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Case Report

Non-diethylstilbestrol exposed vaginal clear cell adenocarcinoma has a common molecular profile with ovarian clear cell adenocarcinoma: A case report

Yuji Ikeda [a], Katsutoshi Oda [a,*], Hiroyuki Aburatani [b], Kei Kawana [a], Yutaka Osuga [a], Tomoyuki Fujii [a]

[a] Department of Obstetrics and Gynecology, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[b] Division of Genome Science, Research Center for Advanced Science and Technology, 4-6-1 Komaba, Meguro-ku, Tokyo 153-8904, Japan

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Introduction

Vaginal cancer accounts for only 1–2% of female genital malignancies (Creasman et al., 1998). Primary vaginal clear cell adenocarcinoma (PVCCA) is particularly uncommon, as 80–90% of vaginal cancers are squamous cell carcinoma (Creasman et al., 1998). PVCCA generally occurs in young women with genital tract anomalies and intrauterine diethylstilbestrol (DES) exposure and is very rare in women with no history of DES exposure (Hanselaar et al., 1997). Neither the optimal therapeutic strategy nor the molecular characteristics of this disease have been elucidated. Four reported cases of non-DES-exposed PVCCA were associated with congenital genital tract anomalies (Uehara et al., 2010; Tanaka et al., 1994), suggesting that congenital genital anomalies are common to both DES-exposed PVCCA and non-DES-exposed PVCCA. Despite the apparent familial nature of this disease, the genetic characteristics of PVCCA are still unknown. Clear cell adenocarcinoma (CCA) is a common histologic type of renal and ovarian carcinoma. Renal CCA (RCCA) frequently exhibits chromosomal loss at 3p (92.2%), which includes *VHL*, and gain at 5q (60.2%), whereas ovarian CCA (OCCA) commonly exhibits gain at 20q (36%), which includes *ZNF217*, and deletion at 9p, which includes *CDKN1A*/*CDKN1B* (Moore et al., 2012; Kuo et al., 2010). *VHL* mutation is common in RCCA (57%), whereas *PIK3CA* mutation is common in OCCA (33%) (Gnarra et al., 1994; Kuo et al., 2009).

We present a case of a young woman with a congenital genital anomaly diagnosed with PVCCA. She was treated with concurrent chemoradiotherapy (CCRT) and remains recurrence free to date. We examined the tumor for chromosomal copy number alterations (CNA) and genetic mutations and compared the alterations with those commonly reported for RCCA and OCCA.

Case report

A 25-year-old woman was referred to our hospital with abnormal vaginal bleeding. Her medical history included a right ectopic ureteral orifice repaired by surgery during childhood, and she was also diagnosed with a septate uterus. She had no history of prenatal DES exposure or sexual intercourse. Colposcopy showed an entirely circumferential vaginal tumor, primarily at the distal side (Fig. 1A-1) and not affecting the uterine cervix. Vaginal biopsy showed large cells with clear cytoplasm, enlarged nucleoli, and tubular structures lined by hobnail cells (Fig. 1A-2). Magnetic resonance imaging (MRI) revealed a tumor, >6 cm in size, expanded inside the vagina without parametrial invasion (Fig. 1A-3). Computed tomography (CT) also showed the presence of the tumor as well as right renal atrophy and compensatory hypertrophy of the left kidney, but no metastasis was detected by positron emission tomography–CT. The cancer was diagnosed as stage I PVCCA (International Federation of Gynecology and Obstetrics). Considering the complexity of surgery and the limited therapeutic effects of radiotherapy alone, CCRT was selected as the treatment strategy after obtaining informed consent from the patient. Weekly cisplatin (40 mg/m^2, 6 cycles) and a combination of external radiotherapy (1.8 Gy, 28 times) and high-dose-rate intracavitary brachytherapy (6 Gy, 6 times) were administered. After 1.5 months, colposcopy, vaginal biopsy, and MRI (Fig. 1B-1, B-2, B-3) showed a drastic decrease in tumor volume. The following month, vaginal biopsy confirmed a pathological complete response. The patient has been recurrence free for 5 years following CCRT.

