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Case Report

Plexiform architecture in gastrointestinal stromal tumors is not restricted to succinate dehydrogenase-deficient cases

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ABSTRACT

Accumulating evidence reveals the heterogeneous features of gastrointestinal stromal tumors (GISTs), primarily distinguished by their various molecular triggers defining well characterized subgroups. The identification of the pathogenetic group a given GIST belongs to, in combination with the currently adopted GIST prognosticators, is pivotal for the correct management of GIST patients. Epidemiological, anatomical and morphological features are more or less strictly associated with the various possible GIST molecular pathogenesis; therefore, they can concur to addressing molecular analysis or even influence the identification of GIST subsets by themselves. This is particularly true in a cost/benefit perspective aimed at cutting the expenses of pathology labs. Under these circumstances, a correct classical pathological analysis still appears a fundamental step to achieve an optimal GIST characterization.

We herein report a gastric epithelioid *PDGFRA*-mutant GIST displaying the multinodular/plexiform architecture distinctive of succinate dehydrogenase (SDH)-deficient GISTs. Immunohistochemistry and molecular analysis led to the correct tumor characterization. The reported case constitutes a valuable contribution to GIST pathology in that it demonstrates that multinodular/plexiform architecture is not restricted to SDH-deficient GISTs, but can be found also in *PDGFRA*-mutant ones; this is an event to be aware of, given the predilection for gastric location and epithelioid morphology shared by these two GIST subgroups, only the latter of which includes imatinib-sensitive cases.

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Differences in molecular pathogenesis characterize heterogeneous GIST subgroups [1], whose identification, in combination with the currently adopted prognosticators, is pivotal for the correct management of GIST patients [2]. Clinical and morphological features, variously associated with the diverse GIST molecular defects, can help in identifying GIST subsets, either directly or by contributing to orient molecular analysis, especially in a bona fide cost/benefit perspective aimed at cutting the outlay of pathology labs. Therefore, a correct “classical” pathological diagnosis appears still fundamental for an optimal GIST characterization.

Two of the known pathogenetic GIST subgroups are characterized by a predilection for both gastric location and epithelioid cytology: that mutated in the *platelet-derived growth factor receptor alpha* (*PDGFRA*) gene and that featuring succinate dehydrogenase (SDH) deficiency [3]. Of note, part of the former tumors are amenable to the molecular targeted therapy employing imatinib, whereas the latters are usually imatinib-resistant [4, 5]. We herein report a p.Val561Asp exon 12 *PDGFRA*-mutant gastric epithelioid GIST displaying a multinodular/plexiform architecture which had previously undergone incomplete surgical resection that, thanks to its genotype, could be treated by adjuvant imatinib after the second surgery. Our findings show that a multinodular/plexiform pattern, considered distinctive of SDH-deficient cases [5], can be found also in *PDGFRA*-mutant GISTs, contributing to the knowledge of the basic pathology of these tumors.

2. Materials and methods

2.1. Patient

A 42-year-old man presented with abdominal discomfort. Physical and routine laboratory tests were unremarkable. Eight months earlier,

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the patient had undergone laparoscopic resection of a gastric GIST in another hospital. Six months after this surgical procedure, contrast-enhanced abdominal CT scan and endoscopic ultrasound showed a 5 cm gastric tumor, originating from the site of the previous resection in the wall of the greater curvature, bulging into the gastric lumen, consistent with gastric GIST. Thus, eight months after the first surgery, the patient underwent a gastric wedge resection in our hospital. Informed written consent for this study was obtained from the individual tested. The procedures followed were in accordance with the Helsinki declaration of 1975, as revised in 1983.

2.2. Histology and immunohistochemistry

Sections from formalin-fixed, paraffin-embedded specimens were stained with hematoxylin/eosin. For immunohistochemistry, the following antibodies were used: CD117 (DAKO, Glostrup, Denmark, rabbit polyclonal, 1:400), DOG1 (Spring Bioscience, Pleasanton, CA, USA, rabbit polyclonal, 1:100), and SDHB (21A11, ABCAM, Cambridge, MA, 1:1000). Specific pre-immune sera or isotype-specific unrelated primary antibodies were used for the control stainings. For CD117 and DOG1, the detection system consisted of DAKO visualization reagent (dextran polymer conjugated with horseradish peroxidase and goat anti-rabbit and anti-mouse immunoglobulins), for DOG1 preceded by antigen retrieval (10 min in 0.01M citrate buffer, pH6, microwave at 750W), with 3,3′- diaminobenzidine chromogen solution. For SDHB, the Leica BondMax autostainer (Leica Microsystems, Bannockburn, IL) was employed utilizing the BondMax avidin biotin free polymer-based detection system preceded by heat-induced epitope retrieval with Leica retrieval solution (alkaline buffer), using diaminobenzine as the chromogen. Sections were counterstained with hematoxylin.

