Appendiceal mucinous cystadenocarcinoma with mural nodules of anaplastic carcinoma and K-RAS mutation

Gözde Kır[1], Billur Coşan Sarbay[2], Burçin Girgin[1], Filiz Özen[3]

[1]Department of Pathology, İstanbul Medeniyet University Göztepe Research and Training Hospital, İstanbul, Turkey
[2]Department of Pathology, Denizli State Hospital, Denizli, Turkey
[3]Department of Medical Genetics, İstanbul Medeniyet University Göztepe Research and Training Hospital, İstanbul, Turkey

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Dear Editor;

Mural nodules are well-established in ovarian and pancreatic mucinous cystic neoplasms, and they grossly and histopathologically differ from the mucinous component of the tumor, which could be benign or malignant. Malignant mural nodules may include anaplastic carcinoma, clear cell carcinoma, neuroendocrine carcinoma, giant cell carcinoma, carcinosarcoma, and sarcoma (1). Herein, we report the first case of an appendiceal mucinous cystadenocarcinoma with multiple mural nodules comprising anaplastic carcinoma with K-RAS gene mutation status in both components.

The patient was a 45-year-old woman with 3-day lasting acute abdominal pain. She underwent appendectomy, which was performed in another hospital, and 21 paraffin blocks were submitted to our pathology department for microscopic consultation. Histologically, the tumor included two malignant components: a cyst wall and mural nodules. The cyst was lined by papillae with atypical mucinous cells that displayed deep invasion. The invasive component was characterized by cribriform pattern and irregular glands. Additionally, there was significant nuclear atypia. The second component, the mural nodules, was composed of nodules of pleomorphic and rhabdoid cells with large eosinophilic cytoplasm, remarkably enlarged nuclei, and prominent nucleoli. The mitotic rate was 14 mitoses per 10 HPF (Figure 1). The mural nodule component constituted 70% of the tumor area. Notably, lymphovascular invasion was not detected.

Immunohistochemically, the mucinous adenocarcinoma and mural nodule component were positive for cytokeratin 8-18 and keratin Cam 5.2 and negative for desmin. Based on the findings, we diagnosed the patient with appendiceal mucinous cystadenocarcinoma with mural nodules of anaplastic carcinoma.

DNA extraction was done from the paraffin-embedded tissue sections, which were manually and separately microdissected from the invasive mucinous and mural nodule components. Mutation analysis was studied in two different blocks from two components. DNA was isolated according to the standard laboratory procedures and genotyped using multiplex polymerase chain reaction coupled with a primer extension assay for K-RAS genes. The mucinous and mural nodule components exhibited a K-RAS codon 12/13 mutation (G12V, c.35G>T).

Demirel et al. (2) suggested that a malignant mural nodule in an invasive mucinous carcinoma of retroperitoneum may be part of the main tumor rather than a separate mural nodule. To better describe the morphologic and immunohistochemical features of primary retroperitoneal mucinous cystadenomas (PRMCs) and their association with sarcoma-like mural nodules, the authors conducted an immunohistochemical study with a panel of 19 antibodies and a histochemical study for mucin stains. They showed that the immunohistochemical and histochemical profiles of the PRMCs were similar to those of ovarian mucinous neoplasms and mesothelium.

K-RAS gene mutations have been demonstrated in up to 80% of invasive and borderline mucinous ovarian neoplasms (1). Recently, Ardakani et al. (3) investigated the molecular profile of a recurrent ovarian mucinous tumor with a mural nodule of anaplastic carcinoma. They iden-

ORCID IDs of the authors: G.K. 0000-0003-1933-9824; B.C.S. 0000-0002-9498-5570; B.G. 0000-0003-4124-6261; F.Ö. 0000-0001-9187-5387.

