



Case Report

Metastatic Clear Cell Carcinoma of the Primary Vaginal Site with Complete Response to Immunotherapy: A Case Report

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Abstract

Objectives: Vaginal cancer is a rare condition, and data to guide its treatment still are an unmet need. Currently, its approach is usually extrapolated from cervical and anal cancer treatments. Primary clear cell adenocarcinomas of the vagina unrelated to diethylstilbestrol exposure are uncommon. The objective of this paper is to report a case of a clear cell carcinoma of the primary vaginal site metastatic, as well as add to the literature on this scenario with dismal prognosis and scarce data.

Methods: We report a case of a patient with metastatic clear cell carcinoma of the primary vagina not related to diethylstilbestrol exposure, treated with immunotherapy, as well as a review of the pathology and the treatment.

Results: The patient was diagnosed with clear cell carcinoma of the primary vaginal site on a biopsy of a pelvic lesion involving the urethra near the vaginal canal in October 2019. Nivolumab was started in August 2020. PET CT and MRI in August 2021 with response complete on all sites, sustained until the present moment.

Conclusions: Clear cell adenocarcinoma of the vagina is a rare disease with limited treatment options. This case reports a complete response following immunotherapy in a patient with advanced disease refractory to local treatment, in line with the behavior observed in clear cell carcinomas from distinct organs. Further studies are required to understand the pathogenesis and better guide treatment.

Keywords: Clear Cell Carcinoma of the Vagina; Immunotherapy

Introduction

Approximately 1 in 100,000 women will be diagnosed with invasive or in situ vaginal cancer (typically squamous cell histology) [1], with an average age at diagnosis being approximately 60 years. Squamous cell carcinoma is more common with the increasing age of the patient [1], and most cases of vaginal cancer are related to human papillomavirus (HPV), as is the case with cervical cancer [2]. Adenocarcinomas account for 10% of vaginal cancer cases, representing almost all primary vaginal cancers in women under 20 years of age [3], and may arise in areas of vaginal adenosis, Wolffian resting elements, periurethral glands, and foci of endometriosis. Clear cell variants are the best-known type of adenocarcinoma, mainly because of their occurrence in young women exposed in utero to diethylstilbestrol (DES) [4]. Roughly clear cell carcinomas of the vagina present as polypoid masses on the anterior wall of the vagina, and about 70% of patients present in stage I at diagnosis. No randomized clinical trials define the treatment of vaginal cancer, given its rarity. Instead, the treatment approach is extrapolated from cervical and anal cancers [5]. We report a case of a patient with primary metastatic clear cell carcinoma of the vagina unrelated to exposure to diethylstilbestrol, who underwent treatment with immunotherapy with excellent response, along with a review of the pathology and advances of medicine with immunotherapy in this setting.

Case Report

In October/2019, a 55 y female started with massive vaginal bleeding. There were no noticeable elements in her previous medical history, with two previous pregnancies, one miscarriage, and one vaginal birth. A magnetic resonance imaging (MRI) of the pelvis was performed on 10/31/2019, which showed the presence of a rounded lesion involving the urethra, measuring 4.2 x 4.1 x 3.0 cm in the largest craniocaudal, anteroposterior and transverse axes, respectively, with lobulated and well-defined limits, close to the anterior wall of the distal half of the vaginal canal, with loss of the cleavage plane, promoting an impression on the vaginal canal (Figure 1). She underwent a biopsy of the lesion in December 2019, and diagnosis was adenocarcinoma with papillary growth affecting soft tissues of the vagina. Histological and immunohistochemical findings showed a high-grade invasive adenocarcinoma, with the possibility of the lesion being primary of the vagina. Since image exams showed urethral involvement, a primary urothelial tumor was questioned, and a pathological and immunohistochemical review study was requested and carried out on 03/19/2020. Its result was compatible with grade 3 clear cell carcinoma, infiltrating the vaginal wall. The tumor presented a papillary architectural pattern with solid areas, nuclear grade 3,

