CASE REPORT

Synchronous GISTs associated with multiple sporadic tumors: a case report

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Abstract

Gastrointestinal stromal tumors (GISTs) are rare neoplasms; however, they also represent the most common mesenchymal tumors of the gastrointestinal tract originating from the cell of Cajal. GIST incidence ranges around 1% of all gastrointestinal malignancies. Approximately 5% of all GISTs have a hereditary etiology. The remaining 95% of GISTs are considered sporadic events, with up to 75% of cases driven by a constitutional activation of the c-KIT proto-oncogene. GISTs are generally solitary lesions. Nonetheless, multiple sporadic GISTs can occur and present as synchronous or metachronous tumors, usually associated with familial GIST. Here, we report a case of primary prostate and lung tumors associated with gastric and small bowel GISTs, unrelated to any known hereditary syndrome. Also, in the case we describe, the prostatic tumor came before the GISTs, while the lung tumor occurred later in time and led to pulmonary lobectomy plus lymphoadenectomy, with a diagnosis of nonsmall cell lung cancer. With the exception of a slight difference in lymphoid infiltration, the abdominal and gastric GIST nodules shared the same proliferative MIB1 index and mitotic count. However, the genetic analysis revealed that the gastric GIST and abdominal tumors were characterized by two different c-KIT mutations. This molecular heterogeneity supported the hypothesis of two different synchronous GISTs arising from stomach and ileum. At present, the patient is disease free and has already completed the third year of adjuvant therapy with imatinib. This case supports the importance of the analysis of c-KIT mutational status to distinguish metastases from synchronous multicentric GISTs, with relevant implications in therapeutic decisions, as well as the importance of a dedicated multidisciplinary team and of a radiological follow-up after the diagnosis of a primary GIST, to discover a relapse of the GIST or, possibly, additional malignancies.

Keywords: c-KIT, gastrointestinal cancer, gastrointestinal stromal tumors, imatinib, mutational status, PDGFRA, small bowel, synchronous tumors.

Citation

Comandini D, Damiani A, Pastorino A. Synchronous GISTs associated with multiple sporadic tumors: a case report. Drugs in Context 2017; 6: 212307. DOI: 10.7573/dic.212307

Introduction

Gastrointestinal stromal tumors (GISTs) are rare neoplasms; nevertheless, they represent the most common mesenchymal tumors of the gastrointestinal tract [1]. GIST incidence is not easily quantifiable; in general, it includes about 1% of all gastrointestinal (GI) malignancies. The most common site of origin is stomach (60%), followed by small intestine (30%), colon–rectum (5%), and esophagus (1%); however, GISTs may occur anywhere in the GI tract and the abdominal cavity, including the greater omentum and mesentery (4%).

GISTs spread mainly to the liver and the peritoneal cavity. Metastases to the lymph nodes are rare, with the exception of pediatric GIST types, particularly those harboring mutations of the gene encoding for the succinate dehydrogenase (SDH) or with SDH inactivation [2].

GISTs are a variegated group of neoplasms whose prognosis can range from an indolent behavior, with a 15-year survival of 90%, to a more aggressive behavior, with a 15-year survival lower than 10%.

Approximately 5% of GISTs have a hereditary etiology. Known hereditable GIST syndromes are caused by germline mutations in c-KIT proto-oncogene, platelet-derived growth factor receptor α (PDGFRA), neurofibromin 1 (NF1), and SDH subunit genes.

The remaining 95% of GISTs are considered sporadic events, with up to 75% of cases driven by a constitutional activation of c-KIT, 10% of cases driven by a mutation of the PDGFRA gene, and 12% of cases related to mutations of the SDH complex, BRAF or NF1 genes.

GISTs are generally solitary lesions; synchronous GISTs are extremely rare and usually associated with familial GIST, type 1 neurofibromatosis, or Carney’s triad [3].
To the best of our knowledge, there is only one case report of multiple sporadic synchronous GISTs associated with another concomitant tumor [4]. Here, we report a case of primary tumors of prostate and lung associated with gastric and small bowel GISTs not related to any known hereditary syndrome. In the case we describe here, the prostatic tumor came before the GISTs, while the lung tumor occurred later in time.

**Case report**

**Diagnosis**

In August 2013, a 65-year-old male subject presented with weight loss, occasional abdominal pain, dyspepsia, and hemoglobin drop (9.5 mg/dL). The patient immediately underwent CT scan, with evidence of a suspicious gastric submucosal nodule with a diameter of 4 cm. No other abdominal and thoracic suspicious masses were found. In September 2013, the patient underwent partial gastrectomy and omentectomy: during abdominal intraoperative staging, another mass (6 cm) was found among ileal loops in addition to the known gastric lesion, and, at the first surgeon’s opinion, it was considered as a possible accessory spleen. The mass was resected radically, and the surgery was completed without complications.

**Pathologic findings**

At the opening of the stomach, the macroscopic evaluation showed a nodule of 4.3 × 2.3 cm along the greater gastric curvature. The microscopic examination stated that the neoplasm originated from the gastric muscular tissue and infiltrated the submucosa and the mucosa, with concomitant ulceration. The tumor tissue presented spindle cells without necrosis. Proliferative MIB1 index was 12%, and the mitotic count was 2 × 50 high-power fields (HPF). Immunohistochemistry revealed a strong positivity for CD117. Based on these histological and immunohistochemical findings, the diagnosis of gastric GIST was done.

