Clinical Oncology: Case Reports

Case Report

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Metachronous Gastrointestinal Stromal Tumors (GISTS) or Relapse of the Primary Tumor? A Challenging Case of Multiple GISTS in an Elderly Patient

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Abstract

Background: Gastrointestinal Stromal Tumors (GISTs) are the most common mesenchymal cancers of the gastrointestinal tract and the majority of them carries pathogenic mutations of KIT and PDGFRA genes. Sporadic Multiple Primary GISTs (MPGs) are a rare entity that could occur in adult patients characterized by multiple synchronous lesions generally located in the same organ and even more rarely by metachronous neoplasms. The differential diagnosis among MPGs and disseminated disease or recurrent primary GIST is critical as it affects clinical management.

Case report: Here, we present a case of an 86-year-old female who underwent emergency surgery in June 2016 for a giant GIST of the stomach occupying most of the left side of the abdomen. After two years, during adjuvant imatinib 400 mg daily, emergency sigmoid resection was performed due to subacute obstruction and a colonic GIST carrying the same KIT mutation (deletion 557-558 at exon 11) of the previous gastric neoplasm was detected. In this case, we hypothesized the primary nature of the two tumors despite being metachronous and occurring in different organs. However, the same mutational pattern suggested a clonal relationship between the two neoplasms. The onset of a third duodenal lesion, that could corroborate the assumption of the primary metachronous nature of the disease, still remains an unsolved question since its malignancy was not confirmed.

Conclusion: Differentiating among metachronous multiple primary GISTs or relapse on imatinib is relevant for staging and choosing the most proper therapeutic approach. Further investigations are surely needed in order to asses a diagnostic tool that may help clinicians to distinguish this rare entity (both synchronous or metachronous) from recurrences. In this scenario, molecular analysis may add essential data to discriminate sporadic MPGs and recurrent or metastatic GISTs.

Keywords

GIST; Multiple primary; Sporadic; KIT mutations

Introduction

Gastrointestinal Stromal Tumors (GISTs) are the most common mesenchymal cancers of the gastrointestinal tract, deriving from the interstitial cells of Cajal [1]. GIST diagnosis is established on morphology and immunohistochemistry including CD117 (KIT) and DOG1 positivity. The median age of occurrence is 60-65 years, with an estimated annual incidence of approximately 1/100.000/year and a slight male prevalence [1,2]. However, 20%-30% of GIST cases are clinically asymptomatic and are detected incidentally or diagnosed at autopsy [3].

Recently, several molecular studies have identified key pathogenic and presumably target mutations. Specifically, the majority of GISTs harbors oncogenic mutations of KIT and PDGFRA genes (85% and 3%-5% respectively), while about 10%-15% of cases are still genetically unclassified and are so-called wild type GISTs (WT GISTs) [4]. Several authors suggested that they may carry additional less common driver mutations including RAF, SDH and NF1 mutations [5].

Noteworthy, studies focusing on the role of genetic and epigenetic events of SDH subunits coding genes have provided a classification of GISTs into two clusters: SDH-competent and SDH-deficient. The first one includes tumors with KIT, PDGFRA, NF1, and BRAF mutations. Conversely, all the other cases are classified as SDH-deficient GISTs [6].

The introduction of imatinib, a selective Tyrosine Kinase Inhibitor (TKI), has represented a breakthrough in the management of GISTs, changing dramatically their natural history [7]. However, response to imatinib depends on the different mutational pattern (both on the type of mutation and on which codon is affected) of each tumor, thus suggesting a crucial role of genotype analysis in the diagnostic workup of all GISTs to predict the efficacy of targeted therapies for the individual patient [8].

Case report

We describe a case of an 86-year-old female who referred to our Department in June 2016 with a 3-month history of abdominal bloating, pain and vomiting. At clinical examination, the abdomen appeared tense with a not well-defined, lobulated, transversely mobile, and painful to the touch, mass occupying the mesogastric region and most of the left side of her abdominal cavity. Laboratory analyses showed a slight increase in CA125 (53 U/mL) and the presence of moderate anemia (8,2 g/dL).

Abdominal ultrasonography revealed a dishomogeneous vascular-rich thickening of the gastric wall protruding into the peritoneal cavity. Subsequent CT scan confirmed the presence of a bilobed, 18 × 14 × 25 cm in size mass with heterogenous enhancement due to several necrotic areas and an exophytic growth completely filling the left hypochondriac, lumbar and iliac region, that appeared indissociable from pancreatic body and tail, as well as from gastric body and fundus. Direct contiguity with the first portion of duodenum, spleen, spleen vessels, left kidney, splenic flexure and descending colon with the consequent displacement of them was also reported. Furthermore, subcentimetric adenopathies were detected in the left paracolic gutter, celiac region, mesentery and left cardio-phrenic space. The radiologic pattern was consistent with mesenchymal neoplasia (Figure 1).

