Gastroenterology Report, 9(4), 2021, 377–379

doi: 10.1093/gastro/goaa086
Advance Access Publication Date: 14 December 2020
Brief Report

BRIEF REPORT

A rare case of omental extra-gastrointestinal stromal tumor showing two coexisting mutations on exon 14 of the PDGFRA gene

Gianluca Caruso[1,†], Luca Pacini[2,†], Angelo Iossa[3], Claudio Di Cristofano[1,4], Daniela Bastianelli[2], Gianfranco Silecchia[3], Maria Mele[5], Vincenzo Petrozza[1,4], Antonella Calogero[2,4] and Elena De Falco[2,4,6,*]

[1]Pathology Unit, ICOT Hospital, Sapienza University of Rome, Latina, Italy; [2]Clinical Pathology Unit, ICOT Hospital, Sapienza University of Rome, Latina, Italy; [3]Division of General Surgery and Bariatric Centre of Excellence, Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Rome, Italy; [4]Department of Medical-Surgical Sciences and Biotechnologies, Faculty of Pharmacy and Medicine, Sapienza University, Latina, Italy; [5]Laboratory of Clinical Pathology, ICOT Hospital, Latina, Italy; [6]Mediterranea Cardiocentro, Naples, Italy

*Corresponding author. Department of Medical-Surgical Sciences and Biotechnologies, Faculty of Pharmacy and Medicine, Sapienza University, C.so della Repubblica 79, Latina 04100, Italy. Tel: +39-0773-1757234; Fax: +39-0773-1757254; Email: elena.defalco@uniroma1.it
†These authors contributed equally to this work.

Introduction

Gastrointestinal stromal tumors (GISTs) are neoplasms arising from mesenchymal cells localized into the muscularis propria of the gastrointestinal (GI) tract [1]; 5% of GISTs are extra-GISTs (EGISTs), as they differently originate from adipose tissue adjacent to the GI tract (omentum and mesentery) or from the pancreas [2]. So far, both GISTs and EGISTs have been managed indistinctively by combining surgery, histopathological distinctive features, imaging, and molecular analysis. Moreover, despite the contribution of defined genetic backgrounds whose influence is acknowledged in this type of tumor (i.e. Carney's triad or familiar form of GIST), the pathobiology of both GISTs and EGISTs is not yet fully understood. We describe an interesting case of an extensively diffuse EGIST involving only omentum and mesocolon with multinodular growth and peculiar histological features, and for which a deeper histopathological/molecular analysis is reported.

Case presentation

A 74-year-old female with a historical diagnosis of multiple myeloma was referred for anemia, alvus disorders (diarrhea and constipation), weight loss (15 kg in 6 months), and palpable mass of the right flank that had appeared 8 weeks before. On medication for multiple myeloma since 2016 (melphalan combined with prednisone and bortezomib × 9; carfilzomib/lenalidomide/desametasone × 6 until complete remission), she also had type II diabetes, treated with oral medications and open cholecystectomy in the 1980s. Physical examination revealed the presence of a large mobile non-painful mass in the right flank apparently from the right colon, without signs of occlusion or intestinal bleeding. Blood analysis showed: hemoglobin 7.9 g/dL, white blood cells $2.3 \times 10^3/\mu$L, glycemia 191 mg/dL, and a low potassium level of 2.8 mEq/L.

We first treated the glycemia by insulin infusion and, second, we investigated the signs of anemia. By lower GI

