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Case Series

Primary Clear Cell Carcinoma with no Diethylstilbestrol Exposure; Case Series

Malihe Hasanzadeh[1], MD; Amir Hussein Jafarian[2], MD; Leila Mousavi Seresht[3], MD

[1]Department of Obstetrics and Gynecology, Fellowship of Gynecology Oncology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran;
[2]Department of Pathology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran;
[3]Department of Obstetrics and Gynecology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Correspondence:
Leila Mousavi Seresht, MD;
Department of Obstetrics and Gynecology, Faculty of Medicine, Ahmadabad Street, Ghaem Hospital, Postal code: 91766-99199, Mashhad, Iran
Tel: +98 51 380124777
Fax: +98 51 38430569
Email: lmousavi.lm@gmail.com
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Abstract

One of the rare neoplasms of cervix uteri and vagina is clear cell carcinoma; mostly in patients with a positive past medical history of intrauterine diethylstilbestrol (DES) exposure which reveals the importance of other unknown risk factors of gynecologic neoplasms. 2 Asian women referred to the gynecology-oncology department. The first one came with a complaint of prolonged vaginal discharge and the second one with irregular bleeding. Neither did report a history of DES-exposure. On vaginal examination, it was found that both cases had mass which biopsied for histologic study. They were diagnosed with primary Clear Cell Carcinoma of Vagina in the first case and Cervix uteri in the other one. Both patients underwent cytoreductive surgery soon after diagnosis.

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Keywords ● Clear cell adenocarcinoma ● Diethylstilbestrol ● Vagina ● Cervix uteri

What's Known

- The most common reason for clear cell carcinoma in gynecologic organs is exposure to Diethylstilbestrol in the past. Malignancies with clear cell feature manage high-grade neoplasms due to their worse prognosis.

What's New

- Primary Clear cell carcinoma of gynecologic organs in patients without the history of Diethylstilbestrol exposure is very rare and needs more evaluation for their best management. In the present article, two cases of gynecologic organ clear cell carcinoma with no recurrences after radical surgery and adjuvant therapy are reported.

Introduction

Adenocarcinoma of gynecologic structures is a rare malignant tumor (less than 15% of all cervical malignancies and rarer at vagina).[1] Primary Clear Cell Carcinoma (CCC) is too rare; it accounts for approximately 2-9% of adenocarcinoma.[2] This cancer usually has been reported in women with past medical history of diethylstilbestrol exposure (DES), but there must be some other unknown etiology for that. On histopathologic examination, this tumor shows cells with clear cytoplasm and hobnail cells, and it must be distinguished from other differential diagnoses. Immunohistochemically staining is needed in doubtful cases.[2] Authors had reported some rare cases which could be helpful in suggesting any association between CCC and race, infection, and sexual activity. On the other hand, CCC could also act as the best treatment modality because the best prognosis is not standardized yet. This study aimed to report two rare cases of CCC without the most well-known risk factors and compare the etiology, treatment approach, and prognosis of them with prior literature.

Case Presentation

Case 1

A 49-year-old nulligravida woman referred to Mashhad University of Medical Sciences, Iran, Hospital, gynecologic-oncology department in 2017, Aug. She had a complaint of prolonged purulent watery vaginal discharge and vaginal

bleeding after an intercourse that had happened a year before. Since 2012, she had become menopause. She had no significant prior medical history, except the history of anti-depressant therapy (sertraline). She did not report any history of hormonal contraception usage either. She was a passive smoker by her partner. Her history of the first sexual intercourse experience was not reliable. She reported her engagement time to have happened in 2015 and did not respond to sexual field questions anymore. She had a significant low socioeconomic condition. There was no genitalia structural abnormality on her physical examination. Speculum examination showed a 2×2 cm, polypoid shape, mass, arising from the post fornix at the left side of upper vagina not affecting the uterine cervix and parametriom. Per rectal examination, no additional finding was detected. Malignancy diagnosis was the first suggestion for detecting her pathology, but its source as the primary vaginal or metastatic one was the essential question. Pap smear from Exo/Endocervical canal and the lesion sampling were performed. Pelvic Magnetic Resonance Imaging (MRI) for better estimation of the tumor local extension and respectability and abdominal computed tomography (CT) and chest X-ray (CXR) for exact assessment of distant metastasis were recommended. MRI of the pelvis showed a vaginal mass 1-2 cm in size expanded inside the vagina without parametrial extension; no distant metastasis showed on abdominal CT scan and CXR (figure 1).

