CASE REPORT

Clear cell adenocarcinoma of cervix in 1-year-old girl without in utero exposure to diethylstilbestrol: an uncommon tumour at an uncommon age and site

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SUMMARY

Adenocarcinoma of cervix constitutes about 10–15% cases of carcinoma cervix. Clear cell variant is even a rarer variant of adenocarcinoma. It rarely occurs in the paediatric age group and a known risk factor is in utero exposure to diethylstilbestrol (DES). We report here a case of primary cervical tumour in a 1-year-old girl, which was initially suspected to be an embryonal rhabdomyosarcoma botryoides. Histopathology with immunohistochemical analysis revealed clear cell adenocarcinoma. There was no maternal history of DES intake during pregnancy. We discuss the histopathological characteristics and clinical course of this unusual tumour.

BACKGROUND

Cancer of the cervix is the most common gynaecological malignancy worldwide.¹ However, its occurrence in the paediatric age group is rare.² Adenocarcinoma of cervix is present in 10–15% cases of carcinoma cervix in all age groups and only 4% of these are clear cell variant.^{2–3} The most common site of clear cell adenocarcinoma (CCAC) in the female genital tract is ovary, followed by uterus, vagina and cervix.⁴ It has bimodal age distribution, that is, the first peak in young women (who usually have history of exposure to diethylstilbestrol (DES) in utero) and the second peak in the postmenopausal age group (in whom history of exposure to DES exposure is usually absent).^{2–4} This case is extremely rare due to the age of the patient at presentation, location of the tumour, the subtype of adenocarcinoma and absence of in utero exposure to DES.

CASE PRESENTATION

A 1-year-old girl presented with intermittent heavy vaginal bleeding from the past 1 month. On examination, the bladder was palpable up to the umbilicus. There was no family history of gynaecological or any other malignancy. The age of mother at the time of pregnancy was 28 years, and it was her first pregnancy. She was not undergoing any fertility treatment to achieve pregnancy, and had no difficulties in getting pregnant. There was no history of use of birth control medicines, venereal diseases or malignancy in the mother. There was no maternal history of any drug, DES exposure, smoking, alcoholism or hypertension during pregnancy. The course of pregnancy was normal, and she had

normal vaginal delivery at 40 weeks of pregnancy. The girl weighed 2.8 kg at birth.

INVESTIGATIONS

Laboratory tests included serum creatinine (0.5 mg/dL), urea (15 mg/dL), total bilirubin (0.6 mg/dL), sodium (147 mEq/L), potassium (4.1 mEq/L), haemoglobin (9.8 gm/dL), and total leucocyte count (9800/Cumm). Ultrasound scan of the abdomen and pelvis revealed a well-defined hyperechoic lesion measuring 12×17×20 mm between the rectum and urinary bladder. Cervix was not visualised separately from the mass. Contrast-enhanced CT of abdomen and pelvis revealed a heterogeneously enhancing mass measuring 15×19×23 mm in the cervix with extension into the lower uterine segment. There were no enlarged pelvic lymph nodes. Bilateral ovaries were normal. There was no infiltration into the surrounding organs. This mass was compressing the bladder neck (without infiltration) with dilated bladder and normal bilateral kidneys and ureters (figure 1). Vaginoscopy showed a very friable broad-based mass arising circumferentially from the cervix.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis based on radiology was embryonal rhabdomyosarcoma botryoides and germ cell tumour. However, vaginoscope-guided biopsy revealed a CCAC of the cervix.

TREATMENT

She underwent radical hysterectomy by transabdominal route with pelvic lymph node dissection. The gross specimen showed friable, yellow-white growth involving the cervix with extension into the lower uterine segment. The upper uterine segment, bilateral fallopian tubes and vaginal cuff were free of tumour (figure 2). Histopathological examination of the cervix showed the tissue was lined by partly ulcerated stratified squamous epithelium with underlying stroma infiltrated by tumour cells arranged in tubules, nests and acini. These acini were of variable shapes and some showed cystic dilation. Individual tumour cells were round, with moderate amount of eosinophilic to clear cytoplasm, moderately pleomorphic round to oval nuclei, coarse chromatin and prominent nucleoli (figure 3). Focal hob nailing was seen. Mitoses were occasional (2–4/10 hpv). Large areas of necrosis and foci of haemorrhage were seen. On

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Figure 1 CT abdomen and pelvis—axial section (A and B) and coronal section (C) revealed heterogeneously enhancing mass measuring $\sim 1.5 \times 1.9 \times 2.3$ cm arising from the cervix with extension into the lower uterine segment (red arrow). There was no pelvic lymphadenopathy and no infiltration into the surrounding organs. Cervical mass was compressing the bladder neck (without infiltration) with dilated bladder (yellow arrow).

immunohistochemical evaluation, the tumour cells were positive for pancytokeratin and non-reactive to cytokeratin 7, cytokeratin 20, α -fetoprotein, CD30, β -subunit of human chorionic gonadotropin, carcinoembryonic antigen, vimentin, myogenin, oestrogen receptor, progesterone receptor, p16, p53, p63, CD10 and melan A (figure 4). Based on the histomorphology and immunohistochemistry, a diagnosis of CCAC of cervix stage 1 (T1 N0 M0) was made.