Clear cell adenocarcinoma (CCA) is a common histologic type of renal cell and ovarian carcinomas. Therefore, we hypothesized that PVCCA may share common genetic characteristics with CCA arising in

* Corresponding author. Fax: +81 3 3816 2017.
E-mail addresses: yujida-tky@umin.ac.jp (Y. Ikeda), katsutoshi-tky@umin.ac.jp (K. Oda), haburata-tky@umin.ac.jp (H. Aburatani), kkawana-tky@umin.ac.jp (K. Kawana), yutakaos-tky@umin.ac.jp (Y. Osuga), fujiit-tky@umin.ac.jp (T. Fujii).

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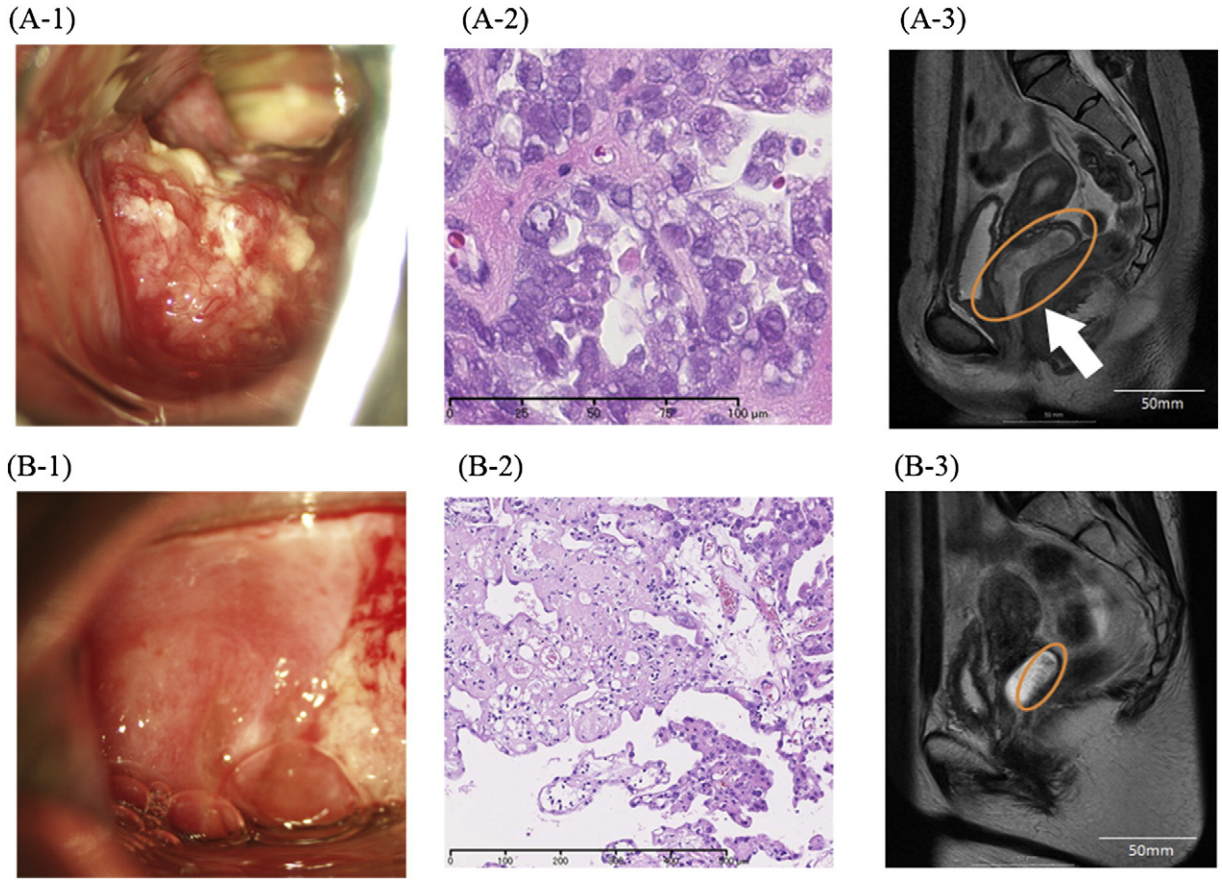

