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Case Report

Two cases of high grade tubo-ovarian serous carcinoma with extensive clear cell carcinoma-like morphology, possibly accentuated in the neoadjuvant setting

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1. Introduction

High grade tubo-ovarian serous carcinoma (HGSC) and ovarian clear cell carcinoma (CCC) are widely accepted as distinct, essentially non-overlapping clinicopathological entities with different pathogenetic origins [1–3]. Nevertheless, their distinction on morphological grounds can occasionally be challenging. This distinction is not merely academic as HGSC and CCC can show significantly different responses to chemotherapy. Specifically, CCC may show resistance to chemotherapeutic regimens routinely used for patients with HGSC [4,5]. The above-mentioned diagnostic difficulty is due in a large part to the occasional finding of CCC-like areas in cases of HGSC, in particular, in the form of optically clear cytoplasm [1]. Fortunately, even when exhibiting such morphology, HGSC often retains a characteristically high mitotic index [1], a feature uncommon in most cases of CCC [6].

However, the propensity of HGSC to mimic CCC may be accentuated in the neoadjuvant setting, potentially compounding the diagnostic difficulty even further in cases in which a pre-treatment biopsy is not readily available. Post neoadjuvant cases of HGSC may show extensive clear cell cytoplasmic changes [7,8]. Furthermore, the mitotic index of treated ovarian carcinomas may be considerably diminished [7]; this latter point is of special interest since, as already mentioned, the characteristically high mitotic index of HGSC relative to CCC is a very useful distinguishing feature [6].

To be clear, we acknowledge that, regardless of the clinical setting, the vast majority of cases of HGSC and CCC may be readily distinguished by a panel of immunohistochemical (IHC) markers [1,9]. However, some features are so morphologically characteristic of CCC that pathologists may be tempted to forego an IHC workup. These include extensive papillary architecture with a simple, optically clear epithelial lining showing hobnailing, open tumor rings, moderate nuclear atypia, a relatively low mitotic index and abundant hyaline globule formation. Here, we report two cases of patients with HGSC that exhibited various combinations of this very morphology. While both patients had received neoadjuvant chemotherapy, one of the patients had undergone a pre-treatment omental biopsy in which at least some of the variant morphological features were already present. While we suspect that the CCC-like morphology was accentuated by the effects of chemotherapy, these cases highlight the ability of HGSC to mimic many more of the morphological features of CCC than the frequently reported optically clear cytoplasm. We emphasize the utility of a targeted IHC panel in approaching cases of upper gynecologic tract carcinomas, even when many of the classical morphologic features of CCC are present, especially in the neoadjuvant setting.

2. Case report

2.1. Case 1

A 71-year-old woman with an unknown *BRCA* mutation carrier status and no known history of endometriosis presented with new onset lower abdominal pain before bowel movements. Her clinical history was significant only for diverticulosis. Computed tomography (CT) imaging of her abdomen demonstrated findings compatible with peritoneal carcinomatosis and her reproductive organs were without detectable abnormalities. Her CA 125 was elevated (2356 U/ml).

An omental biopsy was positive for carcinoma. By IHC, the carcinoma was diffusely and strongly positive for PAX-8, P53 and WT-1 (Fig. 1d–f). A diagnosis of high grade serous carcinoma was rendered. While some clear cell carcinoma-like morphological features were present on our retrospective review of the case [i.e. delicate papillary architecture, focal cytoplasmic clearing, moderate nuclear atypia, hyaline globule formation and a conspicuous absence of mitotic figures (Fig. 1a–c)], no mention of these findings was made by the signing pathologist at the time of diagnosis.

The patient received three cycles of carboplatin and paclitaxel, followed by repeat CT imaging, which showed an interval decrease in the tumor burden within the abdomen and pelvis. She underwent an exploratory laparotomy for optimal debulking, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, appendectomy, and fulguration of tumor nodules.

Upon gross examination, the uterus and adnexa were unremarkable

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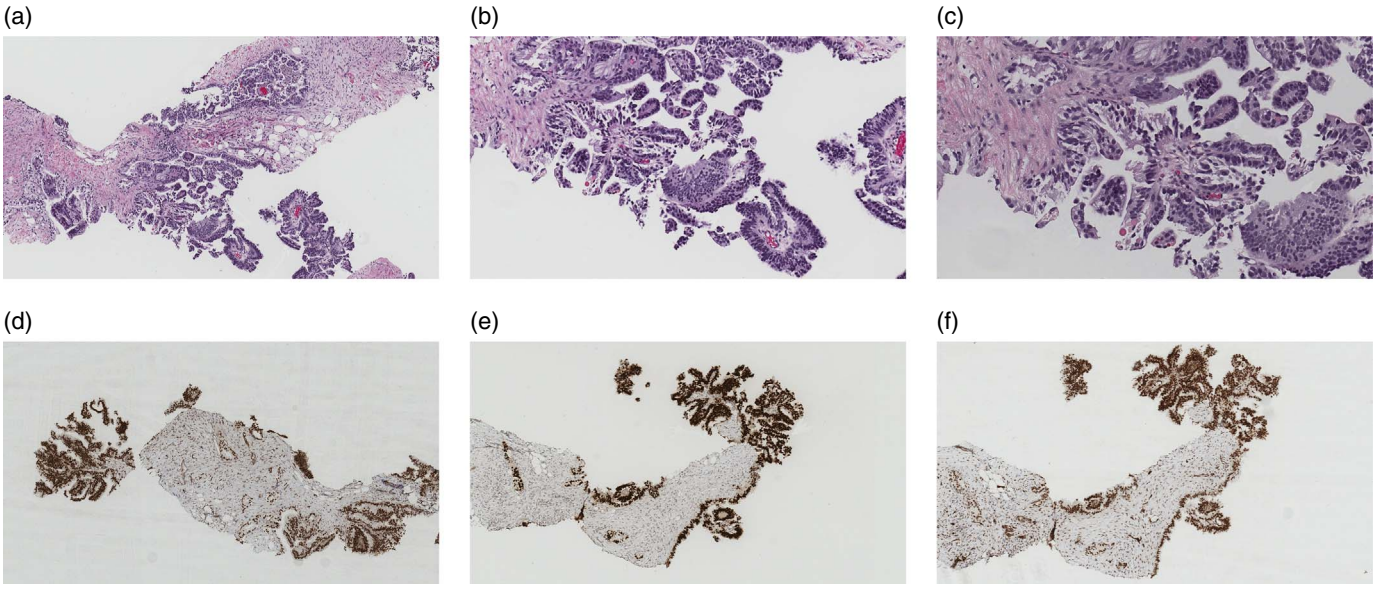

