Case Report

Clear cell adenocarcinoma of uterine cervix in a 19-year-old virgin unrelated to diethylstilbestrol exposure

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ABSTRACT

Clear-cell carcinoma of cervix (CCC) is rarely seen in clinical practice nowadays, especially post the diethylstilbestrol (DES) era. Its association is well established with DES exposure in the adolescent age group. We report a rare case of CCC in a 19-year-old Asian female with no history of exposure to DES. She underwent radical hysterectomy with unilateral salpingoopherectomy and was kept on follow-up and had shown no signs of recurrence even after 1 year of follow-up. Relevant literature is reviewed including possible etiology, appropriate treatment, and prognostic factors.

Key words: Adolescent, Clear-cell carcinoma cervix, diethylstilbestrol exposure

INTRODUCTION

Clear-cell carcinoma (CCC), also called "mesonephric" carcinoma of the cervix and vagina has long been considered a rare entity. It accounts for 4% of all cervical adenocarcinomas. In adolescent females, it is frequently associated with exposure to diethylstilbestrol (DES). Here, we report a rare case of CCC in a 19-year-old virgin with no history of maternal exposure to synthetic nonsteroidal estrogens and DES.

CASE REPORT

A 19-year-old virgin presented with the chief complaint of menorrhagia. She was apparently well 2 years back when she started having excessive and irregular bleeding per vaginum (PV). Easy fatigability and decreased appetite were also reported. There was no history of discharge PV, pain abdomen, bowel, and bladder complaints. She attained menarche at 14 years of age. Her previous menstrual cycles were regular with 5 days bleeding period with a regular and moderate flow.

On examination, she had moderate pallor. Per speculum examination revealed cauliflower-like growth involving the whole cervix approximately 5 cm × 5 cm in size. It was friable and was bleeding on touch. All fornices were obliterated. Vaginal mucosa appeared free of disease. Per rectal examination revealed normal rectal mucosa. Bilateral parametrium appeared free of disease clinically. Rest of the systemic examination was normal.

Her Hb was 8 g%. Cancer antigen 125 was 10.6 U/ml. Other routine blood investigations were normal. Contrast-enhanced computed tomography (CT) pelvis showed a normal-sized uterus with bulky cervix showing a hyperdense mass lesion measuring 4 cm × 5 cm. Other pelvic and intra-abdominal organs were normal.

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Cervical biopsy showed features suggestive of CCC. There were no abnormalities on intravenous pyelography, cystoscopy, and colonoscopy.

In view of Stage Ib2 disease, radical abdominal hysterectomy with right salpingoopherectomy with pelvic lymphadenectomy was performed. Gross examination revealed a cauliflower-like proliferative growth arising from anterior lip of cervix measuring 4 cm × 3 cm in size. Endocervical canal was irregular, hard, and indurated.

Microscopic examination was suggestive of CCC cervix with invasion into endometrium and inner half of myometrium of lower uterine segment [Figures 1 and 2]. Tumor was extending up to serosa. Vaginal flap, parametrium, and the thirty pelvic lymph nodes examined were free from tumor invasion.

Following postoperative recovery, she was discharged on symptomatic treatment. Three months after surgery, her positron emission tomography (PET) CT was done and it did not show any evidence of local residual or metastatic disease. In view of young age, no residual disease on PET scan and CCC being chemo- and radio-therapy resistant, she was kept on 2 monthly follow-up. At present, she is on follow-up for last 1 year and disease-free with a good quality of life.

DISCUSSION

Carcinoma cervix is the most common malignancy in Indian females with around 85% tumors having squamous pathology. Although rare, adenocarcinoma incidence is increasing nowadays.[1] Around 4% adenocarcinomas are clear cell type. Hameed's reviews indicate that this disease has bimodal peak of age incidence,[2] 20–30 years and 60–70 years, as opposed to other cervical adenocarcinomas which have their peak incidence at ages 40–50. The early peak includes all DES-exposed patients.

Due to this strong association, DES had been banned in pregnant females since 1970. Nowadays, over 40 years after ban, DES-associated CCC is observed much less frequently than non-DES-associated CCC.

Previous studies had suggested important differences in the patterns of spread and recurrence in these two populations and no clear recommendations for optimal management exist. There have only been a few small series reported in recent years.

