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MYOM YANLIŞ TANISI ALAN SERVİKS VE VAJİNANIN BERRAK HÜCRELİ ADENOKARSİNOMU: VAKA SUNUMU VE LİTERATÜR TARAMASI

CLEAR CELL ADENOCARCINOMA OF CERVIX AND VAGINA MISDIAGNOSED AS MYOMA: CASE REPORT AND LITERATURE REVIEW

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ÖZET

Berrak hücreli adenokarsinom (BHA), serviks ve vajenin nadir görülen bir müsinöz adenokarsinom alt tipidir. En sık görülen belirtisi anormal vajinal kanamadır. Bu yazıda myoma uteri tanısı ile yapılan cerrahi sonrasında tanı alan bir serviks ve vajen BHA vakasını ve literatür derlemesini ortaya koyduk. BHA oldukça nadir bir hastalık olması nedeniyle, standart tarama testleri, tanı ve tedavi yöntemleri henüz tam olarak ortaya konulamamıştır. BHA'nın bu özellikleri preoperatif tanısını zorlaştırmaktadır. Bundan dolayı, BHA tanısının doğru konulabilmesi, etkin yönetimi ve tedavi stratejilerinin tam olarak belirlenebilmesi için çok merkezli başka metaanalizlere ihtiyaç vardır.

Anahtar Kelimeler: Berrak hücreli adenokarsinom; Dietilstilbestrol; Serviks; Vajina.

ABSTRACT

Clear cell adenocarcinoma (CCA) is a rare variant of mucinous adenocarcinoma of the cervix and vagina. The most common presenting symptom is abnormal vaginal bleeding. Here, we report a case and literature review of CCA of cervix and vagina which was incidentally diagnosed after surgery performed for myoma uteri. Since CCA is an extremely rare disease, standard screening tests, diagnostic tools and treatment methods have not been completely established yet. These features of CCA make it difficult to diagnose preoperatively. Hence, additional studies are needed to diagnose CCA correctly and determine definitive management and treatment principles through meta-analysis using multicenter data.

Key Words: Cervix; Clear cell adenocarcinoma; Diethylstilbestrol; Vagina.

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INTRODUCTION

Cervical cancer is currently the 3rd leading cause of death related to gynecologic cancers among women in the United States. Unless the immune system is weekened or comprimised, the vast majority of cervical cancers progress very slowly and thus, they can be detected even before they become life-threatening (1). Clear cell adenocarcinoma (CCA) is a rare variant of cervical adenocarcinoma and comprises about 3-10% of all cases (2-4). It generally occurs in young women whose mother took diethylstilbestrol (DES) when pregnant and this link is first described in 1971 (5). After the discontinuation of DES use, the incidence went down, and such cases with in utero DES exposure have seen rarely during the past several years. On the other hand such tumors can also develop in women not exposed to DES in utero (3, 6, 7). The etiology and pathophysiology are still unclear. In addition to in utero DES exposure, multiple predisposing factors such as tumor protein 53 (p53) gene mutation, overexpression of B-cell lymphoma-2 (bcl-2) protein, and human papilloma virus (HPV) infection were reported (8–13). Because of its rarity, the nature and clinical course of the disease have not been completely clarified. There is still no consensus on the best treatment option particularly in advanced disease and the prognosis is generally poor. However, good outcomes and survival have been reported for radical surgery in early stage disease (3, 14).

CASE PRESENTATION

A 25 year-old virgo woman complaining of irregular vaginal bleeding and discharge with a malignant pelvic mass was referred to our gynecologic oncology department. Prior exploratory laparotomy performed due to the diagnosis of myoma uteri associated with menometrorrhagia revealed a mass mimicking malignancy and incisional biopsy was taken. The hispathological examination revealed cervical or vaginal clear cell adenocarcinoma. The patient had no history of prenatal DES exposure.

