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Case report

Simultaneous p53 and KRAS mutation in a high-grade serous carcinoma with deceptive appearance of a low-grade carcinoma. A case report

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SUMMARY

Low-grade and high-grade serous carcinomas have unique clinical, morphological, underlying molecular alterations, and vastly different biologic behavior (Prat et al., 2018, Vang et al., 2009). The differentiation into high and low-grade serous carcinoma is important for clinical management and prognosis and is easily recognized by practicing pathologists. High-grade serous carcinoma is characterized by marked nuclear atypia and pleomorphism, frequent, often atypical mitosis with papillary or three-dimensional clusters, p53 mutation, and block-like p16 staining. In contrast, low-grade serous carcinomas have a different morphologic appearance with micropapillary formation, small nests of tumor cells having low to intermediate grade nuclei, and absence of significant mitosis. Low-grade serous carcinoma is often associated with micropapillary variant of ovarian serous borderline tumor. The low-grade serous carcinoma shows wild type p53 expression, patchy p16 staining, and often *K-RAS*, *N-RAS*, and/or *B-RAF* mutation. Here we report a case of mullerian high grade serous with a deceptive morphology resembling low-grade serous carcinoma with micropapillary features and moderate nuclear atypia. However, the tumor is simultaneously p53 and *K-RAS* mutated. This case illustrates three critical issues; a) potential to be mistaken as a low-grade serous carcinoma because of morphologic appearance and relative uniform cytologic feature. b). raise the question of true progression of low-grade to high-grade serous carcinoma, a rare phenomenon as described in the literature, and c). whether the biologic behavior and/or response to therapy would differ from the classic forms.

1. Background

High-grade serous carcinomas (HGSC) have typical histological features with complex solid or cystic, often papillary architecture, pleomorphic high nuclear grade, and abundant mitosis, including atypical ones. These tumors show diffuse intense p53 staining, absent staining (Null) or cytoplasmic staining (Köbel et al., 2016) indicating p53 mutation. The distinction between low- and high-grade serous carcinoma is usually straightforward because of differences in architectural, cytological and immunohistochemical profile (Altman et al., 2013; Prat et al., 2018). The histologic features of low-grade serous carcinoma include micropapillary architecture and mild to moderate nuclear atypia, and infrequent mitosis (Malpica et al., 2004). Solid sheets with slit-like spaces may be present (Gadducci and Cosio, 2020; Arslanian et al, 2022). Wild type p53 expression, and often mutations in KRAS, NRAS, and BRAF genes are seen.

The biological behavior, patient management, response to therapy, and overall prognosis of these two tumors are vastly different. It is imperative to have an accurate diagnosis before the initiation of treatment. The current case illustrates a unique scenario where the tumor shows morphological pattern of a low-grade serous carcinoma but has simultaneous p53 mutation by immunohistochemical staining (IHC) and K-RAS mutation by molecular testing. The combined pattern of p53 mutation and *K-RAS* mutation is highly unusual as documented by The Cancer Genomic Atlas study (Cancer genomic Atlas 2012).

2. Case report

A 77-year-old patient with a remote history of uterine cervical cancer, treated in 1977 at another facility, presented with abdominal cramps and, on CT scan showed calcification in the left pelvis. This was followed by MRI that again showed calcifications as well as a 3 cm mass in the right pelvis. For uterine cervical carcinoma, she was treated by hysterectomy in the past; no pertinent treatment history was available. This G3, P3 patient had her last Pap done in 2019 was normal. On physical examination there was no tenderness or palpable mass in the

