

## Case report

# Menstrual function preservation treatment of a primary vaginal clear cell carcinoma with ovarian transposition and vaginal brachytherapy

Dimitrios-Efthymios Vlachos<sup>a,\*</sup>, Athanasios Protopapas<sup>a</sup>, Georgios Vlachos<sup>a</sup>, Kyrillos Sarris<sup>b</sup>, Maria Sotiropoulou<sup>c</sup>, Maria Terzi<sup>d</sup>, Dimitris Loutradis<sup>a</sup>

<sup>a</sup> 1st Department of Obstetrics and Gynecology, University of Athens, Greece

<sup>b</sup> Department of Radiotherapy, General Hospital "Alexandra", Athens, Greece

<sup>c</sup> Department of Pathology, General Hospital "Alexandra", Athens, Greece

<sup>d</sup> Department of Pathology, 'Hygeia' Diagnostic and Therapeutic Centre of Athens - Hygeia, Greece

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## ABSTRACT

Early stage vaginal carcinomas are typically treated with radical surgical procedures or radiation therapy. Both modalities impair the reproductive ability of the patients. We hereby report a case of menstrual function preservation in a 24-year-old patient with an early-stage primary vaginal clear cell carcinoma. We treated the patient with intravaginal brachytherapy after appropriate laparoscopic surgical staging and separate transposition of the ovaries and tubes.

The patient is now 6 years without any evidence of disease. She reports minor complaints during sexual intercourse, while her menstruation and hormonal profile are normal.

## 1. Introduction

Primary clear cell adenocarcinoma of the vagina (vCCA) is a rare tumor that accounts for 1% of all vaginal carcinomas (Hanselaar et al., 1997). vCCA is associated with diethylstilbestrol (DES) exposure, congenital anomalies of urogenital tract, and metaplasia of endometriotic nodules (Uehara et al., 2010).

The main symptoms that lead patients to seek medical care are abnormal vaginal bleeding, discharge and/or dyspareunia. About 10–25% patients are asymptomatic, and the tumor is detected during regular checkup. Vaginal examination reveals a protruding nodule at the anterior upper third of the vaginal wall, and the diagnosis is confirmed via punch biopsy.

The disease incidence has a bimodal distribution with peaks in the third and seventh decades of life. (Hanselaar et al., 1997) This indicates that vCCA may be detected in young patients before childbearing. For such patients, conservative treatments, including radical colporrhectomy, wide local excision or brachytherapy, have been successfully implemented.

## 2. Case report

A 24-year-old Greek female student with postcoital vaginal bleeding and no other complaints presented to our department. She was of normal physical status (ACOG PS = 0, BMI = 24, Karnofsky = 100%). Her medical history was free of any operative procedures or medical problems, and she did not report any chronic pharmacological treatment. She had regular Pap smears since the age of 21 years and had never been pregnant. Her family history was unremarkable, and her mother reported that she had never consumed DES.

Pelvic examination revealed a 2 cm wide hemorrhagic nodule, which protruded in the upper left third of the vagina. The inner genitalia and parametria showed no signs of infiltration, and cervix, vulva and the rest of vagina were also unremarkable. A colposcopic examination of the cervix and vagina revealed only the nodule on the vaginal wall and a punch biopsy was performed (Fig. 1). Histopathologic examination revealed a poorly differentiated adenocarcinoma with morphological and immunohistochemical characteristics compatible with a clear cell carcinoma. The tumor exhibited positive immunoreactivity for CK7, CEA, focal positive for CD15, and negative immunoreactivity for Vimentin, CD10, CK5/6, Calretinin, WT1, RCC, and ER (Fig. 2)

The patient was further evaluated with abdominal magnetic

\* Corresponding author at: 80 Leoforos Vasilissis Sofias Str., 11526 Athens, Greece.

E-mail addresses: [vlachos.dg@gmail.com](mailto:vlachos.dg@gmail.com) (D.-E. Vlachos), [prototha@otenet.gr](mailto:prototha@otenet.gr) (A. Protopapas), [dimitri@otenet.gr](mailto:dimitri@otenet.gr) (D. Loutradis).

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resonance imaging (MRI), positron emission tomography-computed tomography scan, and tumor markers, which were all found to be negative. To eliminate endometrial and endocervical pathology, diagnostic hysteroscopy and curettage were performed with negative results.

