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Non-diethylstilbestrol exposed vaginal adenocarcinoma in young patients associated with unilateral renal agenesis: two case reports and literature review

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Summary

Background: Adenocarcinoma, accounts for up to14% of all vaginal cancer. In young patients, common histological feature is clear cell adenocarcinoma (CCA) while mesonephric adenocarcinoma (MA) is very rare. The authors report two patients in their early twenties with unilateral renal agenesis and vaginal adenocarcinoma not exposed to diethylstilbestrol (DES). *Cases*: Two patients with vaginal adenocarcinoma were treated, with external beam radiotherapy of pelvis combined with brachytherapy to a radical dose. In 2000, 25-year-old female, was admitted for radiotherapy after incomplete excision of the tumor localized in left vaginal apex and fornix. Histopathology confirmed CCA and classified as clinical Stage II. CT revealed left renal agenesis.The patient is alive and disease-free 15 years after therapy. Vaginal, urethral stenosis, and hydronephrosis occurred and ureteral stent was inserted. In the second patient, 22-year-old, in 2004, after biopsy of bulky tumor of vagina and histology, revealed MA in Stage III and CT scan also confirmed right renal agenesis. Radiotherapy was followed by chemotherapy. After 11 years, patient is disease-free with vaginal stenosis and incipient renal hydronephrosis. *Conclusion*: Radiotherapy is effective treatment in advance vaginal adenocarcinoma, however, with high morbidity. The authors advise rigorous gynecologic exams in young females with renal agenesis as there may be a risk of malignant changes in vagina.

Key words: Vaginal adenocarcinoma; Renal agenesis; Radiotherapy.

Introduction

Vaginal cancer constitutes for approximately less than 2% of all gynecologic malignancies. Adenocarcinoma type is rare tumor and accounts for only 14% of all vaginal cancer. In young patients (19-20 years of age), the histologic features mostly belong to the clear cell adenocarcinoma (CCA), while mesonephric adenocarcinoma (MA) is extremely rare [1]. Reports described that about two-thirds of CCA were related to prenatal exposure to diethylstilbestrol (DES). The natural history of non-DES-exposed CCA and MA has not yet been clarified.

Common association of these rare tumors with variety of Müllerian duct anomalies was reported. Ipsilateral renal agenesis was observed sporadically [2-4].

In the literature, adenocarcinoma was described as having significantly worse outcome compared to squamous cell carcinoma. Early clinical stages, after primary surgery, or combination of radiotherapy and surgery, tend to have good outcome, with overall survival of 80-87%. Advanced stages of disease, treated with radio-chemotherapy, had less satisfactory treatment outcome [5]. The optimal treatment approach, still under investigation, depends on clinical stage, patient's age, and it is influenced by previous belief that this tumor has aggressive behavior even in the early stage. Recent investigation of molecular nature of this tumor may incorporate new approach in treatment [6].

Here, the authors report two cases of adenocarcinoma of vagina, with no history of in-utero exposure with DES, but associated with unilateral renal agenesis treated with radiotherapy.

Case Report

From 2000-2004, two young patients with histologically confirmed vaginal adenocarcinomas were admitted to the present department of radiotherapy. The initial exam and biopsy of the tumor were done in regional hospitals and histology was reviewed at the present pathology department. There was no previous history of prenatal exposure with DES. The clinical evaluation and diagnostic procedure included pelvic examination, chest radiography, abdominal and pelvic CT or US, and the routine blood work. The tumor stage was assigned according to FIGO system. Treatment approach and options were determined by tumor board after literature search, as there are no established guidelines for treatment management of this type of cancer. Patients were followed up at three- to four-months interval for two years, in six-month intervals for three years, and after that yearly.

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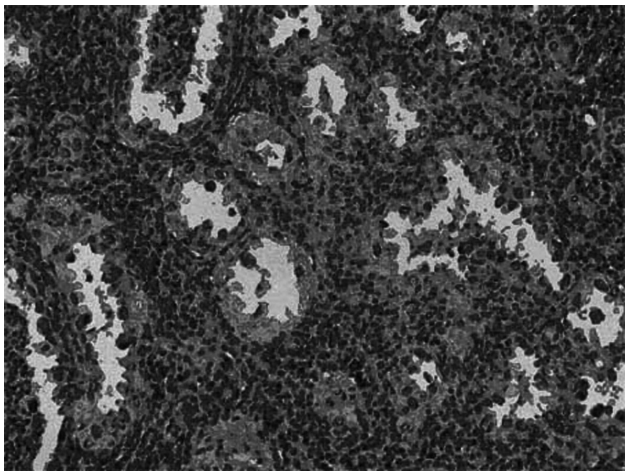

Figure 1. — Adenoid structure with abundant eosinophilic, clear cytoplasm and "hobnail" cells (HE).