Submitted: 14 May 2020; **Revised:** 20 July 2020; **Accepted:** 28 July 2020

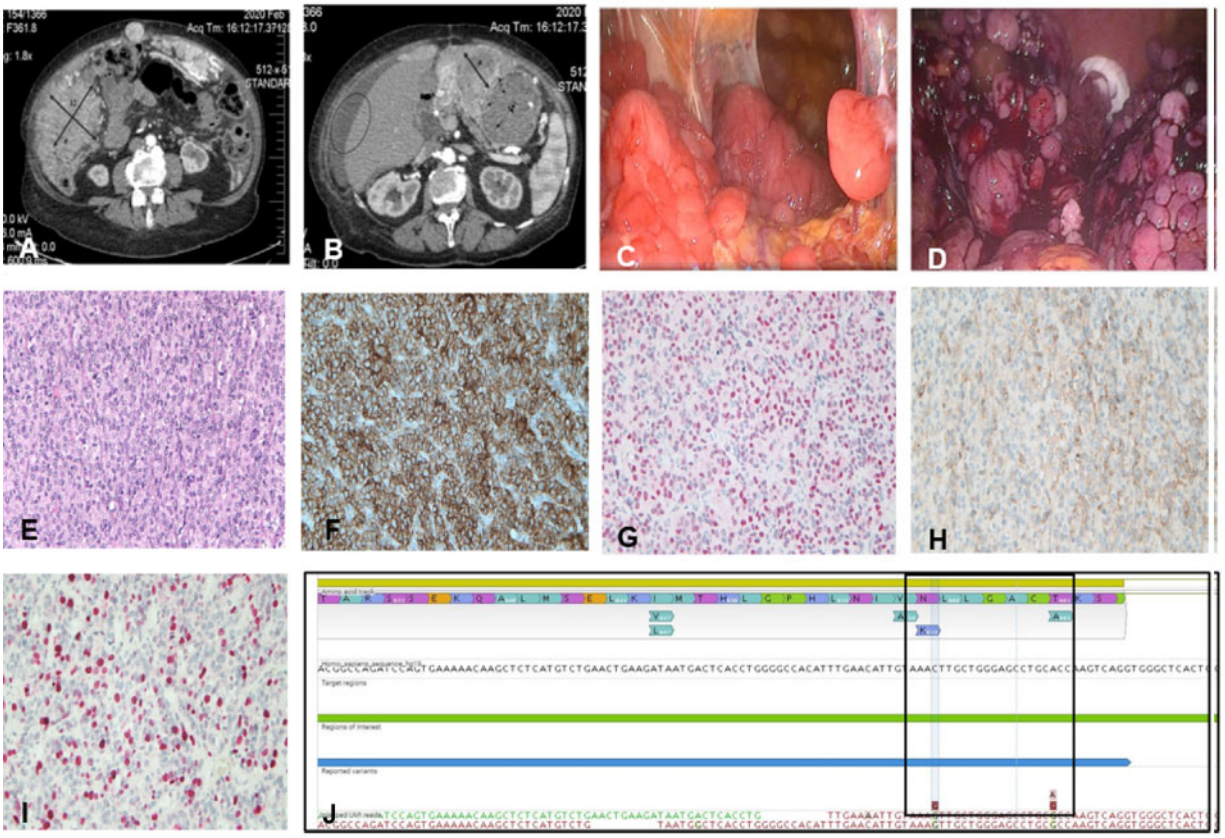

Figure 1. Radiological, histopathological, and molecular examinations of the 74-year-old female patient with extra-gastrointestinal stromal tumor. CT scan showing (A) large colonic and (B) hepatoduodenal ligament mass together with a free-fluid collection. (C) and (D) Intraoperative photos showing a large hepatoduodenal mass and multiple omental nodules. (E) Representative images of the histopathological analysis of the hematoxylin/eosin staining displaying epithelioid features of the tumor tissue, strong positivity for DOG-1 (F) and CyCD1 (G), locally positive for CD117 (H) and positive Ki67 (I). All images magnification 20×. (J) Next-generation sequencing analysis (black box) showing in the exon 14 of the PDGFRA gene both the nucleotide changes c.1977C>G (amino-acid change p. N659K) of pathogenic significance and the c.1993A>G (amino-acid change p. T665A) of uncertain significance.

endoscopy, we excluded bleeding and abnormalities of the GI-tract mucosa. No primary masses or *ab estrinseco* protrusions were found. Computed tomography (CT) scan showed ascites and multiple abdominal masses, with the biggest (D_{max} 120 × 85 mm) attached to the right colon, without signs of infiltration, suggesting a non-specific carcinomatosis (Figure 1A and B). Explorative laparoscopy revealed hemoperitoneum (2.4 L) and confirmed multiple nodular lesions of the mesentery, peritoneum, and two large masses attached to the colonic mesentery and to the hepatoduodenal ligament (Figure 1C and D). Multiple biopsies including mesocolonic/omental adipose tissue with extensive nodular changes, together with abdominal fluid (ascites) samples were evaluated by histopathological analysis (Figure 1E). The post-operative course was normal with progressive blood-analysis normalization after transfusion of 2 blood units (hemoglobin 9.4 g/dL) and a rearrangement of antidiabetic therapy.