At the macroscopic evaluation, the abdominal nodule had a diameter of 6 cm. The microscopic examination revealed a spindle cell population very similar to the gastric GIST, leading to rule out the surgeon hypothesis of an accessory spleen. Moreover, the nodule was characterized by an immunohistochemical profile (CD117 positivity), a MIB1 index (12%), and a mitotic count (2 × 50 HPF) perfectly overlapping with the gastric GIST. A slight difference was found between the two nodules, as a little lymphoid infiltration was present in the abdominal nodule, and this finding led the pathologist to hypothesize a nodal GIST metastasis. Both nodules were surrounded by a pseudocapsule.

**Oncological evaluation and differential diagnosis**

The above-mentioned patient came to our attention in October 2013 for oncological evaluation (the surgical intervention had occurred in a different hospital), and we were doubtful, because a GIST at the stomach with low mitotic index unlikely may have spread metastasis, and, in second place, nodal metastasis are rare in GISTs [2]. Therefore, we hypothesized a differential diagnosis including GIST nodal metastasis, GIST peritoneal metastasis, and a synchronous ileal GIST. Furthermore, to clarify the link between the primitive GIST and the abdominal nodule, the analysis of c-KIT mutational status for both neoplasms was requested. In the meantime, a postoperative CT scan was performed, revealing the absence of additional suspicious masses.

**Analysis of c-KIT mutational status**

The analysis of c-KIT mutational status was performed by PCR automatic direct sequencing, for the exons 8, 9, 11, 13, 14, and 17. The analysis of the tissue deriving from both gastric GIST and abdominal neoplasm revealed that the tumors were characterized by two different c-KIT mutations.

In particular, the gastric GIST harbored an insertion of 6 bp in exon 9 of c-KIT (c.1509_1510insGCCTAT). This mutation leads to an in-frame insertion of 2 amino acids between codon 503 and codon 504 of the protein sequence (p.Y503_F504insAY).

The ileal tumor harbored a substitution in exon 11 of c-KIT (c.1679T>A). This mutation leads to the Valine→Aspartic acid replacement in codon 560 of the protein sequence (p.V560D).

The two different c-KIT mutations (in exons 9 and 11), we described above, weakened the hypothesis of a metastasis from gastric GIST. In that case, both tumors should have harbored the same type of mutation, while the molecular heterogeneity, revealed by the analysis of the c-KIT mutational status, supported the hypothesis of two different synchronous GISTs arising from stomach and ileum.

**Adjuvant therapy and follow-up**

In November 2013, considering a risk of recurrence of the ileal mass ranging from 20 to 40% [5] (in this specific case, the risk is about 30%), an adjuvant therapy with imatinib at 400 mg every day continuously was started.

After 15 months of adjuvant treatment, a scheduled CT scan showed a small nodule (14 × 9 mm) in the medium right pulmonary lobe. The PET scan was negative, and the differential diagnosis was between a solitary lung metastasis by GIST and a primitive lung cancer.
In consideration of the low frequency of lung metastasis in GIST, we proposed to the patient a surgical approach. In April 2015, the patient underwent pulmonary lobectomy plus lymphadenectomy with a diagnosis of nonsmall cell lung cancer (pT1a-G2-N0). No indication for adjuvant chemotherapy was given.

At present, the patient is disease free and ends the third year of adjuvant therapy with imatinib.

Discussion

Multiple sporadic GISTs are a rare but well-recognized clinical presentation of GISTs and can occur as synchronous or metachronous tumors.

Results of several descriptive, single-institution case series suggest that patients with sporadic GISTs develop additional synchronous or metachronous malignancies with frequencies far exceeding the cited one in nine lifetime chance of developing other primary cancers [6]. A population-based study published in 2015 revealed a 17.1% occurrence of other cancers in GIST patients and provided evidence for an increased cancer risk in the GIST population [6].

The diagnosis of GISTs arising simultaneously from different GI tract is an exceptional event. To our knowledge, only a few reports of synchronous GISTs have been published so far; among them, Kang and colleagues described 12 patients with synchronous GISTs, including 5 cases of type 1 neurofibromatosis, 2 cases of familial germline mutations, and 5 cases of sporadic mutations of c-KIT [3].

There is only one case report of multiple sporadic synchronous GISTs associated with another concomitant tumor [4], but there are no reported cases of sporadic synchronous GISTs associated with multiple other tumors. Of interest, the case we described in the present report developed the prostatic tumor before the GISTs and the lung tumor later in time.

Sporadic multicentric GISTs are an important differential diagnosis to familial and syndromal GIST variants or even to recurrent/metastatic disease [7]. This is essential for a correct therapeutic approach, and a molecular analysis is needed to distinguish between multiple primary GISTs and multiple recurrent or metastatic GISTs.

Our single experience of sporadic synchronous multicentric GISTs led us to define four key points to be addressed for a correct clinical approach to such a complex and rare event:

1. It is strongly recommended that such a rare pathology is treated by the different components of a GIST Unit;
2. For patients reaching a GIST Unit after the surgical operation, an exhaustive and complete description of the surgery should be provided as it has a major clinical relevance for the differential diagnosis and for disease staging. Especially in cases in which the surgical description or the histological exam has an “atypical” behavior in reference to GIST common features, it is important to talk with the surgeon or with the pathologist;
3. The analysis of c-KIT and PDGFRA mutational status is very important to distinguish metastases from synchronous multicentric GISTs, with relevant implications in therapeutic decisions;
4. A radiological follow-up after the diagnosis of a primary GIST is of major importance to discover a relapse of the GIST or, possibly, additional malignancies. A suspicious evidence is not necessarily related to a GIST: for example, abdominal nodes are really rare, and their finding during the follow-up of a GIST is probably unrelated to it.
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