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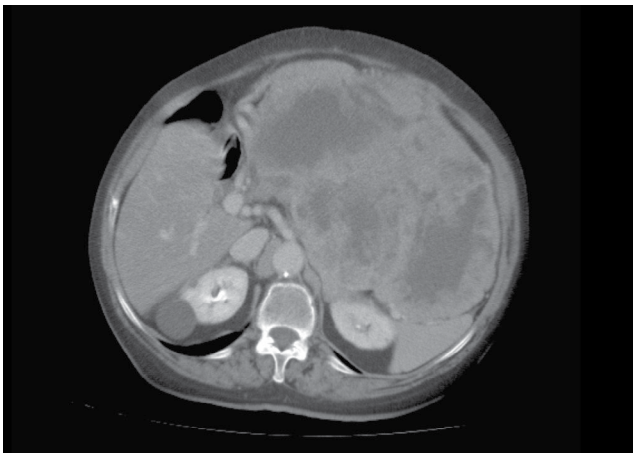

Figure 1: CT scan showing a dishomogenous mass occupying most of the left side of the abdomen.

Shortly after, an emergency wedge resection of the gastric fundus with ENDO GIA stapler and excision of the mass was performed. However, infiltration of the left side of the diaphragm and of kidney vessels was found and tumor rupture occurred.

Histopathologically, a 35 × 25 cm sized neoplasm arising from the gastric submucosa composed of both fusiform and epithelioid cells with focal atypias was described. Mitotic count was around 74/50 HPF with detectable necrosis and hemorrhagic areas. At immunohistochemical staining, tumor cells were diffusely and strongly positive for CD117, DOG1, and CD34, while negative for actin, desmin, calponin, and S100. Gastric mucosa and serosa showed only aspecific inflammatory modifications without signs of tumoral infiltration. Perigastric lymph nodes displayed hyperplastic changes in the absence of metastatic involvement and, despite tumor rupture; peritoneal fluid cytology was negative for cancer cells. Overall, these findings were consistent with a high-grade GIST according to Miettinen's classification [9-11] (Figure 2).

In July 2016, post-operative imatinib 400 mg daily was started with regular clinical and biochemical evaluation. Dose intensity was maintained without adverse events, except for mild diarrhea (grade I according to CTACAE) [12].

Regular follow up was performed every 3 months with no evidence of disease recurrence until November 2018 when abdominal CT scan revealed a polilobated well-circumscribed mass of 11 × 8 × 12 cm in size, with dishomogeneous enhancement abutting the sigmoid colon with extrinsic compression. Thickening of the stomach wall with endoluminal growth as well as an isolated mammillated lesion at the inferior duodenal flexure was also detected. Endoscopic Ultrasound (EUS) with concomitant biopsy of stomach and duodenum was performed and the histological examination was negative for neoplastic lesions.

After one week, the patient presented to the emergency department complaining about abdominal bloating, pain and severe constipation. Clinical examination was consistent with subacute intestinal obstruction and the patient underwent emergency sigmoid resection with colonic anastomosis.

The pathology report described a 10 cm sized neoplasm composed of both fusiform and epithelioid cells, growing into the colonic subserosa towards the smooth layer without invading it, with a storiform growth pattern. Mitotic count was around 150/50 HPF with detectable necrotic and hemorrhagic areas. Immunohistochemistry showed positivity for CD117, DOG1, and CD34. All these characteristics were compatible with the diagnosis of a high-risk stage IIIB GIST according to Mitteinen's classification (Figure 3).

Adjuvant imatinib was not started due to the poor clinical conditions and age of the patient and intensive follow-up was recommended.