Histological study of the sampled tissue revealed large cells with clear cytoplasm, enlarged nucleoli, and tubular structures lined by hobnail cells. Cervical cytology was normal. The diagnosis was early stage primary CCC of vagina due to neither cervical involvement nor prenatal DES exposure history or sign of genital anomaly.

Radical hysterectomy with at least excision of about 4 cm of the vaginal wall, with bilateral

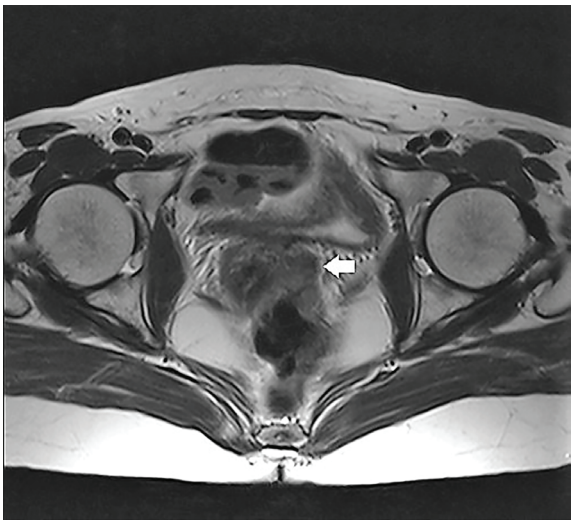

Figure 1: Sagittal view of Pelvic MRI showed vaginal fornix expansion probably due to mass in the lateral of the cervix which had expanded the vagina without cervical and parametrial extension.

oophorectomy (due to her menopausal status), complete pelvic lymph node dissection, and Para-aortic lymph node sampling were done for her. The permanent pathology confirmed residual clear cell carcinoma foci in the vagina with no more local extension (figure 2).

An occasional finding in the pathologic study of uterus was adenomyosis pattern in myometrium. Neoplastic involvement of Pelvic & Para-aortic lymph node was shown in a permanent report in regard of her pre-op imaging study.

After the non-complicated surgery and uneventful post-operative hospitalization, the patient referred to the Radiotherapy department and concurrent chemo-radiotherapy treatment planned for her. The patient is still under observation after 10 months of treatment and remains free from disease.

Case 2

A 48-year-old multiparous woman was consulted in Mashhad University of Medical

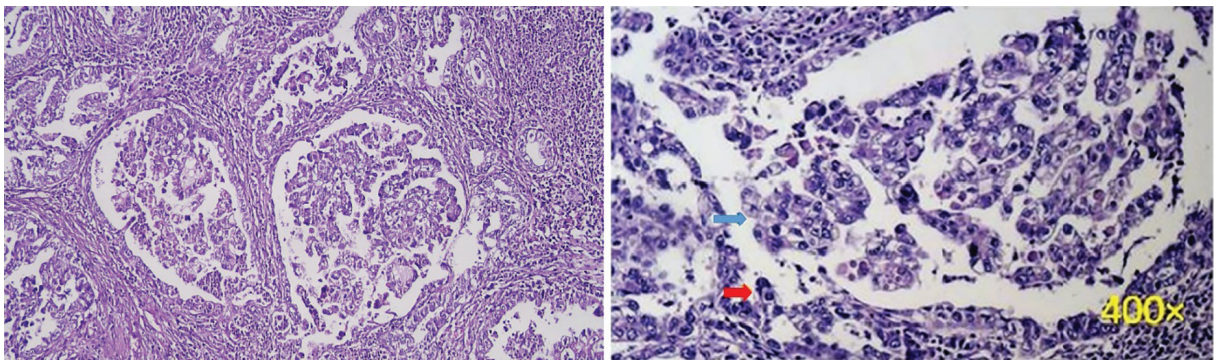

Figure 2: CCC of vagina showed invasive carcinoma with tubulopapillary architecture, hobnail nuclei cell (The red arrow), and Clear cells (The blue arrow). (H&Ex100& ×400)

Sciences, Iran, gynecology oncology department with the complaint of abnormal vaginal bleeding for 6 months during 2017, July. The patient did not have important past medical history. Her last sexual activity was 17 years ago. She reported her husband's smoking behavior (passive smoking). She had no history of hormone contraceptive usage. Gynecologic examination showed no obvious visual abnormality in genitalia, vagina, and cervix. The lone finding was a bulky cervixor uterine isthmus without parametrial involvement. Her last cervical pap smear in one month before the consultation was normal.

