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Vaginal clear cell adenocarcinoma in a young woman with a Müllerian duct anomaly and no history of in utero diethylstilbestrol exposure: a fertility-sparing approach

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Summary

Since most cases of primary vaginal clear cell adenocarcinoma (PVCCA) occur during the reproductive years, it is necessary to evaluate the safety and efficacy of potential fertility-sparing approaches. Herein, the authors report a case of a young woman with a Müllerian duct anomaly and a primary diagnosis of PVCCA without a history of in utero diethylstilbestrol (DES) exposure. She was treated with a fertility-sparing approach involving organ-preserving surgery and oocyte cryopreservation in conjunction with adjuvant pelvic radiotherapy. To date, disease recurrence has not been documented.

Key words: Primary vaginal clear cell adenocarcinoma (PVCCA); Müllerian duct anomaly.

Introduction

Clear cell adenocarcinoma is an uncommon malignancy involving the vagina that is closely related to in utero exposure to diethylstilbestrol (DES) [1]. Data suggest that DES exposure is also associated with Müllerian duct anomalies [2].

Primary vaginal clear cell adenocarcinoma (PVCCA) that is unrelated to DES is a rare finding [3]. Moreover, the presence of this vaginal cancer histotype in association with Müllerian duct anomalies and urogenital malformations in the absence of DES exposure is even rarer. Patients with PVCCA usually undergo radical surgery. Therefore, in the literature, no data are available regarding a conservative approach.

Case Report

A 28-year-old nulliparous woman was referred to the Department of Obstetrics and Gynecology in the Gynecologic Oncology Unit at A.O. Pugliese Ciaccio at Magna Graecia University in Catanzaro for atypical vaginal bleeding.

At the age of two years, a Müllerian duct anomaly characterized by bicornuate uterine and vaginal sept (Figure 1) associated with a renal abnormality was diagnosed, and surgery for renal malformation was performed.

During the pelvic examination there were no abnormal findings in the visible part of the uterine cervix, but pelvic ultrasound showed an abnormal endometrial thickness. Based on patient symptoms and ultrasound evaluation, the authors decided to perform a hysteroscopic-guided endometrial biopsy both in the right and the left hemi-uterine cavities. During hysteroscopic evaluation, the vagina was also examined and a polypoid area in the upper lateral vaginal wall was observed. Moreover, a targeted vaginal biopsy was performed. The vaginal biopsy specimen showed "poorly differentiated clear cell adenocarcinoma" (Figure 2), while the endometrial tissue was negative for neoplastic lesions.

Based on the results of the recommended diagnostic workup, a

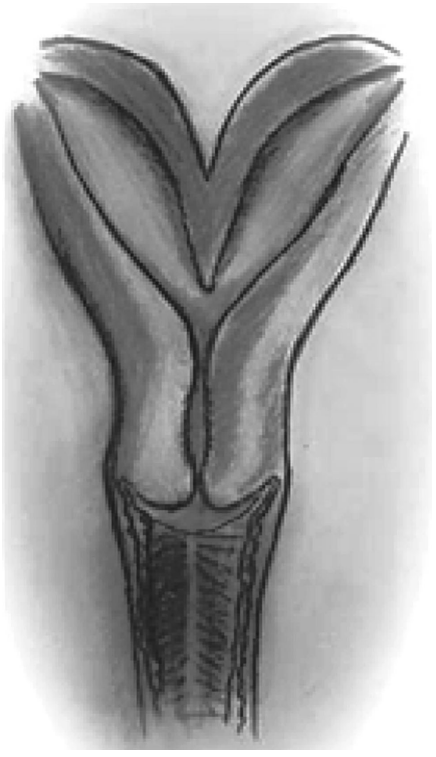

Figure 1. — Graphic representation of the Müllerian duct anomaly characterized by uterine bicornuate and vaginal sept.

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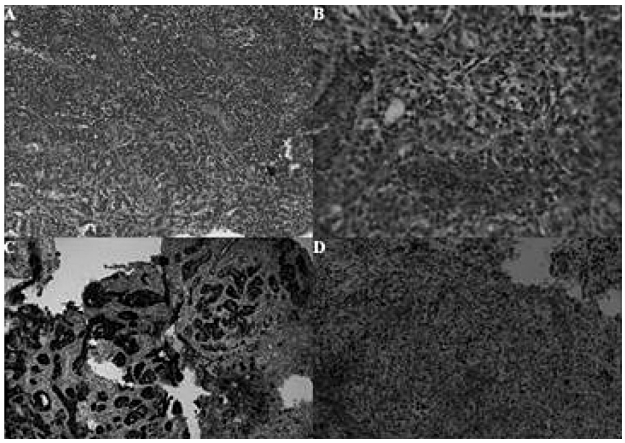

Figure 2. — Microscopic imaging findings. (A and B) Biopsy of vaginal lesion showing invasive carcinoma with glandular differentiation clear cell pattern (magnification of ×20 and ×40, respectively). (C) Immunoistochemical analysis for cytokeratin 7: positive (magnification of ×10). (D) Immunoistochemical analysis for p53: positive (magnification of ×20).