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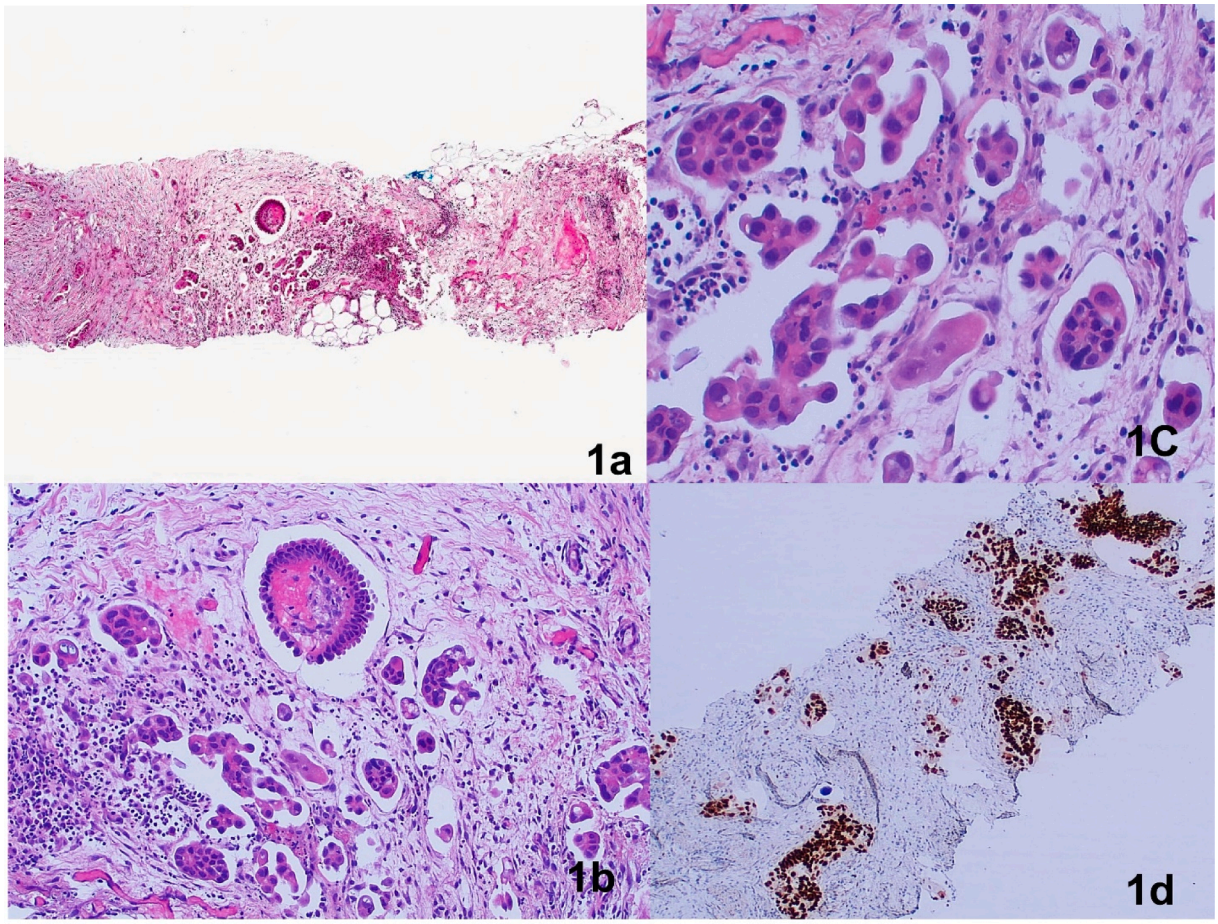

Fig. 1a-d. Low grade serous morphology on initial biopsy 1a: H&E (Scanning image). 1b and 1c: The papillary structures show low to intermediate grade nuclei of LG serous carcinoma and then next to it are cells of higher nuclear grade, seen as a collection of fewer cells without any pattern. (H&E 10x and 20x respectively). 1d: Diffuse p53 staining on both components is consistent p53 mutation (IHC 4x).