Pelvic ultrasonography showed fluid in the uterus with thick endometrial lines, so endometrial sampling was performed for her. Histopathological examination revealed CCC of high grade in endometrial and endocervical curettage samples which was confirmed by Immunohistochemistry staining study; negative ER, PR. Ck20 and positive P16 and CEA. No more data were obtained on pelvic MRI and abdominal CT scan study. The incidental abnormal finding was an elevated CA125 in her laboratory test. She was classified as FIGO stage IB1 of the cervix, and laparotomy was planned for her. Intra-operatively, a barrel-shaped cervix versus a small uterus was seen. Thus, radical hysterectomy (type 3) with parametrial resection and complete pelvic LND and Para-aortic LN sampling were performed by Gyneco-oncologist.

Histopathological examination in Microscopic view showed different sizes of tumoral cells with clear cytoplasm, large round nucleus with pleomorphism, hyperchromasia, frequent Mitotic activity, and prominent nucleoli (hobnailing appearance) in tubulocystic growth pattern); which confirmed 'high-grade CCCC' (figure 3). The gyneco-pathologist also reported the main bulk of tumor in the uterine cervix (the largest diameter was less than 4 cm) versus limited tumoral involvement of the isthmuses of the uterus. The other surgical sample was free of tumor. Adjuvant chemo radiotherapy was the next step in her management, and after 6 months of follow-up, she didnot show any sign of recurrences.

Written, informed consents were obtained from the patients for writing and publication of this case series.

Discussion

This study presents two new cases of rare primary clear cell carcinoma of the vagina and cervix uteri.[1, 2]

Previous articles reported the age of 26th as the commonest age for this malignancy, which confirms the hypothesis of early age (intrauterine) DES- exposure as the commonest etiology for this type of cancer. But, recently, the presented age have risen as it was the case in this study cases, which suggests more studies about CCC risk factors[1-3] are needed. In the present article, two cases of gynecologic