high mitotic count, mucinous areas, and intense fibroblastic stromal reaction with vascular neof ormation and lymphoid aggregates. Tumor-infiltrating lymphocytes stromal (TILs) was 15%, tumor necrosis foci <5%, without peritumoral vascular embolization. The immunohistochemical profile was positive for PAX-8, CEA, napsin, HNF1B (HNF1 homeobox B (hepatocyte nuclear factor 1 homeobox B), and p53 (Figure 2). The morphological findings and immunohistochemical profile indicated a primary gynecological site. A PET-CT in March 2020 showed an increase in glycolytic metabolism in a heterogeneous expansive lesion in the anterior compartment of the pelvic excavation, determining incarceration of the urethra, without a cleavage plane with the vesical floor, as well as the vaginal canal, with also hypermetabolic bilateral pelvic and left inguinal lymph node disorders, compatible with secondary neoplastic involvement. The patient was then submitted to chemoradiotherapy treatment with weekly cisplatin from 04/01/2020 to 05/01/2020, with improved vaginal bleeding since radiotherapy started. PET-CT for response assessment, performed on 05/22/2020, showed a marked increase in glycolytic metabolism, more irregular and expressive than in the previous study in an expansive lesion in the anterior compartment of the pelvis, with increased dimensions, as well as pelvic and bilateral inguinal lymph nodes increased in number and measurements compared to the previous study, compatible with disease progression based on RECIST 1.1. The patient remained in excellent general condition, except for the locally advanced neoplasia, which was not amenable to surgical resection without an exenterative procedure. The patient initiated chemotherapy (3 cycles of carboplatin and paclitaxel) and presented no objective response. Faced with a rare disease, a patient already exposed to treatment with chemotherapy and radiotherapy without objective response, and based on positive results observed with immunotherapy in clear cell cancer from different tumor sites, the oncology team opted for immunotherapy. In August/2020, nivolumab 480mg monthly was started. Response evaluation tests were performed in October/2020, with suspected pulmonary progression on computed tomography (CT) of the chest, due to the appearance of bilateral pulmonary nodules. On the other hand, an excellent local response was achieved with an MRI of the abdomen and pelvis showing a reduction from 14.3 cm³ to 3.0 cm³ in the lesion volume involving the urethra and the middle and distal thirds of the vagina (Figure 3). There was also a slight reduction in other secondary lesions and secondary lymph nodes. She continued on immunotherapy, with excellent response in exams of April/2021, with chest CT no longer visualizing bilateral pulmonary nodules, and MRI of the abdomen and pelvis also not evidencing the lesion involving the urethra. Other secondary lesions reduced in size, including secondary lymph nodes, the biggest in the right lateral anterior aspect close to the pubic symphysis, measuring 1.4 x 1.0 cm (previously 2.4 x 1.3 cm). The patient remained in excellent condition, asymptomatic,

and without toxicities from the immunotherapeutic treatment. PET-CT was performed on 06/25/21 with complete response in all sites and increased glycolytic metabolism in the paraaortic lymph node, measuring 6.2 x 9.5 mm with SUVmax 4.66, previously absent, suggesting a secondary neoplastic implant. Abdomen and pelvis MRI of 07/28/21 showed reduction of all lymph nodes, including the one shown in PET-CT, measuring 4.0 x 6.0 mm. There was no appearance of new lesions. The patient remains on immunotherapy, with no evidence of disease in the last control exams.

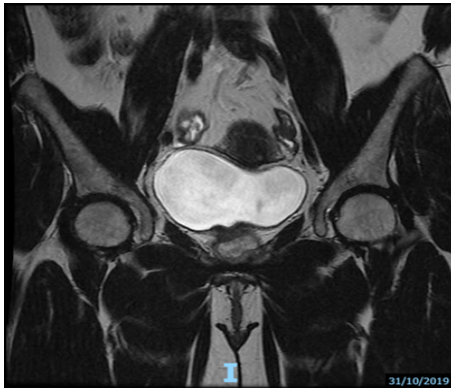


Figure 1: Lesion involving the urethra, volume 14.3 cm³, close to the anterior wall of the distal half of the vaginal canal.