Due to the patient's young age and nulliparity we were reluctant to proceed with a radical procedure and opted instead for a conservative treatment. The case was presented to our institution's multidisciplinary tumor board, and it was decided that after appropriate lymph node and peritoneal staging, vaginal brachytherapy could be implemented. The patient was informed about the therapeutic alternatives and consented to the proposed treatment modality.

Laparoscopic pelvic lymphadenectomy, omentectomy, and extrapelvic transposition of the ovaries were performed. The tubes were conserved and transfixed to the anterior abdominal wall separately from the ovaries (Fig. 3A-D). The procedure lasted approximately 1 h and 50 min, with an uneventful postoperative course. The pathologic examination showed no lymphatic or peritoneal dissemination and negative peritoneal cytology. (Fig. 3A-D)

After 3 weeks of recovery, the patient received intracavitary brachytherapy for the vaginal lesion. A 2.5-cm Brunette cylinder was used for the treatment. She received 3400 cGy of radiation in 6 sessions. The radiotherapy was well tolerated, and the patient did not have any major side effects.

The patient had been regularly followed-up for 6 years under our care. Radiological tests (MRI) and tumor marker remain unremarkable. Physical examination reveals atrophy of the vaginal epithelium and low-grade stenosis at the level of vaginal vaults. The hormonal status of the patient was checked with E<sub>2</sub>, FSH and AMH 6 months after the completion of IBT and found to within normal range. (E<sub>2</sub>:39.1 pg/mL; FSH: 7.8 mIU/mL; AMH: 4.5 ng/mL). Annual hormonal checks have not revealed serious decline of ovarian function. Although the patient has not been pregnant yet, she does not report any menstrual or sexual disorders.

### 3. Discussion

Vaginal adenosis (VA) is defined as the presence of cylindrical epithelium in cervicovaginal squamous cell epithelium, mostly in anterior third of the vagina. It appears to be the dominant precursor lesion of vCCA in DES-exposed patients and those with urogenital malformations. About 9% patients and 2% patients have VA in the middle and lower third of the vagina, respectively. (Robboy et al., 1982) This is concurrent with the vCCA topographic incidence.

The pathogenetic mechanism of VA formation needs further

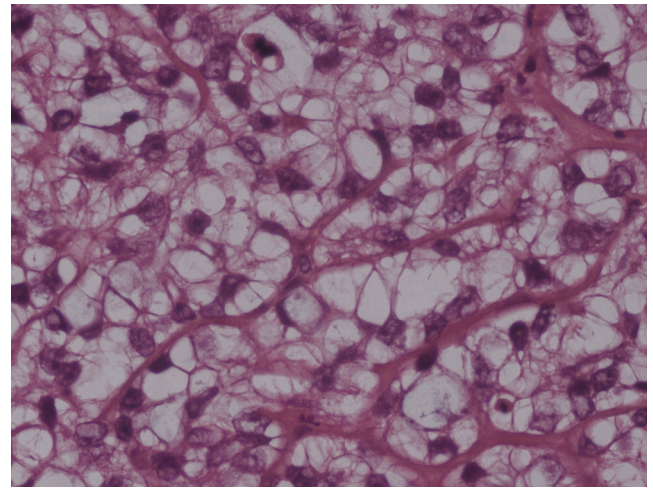


Fig. 2. Neoplastic cells exhibiting a "hobnail" pattern.

elucidation. In Mullerian duct epithelium (MDE), uterine and cervicovaginal epithelia differentiate from stem cells. Kurita et al. (Zhang et al., 2017) have reported that p63 gene is responsible for the differentiation of the lower genital tract epithelium to the squamous cell type. Three signaling pathways have been identified that accompany p63 activation: (a) BMP4-SMAD, (b) activin A-RUNX1 (runt-related transcription factor 1) and (c) FGF7/10-MAPK pathways. (Kurita et al., 2004; Laronda et al., 2013; Terakawa et al., 2016). DES has been found to inhibit the p63 transcription factor, forcing MDE to differentiate to uterine columnar cells. (Kurita et al., 2004; Kurita, 2011)

Historically, intrauterine DES exposure has been associated with vCCA. DES was mainly administered in the USA, the Netherlands and Norway to prevent miscarriage and other pregnancy complications. Fortunately, the risk of developing a vCCA is rare, in the order of 1–1.4/1000 by the age of 40 years (Herbst, 1999).