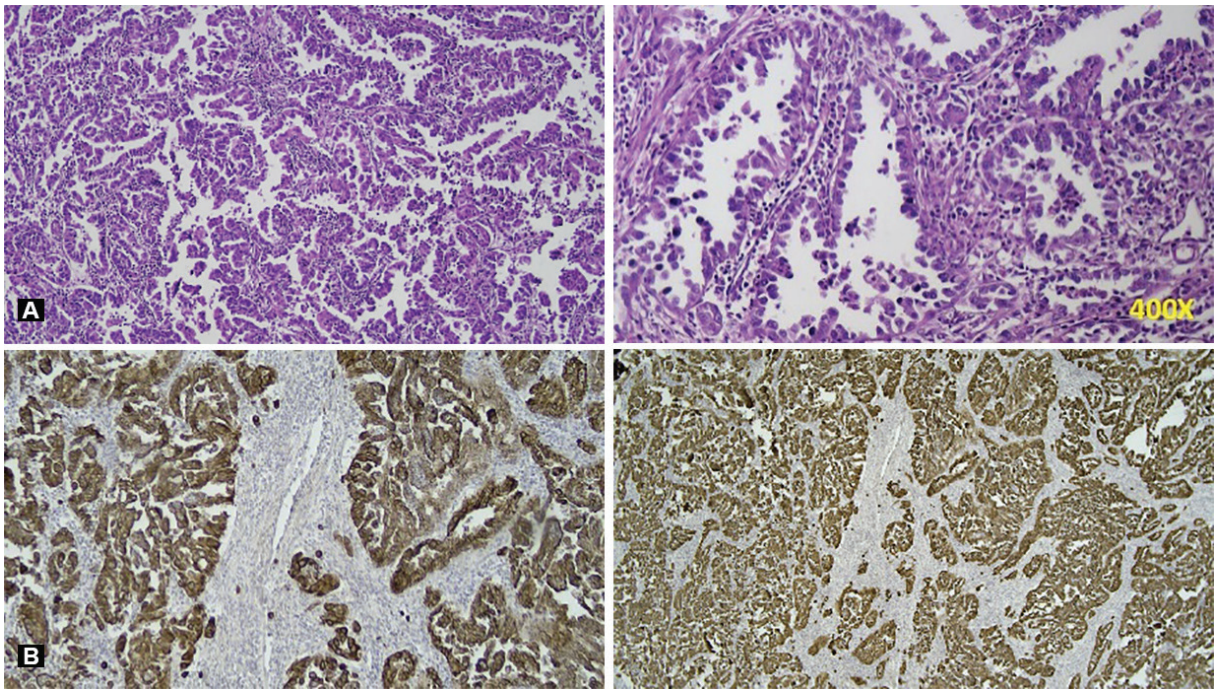

Figure 3: A) Clear cell carcinoma of cervix showed infiltrative tubulopapillary carcinoma with eosinophilic cytoplasm with hobnail nuclei. (H&Ex100 & ×400) B) Immunohistochemical staining showed diffuse Napsin A (top) and CK7 (bottom) staining of tumor cell. (×100)

organ clear cell carcinoma without the history of DES-exposure with no recurrences after radical surgery and adjuvant therapy are reported.

The most common presentation of CCC is the same as other neoplasms of this structure: atypical vaginal discharge and/or bleeding as reported in the present case series.[3] (The simple initial step for the diagnosis after the physical examination is cervical pap-smear and HPV testing, but normal cervical cytology could not rule out malignancies of adenocarcinoma type. The HPV infection role in CCCs development is not confirmed to date and there is controversy over this issue in the literature (especially HPV type 18 & 31). The other possible etiology in some case reports are advanced age, epidemiological risk and socioeconomic status, multiple sexual partners, nuliparity, smoking and contraceptive usage in addition to adenomyosis and endometriosis for endometrial CCC.[3-5] Both cases in the present study were passive smokers and had a low socioeconomic condition. Hormonal contraceptive had used only by one of them; its role must be studied more in future to confirm.

Tumor marker (CA125) was elevated in second case, but the usefulness of this tumor for this cancer diagnosis or management is based on few case reports and is questionable.[6]

Clear cytoplasmic cells with tubulocystic pattern are the CCCs microscopic character. The immunohistochemistry staining by CK7, CAM5.2, 34 beta E12, CEA, C-A125, Leu-M1 and Vimentin (positivity), P53 and Bcl-2 (overexpression) and CK20, β-HCG and Alpha 1-fetoprotein (negative staining) are suggestive for CCC and could distinguish this malignancy from other differential diagnoses such as Aria-Stella reaction, micro glandular hyperplasia, and mesonephric hyperplasia in adults, and Yolk sac tumor, sarcoma botryoides, and embryonal rhabdomyosarcoma in children, and metastatic renal cell carcinoma in all ages. Although staining for ER/PR and HER2 Neu shows variable positivity.[7]

Because of CCC rarity, the individual experiencebased on case reports is the main source of management; no approved guideline persists.

The prognostic factor in all malignancies are stage, tumor size, growth pattern, nuclear atypia, mitotic activity, and lymph node involvement, so the worse prognosis in CCCs in regard of other malignancies' subtypes is controversy.[2, 4] The prognosis in the early stage has reported to be near 80-85% by either radical hysterectomy and lymph node dissection, radiotherapy,[3] or radical trachelectomy (by the aim of maintaining fertility and with/or without chemotherapy). Fertility-sparing surgery in early stage of CCC in young patient is recommended by the National Comprehensive Cancer Network (of Fort Washington) in 2013, too.[3, 8] The main treatment in early-stage adenocarcinoma is radical hysterectomy, but it is important to put emphasis on adjuvant chemoradiotherapy in high-risk patients to reduce the risk of distant metastasis.[2]

Disease-free and overall survival after positive versus negative lymph node detection is 31% versus 92% (P<0.001) and 80% versus 100% (P=0.02), respectively. The most expected recurrence time is 1 year after the definite treatment. The most common site for CCC early recurrences are lung, liver, and the skeletal system, but close follow-up for a long time is necessary. Recurrences in pelvis and vagina were mostly seen in about 4 years after the remission.[4]

As the prognosis of CCC is controversial in different Studies,[1, 2] long life follow-up the is planned for the presented cases in this study, and now, after 10 months of monitoring, they have reported no recurrence.

Conclusion

Due to the sporadic cases of no DES exposure CCC, the probable etiology and the most effective mode of treatment remains unknown and depends on the patient's factors such as tumor size, surgeon, and oncologist team working experiences.

Conflict of Interest: None declared.

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