Histopathological analysis

The paraffin sections showed proliferative markedly atypical epithelioid cells diffusely positive for Vimentin, DOG-1 (Figure 1F), and Cyclin D1 (Figure 1G), and only partially for CD117 (c-KIT) (Figure 1H). In order to rule out a potential involvement in the evolution of the disease of the pre-existing multiple myeloma, staining for both CD138 and CD38 was also performed, showing a negative expression of these. The mitotic count was 80/5 mm^2 with 20% positivity for Ki-67 (Figure 1I). The radiological and laparoscopic absence of GI-tract involvement, the positivity for DOG-1 and Cyclin D1 strongly suggested high-grade EGIST [3]. In addition, an extensive panel of additional multiple markers was evaluated, showing negative expression (data not shown).

Importantly, the diagnosis of EGIST was confirmed by the molecular analysis performed by next-generation sequencing (NGS, Qiagen) on the selected neoplastic area. Results showed that the pathogenic missense mutation p. N659K on exon 14 of the PDGFRA gene with a gain of function of the protein was present (Figure 1J). However, a further missense mutation (p.T665A) with uncertain significance was present on the same exon 14 of the PDGFRA gene. Several additional variants of uncertain significance were also found, as described in Table 1. The molecular analysis confirmed wild-type genotype for CD117. According to the NGS analysis, the patient is being currently treated with imatinib (400 mg) and maintained as long as no evidence of progressive disease or unacceptable toxicity will be shown.

Discussion

Primary omental EGISTs are rarely described worldwide; the most recent report was derived from a cohort of 112 cases and 114

Table 1. Variant details on the tumor biopsy performed by next-generation sequencing

Gene	Exon	Nucleotide change	Amino-acid change	Allele fraction (%)	Classification	Effect on protein
PDGFRA	14	NM_006206.6: c.1977C>G	p.N659K	49	Pathogenic	Gain of function
PDGFRA	14	NM_006206.6: c.1993A>G	p.T665A	50	VUS	Gain of function
ALK	29	NM_004304.5: c.4587C>G	p.D1529E	51	Benign	Gain of function
EGFR	15	NM_005228.5: c.1856_1857delTGinsCA	p.L619P	3.59	VUS	Normal function
ERBB2	17	NM_004448.3: c.1963A>G	p.I655V	51	Benign	Gain of function
FGFR1	NA	NA	Loss	NA	VUS	Loss of function
GNAQ	5	NM_002072.4: c.728A>G	p.D243G	15	VUS	Normal function
PIK3CA	7	NM_006218.4: c.1173A>G	p.I391M	8.46	VUS	Normal function
Additonal genes*	–	–	–	–	All wild-type	–

*AKT1, BRAF, CTNNB1, DDR2, ERBB3, ERBB4, ESR1, FBXW7, FGFR2, FGFR3, FLT3, GNA11, HRAS, KIT, KRAS, MAP2K1, MAP2K2, MET, NOTCH1, NRAS, RAF1, SMAD4, STK11.
NA, not applicable; VUS, variant of uncertain significance.

