.

3. Discussion

MPGs generally occurred in a sporadic or familial setting or associated with hereditary syndromes.

Most GISTs occur sporadically and multiplicity is very rare.

Frequently, MPGs could be observed in pediatric patients or in patients affected by hereditary GISTs, NF1, or paraganglioma/sarcoma and Carney's triad syndromes [5–7]. Contrary to the familial GISTs, no mutations of KIT or PDGFR-α have been reported in the majority of the syndromic, pediatric and NF1-related GIST variants.

All these are well-defined entities that can be easily distinguished from common sporadic GISTs based on their peculiar clinicopathological features.

As a matter of fact, patients, according to the mutation type, could show some clinical characteristics such as urticaria pigmentosa, mastocytosis, and/or skin hyper pigmentation.

Moreover, GISTs in these cases generally develop at early age.

Presence of multicentric GISTs has also been observed and described in familial settings. These patients usually develop tumors in the small intestine, which may be associated with hyperplasia of ICC.

Patients with germline mutations of KIT, similarly to sporadic gist patients, may have genetic variations of the juxtamembrane domain (exon 11), although mutations involving the extracellular domain (exon 9), kinase I domain (exon 13), and kinase II domain (exon17) of KIT gene.

C-KIT gene is a tyrosine kinase receptor normally expressed by the interstitial Cajal cells known as the origin of GISTs.

The sporadic multiple GISTs are generally low in number, localized in the stomach or small intestine with a benign histology and positive for CD-117.

Multiplicity in sporadic GIST patients without family history or NF-1 is uncommon and it was described only in few reports.

At the beginning, gastrointestinal mGISTs were considered as advanced, metastatic disease because they were viewed as the dissemination from the single biggest GIST. This paradigm was changed by the presence of two reports in which authors described multifocal GISTs in the same patient with well defined clinical and pathological characteristics.

Kang's [8] work described the coexistence of multifocal GIST with different KIT mutations showing the different origin of each neoplasia.

Haller [9] reported 4 cases of multifocal sporadic GISTs.

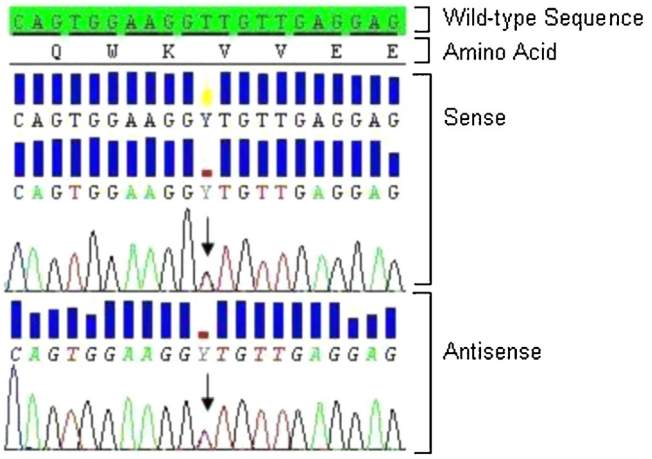

Fig. 2. Sequencing of exon 11 shows a heterozygous mutation in tumor tissue DNA: a T–Y (T or C) base-pair change (black arrow), resulting in a substitution of Valine for Alanine at position 559 (V559A).

Different mutations of KIT and PDGFR-α were present among individual tumors of each patient, and germline mutation of KIT and PDGFR-α could be excluded.

Thus, the presence of different Kit and PDGRF-α mutations in multiple GISTs of the same patient, the lack of mutation in normal tissue and the absence of ICC hyperplasia addressed to coincidental multicentric occurrence of sporadic GISTs.

Often in sporadic mGISTs adults there was a bigger neoplasia that caused the clinical symptomatic patient state.

Gasparotto et al. [10] in her work explained the origin of sporadic MPGs. She suggested that in these patients widespread priming of GIST precursor mesenchymal cells could be implicated in sporadic mGISTs origin.

The existence of tumor multiplicity in the context of adult GIST suggests that, in the presence of multifocal presentation, an accurate molecular characterization of the different tumor localizations should be taken into account for proper patient staging and planning of therapy.

