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Divergent gastrointestinal stromal tumors in syndromic settings

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The vast majority of gastrointestinal stromal tumors (GISTs) occur as sporadic tumors. Rarely, however, these neoplasms can arise in syndromic contexts. Under these circumstances, GISTs are often multiple and associated with accompanying signs peculiar of the hosting syndrome. Moreover, syndromic GISTs themselves tend to show heterogeneous features depending on the underlying condition.

Multiple inflammatory fibroid polyps (IFPs) and a jejunal spindle-cell GIST were resected in a germline *PDGFRA*-mutant individual. Although the association of IFP and GIST is typical of this genetic setting (*PDGFRA* mutations can in fact trigger both these tumor types), *PDGFRA*-mutant GISTs are usually epithelioid and gastric. This discrepancy was settled evidencing a somatic *KIT* mutation in the GIST.

The awareness of possible somatic mutations can be critical in the management of high-risk/malignant GISTs arising in syndromic settings. GIST features unusual for a given GIST-predisposing syndrome are a valuable tool in the hands of physicians for suspecting these "extra" triggers, which could not be sought for once a diagnosis of GIST-prone syndrome is well established, in a bona fide cost/benefit perspective.

Keywords Syndromic gastrointestinal stromal tumors, familial gastrointestinal stromal tumors, divergent gastrointestinal stromal tumors, PDGFRA, germline mutations

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of gastrointestinal tract. They feature heterogeneous distinctive triggering mechanisms, implying prognostic and therapeutic differences (1). Rarely, GISTs occur in predisposing syndromes, hereditary or not.

Among hereditary GISTs are germline-mutant syndromes involving *KIT*, *PDGFRA*, *succinate dehydrogenase* (*SDH*) complex or *neurofibromatosis type 1*(*NF1*) genes (1). The latter two conditions cause Carney–Stratakis syndrome (CSS) and NF1-associated GISTs, respectively. Conversely, epigenetic inactivation of *SHDC* at tumoral level is implied in the pathogenesis of another GIST-prone condition: Carney's triad (CT) (2); recently, germline variants of *SDH* genes have been described also in CT patients, although in a minority of cases (3). Whatever the cause, associated syndrome-specific signs, such as altered skin pigmentation and mast cell disorders in germline *KIT* mutations (4), inflammatory fibroid polyps (IFPs) and large hands in germline *PDGFRA* mutations (5), café au lait skin macules and cutaneous neurofibromas in NF1 (6), paragangliomas in CSS and CT and pulmonary chondromas in CT (7), are typically present. The resulting clinical picture is often strongly suggestive for a given GIST-predisposing syndrome even without/before evidencing GISTs. Genotyping is usually confirmatory.

Malignant GISTs can occur with varying frequencies in every GIST-predisposing syndrome, making molecular targeted therapy necessary. Once a diagnosis of GIST-prone condition is established, the latter can be planned according to the known syndromic trigger in a bona fide cost/benefit perspective. But sporadic GISTs can arise in syndromic settings, ultimately bearing multiple tumorigenic mechanisms. This can have relevant consequences on patients' management.

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Herein we report a GIST arisen in a germline *PDGFRA*-mutant context bearing an additional somatic *KIT* exon 11 mutation. This scenario gave us the opportunity to underline the features which can lead to clinically suspect additional somatic mutations/pathogenic mechanisms in GISTs arising in GIST-prone syndromes, prompting not to rely only on a known syndromic setting for establishing a therapeutic strategy, when necessary, ultimately avoiding possible dramatic mistreatments.

Materials and methods

Patient

A 67-year-old man presented with a syncopal episode and recurrent melena. Physical examination was unremarkable. Routine laboratory tests revealed thrombocytopenia (66,000/mm^3) and mild anemia (hemoglobin 9.9 g/dL). Esophagogastroduodenoscopy, video-capsule endoscopy and contrast-enhanced CT scan showed multiple ≤1.5 cm gastric polyps and two (enhancing) jejunal (25 mm) and ileal (40 mm) tumors. Patient underwent a double small bowel resection. Follow-up monitored multiple small intestinal and gastric polyps (Figure 1A). Four years later, a gastric polyp, enlarged to 20 mm, was removed. Currently, at 84 months' follow-up, the patient is well.

Histology and immunohistochemistry

Sections from formalin-fixed, paraffin-embedded specimens were stained with hematoxylin/eosin. The following antibodies were used: CD117 (DAKO, Glostrup, Denmark, rabbit polyclonal, 1:400), DOG1 (Spring Bioscience, Pleasanton, CA, USA, rabbit polyclonal, 1:100), and CD34 (Novocastra, Newcastle, UK, 1:50). Antigen retrieval was performed for DOG1 (10 minutes in 0.01 M citrate buffer, pH 6, microwave at 750 W). Specific pre-immune sera or isotype-specific unrelated primary antibodies were used for the control stainings. The detection system consisted of DAKO visualization reagent (dextran polymer conjugated with horseradish peroxidase and goat anti-rabbit and anti-mouse immunoglobulins) with 3,3′-diaminobenzidine chromogen solution. Sections were counterstained with hematoxylin.