Corresponding Author: **Billur Coşan Sarbay; billurcosan@hotmail.com**
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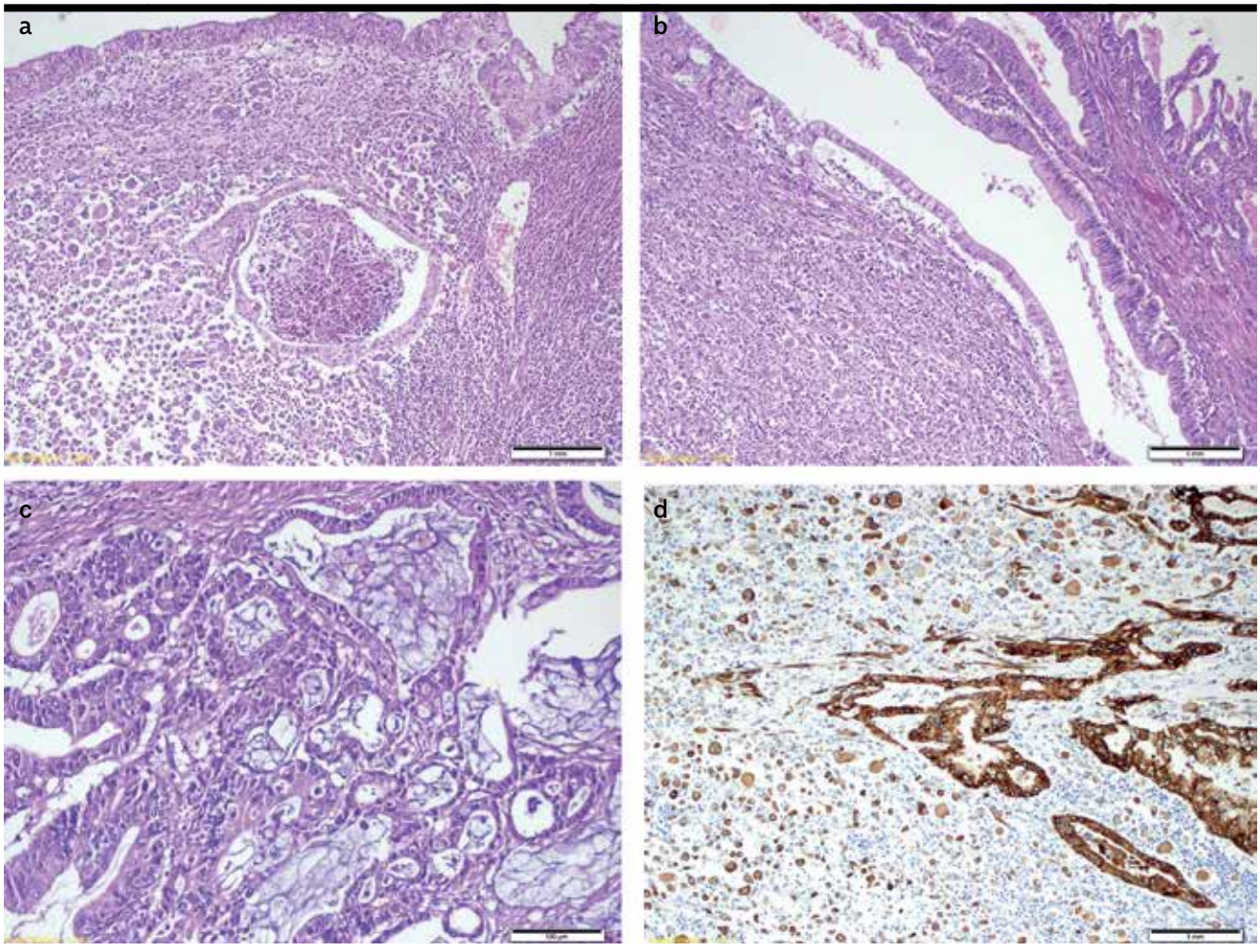

Figure 1. a-d. The glandular component of mucinous carcinoma with surrounding dispersed cells with rhabdoid appearance of mural nodule. Hematoxylin and eosin staining, ×200 (a); mucinous cystadenocarcinoma (upper right) concomitant with anaplastic mural nodule (left); hematoxylin and eosin staining, ×200 (b); Cribriform pattern in mucinous cystadenocarcinoma; hematoxylin and eosin staining, ×200 (c); mucinous and anaplastic components were strongly positive for keratin Cam5.2 by immunohistochemistry (d)

tified a similar K-RAS mutation in anaplastic carcinoma and previously resected mucinous tumor, and they suggested that it may show dedifferentiation rather than a collision tumor. Similarly, Desouki et al. (4) reported the K-RAS gene mutation status in case of ovarian mucinous adenocarcinoma with mural nodule of high-grade sarcoma. Both components demonstrated a mutation in codon 12 of the K-RAS gene. In another report by Resouki et al. (1), the authors studied K-RAS gene mutation in a case of invasive mucinous carcinoma with mural nodules of anaplastic carcinoma. They detected p.G12V, c.35G>T mutation in the two components of the tumor. Based on the same K-RAS gene mutation in the components in both cases, the authors concluded that some malignant mural nodules exhibit a form of dedifferentiation in mucinous tumors rather than a collision of two divergent tumor types (1,4). Similarly, in our case, both tumor components displayed a mutation in codon 12 of the K-RAS gene with the same nucleotide substitution (G12V, c.35G>A). Therefore, we suggest that mural nodule of appendiceal mucinous tumor represented a form of dedifferentiation rather than a separate tumor.

In spite of treatment with adjuvant chemotherapy or radiotherapy in patients with anaplastic carcinoma mural nodules, the reported prognosis is poor (1). As in ovarian tumors, the definite detection of the differentiation of the cells of these mural nodules presumably has prognos-

tic implications; hence, all mural nodules require careful histological evaluation. In addition, patients with tumors displaying K-RAS mutations may benefit from directed therapies. Further research is warranted on this topic.

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