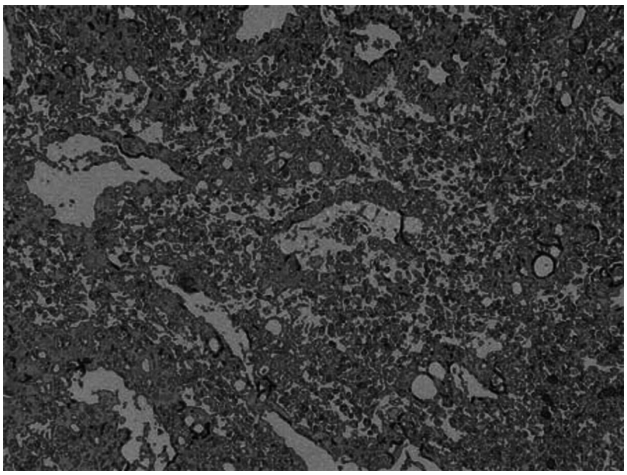

Figure 2. — Immunoreactivity to CK7 antibody.

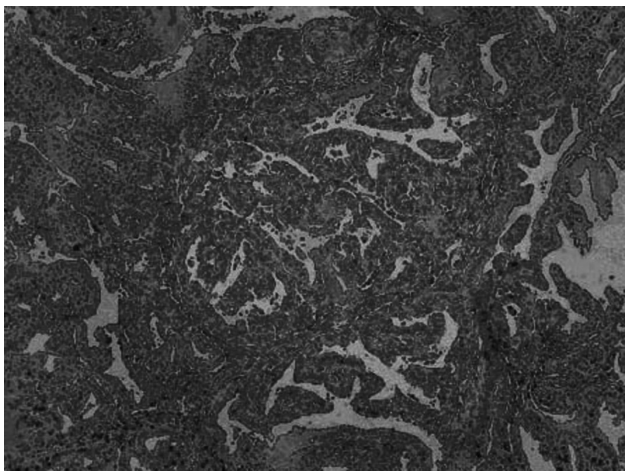

Figure 3. — Ductal branching structures lined with malignant cells with mild atypia (HE).

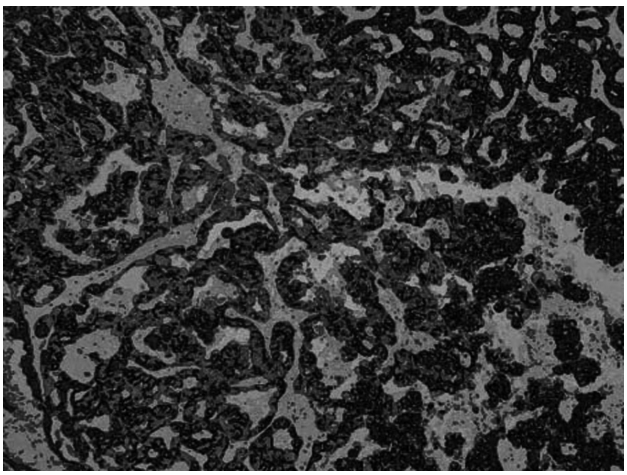

Figure 4. — Immunoreactivity to CK7.

Case 1

In 2000, a 25-year-old female, para 1, was submitted for postoperative radiotherapy after incomplete excision of the tumor, localized in the left vaginal apex and fornix, clinically classified as FIGO Stage II vaginal cancer. The surgically resected tissues of vagina revealed CCA. Microscopically, the adenoid structure was composed of cells with clear or eosinophilic cytoplasm with large nuclei and visible nucleoli. Also, "hobnail" cells were visible (Figure 1). Cells were immunoreactive to CK7 antibody (Figure 2). On bimanual vaginal and rectal examination, cervix and remaining vagina were free and minor left lateral thickening of paravaginal and paracervical spaces were noticed. Previous biopsy of the cervix confirmed CIN III but repeated pathological exam was normal. US and CT revealed no evidence of primary or metastatic disease, however, left renal agenesis was found.