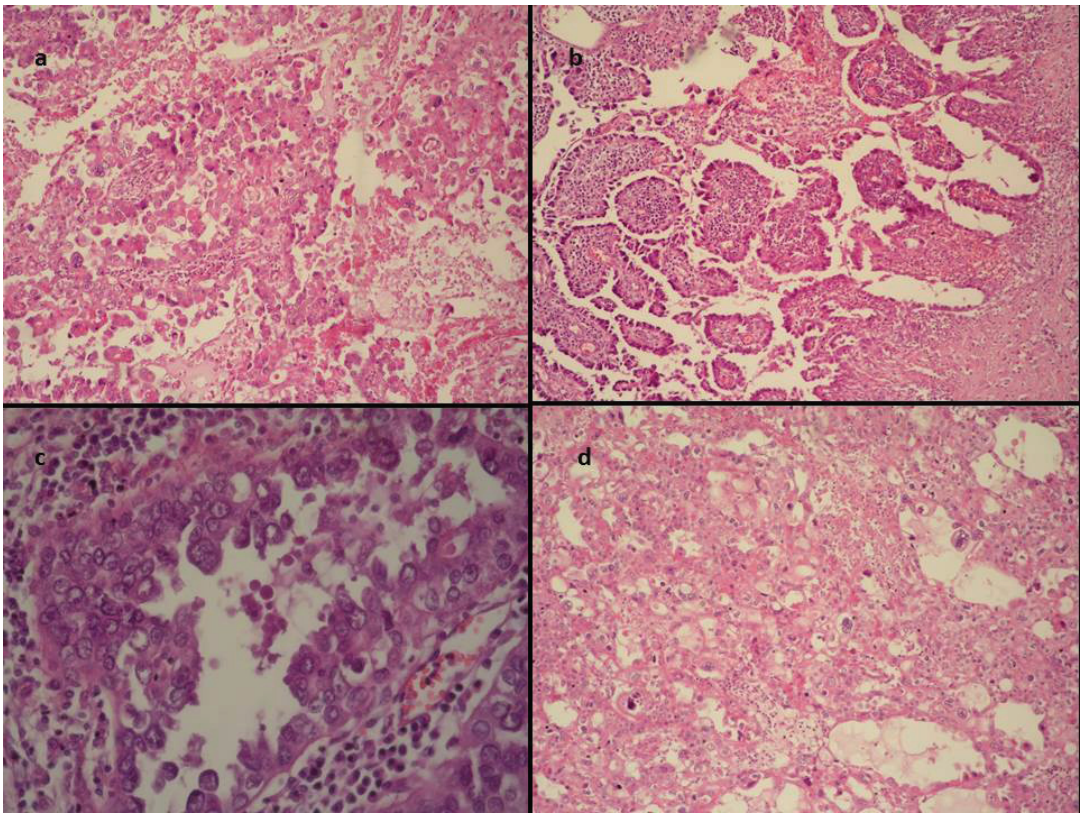
Careful inspection of the external genitalia resulted in no abnormal findings. A pelvic mass approximately 8 cm in size was palpable on the right lower quadrant of the abdomen. She had no pap-smears previously. Her serum cancer antigen (CA) 125 level was elevated (466 U/mL). CA 15-3, CA 19-9 and carcino embrionic antigen (CEA) levels were normal. To assess the stage, the extension of the disease and possible metastases, some preoperative imaging methods were performed. Abdominal magnetic resonance imaging revealed absence of left kidney with compensatory hypertrophy of the right kidney and a 9x8x5 cm pelvic mass. Thoracic computed tomography (CT) showed no abnormal findings.

A low median-line incision for explatory laparotomy was performed. Peritoneal fluid cytology was reported as 'benign'. The uterus bicornis bicollis malformation was reported. The ovaries were normal in size and have normal visual apereance. There was a solid mass about 9 x 8 cm in size originated from the cervicovaginal area extending distal to the vagina. The 4 cm distal part of the right ureter was encased but not infiltrated by the tumor and the remaining part was dilated to 1.5 cm. Left sided renal agenesis was confirmed and the left ureter was seen at the level of left common iliac artery. Besides, the proximal vagina was dilated towards the right paravaginal area. Total abdominal hysterectomy, proximal vaginectomy, bilateral salpingectomy, bilateral pelvic and paraaortic lympadenectomy were performed. To prevent early menopause because of possible need for low abdominal radiation therapy, ovaries were transposed. Further pathologic examination of the cervix and proximal vagina from the hysterectomy specimen showed CCA of the cervix and vagina (Figure 1). Examination of the 21 pelvic and paraaortic lymp nodes did not reveal any metastasis. There was no evidence of residual tumor in the surgical margins. Surgical staging revealed International Federation of Gynecology and Obstetrics (FIGO) stage IB2 CCA.