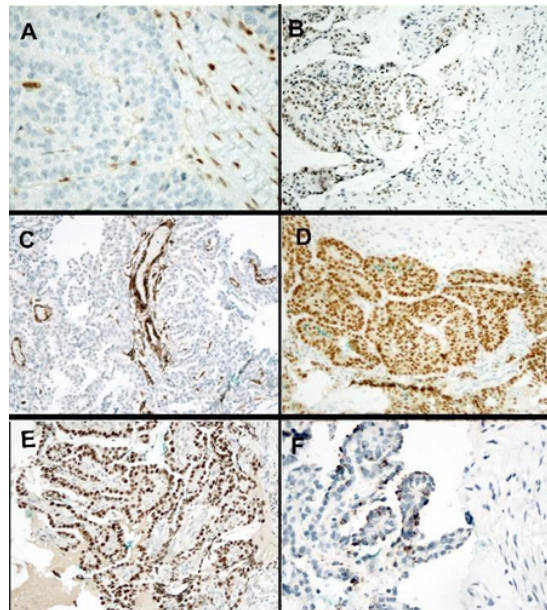


Figure 2: Immunohistochemical profile of tumor cells showing A) negative estrogen receptor contrasting with positive stromal cell; B) p53 wild type characterized by weak to moderate nuclear staining in part of cells; C) negative WT-1 (positive internal control of endothelial cells); D) positive PAX-8; E) HNF1B diffusely positive; F) positive napsin with a dot-like pattern of staining.

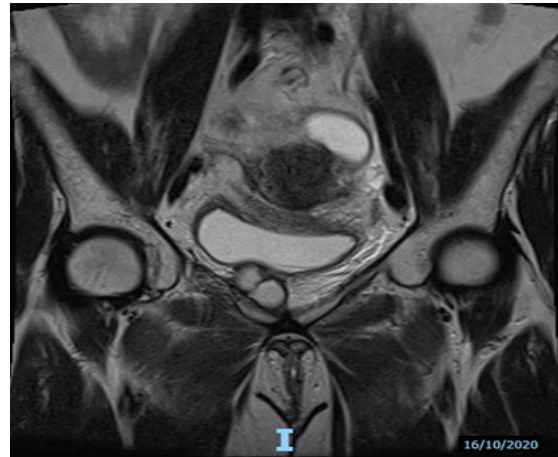


Figure 3: Reduction to 3.0 cm³ in the lesion volume involving the urethra and the middle and distal thirds of the vagina.

Discussion

Vaginal clear cell adenocarcinoma was first reported before the 1960s. Still, from 1966 onwards, its incidence increased dramatically, coinciding with the advent of the use of DES, a drug used to prevent recurrent miscarriages, widely used until the early 1970s. With a different proven role in the development of this carcinoma, the administration of diethylstilbestrol was prohibited [6]. Primary clear cell adenocarcinoma of the vagina unrelated to DES exposure is uncommon, and when over 50 years-old, it is even rarer, accounting for 5-10% of all vaginal cancers [7]. There is a bimodal age distribution, with the first peak at 26 years and the second peak at 71 years of age. Histologically and immunohistochemically, they are identical to those involving the cervix, ovaries, and urinary tract, including the kidneys. Little is known about the nature of clear cell adenocarcinoma of the vagina that occurs without DES exposure, as information about clinical behavior, pathology, and prognosis in this setting are sparse and inconsistent [8]. Recent studies suggest tumor association with DES is related to the disease's natural history. Non-associated ones may be related to adenosis and other congenital malformations, such as a didelphic uterus with a double vagina, renal agenesis, and situs inversus. The macroscopic size of the tumor ranges from microscopic to 10 cm, characterized by a polypoid, nodular, flat, or ulcerated mass. Microscopically, it presents a predominantly tubulocystic pattern, followed by solid and papillary patterns. However, a mixture of types is typical. Nuclear pleomorphism is variable, with the number of mitoses usually less than 10/10 in high-power fields. In immunohistochemistry, primary clear cell adenocarcinoma of the genitourinary tract for all sites presents positive CK7, CAM5.2, 34 beta E12, CEA, CA125, Leu-M1, and Vimentin. They overexpress p53 and BCL-2 and exhibit variable positivity for hormone receptors (estrogen and progesterone) [9].

