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Case study

Early signet ring cell carcinoma arising from colonic adenoma: the molecular profiling supports the adenoma-carcinoma sequence☆,☆☆

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Summary Among colorectal cancers, the prevalence of signet ring cell carcinoma (SRCC) is lower than 1%; to date, only 6 cases of early SRCCs arising in colonic adenoma have been reported. In spite of the well-established understanding of the phenotypic and genetic changes occurring in conventional colonic carcinogenesis, the molecular landscape of colon SRCC is still far to be elucidated. We describe the histologic and immunohistochemical phenotype and the molecular profile of a case of intramucosal SRCC developed within a 4.5-cm large sigmoid adenoma. The DNA sequencing of the 2 microdissected neoplastic components (adenomatous and SRCC) showed the same G12V *KRAS* mutation. Interestingly, although the adenomatous epithelium showed unequivocal p53 overexpression, no signet ring cancer cells featured p53 nuclear immunostain. This molecular pattern supports the unique histogenesis of the 2 coexisting neoplastic oncotypes, also suggesting that the signet ring cell component is derived from the molecular de-differentiation (p53 loss) of the preexisting adenomatous lesion.

1. Introduction

Signet ring cell carcinoma (SRCC) is a poorly differentiated variant of colorectal cancer (CRC) accounting for less than 1% of all the colorectal malignancies [1]. Histologically, *SRCC* is defined as solid adenocarcinoma with more than 50% of tumor cells consisting of noncohesive mucosecreting cells with peripherally displaced nuclei [2].

[1] The first 2 authors contributed equally.

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The first description of SRCC as a distinct colon cancer histotype dates back to 1951 by Laufman and Saphir [3]; since then, only occasional cases or small series have been reported. Colorectal SRCCs are usually diagnosed at advanced stage and are associated with poor prognosis [2,4,5].

In spite of the well-established understanding of the phenotypic and genetic changes occurring in conventional colonic carcinogenesis, the molecular landscape of colon SRCC is still far to be elucidated. We report the histologic, immunohistochemical, and molecular features of a case of SRCC arising within a colorectal adenomatous polyp.

2. Case report

Because of a positive fecal occult blood test result, a 78-year-old white man underwent colonoscopy, which revealed a sessile polyp (4.5 cm of diameter) of the sigmoid colon. Because of the polyp's size, only biopsy samples were obtained (7 biopsy samples ranging from 0.1 to 0.3 cm). The histology assessment documented a "combined" neoplastic lesion consisting of both a major villous adenoma component merged to small foci of SRCC (Fig.).

The patient underwent Hartmann colectomy. From the surgical specimen, serial sections of the entire polypoid lesions were obtained. The histology assessment confirmed the adenomatous lesion (including both low- and high-grade intraepithelial neoplasia) adjacent to scattered foci of signet ring cancer cells invading the lamina propria. None of the 13 harvested lymph nodes showed metastatic lesions. Adenomatous epithelium featured evident nuclear immunoreaction for p53 protein expression (clone DO-7; DakoCytomation, Glostrup, Denmark; prediluted), but no nuclear stain was revealed in the SRCC component (Fig.). A strong and diffuse E-cadherin (clone NCH38; DakoCytomation; working dilution 1:200) membranous expression was observed in both components (Fig.). Furthermore, neither adenomatous nor signet ring cancer components showed β-catenin nuclear expression (clone β-catenin-1; DakoCytomation; prediluted). The immunohistochemical analysis of the 4 mismatch repair proteins (MSH2, clone FE11; MSH6, clone EP49; MLH1, clone ES05; hPMS2, clone EP51; DakoCytomation; prediluted) resulted in a strong and diffuse nuclear immunoreaction in both components.

No local or distant cancer recurrence has been documented after an 18-months follow-up.

DNA was obtained from the formalin-fixed, paraffin-embedded samples after enrichment for neoplastic cellularity. Suitable areas for microdissection were marked on the archival hematoxylin and eosin slide, which served as template. The corresponding tissue block was serially cut to 5-μm-thin sections. Unstained sections were therefore deparaffinized and slightly counterstained with hematoxylyn. Tumor cells were dissected manually using a sterile syringe needle, and at least 70% of neoplastic cells were collected from both the adenomatous and SRCC components. DNA was extracted using the QIAamp DNA formalin-fixed, paraffin-embedded tissue kit (Qiagen, Milan, Italy).

Both components were analyzed for *KRAS* (exons 2, 3, 4), *NRAS* (exons 2, 3, 4), and *BRAF* (exon 15) status by both pyrosequencing (Diatech Pharmacogenetics, Jesi, Italy) and Sanger sequencing (Applied Biosystems 3130xl Genetic Analyser; Life Technologies, Monza, Italy) showing the G12V *KRAS* point mutation by both methods (Fig.). Pyrosequencing determined a comparable mutated allele frequency in both components (46% versus 42%). DNA obtained from surrounding normal colon mucosa was analyzed and showed a wild-type status of the *KRAS* gene.

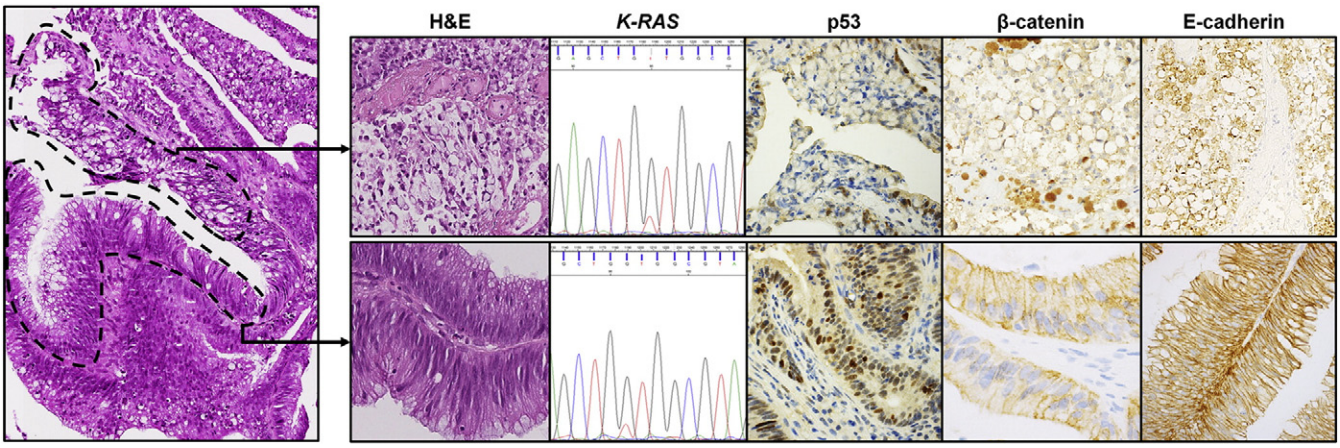

Fig. Adenomatous and signet ring features observed in the same gland on the hematoxylin and eosin–stained section. The corresponding results of the *KRAS* exon 2 mutational analysis at Sanger, and p53, β-catenin, and E-cadherin expression at immunohistochemistry are shown. Both components were characterized by a G12V *KRAS* point mutation; the adenomatous component showed a diffuse, moderate to strong nuclear immunoreaction for p53, whereas the signet ring one was completely negative. Both components showed a strong β-catenin and E-cadherin membranous expression. Original magnifications ×20 and ×40.