2.3. Genetic analysis

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 at least 70% disease-specific tissue, were analyzed. Mutational analysis was also performed in normal tissue (gastric wall and 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 [6, 7]. Briefly, DNA (100–200 ng) of normal and pathological areas was amplified in a mixture containing 1 × 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 of 25 l. PCR conditions were: an initial denaturation of 95 °C for 8 min, followed by 35 cycles of 95 °C for 40 s, 55 °C for 40 s and 72 °C for 40 s. After visualization onto agarose gel, PCR products were treated with ExoSAP-IT (USB Corp, Cleve- land, Ohio) following the manufacturer's protocol, amplified with BigDye Terminator version 3.1 cycle sequencing kit (Applied Biosystems) using forward and reverse primers, and sequenced with an ABI PRISM 3100-Avant Genetic Ana- lyzer (Applied Biosystems). Water was used as negative control.

3. Results

3.1. Pathology

An intramural, 33 mm tumor was resected together with an 85 mm portion of gastric wall. The lesion was centered in the muscularis propria and showed a plexiform architecture, consisting of multiple juxtaposed nodules (Fig. 1A, B); these nodules were made up of epithelioid cells (Fig. 1C); CD117 immunostaining was only patchy and mostly faint (Fig. 1D; occasional nuclear pleomorphism was evident); SDHB positivity was intense and diffuse (Fig. 1E); DOG1 was positive (not shown). Mitotic activity reached 3/5 mm^2. These features were consistent with gastric epithelioid GIST, SDH-proficient.

3.2. Genetic analysis

A point mutation (c.1682 T > A) determining a Val for Asp substitution at 561 (p.Val561Asp) in *PDGFRA* gene (Fig. 2) was found in tumor, but not in normal tissue (not shown).

4. Discussion

We herein report a *PDGFRA*-mutant, SDH-proficient GIST simulating a SDH-deficient one because of its morphological features.

After the seminal discovery of both *KIT* mutations and KIT expression in GISTs in 1998 [8, 9], pivotal for both their reliable identification and effective molecular-targeted treatment, these tumors revealed a rather heterogeneous group of neoplasms, driven by several possible, mutually exclusive molecular triggers [1]. The various pathogenetic GIST subsets differ in epidemiology, pathology and clinical features. Two GIST subgroups are distinguishable because of their propensity for epithelioid cytology and gastric location: *PDGFRA*-mutant and SDH-deficient ones. The former tumors, although prevailing in the stomach, can also occur in the bowel, are often negative or only patchy and mildly positive for CD117, and can respond to imatinib depending on the type of *PDGFRA* mutation [4, 10]. Conversely, SDH-deficient GISTs are virtually exclusively gastric, stain diffusely and intensely for CD117, and are almost invariably imatinib-resistant; additionally, they peculiarly show a multinodular, plexiform architecture and tend to affect young people, mostly manifesting before the age of 40 years; finally, current GIST risk classifications fail to predict their clinical behavior [5, 11, 12].

The herein reported *PDGFRA*-mutant GIST presented with deceiving features, simulating a SDH-deficient GIST. In fact, it displayed a multinodular, plexiform architecture (Fig. 1A, B), considered distinctive of the latter GIST type [5]; also compatible with SDH-deficiency were its gastric location and epithelioid cytology (Fig. 1C), and the relatively young age of the patient. However, the detected patchy and mostly weak CD117 positivity (Fig. 1D) was not typical of SDH-deficient GISTs, being rather suggestive of a concealed mutation of *PDGFRA* [10, 13]. SDHB intense and diffuse immunostaining confirmed the presence of a functional SDHB enzymatic complex (Fig. 1E). Finally, molecular analysis revealed a point mutation (c.1682 T > A) determining a Val for Asp substitution at 561 (p.Val561Asp) in *PDGFRA* exon 12 (Fig. 2).

To the best of our knowledge, only one multinodular/plexiform *PDGFRA*-mutant GIST has been signaled so far [14]. Unlike the case reported herein, that GIST displayed a prominent myxoid matrix, a feature consistent with the “myxoid epithelioid” subtype of *PDGFRA*-mutant GIST [15] which, combined with the multinodular architecture present in that particular case, simulated a plexiform fibromyxoma [16] rather than a SDH-deficient GIST.

The multinodular, plexiform morphology of the GIST we report is likely to have played a role in the incompleteness of the surgical resection the patient had previously undergone. Similarly, surgery is often only apparently curative in SDH-deficient GISTs, typically plexiform in architecture; however, under the latter circumstances, the propensity to lymph node metastases and the frequent presence of a syndromic setting determined by a systemic SDH dysfunction often contribute to surgical failures [5]. With regard to the case reported herein, the detection of a wild-type *PDGFRA* in normal tissue ruled out the possibility that the multiple tumor nodules found in the gastric wall represented multiple GISTs in the setting of a germline *PDGFRA* mutation.

Considering the above-mentioned previous incomplete tumor resection, an adjuvant therapy with imatinib has been initiated in the reported case. The detection of a Val for Asp substitution at 561 (p.Val561Asp) in *PDGFRA* has revealed decisive for allowing this