External beam radiation (EBRT) of pelvis, with two beam arrangement (anterior and posterior) at dose of 45 Gy in 22 fractions was done. According to initial vaginal examination, HDR brachytherapy (Ir-192) consisted of five applications (one per week) with intrauterine tube and colpostat, to a dose of 35 Gy.

The follow up consisted of extensive radiological and gynecological examinations. The patient is alive and disease free after 15 years. Vaginal, urethral stenosis, and hydronephrosis occurred after five-years and ureteral stent was inserted at the right kidney.

Case 2

A 22-year-old female, para 0, biopsy revealed advanced malignant vaginal tumor, classified as clinical FIGO Stage III. Based on the morphological and immunohistochemical features, diagnosis of MA was made (Figure 3). Tumor consisted of tubular structures lined with one or two layers of malignant cells. Immunohistochemistry staining revealed positivity of tumor cells for CK7 antibody, negativity for CK20 and CD10 antibody (Figure 4). Estrogen and progesterone receptors were also negative. No normal tissue was identified to determine the possible origin. As this tumor can arise from cervix or vagina, a gynecological exam de-

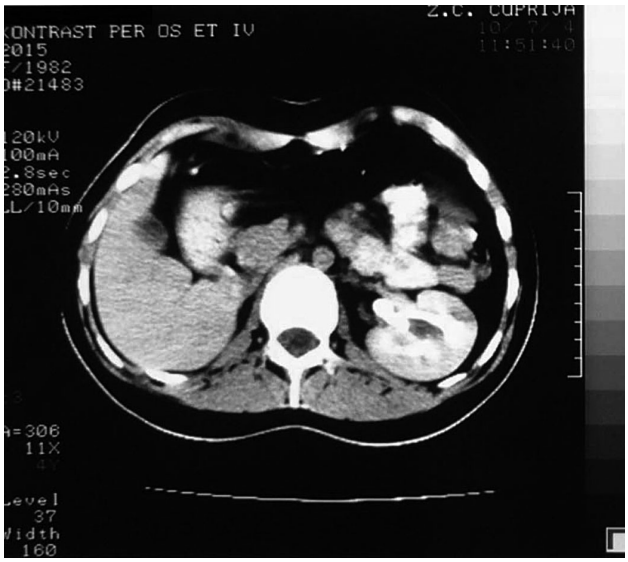

Figure 5. — Initial CT scan reveals agenesis of right kidney.

Figure 6. — Initial CT scan of pelvis before radiotherapy with bulky tumor of vagina.

Figure 7. — CT scan four years after radiotherapy showing vaginal stenosis.

termined the vagina as site of tumor origin. On pelvic exam, a tumor mass involving the whole vagina infiltrated completely the right paracolpium or paravaginal space and parametria. There was no possibility for speculum examination, while on palpation, the cervix seemed to be normal. CT and US confirmed agenesis of right kidney (Figure 5). No evidence of lymph node involvement or metastatic disease was observed.

Initially after one cycle of chemotherapy (cisplatinol 100 mg/m^2), definitive radiotherapy was applied with EBRT to pelvis, with two-field technique and dose of 46 Gy in 22 fractions combined with Ir-192 HDR brachytherapy (vaginal cylinders, uterine tandems) to a dose of 35 Gy (five applications). Acute radiation vaginitis was managed with vaginal douching. As the tumor mass was initially bulky (Figure 6), the irradiation was followed by platinum-based chemotherapy of up to six cycles with observed leucopenia of grade 2.

On follow-up exam after four months, pelvic CT showed no evidence of tumor or metastatic deposit. Vaginal examination revealed vaginal stenos and post-irradiation necrosis. Digital examination and proctoscopy revealed an ulcer of the anterior rectal wall. Severe grade 3 rectal and vaginal toxicity developed, requiring hospital admission. The treatment with vaginal douching and steroid enema of the rectum was done. After one year of intensive local therapy, the thinning of rectal mucosa and rectovaginal septum was ascertained. After 11 years of follow-up, the patient is disease-free with vaginal stenosis (Figure 7) and incipient hydronephrosis of left solitary kidney.

Discussion

Due to the rare occurrence of vaginal adenocarcinoma, information concerning the origin, behavior, and treatment response were less documented.