The patient had an uneventful postoperative course and referred for medical oncology and radiation oncology consultation. She received concomitant pelvic radiotherapy (RT) and chemotherapy (paclitaxel and carboplatin). After 6 months later, her serum CA-125 level raised to 800 U/mL. Abdominal CT scan demonstrated multiple metastatic lymph nodes 3 cm or less in greatest dimension. Another 6 cycles of chemotherapy (paclitaxel and carboplatin) were given for recurrent disease. At the first year of her follow-up visit, CT scan revealed bone metastases in addition to the lymph node metastases. The patient received another 6 cycles of paclitaxel and carboplatin chemotherapy and 0.75 mg/m^2 of topotecan and 50 mg/m^2 of cisplatin therapy. After 8 months doxorubicin (60 mg/m^2), ifosfamide (2500 mg/m^2) and Mesna (400 mg 15 minutes prior to ifosfamide) were given by intravenous infusion every 21 days. The patient died 2 years after diagnosis.

DISCUSSION

CCA of the cervix and vagina is a rare tumor mostly occurs in young women. The pathogenesis still remains unclear. Clinically, patients may present with menometrorrhagia, abdominopelvic pain, or may have no



Figur 1 • Histopathologic appearance of clear cell adenocarcinoma of cervix and proximal vagina on hemotoxylin and eosin stain **a.** Papillary growth pattern in tumor (H&E×100). **b.** Complex papillary structures with hyalene stromal cores (H&E×100). **c.** Characteristic 'hobnail' appearance of nuclei (H&E×400). **d.** Tubulocystic and solid growth pattern of tumor (H&E×100).

complaints in early stages. DES related CCAs generally affect pediatric and adolescent patients. On the other hand, in a study, patients of CCA without perinatal DES exposure showed two peaks; one at 26 years and a second at 71 years (15). In line with this age distribution, our case was 26 years old at diagnosis.

It's difficult to diagnose CCA preoperatively if the physician does not examine patients with particular concern about CCA. Papanicolaou smear is the routine screening method for the diagnosis of cervical carcinoma. However, in rare neoplastic entities such as CCAs, it could be hard to make a precise diagnosis due to infrequent occurrence in daily practice of cytology. Thomas et al. reported that only 6 of 31 CCA patients' (18%) Pap tests were abnormal (16).

Besides, in a study, it is highlighted that 80% of CCA cases showed endophytic and deep infiltrative pattern which increased false negative rate of Pap smear(14). Particularly young virginal patients are often misdiagnosed as functional uterine bleeding, so the correct diagnosis can be delayed (17). Our virginal case had no Pap smear testing. The preoperative diagnosis and the surgical indication was 'uterine leiomyoma and menometrorrhagia'. So the final diagnosis was made with an incisional biopsy during the exploratory laparotomy performed based on a misdiagnosis.

It is reported that CCA of the cervix and vagina occurred in 60% of women exposed to DES in utero and in 12% of women whose mothers were considered to be high risk pregnancies and given unknown medications. It is also emphasised that some contributing factors are also involved in the pathogenesis because the incidence of this tumor was 1 in 1000 in utero DES exposed women (18-20). Our patient had no history of prenatal DES exposure. We reviewed previous series of CCA with or without DES exposure reported in the literature between 1982 and 2014 (Table 1).

The extreme infrequency of CCA suggests that there is no accurate prognosis or standard treatment. About 75-90% of women with CCA are diagnosed at an early stage (stage I and II) (15, 17, 24). Besides, even though the tumor is very small, metastases can occur (17). Hanselaar et al. stated that primary tumor diameter >4 cm was a powerful negative prognostic factor similarly

Table 1 • Overin Malign Transizyonel Hücreli Tümörleri.

