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Research Letter

Mutation-free expression of *c-Kit* proto-oncogene in primary adenocarcinoma of uterine cervix

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Dear Editor,

Imatinib, a small compound that selectively inhibits the activity of a limited number of receptor tyrosine kinases, is currently considered the standard therapy in advanced inoperable forms of gastrointestinal stromal tumors (GISTs) [1]. Despite the importance of anti-c-KIT therapeutics, very few studies have characterized the *c-Kit* oncogene in adenocarcinoma of the uterine cervix (adenoca Ut Cx) and the response to imatinib has not yet been explored, either [2]. Those findings prompted us to investigate c-KIT overexpression and activation as well as the underlying molecular mechanisms in adenoca Ut Cx, in order to identify possible novel treatment options for this kind of tumor.

In this study, tissue microarrays (TMAs) were constructed using a total of 48 formalin-fixed, paraffin-embedded specimens of adenoca Ut Cx. The stem cell factor (SCF) and c-KIT protein expressions were detected by immunohistochemistry (IHC), applying previously mentioned monoclonal mouse anti-SCF and polyclonal rabbit antihuman c-KIT [3]. The *c-Kit* gene mutations within Exon-2, -8, -9, -11, -13, and -17 were analyzed by seminested polymerase chain reaction (PCR) and direct sequencing. The forward and reverse oligonucleotide primers were listed elsewhere [4]. Sequence products were analyzed on an ABI Prism 310 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

Inoue et al [2] reported that neither c-KIT receptor nor SCF ligand were expressed in four (0%), while Went et al [4] demonstrated c-KIT over-expression in one case out of three (33%) of the adenoca Ut Cx. Our observations showed that only one (2.08%) out of the 48 tested cases was c-KIT positive, whereas, the remaining 47 cases were c-KIT negative. This c-KIT positive case exhibited an intense but focal staining pattern (Figure 1). Fortunately, there was enough extra tissue material from the only c-KIT-positive case for a broad spectrum of other ancillary tests. Subsequently, a negative SCF IHC and absence of *c-Kit* gene mutations were also identified.

Of this selected case of c-KIT positive adenoca Ut Cx, the SCF/c-KIT loop activation and *c-Kit* gene activating mutations, which are specifically characteristic of GISTs, were not detected. Even though the precise mechanism of c-KIT over-expression is not yet fully understood, we suggest that the c-KIT signaling may have been activated by other mechanisms, such as a variety of cell regulatory proteins implicated in gene expression, cross-reactivity with an unknown epitope, or epigenetic means.

In conclusion, owing to the limited case number, especially as there was only one c-KIT positive case, the occurrence of this single c-KIT positive case might not be representative of a larger population. The low frequency of expression suggests that imatimab may have a limited value in the management of patients with c-KIT positive primary adenoca Ut Cx.

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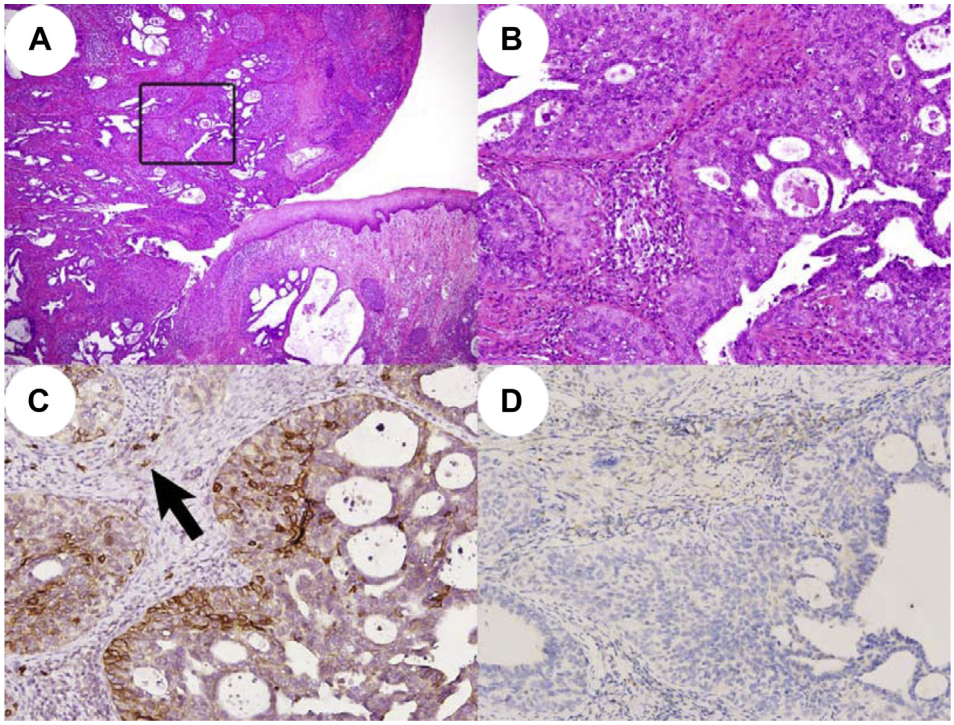

Figure 1. Histologic features of adenoca Ut Cx [hematoxylin and eosin stain (H&E)] stained sections; case code No. 1-1) typically show (A) moderately differentiated adenocarcinoma, characterized by irregular haphazard arrangement of glands and solid nests with cribriform growth pattern. Additionally, there is no apparent desmoplastic stromal reaction. (H&E stain, ×40); (B) a higher magnification view of the area within the square in A illustrating atypical glandular epithelium with eosinophilic cytoplasm and vacuolated nuclei. Dispersed mitoses and apoptotic bodies can be readily found. (H and E stain, ×200); (C) IHC showing that focal tumor cells with significant cytoplasmic staining and accentuation of membranous c-KIT positivity. The arrow head indicates the mast cells used as an internal positive control. (c-KIT stain, ×200); (D) IHC showing the tumor cells with negative expression of SCF. (SCF stain, ×200). IHC = immunohistochemistry; SCF = stem cell factor.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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