Rectovaginal endometriosis has also been associated with vaginal adenocarcinomas. Approximately 1–2% of ovarian and extragenital endometriosis reportedly transform to malignancy. (Yang et al., 2019) Clear cell adenocarcinoma is common in ovarian carcinomas developing from endometriomas. However, in extraovarian sites it accounts for only 4.5% of those cases. (Van Gorp et al., 2004) Moreover, an association between endometriosis and VA has also been reported. (Han et al., 2018)

The oncogenic trigger for the malignant transformation of VA and endometriosis is not yet clarified. Several tumor suppressor genes have

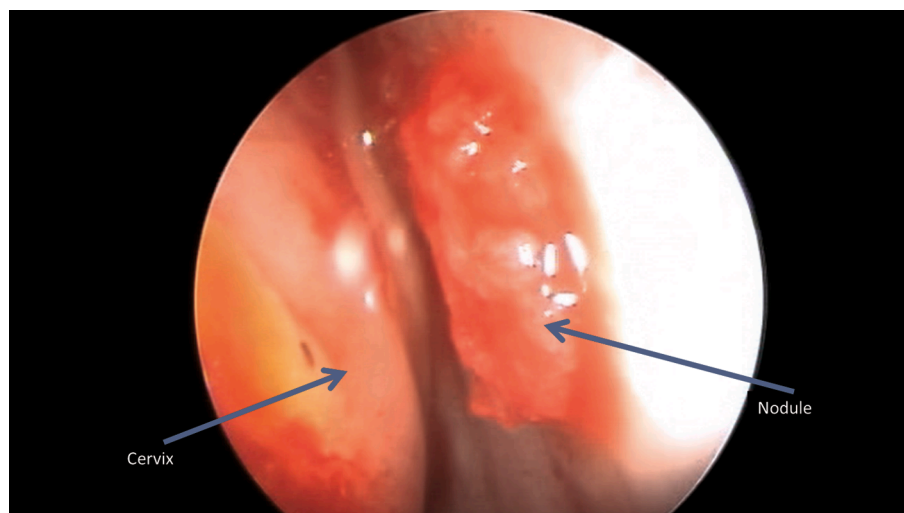
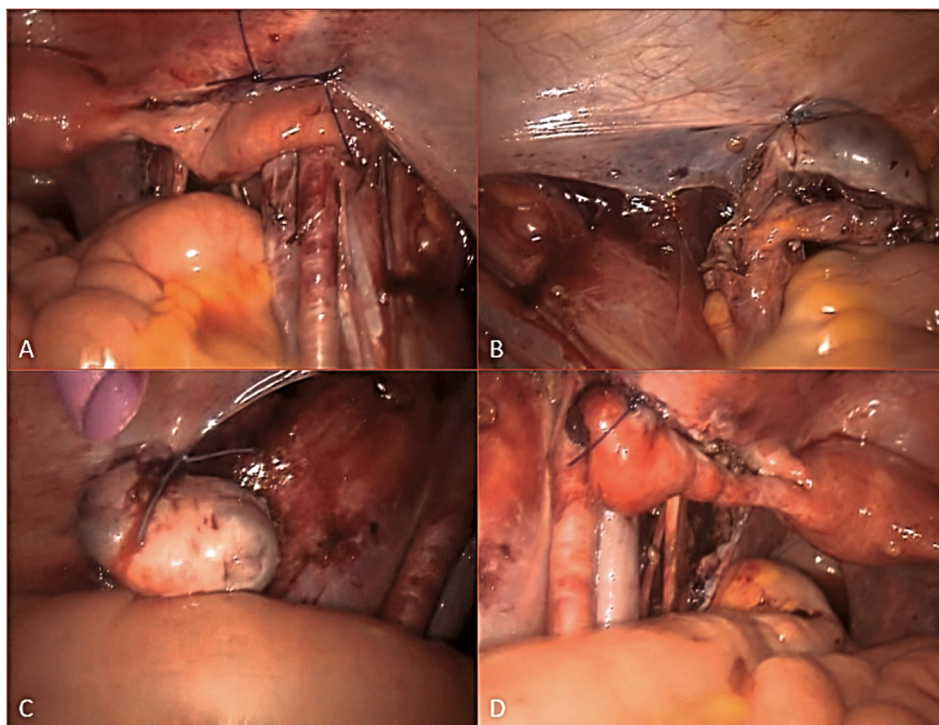


Fig. 1. Colposcopic image of the exophytic vaginal nodule.