pelvis or abdomen. No lymphadenopathy was noted. The labs done at her initial visit were Ca125 = 16 and CEA < 1.7. The pelvic mass biopsy done at an outside hospital and later reviewed at this institution revealed tumor cells in nests and micropapillary architecture, low- to intermediate-grade nuclei, and rare mitotic figures morphologically resembling a low-grade serous carcinoma (Fig. 1a, 1b, and 1c). IHC showed strong, intense p53 staining (Fig. 1d). Three other immunostains were performed with the following immunoreactivity: patchy p16, diffuse PAX-8, and Patchy WT-1. Given the atypical morphology and immune profile, surgical intervention over neoadjuvant chemotherapy was appropriate. She underwent debulking with exploratory laparotomy, bilateral salpingo-oophorectomy, and partial omentectomy. Grossly the tumor has a red-tan nodular appearance with some papillary and granular areas. The cut surface of the omental tumor shows irregular, firm white nodules, red-tan hemorrhagic nodules, and greenish discoloration (Fig. 1e). The resection specimen, on histology, showed areas of micro papillae and small nests of cells with low- to intermediate grade nuclei admixed with papillary architecture and psammoma bodies. In addition, tumor cells with a high-nuclear to cytoplasmic ratio and significant mitosis (25 per 10 high power field) were present as also reported in 2004 (Malpica et al., 2004). Histologically these areas appeared to be an admixture of low- and high-grade serous carcinoma (Fig. 1f and 1g). However, the p53 IHC was diffusely positive throughout with strong intensity (Fig. 1h). Sequencing by polymerases chain reaction (PCR) was done for the investigation of KRAS. The tumor showed KRAS mutation at codon, c.34G > T, exon 2, alteration pGly12 Cys and as well as TP53 mutation. The *RAS* mutation is a common finding in serous ovarian borderline tumors and low-grade serous carcinomas but is uncommon in classic high-grade serous carcinomas (Singer et al., 2003, Nakamura et al., 2016, Cancer genomic Atlas 2012). After debulking surgery, she received Carboplatin and Taxol chemotherapy for 6 cycles/18 weeks.

3. Discussion

The MAPK pathway alteration is characteristic of LGSC of the ovary or peritoneum and is associated with reduced sensitivity to chemotherapy relative to HGSC.

Therapeutic trials of MEK inhibitor trametinib in patients with recurrent low-grade serous carcinoma are underway (Gershenson et al., 2022). Other trials, including RAF/MEK and FAK inhibitors, are being studied in low-grade serous ovarian carcinoma with KRAS mutation (Banerjee, et al., 2021) These therapeutic agents differ from conventional HGSC, including paclitaxel/platinum-based chemotherapy (Mahmood et al., 2020).

The presence of simultaneous p53 and *K-RAS* mutation makes this case unique and potentially creates a challenge to manage the patient successfully because of the uncertainty of how the tumor would respond to chemotherapy.

These mutations may alter the patient prognosis and requiring a change to the management protocol.

The patient is receiving the chemotherapy and tolerating carbotaxol-cisplatin regimen and scheduled to receive six cycles which was started at the beginning of November 2022 and sotoracib (*KRAS* G12-C