The median age of DES-related CCC is 18.9 years.[3] DES is considered as a teratogenic hormone which can cross placenta during embryonal development and inhibits the replacement of Müllerian by squamous epithelium in the vagina.[4]

This patient was 19-year-old and no history of *in utero* exposure to DES was revealed. This history was also confirmed from patient's mother. This indicated some alternate etiological factors involved. Other etiologic factors of carcinoma cervix such as early childbirth, multiparity, and multiple sexual partners were also not present in this patient. There was no history of similar disease in her family.

CCC differs from squamous cell carcinoma of the cervix in many aspects including age of incidence, lack of smoking history, and a lower frequency of abnormal cervical cytology on pap smear.

The potential absence of a precursor lesion and reports showing many non-DES-exposed CCC as endophytic lesions, may explain lower rate of abnormal pap smears.[5] Human papillomavirus (HPV) type 31 DNA also has been

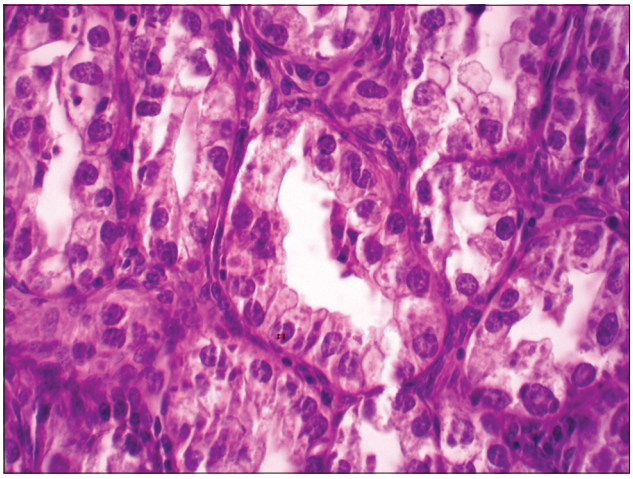

Figure 1: Higher magnification showing clear cells and glandular epithelium (H and E, ×400)

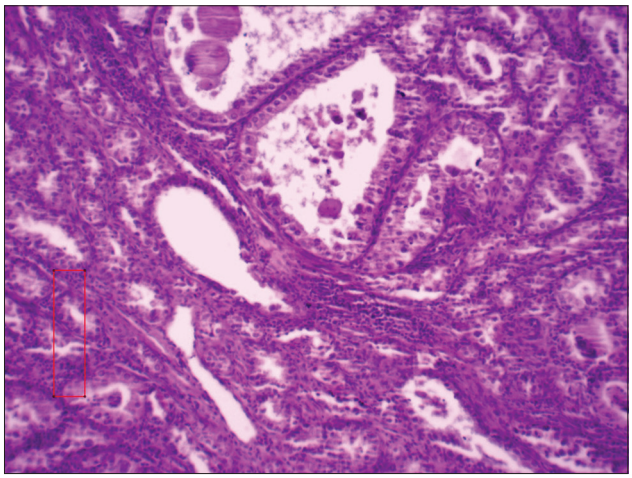

Figure 2: Photomicrograph showing cuboidal and flattened cells with clear cytoplasm (H and E, ×100)

found in CCC, but HPV 31 has low malignant potential, and hence, its association with CCC is unlikely.[6]

Similar to squamous cell carcinoma of the cervix, patients of CCC with positive lymph nodes are at higher risk of recurrence and would appear to benefit from chemoradiation. Paraaortic lymph node dissection is recommended in patients with positive pelvic lymph nodes.[5]

The primary treatment of this patient with Stage Ib2 disease is radical surgery. Outcomes are comparable to other types of cervical adenocarcinoma.[7] As this patient was an adolescent and keeping in view good survival rates in such early disease, ovarian function was preserved to prevent hormone-related complications in later life.

The prognosis of patients with Stages I CCC treated surgically and free of lymphatic dissemination is excellent irrespective of the use of adjuvant therapy. An unfavorable prognosis correspond with high stage, large tumor size, high grade of nuclear atypia, and high mitotic activity.[6] Local recurrences are common within 3 years of diagnosis.

Although DES use has been discontinued in pregnancy, CCC may represent a small, yet growing proportion of cervical cancer cases as the HPV vaccine becomes incorporated into health-care delivery.[5] There may be other unidentified etiological factors which may be responsible for CCC. Whether treatment recommendations for squamous cell and adenocarcinoma of the cervix can be applied in patients with CCC is not clear.

Due to unknown nature of this disease, we need more cases to be reported to evaluate the natural history, etiology, prognostic factors, and to find out more effective treatment and survival rates in this disease.

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Conflicts of interest
There are no conflicts of interest.

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