Fig. 1. Colposcopic, microscopic, and magnetic resonance imaging findings. (A) Before treatment. (B) 1.5 months after concurrent chemoradiotherapy. (A-1) Colposcopy shows a vaginal tumor, with extension beyond the lower third of the vagina. (A-2) Histologically (high power), cancer cells had clear cytoplasm, enlarged nucleoli, and tubular structures lined by hobnail cells. (A-3) The axial T2-weighted image shows a >6-cm vaginal tumor. (B-1) Colposcopy showed tumor disappearance on the right side of the vagina. (B-2) Vaginal biopsy (low power) showed a significant reduction in viable cells. (B-3) The axial T2-weighted image showed a tiny residual tumor (low intensity) with fluid collection (high intensity) inside the vagina.

other organs. We obtained fresh frozen tumor samples via biopsy, after obtaining informed consent and approval by the appropriate institutional ethics committee. Samples were embedded in optimal cutting temperature compound and were cut into 4-μm sections. Genomic DNA was isolated from the tumor and control samples (lymphocyte pellet from the patient's blood) using the QIAamp DNA Easy Kit (Qiagen, Valencia, CA). RNA was also extracted from the tumor using the RNeasy Mini Kit (Qiagen, Valencia, CA). We then performed single nucleotide polymorphism (SNP) typing array to evaluate chromosomal CNA using the Human Mapping 250K NSP Array (Affymetrix, Santa Clara, CA). The SNP array revealed several CNA, including 5 loci with copy number neutral loss of heterozygosity (gain of one allele and loss of the other allele) at chromosomes 1q, 9p, 12p, 16q, and 20q (Fig. 2A and Table 1). Among the CNA, chromosomal gain was noted at 20q13.13–20q13.33, and loss of heterozygosity, at 9p22.1–9p21.3, which include the cancer-related genes, *ZNF217* and *CDKN2A/2B*, respectively (Table 1).

Next, we analyzed mutations in *PIK3CA* (common in OCCA) and *VHL* (common in RCCA) using PCR-direct sequencing (Moore et al., 2012; Kuo et al., 2009). We identified a point mutation in *PIK3CA* at exon 20 (M1004I); no mutations were found in *VHL* (Fig. 2B).

The key findings of this case of non-DES exposed PVCCA are (i) favorable prognosis with CCRT, (ii) extensive chromosomal instability with CNA at loci of well-known cancer-related genes, and (iii) presence of a *PIK3CA* mutation. Vaginal cancer patients are generally treated with radiation (Creasman et al., 1998). Chemotherapy is infrequently used in treatment because of the poor associated outcome (Creasman et al., 1998; Renaud et al., 2009). However, the 5-year survival rate among patients with stage I PVCCA is only 56%, which is significantly worse than that for vaginal squamous cell carcinoma (Hanselaar et al., 1997). Thus, an alternative therapeutic strategy is warranted. Recently, Ghia et al. compared the prognoses associated with CCRT and radiotherapy between vaginal and cervical cancers, and suggested that the improvement in prognosis was lower for vaginal cancer than for cervical cancer (Ghia et al., 2011). However, multivariate analysis by histology suggested that the increase in the progression-free interval associated with CCRT was significantly higher for adenocarcinoma (hazard ratio [HR], 0.05; 95% confidence interval [CI]: 0.004–0.56; $P = 0.02$) than for squamous cell carcinoma (HR, 0.14, 95% CI: 0.02–1.20; $P = 0.07$). Thus, CCRT may be a suitable option for PVCCA.

We analyzed the tumor for chromosomal CNA and genetic alterations. Since non-DES-exposed PVCCA often coexists with congenital genital tract anomalies, such as an ectopic ureteral orifice to the vagina (Uehara et al., 2010; Tanaka et al., 1994), we hypothesized that PVCCA may possess genetic characteristics similar to urogenital CCA, such as RCCA and OCCA. In this patient, we observed extensive chromosomal imbalances, with a chromosomal gain at 20q and loss of heterozygosity at 9p, both of which are common to OCCA. However, neither 3p loss nor 5q gain was observed. These results suggest a similarity of chromosomal imbalances between PVCCA and OCCA. To assess specific genetic alterations common to RCCA and OCCA, we analyzed mutations in *VHL* and *PIK3CA* and found that this PVCCA had a *PIK3CA* mutation (but not a *VHL* mutation), further supporting the hypothesis that PVCCA and OCCA are genetically similar.

Our study has several limitations. Since our findings are based on a single case, given the rarity of PVCCA, the efficacy of CCRT in PVCCA