Genetic analysis

Informed written consent was obtained from the individual tested. DNA was obtained from slides cut from paraffin-embedded tissues. These were treated twice with xylene and then washed with ethanol. DNA was extracted using the QIAamp tissue kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. Pathologic areas, containing nearly 100% disease-specific tissue, were macro-dissected on slides. Mutational analysis was also performed in normal tissue (gastrointestinal wall or mucosa). *KIT* (exons 9, 11, 13 and 17) and *PDGFRA* (exons 12, 14 and 18) genes were amplified using the same primers and PCR conditions described elsewhere (8,9). Briefly, DNA (100–200 ng) of normal and pathological areas was amplified in a mixture containing 1X PCR buffer [20 mM TRIS (pH 8.3), 50 mMKCl, 1.5 mM MgCl2], dNTPs (200 mM each), primers (20 pM each), and 0.5 U Taq polymerase platinum (Invitrogen, Milan, Italy) in a final volume

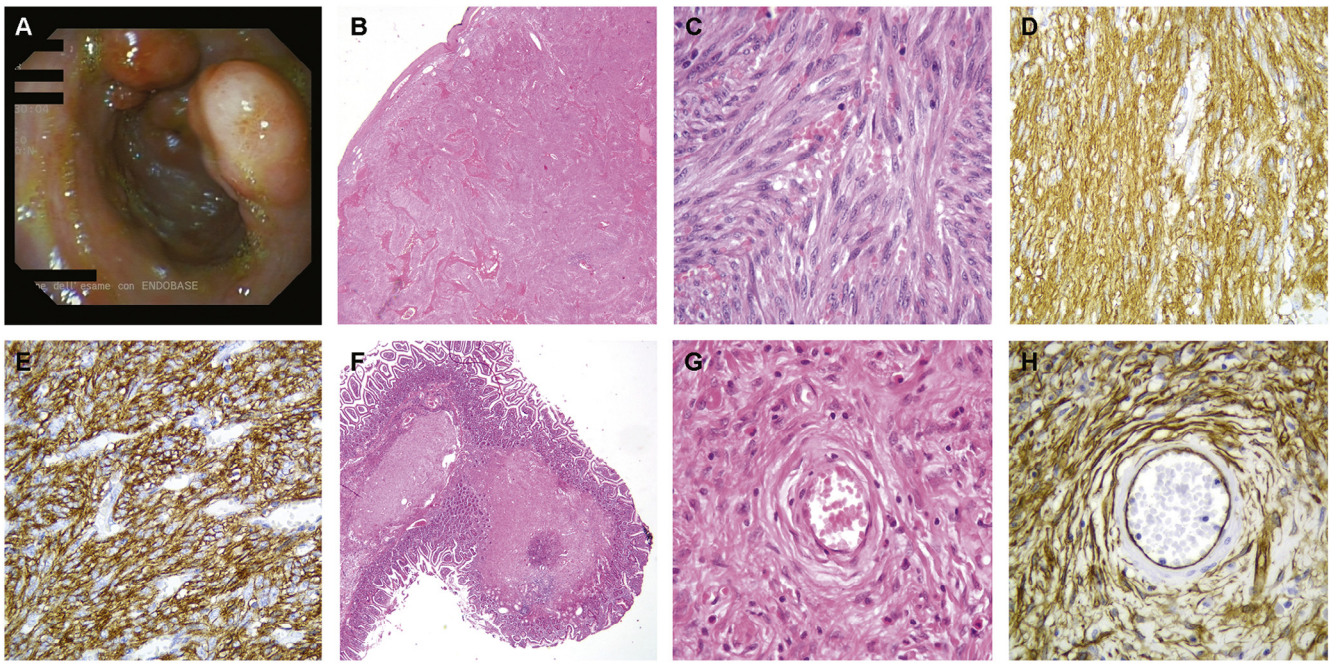

Figure 1 Features of the tumors. (A) Endoscopy revealed several semi-pedunculated gastric polyps. (B, C) H&E stains of the 40 mm jejunal tumor revealed fascicles of elongated cells with moderately eosinophilic cytoplasm, featuring 2 mitoses/5 mm^2 (B, ×20; C, ×400); (D) CD117 and (E) DOG1 were positive (D, E, ×400). (F, G) H&E stains of the 10 mm jejunal polyp showed intermingled fibroblast-like cells and inflammatory cells, with eosinophils and mast cells, in a myxoid collagenous matrix, often with an onion skin pattern around vessels (F, ×20; G ×400); (H) CD34 was positive (×400).