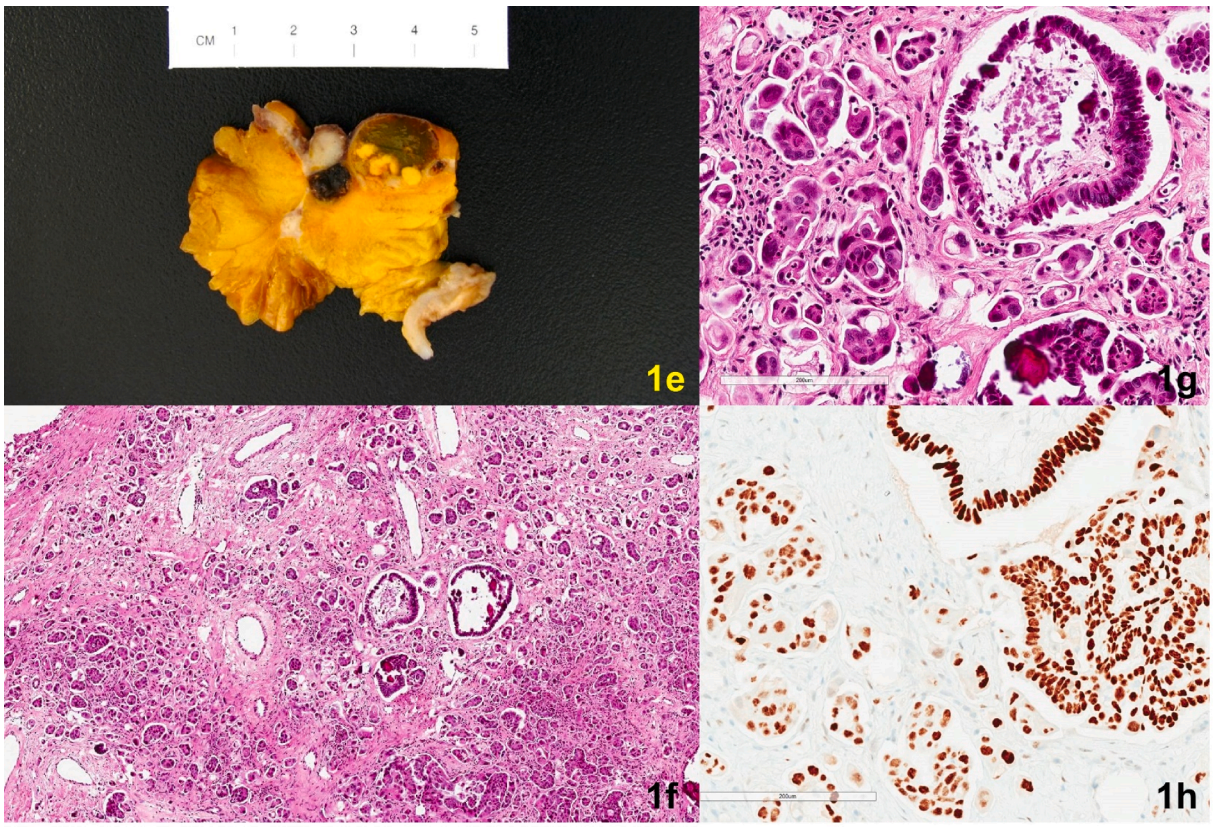

Fig. 1e-h. Resection specimen 1e: Gross photo of omental nodule, 1f: Micropapillary architectural pattern typical of low-grade serous carcinoma (H&E 2x), 1 g: The nuclear grade seen is both low- and high grade. The single larger papilla shows low nuclear grade. (H&E 20x), 1 h: p53 mutant positive in all tumors (IHC 4x).

inhibitor) later, end of November, after undergoing a suboptimal debulking with 1.5 cm for residual disease in the ileal mesentery. Documenting treatment response in this scenario is thus essential for future references. Routine p53 staining can help avoid this potential misdiagnosis on a small biopsy. Notably in this case, there were areas with morphology suggestive of low-grade serous carcinoma, e.g., nests and micropapillary architecture. However, the mutated p53 staining was consistent with high-grade serous carcinoma, it is essential to recognize this morphological subtype and perform routine p53 IHC stain.

The follow-up is limited in this case as the patient is still undergoing treatment. However, it would be interesting to study a cohort of Mullerian carcinomas with mixed high- and low-grade serous morphological features and p53 and *RAS* or *RAF* mutations, and document the treatment response, prognosis, and overall survival.

This case illustrates three critical issues; a) potential for misdiagnosis as low-grade serous carcinoma because of morphologic appearance and relatively uniform cytologic features. b). one may speculate that this is an example of an actual progression of low-grade to high-grade serous carcinoma, a rare phenomenon described in the literature. c). the biological behavior and/or response to therapy may differ from the classic forms. In addition, a caution for practicing pathologists is that p53 mutation status by IHC should be done on a smaller biopsy sample with a tumor showing low-grade serous morphology to avoid misdiagnosis. We recommend that all HGSC with LG morphology be documented and undergo testing for *RAF* and *RAS* mutation so that their actual biologic behavior can be studied in large number of cases, and proper management protocol could be developed.

The patient signed a consent form that allows the use of the material for educational purposes in this academic institution without disclosing the unique identifiers of the patient.

CRediT authorship contribution statement

Shivali Marketkar: Methodology, Writing – original draft. **C. James Sung:** . **M. Ruhul Quddus:** Supervision, Conceptualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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