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

Gianluca Caruso¹,†, Luca Pacini²,†, Angelo Iossa³, Claudio Di Cristofano¹,4, Daniela Bastianelli², Gianfranco Silecchia³, Maria Mele⁵, Vincenzo Petrozza¹,4, Antonella Calogero²,4 and Elena De Falco²,4,6,*

¹Pathology Unit, ICOT Hospital, Sapienza University of Rome, Latina, Italy; ²Clinical Pathology Unit, ICOT Hospital, Sapienza University of Rome, Latina, Italy; ³Division of General Surgery and Bariatric Centre of Excellence, Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Rome, Italy; ⁴Department of Medical-Surgical Sciences and Biotechnologies, Faculty of Pharmacy and Medicine, Sapienza University, Latina, Italy; ⁵Laboratory of Clinical Pathology, ICOT Hospital, Latina, Italy; ⁶Mediterranea 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/dexametasone × 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 × 10⁹/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
endoscopy, we excluded bleeding and abnormalities of the GI-tract mucosa. No primary masses or extrinsic protrusions were found. Computed tomography (CT) scan showed ascites and multiple abdominal masses, with the biggest ($D_{\text{max}} 120 \times 85$ 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
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 heterogeneity 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 PDGFRA gene. Although the PDGFRA gene contributes in bone-

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.

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Conflicts of interest

None declared.

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                | 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  |
| Additional 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.