KIT/PDGFR-α mutation status is an important predictor of responsiveness to imatinib.

Accurate molecular characterization should be done because sporadic MPGs may display different mutations with varying imatinib sensitivity, planning the adeguate therapy although the benign behaviour of GIST.

Our patient showed anemia for the gastric GIST bleeding and only after other tumors were instrumentally and intraoperative discovered. The patient showed the genetic mutation V559A/1676 T>C of the juxtamembrane domain of the exon 11 causing the replacement of Valine with Alanine in the 559 codon as Fig. 2 shows.

Conflict of interest

All the authors have no conflicts of interests.

Funding

The authors declare that they had no any sources of funding for this research.

Consent

A written informed consent was obtained from the patient.

Author contribution

Graziosi Luigina – designed the study, analyzed datas and wrote the study.

Marino Elisabetta – participated to the data analysis.

Ludovini Vienna – analysed the genetic alterations.

De Angelis Verena and Rebonato Alberto – participated to study design.

Donini Annibale – designed the study and reviewed it.

References

[1] T.B. Saleem, I. Ahmed, Gastrointestinal stromal tumour – evolving concepts, Surgeon 7 (February (1)) (2009) 36–41.
[2] M. Miettinen, M. Furlong, M. Sarlomo-Rikala, A. Burke, L.H. Sobin, J. Lasota, Gastrointestinal stromal tumors, intramural leiomyomas, and leiomyosarcomas in the rectum and anus: a clinicopathologic, immunohistochemical, and molecular genetic study of 144 cases, Am. J. Surg. Pathol. 25 (September (9)) (2001) 1121–1133.
[3] E. Wardelmann, Translational research and diagnosis in GIST, Pathologe 33 (November (Suppl. 2)) (2012) 273–277.
[4] A. Italiano, C.L. Chen, Y.S. Sung, S. Singer, R.P. DeMatteo, M.P. LaQuaglia, P. Besmer, N. Socci, C.R. Antonescu, SDHA loss of function mutations in a subset of young adult wild-type gastrointestinal stromal tumors, BMC Cancer 14 (September (12)) (2012) 408.
[5] M. Miettinen, J.F. Fetsch, L.H. Sobin, J. Lasota, Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases, Am. J. Surg. Pathol. 30 (January (1)) (2006) 90–96.
[6] C.M. Byrne, R. Daneshjoo, J. Ma-Wyatt, M. Cox, Gastrointestinal haemorrhage as a presentation of Carney's triad, ANZ J. Surg. 77 (January-February (1-2)) (2007) 88–90.
[7] K. Valverde, M. Henderson, C.R. Smith, S. Tallett, H.S. Chan, Typical and atypical Carney's triad presenting with malignant hypertension and papilledema, J. Pediatr. Hematol. Oncol. 23 (November (8)) (2001) 519–524.
[8] G. Kang, Y.S. Park, E.S. Jung, M. Joo, M.S. Kang, S. Ahn, G.H. Kang, K.M. Kim, Gastrointestinal stromal tumors in children and young adults: a clinicopathologic and molecular genetic study of 22 Korean cases, APMIS 121 (October (10)) (2013) 938–944.
[9] F. Haller, H.J. Schulten, T. Armbrust, C. Langer, B. Gunawan, L. Füzesi, Multicentric sporadic gastrointestinal stromal tumors (GISTs) of the stomach with distinct clonal origin: differential diagnosis to familial and syndromal GIST variants and peritoneal metastasis, Am. J. Surg. Pathol. 31 (June (6)) (2007) 933–937.
[10] D. Gasparotto, S. Rossi, I. Bearzi, C. Doglioni, A. Marzotto, J.L. Hornick, A. Grizzo, C. Sartor, A. Mandolesi, R. Sciot, M. Debiec-Rychter, A.P. Dei Tos, R. Maestro, Multiple primary sporadic gastrointestinal stromal tumors in the adult: an underestimated entity, Clin. Cancer Res. 14 (September 15 (18)) (2008) 5715–5721.