After 3 months, the CT scan displayed an increase in the size of the intramural mass located at the inferior duodenal flexure with concomitant dilated extra and intrahepatic biliary tracts. A physical examination, jaundice was present and a slight progressive increase in bilirubin levels was registered. EUS confirmed the presence of a dishomogeneous lesion growing into the submucosa suggestive for mesenchymal neoplasia. The biopsy was carried out during Endoscopic Retrograde Cholangiopancreatography (ERCP) but it resulted in not diagnostic due to scarcity of the collected material. At that time, imatinib and/or surgery were not considered due to poor clinical conditions. An internal-external percutaneous transhepatic

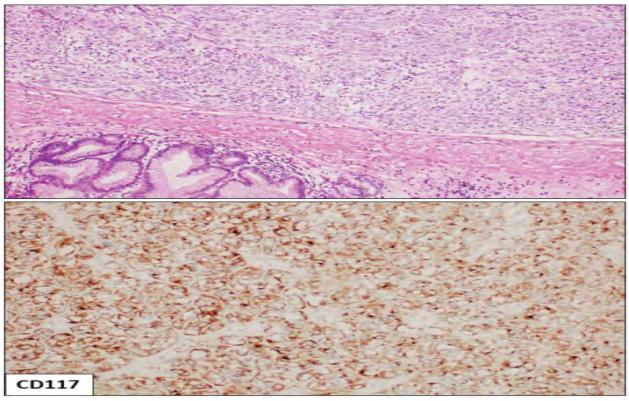

Figure 2: Histological examination showing a nodular neoplasm constituted by spindle-shaped cells, in the thickening of the gastric wall, below the muscolaris mucosae. The neoplasm resulted diffusely positive for CD117.

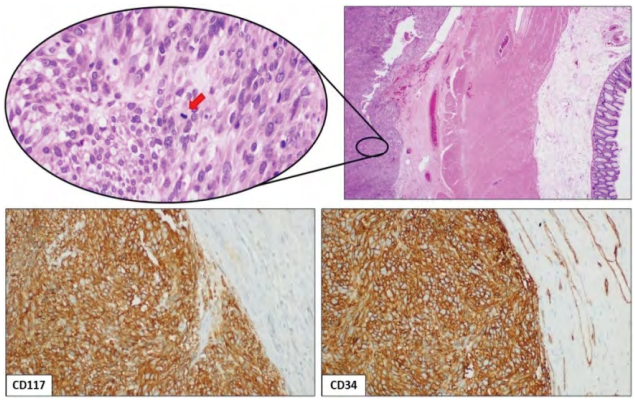

Figure 3: Histological examination showing a neoplastic mass in the thickness of the intestinal wall (upper right). The neoplasm was constituted by spindle-shaped cells with some intracytoplasmatic vacuoles. Some mitoses were present (red arrow) (upper left). Immunohistochemistry showing positivity for CD117 and CD34.

biliary drainage was placed and the patient died within a few weeks after the procedure.

Discussion

Gastrointestinal stromal tumors are commonly solitary, sporadic tumors and the occurrence of multiple primary neoplasms is considered restricted to specific conditions such as familiar GISTs (germline autosomal dominant mutations of KIT or PDGFRA genes) or distinct syndromes including neurofibromatosis 1, Carney triad syndrome and Carney-Stratakis syndrome [1].

The detection at the diagnosis of multifocal (synchronous) lesions in adult patients is generally considered as the result of metastatic spread from a single primary tumor. However, in the latest years, some studies have reported the existence of sporadic Multiple Primary GISTs (MPGs) in adult patients, originating from different primed Cajal Cells or their mesenchymal precursors with independent growth and mutational pattern, thus suggesting a field cancerization phenomenon [13,14]. Furthermore, it cannot be ruled out that sporadic MPGs may also occur as metachronous lesions, despite being a rarer condition [14,15].

The mutational analysis represents a crucial step since concordant immunoreactive pattern as well as similar morphology, tumor size and mitotic index are not sufficient to establish a clonal relationship and discriminate among metastatic disease and second primary neoplasm [13].

Considering KIT and PDGFRA mutations as an early event in GIST cancerogenesis [14,16], we performed NGS analysis to assess a clonal relationship between the two neoplasms occurred in the stomach and, 2 years later, in the sigmoid colon respectively. The mutational pattern of exon 9, 11, 13 and 17 of a KIT gene, as well as exon 12 and 18 of PDGFRA gene, was analyzed in a highly specialized center (INT "Giovanni Pascale", Naples) and W557-K558 deletion at exon 11 of a KIT gene was detected in both neoplasms.

Exon 11, which encodes the juxtamembrane domain of KIT, is the most frequently mutated region reported in about 70-75% of GISTs [17]. Recent data have evidenced that the exon 11 mutant cohort itself is quite heterogeneous in terms of biological behavior. Deletions affecting codons 557-558 of exon 11 account for almost 50% of all exon 11 alterations and are the most common KIT mutations, found in 23-28% of cases. Both codon 557 and 558 play a pivotal role in modulating KIT receptor activity: particularly Tryp557 residue exerts an inhibitory effect in its control while Lys558 may be somehow involved in its constitutive phosphorylation [18,19].