CCA have been commonly described in relation to antenatal DES exposure. The path of developing tumor origin within islands of endometriosis and vaginal adenosis influenced by DES has been shown. CCA unrelated to DES is a rare finding and, according to latest literature, it might be associated with congenital Müllerian duct anomalies, coexisting with vaginal adenosis, and in just a few cases, are reported with presence of renal agenesis [2-4].

Relations between congenital anomalies of the genitourinary tract and vaginal adenocarcinoma were more explored recently. During embryology, uterus and vagina develop from paired Müllerian ducts. Variety of Müllerian duct anomalies (MDAs) or derivates at uterus and vagina in the form of congenital bicornuate uterus, vaginal septum, and vaginal agenesis are documented. Li *et al.* in 17 out of 57 patients determined the association of renal agenesis with the different types of MDA, while an increased

hazard of renal disease was found in present solitary kidney [4]. In a very rare Mayer-Rokitansky-Küster-Hauser syndrome, with karyotype 46, XX, a variety of Müllerian ducts anomalies with skeletal or renal disorders, including agenesis, were reported to be associated with vaginal adenocaracinoma [7]. Uehara *et al.* presented a case of vaginal non-DES CCA with bicornuate uterus, vaginal septum, left ureteral agenesis, and coexisting vaginal adenosis [8]. Watanabe *et a*l. described vaginal non-DES CCA in a Herlyn-Werner-Wunderlich syndrome, which consisted of MDA characterized by uterus didelphys, obstructed hemivagina, and ipsilateral renal agenesis [9]. In conclusion, the authors support the strong association of vaginal adenocarcinoma with MDAs in absence of DES exposure. The patients with renal agenesis could be under higher risk of developing vaginal adenocarcinoma, as the malignant changes in residual Müllerian tissues might be considered [7]. In both of the present patients, the tumor was clinically identified as arising in vagina at ipsilateral side to renal agenesis, but because radical surgery was not performed, no Müllerian or mesonephric remnant was identified.

MA of vagina is the rarest tumor of vagina, appears in younger ages, even in childhood, derived from remnants of the paired mesonephric (Wolffian) ducts, and until now it was well reported in just few cases. It is also found in another part of urogenital tract like cervix, corpus, broad ligament, urinary bladder, urethra, and urethral diverticulum. In the present case, MA was associated with unilateral renal agenesis which supports the hypothesis of their origin from mesonephric remnants. The agenesis of kidney was present also in patient's father, but no further investigation or genetic analyses were done. Besides the strong belief of its aggressive behavior, latest case reports showed their more favorable prognosis [10-12].

Occasionally, there is a confusion and differential diagnoses dilemma between CCA and MA, regarding mostly pathologic characteristics, origin, biological behavior, and therapy. Histology findings of CCA consist of varying degree of cystic, papillary or solid structures. The cell types are either clear cells with abundant clear cytoplasm, round central nuclei or hobnail cells with lesser amount of opaque granular cytoplasm and eccentric nuclei. PAS is positive in both intraluminal secretion and intracytoplasmic globules. Ersahin *et al*. in reported case of MA and made a differential diagnosis of CCA by evaluating absence of clear or hobnail cells and presence of PAS-positive material only in the tubular lumen and not in the cytoplasm [11]. Bifulco *et al*. analyzed well incapsulated MA, and reported immunoreactivity for pancytokeratin, cytokeartin 7 (CK7), CD 10, epithelial membrane antigen, vimentin, and calretinin, while negativity of carcinoembryonic antigen, CK20, estrogen, and progesterone receptors was observed [10]. In both case reports, patients had favorable outcome which supports the hypothesis that MA may be more indolent than it was considered previously and less aggressive treatment could be avoided.

In molecular genetic analysis, Waggoner *et al*. identified that strong overexpression of bcl-2 in CCA can inhibit p53-mediated apoptosis and suggested this as mechanism by which these rare tumors can arise without mutation of the p53 gene [6]. Also, expression of wild-type p53 protein in CCA of cervix and vagina may indicate the subset of tumors with more favorable prognosis compared to gynecologic carcinomas, which contain mutated p53 genes. However, the origin, histology, and molecular evaluation of CCA and MA are mainly uncertain and still under investigation, with ongoing further evaluation of treatment option.