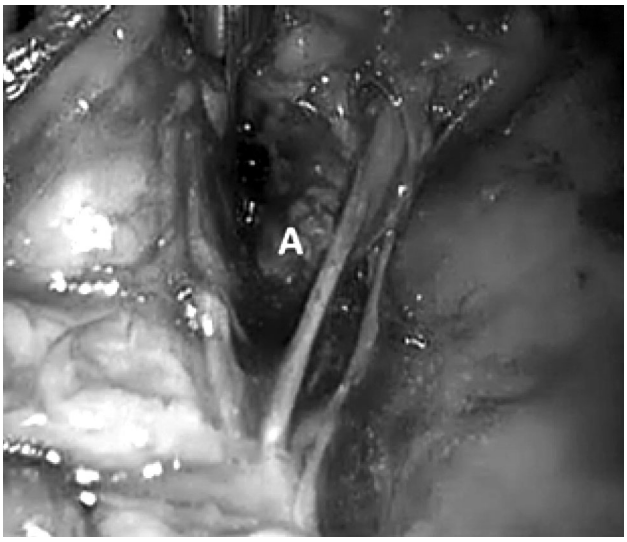

Figure 3. — Laparoscopic imaging finding. (A) Genitofemoral nerve and lateral limit of pelvic lymphadenectomy.

preoperative CT scan, cystoscopy, and rectoscopy were performed, and no loco-regional diffusion was detected. A cervical biopsy revealed only chronic non-specific cervicitis and the case was finally diagnosed as PVCCA, FIGO Stage I [4].

Considering the young age of the patient, the early stage of the cancer and her desire to have children, the authors decided to offer a combined therapy with wide local excision, lymph node sampling, and radiotherapy after obtaining informed consent from the patient. Therefore, cryopreservation of oocytes was proposed. Ovarian stimulation with induction of oocyte maturation using a GnRH antagonist–based protocol was performed after a careful evaluation of the ovarian reserve. No persistent ovarian follicles or pathological ovarian findings were observed before beginning ovarian stimulation. GnRH antagonists are administered to prevent a premature LH surge when the size of the lead follicle reaches 13 mm at day 6 of gonadotropin stimulation (recombinant human FSH), which begins on the second day of the menstrual cycle. Subsequently, surgery involving a laparoscopic approach was performed (Figure 3), and retroperitoneal lymphatic tissue from pelvic side walls was removed. The uterus, tubes, and ovaries were preserved. Then, a vaginal approach was employed to remove a partial local of the vagina with resection of septum.

Surgically resected specimens were negative for carcinoma in the definitive surgical pathology. Therefore, the patient underwent pelvic radiotherapy as an adjuvant treatment. As recommended, the present authors are assessing the patient every three months, for one year, to perform follow-up clinical and ultrasonographic examinations. After five years, no disease recurrence or relapse has been observed.

Discussion

Vaginal cancer accounts for only 1–2% of female genital malignancies [5]. PVCCA is uncommon, as 80–90% of vaginal cancers are squamous cell carcinomas [4] and occur primarily in young females with a history of DES exposure in utero. PVCCA most commonly involves the anterior wall of the upper third of the vagina, with variation in size and morphology (hyperplastic or nodular). Radical surgery is usually performed on affected patients.

In the present case, PVCCA was diagnosed in a patient without exposure to DES in utero. The lesion appeared as a hyperplastic area involving the lateral upper part of the vagina. The patient was only 28 years of age and had a strong reproductive desire. Cancer therapy, either surgical or medical, would have had a negative impact on her fertility. Premature ovarian failure, premature menopause, and subsequent infertility are the major negative long-term effects of genital cancer therapy [6].

After diagnosis of PVCCA was made, the gynecological oncologists cared for the patient at every step of the process throughout the period, from preoperative care to tailoring the adjuvant treatment. The main focus was on devoting maximum effort towards curing the woman.

Gynecological oncologists must always inform patients about the risks related both to the disease and to surgical and medical treatments. In particular, in the present case, they informed the patient of effects of both the disease and treatment on her fertility, offering a potential conservative approach.

Age, pretreatment ovarian reserve, location of the malignancy, and type and duration of adjuvant treatment all have an impact on the decision-making process. To quantify the ovarian reserve, the authors used a new methodology called OvAge that integrates clinical, biochemical, and 3D-ultrasonographic parameters [7]. Biochemical variables include FSH, E2, and anti-Müllerian hormone (AMH), whereas 3D-ultrasonographic variables include the antral

follicle count (AFC), ovarian volume, flow index (FI), vascularization index (VI), and vascularization flow index (VFI). The assessment of ovarian reserve using OvAge prior to beginning ovarian stimulation is necessary to provide a more accurate prediction of ovarian response to controlled ovarian stimulation (COS) and to determine the COS protocol and starting gonadotropin dose.

In the present patient, oocyte cryopreservation rather than blastocyst cryopreservation, was considered because there was no male partner to supply male gametes and her ovarian age was good. Therefore, COS was performed using a GnRH antagonist–based protocol. In contrast to GnRH agonists, GnRH antagonists immediately suppress the pituitary release of FSH and LH and do not require 10–14 days of administration before gonadotropin initiation. Given that GnRH agonists may add up to three additional weeks to the process, using GnRH antagonists decreased the interval between patient presentation and oocyte cryopreservation [8].

Traditionally, because the tumor spreads subepithelially, vaginal cancer is treated with surgery and a total radical vaginectomy and hysterectomy, with lymph node dissection also indicated. The deep pelvic nodes are dissected if the lesion invades the upper vagina, and the inguinal nodes are removed if the lesion originates in the lower vagina. However, this approach irreversibly damages the reproductive capacity of young women. Therefore, these ultraradical surgeries are currently unacceptable in young women with early-stage gynecological cancer with reproductive desire, consequently, after oocyte cryopreservation, combined local therapy with local vaginal excision, lymph node sampling, and radiotherapy was done.

Regular follow-up examinations were performed every three months. After five years, the patient remains recurrence-free. The present experience highlights that PVCCA in young women with a desire to have children may be safely treated with a conservative approach, adjuvant therapy, and strict follow-up. Given the importance of reproduction for many young patients facing cancer, counseling relating to fertility preservation is an essential component of comprehensive cancer care. Moreover, oocyte cryopreservation is a well-established, safe, and an efficacious fertility preservation method. It should be considered for all young women with cancer.

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