**Fig. 3.** A-D. Ovarian transposition with preservation and separate transfixion of tubes. 3A-B: Right side, 3C-D: Left side.

been investigated for possible mutations. Although Ki67 marker is increased, p53 mutations are infrequent (Alduaij et al., 2012). Various studies have reported the accumulation of p53 protein due to enhanced DNA repair mechanism.

The standard treatments for vaginal carcinomas have been modulated based on the experience from cervical cancer patients. Early-stage cases are treated surgically or with chemoradiation. However, most patients present in reproductive age and desire preservation of their fertility. In such cases, treatment modalities like radical trachelectomy or intracavitary brachytherapy have been implemented. (Hanselaar et al., 1997)

Radical trachelectomy is a fertility sparing treatment with low complication rates and has been proven to be oncologically safe with 4.2% mortality and 2.9% recurrence rate. (Pareja et al., 2013) However, the procedure exhibits a 20.5% pooled pregnancy rate due to the increased risk of abortion and preterm labor (Zhang et al., 2017).

Intracavitary brachytherapy (IBT) has been utilized as fertility-preserving alternative treatment. IBT delivers increased doses of radiation locally, and with the improved image-guided targeting, the radiation's deleterious effects on neighboring organs can be diminished. Therefore, in early stage local disease where the parametrial dissemination is minimal, IBT may be used as the only treatment modality. The side effects of IBT are mainly dose- and schema-dependent. Magne et al. reported that 3 out of 7 patients that tried became pregnant spontaneously and delivered healthy babies with cesarean section. (Magné et al., 2012) In the case series by Morice et al., 27 patients with vCCA were treated with BT +/- EBRT. Of them, 20 patients received IBT alone and only 4 out of 27 patients achieved pregnancy.

Pelvic irradiation can cause premature ovarian failure and infertility, depending on the radiation's total dosage, fractioning schedule, patient's age, and radiation field. At the age of 30 years, 14 Gy is gonadotoxic, while a 2 Gy can destroy up to 50% of oocytes. Vaginal IBT delivers more than 5 cGy to the ovaries due to its proximity to the Douglas pouch. To address this problem, ovarian transposition (OT) is implemented. Kumar et al. showed that 94% of the ovaries retained their function after OT and IBT with below 1% risk of occult ovarian metastasis. (Gubbala et al., 2014)

Our patient is now 6 years free of disease. Vaginal examination revealed stenosis and atrophy at the upper part of the vagina; however, the patient did not complain of dyspareunia but only slight postcoital bleeding. Menstrual function was found to be regular, and the hormone levels since the IBT have always been within normal range. The patient has regularly followed-up and has not yet tried to get pregnant. We believe that our patient can also conceive naturally. The fixation of the salpinx in the vicinity of the ovaries may further facilitate natural conception. Due to the vaginal stenosis and epithelial atrophy, cesarean section may be the preferred way of delivery although cases of natural labor after IBT have been reported. (Baughan et al., 1992)

#### 4. Conclusion

Based on the above-mentioned data, radical colpotrachelectomy represents an oncologically safe procedure, but with poor obstetrical results. In vaginal cancer, the procedure's radicality is extended caudally to achieve negative margins, thus increasing the morbidity due to the proximity of the vaginal walls to the bladder trigone and the lower third of rectum. Our approach spares the patient a radical procedure and retains the reproductive potential with minor side effects.

##### CRediT authorship contribution statement

Dimitrios-Efthymios Vlachos: Writing and editing, Athanasios Protopapas: Primary surgeon and reviewing, Georgios Vlachos: Writing - review & editing, Kyrillos Sarris: Writing - review & editing, Maria Sotiropoulou: Writing - review & editing, Maria Terzi: Writing - review & editing, Dimitris Loutradis: Supervision, Writing - review & editing. Informed consent from the patient and ethics committee approval was obtained.

##### Disclaimer:

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## 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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