Historically, adenocarcinoma is treated in the same manner as squamous cell type (SCC). Surgical treatment is recommended for early stages and occasionally as radical treatment for advance tumors. Radiotherapy is the mainstay option of treatment for inoperable stages, with effective outcome but with increasing severe morbidity like genitourinary injury, intestinal toxicity, and fistulas. In the literature, CCA is considered as less sensitive to radiation and it was generally confirmed that vaginal adenocarcinomas have worse prognosis than squamous cell type of tumor [13, 14]. Survival evaluation for CCA and MA regarding its rarity, was cumulative, and results of previous reports considered that these tumors tend to show an aggressive course, with rapid local relapse and distant metastasis, even many years after therapy.

Frank *et al*. analyzed 26 patients with non-DES vaginal adenocarcinoma, treated with combined irradiation (EBRT and BT) and compared with treatment data of SCC. After five years, 39% of patients with adenocarcinoma developed distant metastasis compared with 15% of patients with SCC. Pelvic control rate at adenocarcinoma was 39% and for SCC 81% [14]. On contrary, McNail *et al.* analyzed CCA and MA in 37 pediatric patients (median age 15 years). The estimated three-year survival was 71%. The high contribution of Stage III/IV in this study (24%) was probably due to delay of aggressive diagnostic procedure in young patients. [12]. In metastatic stage of disease, three-year survival was 33%. It was observed that outcomes of patients with DES-related CCA are superior to non-DES associated tumors, while the most important prognostic parameters for five-year survival were clinical stage and grade of nuclear atypia [5].

In conclusion, CCA is reported to be more frequent in younger age with peak incidence in women 19-20 years, but with a second peak for non-DES tumor in postmenopausal age [15]. For young pediatric patients, in early Stage I disease, conservative surgical approach like wide local excision or partial vaginectomy, and lymph node exploration, is recommend as treatment of choice with the aim to decrease morbidity of vagina [12].

In the present cases of non-DES vaginal adenocarci-

noma in Stage II and III, the combined EBRT and BT irradiation with high doses, was effectively applied. However, severe toxicity of rectum, vagina, and urinary tract had developed, with incipient or significant hydronephrosis of solitary kidney. Perez *et al.* observed that incidence of significant morbidity corresponds to dose and stage of the disease: 5% in Stage 0/I, 7% in Stage II, and 10% in Stage III/IV [13]. As Li *et al.* found with unilateral renal agenesis, there is an increased hazard of renal disease in solitary kidney, hence radiotherapy in high survival patents group, has to be balanced with constraints of dose, local irradiation technique, and conformal image based planning to avoid severe toxicity [4]. It is well documented that vaginal cylinders may cause stenosis as the significant surface of the vaginal length receives a high dose. Kirkbride *et al* estimated vaginal stenosis in 30%, vaginal necrosis in 4%, and vesicovaginal or rectovaginal fistula in 2% [16]. In prevention of vaginal morbidity, especially in young patients, daily vaginal douching, dilation, and intravaginal estrogen application can be applied.

The rare case reports summarized that outcome of patients with CCA are better and even with favorable prognosis for MA than thought previously [5, 8, 9]. However, prolonged follow-up is recommended as distant metastases and local recurrence can occur even many years after primary treatment. Jones *et al.* presented three patients with CCA, who developed late local and distant recurrence after a prolonged disease-free interval of seven, five, and four years as metastasis in lung, local recurrence of vagina, and dissemination in abdomen [17].

In conclusion, the present authors report CCA and MA associated with unilateral renal agenesis, which were presented in younger age, in more advanced stage initially, with risk of recurrence and death. Definitive irradiation and chemo-radiation approach was used, based on increasing evidence that the administration of combined therapy will increase treatment efficacy. Long-term survival was successfully achieved with no evidence of locoregional recurrence or systemic failure after 15 and 11 years from treatment. Unfortunately they were not able to avoid the morbidity associated with treatment technique feasible at that time.

Treatment results in every case must be weighed against the complications inducted by higher radiation doses, especially in the cases with renal agenesis. The present authors believe that the management of CCA and MA can be more conservative, especially in early stages, as these tumors might be less aggressive and indolent. A retrospective investigation of all rare cases is necessary for definitive conclusion about the nature, behavior, and optimal treatment approach. They also recommend that in young girls with renal agenesis, rigorous gynecological exam should be done periodically.

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