mesenteric GISTs [4] and phenotypically heterogenous, with CD117, CD34, S100, desmin, and SMA variably expressed [5]. This case displayed a more DOG-1 restricted phenotype, confirming the hystopathological heterogenity of EGIST and also suggesting that the $CD117^{+}/CD34^{+}$ mesenchymal cells fraction, considered the potential precursors of EGIST, is likely not fully preserved. Importantly, histogenesis and mutational status were matched, confirming the pathogenic role of primary and activating mutations in PDGFRA exon 14 that are specific to omental EGIST, but also very rare (<1%), especially if arising as mutually exclusive with CD117 [6] and involving the single nucleotide substitution (N659K) only described in 15 cases. Interestingly, the patient also harboured a concomitant mutation on the PDGFRA exon 14 with uncertain pathogenic significance and was unlikely to be ascribable to imatinib resistance (no previous therapy), which involves different codons [7]. Only in two non-EGIST clinical cases have both mutations been described [8]. Our report represents the first EGIST harbouring two mutations on the same exon 14 of the PDGFRA gene. Although the PDGFRA gene contributes in bone-marrow-derived mesenchymal stem-cells differentiation [9], the observed mutation might not be correlated with the multiple myeloma, suggesting that the EGIST did not occur as a consequence of the first neoplasm, but rather with independent mutational features. Notably, immunocytochemistry has never been observed in germline PDGFRA-based mutations [10], likely in line with the partial expression of CD117 shown in the tissue, therefore strengthening the hypothesis of different precursors in this EGIST. In conclusion, the combination of histopathological and mutational analysis represents the most paramount prognostic factor to address the best suitable clinical therapy for patients. Our case confirms EGIST as a primary and independent tumor with intrinsic features even in the presence of an additional and pre-existing neoplasm.

Authors' contributions

G.C. performed histopathological analysis of the case and contributed to the writing the manuscript; L.P. and D.B. performed the molecular analysis; A.I. and G.S. performed surgery and clinical history of the case and contributed to the writing the manuscript; M.M. performed the laboratory blood analysis; C.D.C., V.P., and A.C. contributed to the writing the manuscript; E.D.F. wrote the manuscript and contributed to the design and conception of the study.

Funding

This study has been supported by Sapienza University, Department of Medical-Surgical Science and Biotechnologies, Latina, Italy.

Acknowledgements

Authors thank the patient and her family for their kind and generous collaboration with this study.

Conflicts of interest

None declared.

References

1. Bamboat ZM, Dematteo RP. Updates on the management of gastrointestinal stromal tumors. *Surg Oncol Clin N Am* 2012;**21**:301–16.
2. von Mehren M, Joensuu H. Gastrointestinal stromal tumors. *J Clin Oncol* 2018;**36**:136–43.
3. Kisluk J, Zinczuk J, Kemona A *et al.* Expression of CD117, DOG-1, and IGF-1R in gastrointestinal stromal tumours—an analysis of 70 cases from 2004 to 2010. *Prz Gastroenterol* 2016;**11**:115–22.
4. Ambrosio M, Testa AC, Moro F *et al.* Imaging in gynecological disease: clinical and ultrasound features of extra gastrointestinal stromal tumors (eGIST). *Ultrasound Obstet Gynecol* 2020 Jan 7.doi.10.1002/uog.21968. Online ahead of print
5. Wu CE, Tzen CY, Wang SY *et al.* Clinical diagnosis of gastrointestinal stromal tumor (GIST): from the molecular genetic point of view. *Cancers (Basel)* 2019;**11**:679.
6. Heinrich MC, Corless CL, Duensing A *et al.* PDGFRA activating mutations in gastrointestinal stromal tumors. *Science* 2003;**299**:708–10.
7. Lasota J, Miettinen M. Clinical significance of oncogenic KIT and PDGFRA mutations in gastrointestinal stromal tumours. *Histopathology* 2008;**53**:245–66.
8. Huss S, Wardelmann E, Goltz D *et al.* Activating PDGFRA mutations in inflammatory fibroid polyps occur in exons 12, 14 and 18 and are associated with tumour localization. *Histopathology* 2012;**61**:59–68.
9. Farahani RM, Xaymardan M. Platelet-derived growth factor receptor alpha as a marker of mesenchymal stem cells in development and stem cell biology. *Stem Cells Int* 2015;**2015**:1–8.
10. Ricci R, Martini M, Cenci T *et al.* PDGFRA-mutant syndrome. *Mod Pathol* 2015;**28**:954–64.