OUTCOME AND FOLLOW-UP

The patient is free from local recurrence and distant metastasis on imaging studies at 8 months of follow-up.

Figure 2 Radical hysterectomy specimen measuring 2×2×1.5 cm. The specimen showed friable, yellow–white growth involving ectocervix and endocervix with extension into lower uterine segment.

DISCUSSION

CCAC has bimodal age distribution. The first peak occurs at 17–37 years (26 years mean age) and second peak occurs at 44–88 years (71 years mean age).⁵ In utero exposure to DES, which is a potential teratogen is usually present in primary CCAC of cervix in young women, while history of DES exposure is mostly absent in the older age group.⁵ Few cases of primary CCAC in the adolescent age group without exposure to DES have been reported in the literature.⁴ Adolescents commonly present with bleeding per vaginum and are often misdiagnosed as anovulatory bleeding or precocious puberty. This leads to delay in diagnosis. However, CCAC has never been reported earlier in the infantile age group.

DES administration began in the Netherlands during 1947. Herselaar *et al*⁵ reviewed CCACs in the cervix and vagina in the Netherlands and reported 88 cases. Out of 88 cases, 32 patients had CCAC of cervix; 56% of these patients (n=18) had history of DES exposure and 44% occurred in those not exposed to DES (n=14). Although the age group range for CCAC of cervix was not specified, the age of youngest patient in their study was 8 years.⁵ Herbst reported 547 cases of CCACs registered in the University of Chicago. He found that maternal intake of DES or a similar compound during pregnancy was present in 60% of the cases. In 12% of the cases, the mother had been treated with some other hormone or unknown medication. In the remaining cases, there had been no exposure to hormones.⁶ Herbst *et al*⁷ described association of adenocarcinoma of vagina with maternal stilbestrol therapy in eight patients in 1971. Vaginal CCAC has been reported in a patient as young as 1 year.⁸ However, to the best of our knowledge, our patient represents the youngest case of CCAC of cervix in the English literature.

The differential diagnosis of tumours with clear cell morphology includes mixed germ cell tumours (yolk sac tumour, choriocarcinoma and embryonal carcinoma), squamous cell

Figure 3 H&E stained sections from cervix showing (A) partly ulcerated stratified squamous epithelium with underlying nests of tumour cells and intervening areas of necrosis; (B) nests and acini of tumour cells with surrounding areas of necrosis; (C) round to oval tumour cells with moderate amount of eosinophilic to clear cytoplasm, coarse chromatin and prominent nucleoli.

Figure 4 Immunohistochemical stains (A) pan-cytokeratin positive, (B) vimentin negative, (C) α -fetoprotein negative, (D) CD30 negative, (E) oestrogen receptor negative, (F) p63 negative.

carcinoma with clear cell change, mesonephric carcinoma and melanoma. Germ cell tumours were ruled out by the negative expression of CD30, α fetoprotein and β human chorionic gonadotropin. Squamous cell carcinoma with clear cell changes usually shows intercellular bridges and some amount of keratinisation. Also, an acinar pattern and p63 negativity ruled out the possibility of squamous cell carcinoma in this case. Mesonephric carcinoma originates from mesonephric duct remnants and is a rare tumour of cervix.³ The tumour cells are positive for CD10 and vimentin. However, in our case, tumour cells were negative for both. Melanoma (amelanotic variant) can also rarely be seen in cervix and can show similar morphology. However, melan A negativity in this case ruled out melanoma as a possible diagnosis.

Treatment of CCAC is similar to cervical cancer. As mainly patients with CCAC of cervix are of the young age group, the mainstay of treatment is surgery.² In stages 1 and 2, radical hysterectomy with pelvic lymphadenectomy is usually performed but the most preferred approach in young patients is fertility sparing radical trachelectomy. Ovaries are not removed in most cases. Local recurrence often occurs in first 3 years from initial diagnosis.⁵ Patients presenting with advanced stage are treated with chemoradiotherapy with paclitaxel and carboplatin regimens.² This patient underwent radical hysterectomy because of infiltration of lower uterine segment.

Prognosis of CCAC depends on the stage at presentation, size of tumour, nuclear atypia, growth pattern and mitotic activity. Large tumour size, high mitotic activity and nuclear atypia are associated with poor prognosis. A tubulocystic growth pattern has good prognosis as compared with solid or mixed growth patterns.⁵ Our patient had tubulocystic pattern, occasional mitotic

activity and moderate nuclear atypia. The overall clinical course of CCAC of cervix is more aggressive and associated with worse prognosis than non-CCAC and squamous cell carcinoma, except in early stages where the prognosis is similar.⁴ The survival of women with CCAC of cervix with exposure to DES is better than non-DES exposure probably due to early detection.³

Learning points

- ▶ The possibility of a cervical malignancy must be kept in the differential diagnosis of vaginal bleeding in a female infant.
- ▶ Clear cell adenocarcinoma of cervix is an extremely rare tumour which should be considered in the differential diagnosis of cervicovaginal lesions in children, even in the absence of history of in utero exposure to diethylstilbestrol.
- ▶ Prognosis is good when it is diagnosed early and managed aggressively with radical surgery.

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Competing interests None declared.

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