There is growing evidence suggesting that 557-558 deletions could be significantly associated with poorer prognosis and metastatic behavior when compared with patients harbouring other exons 11 mutations or any other KIT alterations. This correlation could be explained by the ability of mutation 557-558 to confer resistance to TKI therapy, being imatinib effective only on non-phosphorylated KIT receptor [19-22].

The presence of the same molecular alterations conferring resistance to TKI therapy, as well as the tumor rupture, occurred during surgery and the subserosal location of the second lesion, being colon a quite uncommon site of occurrence of GISTs, seemed to suggest the existence of a clonal relationship between the two neoplasms. Moreover, according to the most recent version of ESMO-EURACAN guidelines [1], the peritoneal occult disease could not be completely excluded in the case of spillage of tumor cells into the peritoneal cavity and, for these patients, adjuvant imatinib should be considered.

However, the finding of the same alterations, which supports the existence of a clonal relationship between the lesions, is not enough to consider the second tumor as a relapse. Furthermore, since microscopic hyperplastic areas of CD117 positive spindle cells are often detected in the proximity of sporadic GIST, we evaluated if multifocal hyperplasia of Cajal cells was present in our samples [14]. We hypothesized that a common preneoplastic multifocal lesion harbouring the same priming and early-occurred mutation could be responsible for the two neoplasms thus accounting for their metachronous presentation. Anyway, there was no evidence of hyperplastic Cajal cells in the samples examined.

Unfortunately, microsatellite status was not evaluated even though some studies suggest that similarly to KIT and PGFRA mutations, losses of some chromosomes such as 14 and 22 are an early event in GIST tumorigenesis and the knowledge of their status might be useful to understand if paired tumors are likely to be clonally related [14].

Finally, despite the presence of the same deletions, the occurrence of a third lesion arising from the duodenal submucosa was suggestive for the multiple primary sporadic natures, although its malignancy was not proven by pathology.

Another interesting point of discussion is surely represented by the role that differential diagnosis among primary and secondary nature could play in choosing the best therapeutic strategy.

Since pre-operative TKIs are the standard of care in primary locally advanced GISTs harbouring sensitive mutations, the discrimination between a primary metachronous lesion or a relapse during imatinib 400 mg daily could have affected treatment approach: Sunitinib or increased imatinib dose to 800 mg daily in case of progressive disease and theoretically imatinib 400 mg daily in case of primary metachronous GIST [1,23-25].

However, in our patient, pre-operative TKIs were not considered as emergency surgical procedures were required due to subacute occlusion occurrence. Furthermore, in the last years, surgery has gained growing importance also in the advanced/ metastatic setting although TKIs remain the mainstay of therapy. Recent retrospective studies have suggested that complete surgical resection (R0-R1) of GIST relapses was associated with a survival benefit compared to patients receiving R2 resections or TKI therapy alone [26-29]. Therefore, in selected patients with the potentially resectable disease after 6-12 months of pre-operative TKIs, the surgical approach could be considered as well as it could represent a valuable option in limited progression during TKIs as first-line treatment.

As a consequence, if the second colonic lesion was truly a relapse, radical surgery would have represented, in any case, an effective strategy to take into account.

Conclusion

In conclusion, sporadic MPGs are an uncommon entity that could occur in adult patients characterized by multiple synchronous lesions generally located in the same organ and even more rarely by metachronous neoplasms. The differential diagnosis among sporadic MPGs and disseminated disease is relevant since it affects staging as well as clinical management.

In this case report, we postulated the primary nature of the two neoplasms occurred in our patient, despite being metachronous and arising in different sites. However, the same deletion at codon 557 and 558 was found in both the tumor samples examined, thus suggesting a clonal relationship between the two entities. Moreover, the recent evidence that these alterations are strictly related to a poorer prognosis and a worse response to adjuvant imatinib could support the hypothesis of recurrent GIST. The onset of a third duodenal lesion, that could corroborate the assumption of the primary metachronous nature of the disease, still remains an unsolved question since its malignancy was not confirmed.

Differentiating among primary metachronous GIST or relapse on imatinib may be crucial for the choice of the best systemic and surgical approach, although in our case it was not technically feasible for the occurrence of emergency conditions.

Further investigations are surely needed in order to asses a diagnostic tool that may help clinicians to distinguish this rare entity (both synchronous or metachronous) from recurrences and choose the most proper therapeutic management. In this scenario, a molecular analysis should be standard practice in the diagnostic work-up of all GISTs as it may add essential data to discriminate among sporadic MPGs and relapses.

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