Author	N	Publication (year)	Age (years)	DES	Stage (n)	Treatment	Outcome
Johnston et al. (21)	28	1982	7-28	n = 9 (+) n = 13 (-) n = 1 (unknown)	I (14), II (9), III (5)	All patients TAH and PLND + RT (n = 9); +CT (n = 1)	5-y OS, 77%
Kaminski and Maier (4)	23	1983	13-80	DES (-)	I (15), II (5), III (1), IV (2)	Early stages: Surgery± RT Advanced stages: RT	5-y OS; 55% for stages I, II All patients with stage III–IV died within 1 year
Hanselaar et al. (22)	55	1991	8-33	55% DES (+)	I (17), II(31), III (4), IV (3)	Not mentioned	Not mentioned
Hanselaar et al. (15) (update of 1991 series)	88	1997	14-37	n = 47 DES (+) n = 41 DES (-)	I (36), II (41), III (6), IV (4)	Not mentioned	5-y OS; Stage I, 56%, stage II, 61%, stage III, 67%
Reich et al. (5)	15	2000	31-64	DES (-)	IB (8), IIB (7)	RAH and PLND ± according to the presence of risk factors; pelvic RT or CT	5-y OS, 67%
Thomas et al. (16)	34	2008	0-79	n = 2 (+) n = 10 (-) n = 22 (unknown)	I (24), II (2), III (6), IV (2)	TAH ±BSO (P and/or PA LND was performed at surgeon's discreation) ± according to the presence of risk factors; pelvic RT or CT	5-y PFS, 65% 5- y OS, 75%
Jiang et al. (23)	32	2014	12-74	DES (-)	I (18), II (11), III (2), IV (1)	22 of 25 IA2-IIA2 underwent surgery (19 RAH, 3 FPS, 21 P, and 3 PA LND), 3 received CT+ RT 7 (2 IB1, 2 IB2, 2 IIA1, 1 IIA2) received NAC 10 RT, 3 RT+CT Advanced CCA: 4 IIB, 2 III and 1 IVB underwent CT (3), RT plus TAH (1), and supportive treatment (1)	5-y PFS;72.2% (early stages, 81.5%, advanced stage, 40.0%)

BSO, bilateral salpingooferectomy; CCA, clear-cell adenocarcinoma; CT, chemotherapy; DES, diethylstilbestrol; FPS, fertility-preserving surgery; LND, lymph node dissection; NAC, neoadjuvan chemothrapy; OS, overall survival; P, pelvic; PA, para-aortic; PE, peritonectomy; PFS, progression-free survival; RAH, radical abdominal hysterectomy; RT, radiotherapy; TAH, total abdominal hysterectomy

to those patients with squamous cervical cancer (15, 23). In line with this statement our case with 8 cm tumor had early recurrences, distant metastases, and poor prognosis. Positive lymph nodes, >4 cm primary tumor diameter, parametrial involvement, positive surgical margins, cervical stromal involvement and lymphovascular space invasion are well-known risk factors that indicate the need for adjuvant therapy in early stage patients of CCA.

In recent reports, the treatment of CCA has been similar to that of endocervical adenocarcinomas and surgery is the standard treatment modality (3, 14, 25).

Types of surgery can vary from author to author depending on the experience and patient characteristics. In our case, the patient underwent total abdominal histerectomy, proximal vaginectomy, bilateral salpingectomy, bilateral pelvic and paraaortic lympadenectomy. The treatment of those women who are eligible for fertility-sparing and local RT after ovarian transposition have also been successful after the excision of the primary tumor and pelvic and/or paraaortic lymphadenectomy.

In conclusion, it can be difficult to make a precise diagnose for CCA before the final histopathological examination of the specimen is done. A routine Papsmear testing has low power in detecting CCA. Therefore, an additional deep biopsy (cone biopsy or endocervical curettage) is necessary to diagnose when there is any clinical suspicion of CCA. Additional studies will be needed to diagnose CCA correctly and determine definitive management and treatment principles through meta-analysis using multicenter data.

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