Fig. 1. Case 1, pre-treatment biopsy. A. Low power magnification showing delicate papillary architecture (H&E). B. Intermediate power magnification showing focal cytoplasmic clearing, moderate nuclear atypia, hyaline globule formation and a conspicuous absence of mitotic figures (H&E). C. High power magnification showing the hyaline globules in greater detail (H&E). D–F. IHC, showing diffuse and strong nuclear staining for PAX-8 (D), p53 (E) and WT-1 (F).

but the omentum revealed a 14 cm firm, red to yellow lesional area. Microscopically, the tumor in the omentum exhibited morphology similar to that seen in the pre-treatment biopsy, including an extensively papillary growth pattern with a predominantly simple epithelial lining consisting of only one to a few layers of cells with clear cytoplasm, a low mitotic index (1 mitotic figure per 10 high power fields), only moderate nuclear atypia and easily identifiable hyaline globules (Fig. 2a–c). In the left fallopian tube, foci of serous tubal intraepithelial carcinoma (STIC) with treatment effect were identified (Fig. 2d–e). Numerous psammomatous calcifications were present. No histological evidence of endometriosis was seen.

By IHC, the tumor showed strong diffuse nuclear staining with p53 and WT-1 and moderate diffuse nuclear staining with ER and PAX-8; glypican-3 was predominantly negative, with a few very focal areas of cytoplasmic staining (Fig. 2f–l). Focal granular cytoplasmic staining with AMACR was present and HNF1-beta, Napsin A and CDX2 were negative.

Residual tumor was also identified in both ovaries and fallopian tubes, the cul-de-sac peritoneum and the serosal surface of the appendix. The uterus and cervix were not involved. The patient is alive with no evidence of disease 7 months following surgery.

2.2. Case 2

A 68-year-old woman with an unknown *BRCA* mutation carrier status and no known history of endometriosis presented with complaints of malaise, loss of appetite, bloating and constipation over the duration of a few months. Her clinical history was significant for a rectal carcinoid that had been surgically removed several years ago. On physical examination she was found to have ascites.

CT imaging revealed a moderate amount of ascites with a diffuse peritoneal reaction, but no clearly evident features of malignancy. Diagnostic paracentesis performed at an outside hospital confirmed the presence of malignant cells consistent with an adenocarcinoma. Serum CA 125 was elevated (2178 U/ml). A presumptive diagnosis of an ovarian primary was made and the patient was started on neoadjuvant chemotherapy. She received three cycles of carboplatin and paclitaxel prior to undergoing debulking surgery including an exploratory laparotomy, total hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, and optimal surgical cytoreduction.

Upon gross examination, the left ovary measured 3.8 cm in greatest dimension and showed cystic lesions with smooth inner linings. The right ovary measured 3.6 cm in greatest dimension and had a mixture of cystic and solid areas; the cystic areas had smooth inner linings. The bilateral fallopian tubes and uterus were unremarkable. The omentum had several firm tan-white nodules possibly representing tumor implants, ranging from 0.5 to 2.1 cm.

Microscopically, the tumor involved both ovaries and fallopian tubes, the uterine serosal surface and the omentum. The tumor showed morphological features similar to those seen in case 1 including an extensively papillary growth pattern with a predominantly simple epithelial lining, a low mitotic rate (3 mitoses per 10 high power fields), predominantly moderate nuclear atypia and conspicuous hyaline globules; additionally, the tumor showed a hobnailed growth pattern and numerous open tumor rings (Fig. 3a–e). In contrast to case 1, there were also other areas with a more solid growth pattern, severe nuclear atypia and an elevated mitotic index (up to 57 mitoses per 10 high power fields; Fig. 3f). Cells with optically clear cytoplasm were less conspicuous as compared to case 1, but were focally present. Numerous psammomatous calcifications were also present. No histological evidence of endometriosis was seen.

By IHC, the tumor showed strong diffuse nuclear staining with p53 and ER, moderate focal nuclear staining with HNF1-beta and only weak focal nuclear staining with WT-1 (Fig. 3g–i). AMACR, Napsin A, glypican-3 and CDX2 were all negative. Focal STIC was identified in the left fallopian tube, supported by aberrant p53 overexpression by IHC (Fig. 3j–k). The patient passed away due to complications related to her carcinoma 4 months following her surgery.

3. Discussion

Here we report two cases of HGSC with morphological changes very reminiscent of CCC, over and above the oft-reported finding of optically clear cytoplasm. Specifically, our cases exhibited vast areas of tumor (the entire tumor in one case) with extensive papillary architecture, a simple epithelial lining composed of 1 or a few layers of cells with variably optically clear cytoplasm, moderate nuclear atypia, a relatively low mitotic index and abundant hyaline globule formation. Open tumor rings and a hobnailed growth pattern were also seen in one case (case 2). While both patients had received neoadjuvant chemotherapy prior