At the molecular level, Watanabe et al. suggested that the stability of microsatellite loci and the overexpression of p53 protein without TP53 gene mutation is a cellular biological characteristic of sporadic carcinomas [10], presenting a poor prognosis and worse results than those seen in patients with other primary carcinomas of the vagina, with more common local and metastatic recurrence rates [11]. Recent studies reported promising gains with immunotherapy in cervical and endometrial tumours, including the phase III study KEYNOTE-826, with positive results for immunotherapy in persistent, recurrent, or metastatic cervical cancer the addition of pembrolizumab to the carboplatin/cisplatin + paclitaxel regimen with or without bevacizumab has been shown to response rate, overall survival, and progression-free survival [12]. Recently, a randomized phase III trial compared cemiplimab (anti-PD-1) with the investigator's chosen therapy and demonstrated a gain of second-line overall survival for the first time, with an increase in the response rate and better quality of life [13]. Pembrolizumab is approved in some countries in the context of controlled disease, after the following criteria: pembrolizumab 200 mg IV every 3 weeks for patients whose tumors express PD-L1 CPS \geq 1. As for advanced endometrial cancer, immunotherapy has been successful in the last few years. The phase III trial 309–KEYNOTE-775 has shown that treatment with lenvatinib plus pembrolizumab led to significantly longer progression-free survival (PFS) and overall survival (OS) than chemotherapy of the treating physician's choice, both for the population with mismatch repair–proficient (pMMR) disease and in the overall study population of patients with advanced endometrial cancer who had disease progression after the receipt of previous systemic platinum-based therapy [14]. Furthermore, regarding clear cell gynecological cancers (CCGC), the phase II PEACOC trial included 48 patients with advanced cancer who had received at least one line of previous chemotherapy. Although small, the trial suggests that pembrolizumab is effective in heavily pre-treated patients with advanced CCGC: 43.8% of patients were alive and progression-free at 12 weeks [15]. Based on these studies and significant response data with immunotherapy in renal clear cell carcinoma, there was an extrapolation of data for treating our patient, considering the lack of robust evidence. Given its aggressiveness and histological behavior similar to clear cell adenocarcinomas from the urogenital tract, further studies are essential for a more accurate treatment decision. Notably, the clear cell histology remarkably shows resistance to chemotherapy and radiotherapy in advanced disease.

Conclusion

Clear cell adenocarcinoma of the vagina is a rare disease with limited treatment options. This case reports a complete response following immunotherapy in a patient with advanced disease refractory to local treatment, in line with the behavior observed in clear cell carcinomas from distinct organs. There is

still an unmet need in the literature, and further studies are required to understand the pathogenesis and better guide treatment.

Highlights

Vaginal cancer is a rare condition; its approach is usually extrapolated from cervical and anal cancer treatments.

Primary clear cell adenocarcinoma of the vagina unrelated to DES exposure is uncommon, and when over 50 years-old, it is even rarer, accounting for 5-10% of all vaginal cancers. Histologically and immunohistochemically, clear cell adenocarcinoma of the vagina are identical to those involving the cervix, ovaries, and urinary tract, including the kidneys.

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