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Case Report

Primary clear cell adenocarcinoma of the vagina in a young female with uterus didelphys

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ABSTRACT

Introduction: Adenocarcinomas of clear cell type are uncommon tumors accounting for 5-10% of all vaginal tumours which in turn account for approximately 2% of all gynaecologic malignancies. Though Clear cell Adenocarcinomas arising in the setting of previous Di-Ethyl–Stilbesterol [DES] exposure have been reported quite often, only few cases of these not associated with DES have been documented. Amongst non-DES exposed patients, CCAs are said to be sporadic or in association with endometriosis in women of peri/postmenopausal age or in association with some congenital genitourinary anomalies mostly affecting young females.

Case Report: A 16 year old female presented with heavy bleeding per vaginum since 2 months. On per vaginal examination a polypoidal mass was felt on posterior wall of vagina. Ultrasonography revealed the presence of a uterus didelphys in addition to this mass. Polypectomy was done. On microscopy, a diagnosis of clear cell adenocarcinoma was made which was confirmed on immunohistochemistry. There was no history of any DES exposure in the mother.

Conclusion: We present here a case of an adolescent female with uterus didelphys and no DES exposure who was diagnosed as a case of Vaginal Clear cell Adenocarcinoma. The rarity of this tumour among DES-exposed cases and its presence in non-exposed patients warrants a more thorough search for the underlying pathology.

1. Introduction

Vaginal tumours are rare accounting for approximately 2% of all gynaecologic malignancies. 85-90 % of women with vaginal cancer present with Squamous cell carcinoma.[1] Adenocarcinomas of clear cell type are uncommon, accounting for 2-9 % of vaginal malignancies.[2] Clear cell adenocarcinomas (CCAs) arising in the setting of in-utero exposure to Diethylstilbestrol (DES) is well documented, Herbst et al. being the first to report CCAs occurring in women whose mothers were exposed to DES during pregnancy. In 1983, Kaminski and Maier were the first to reveal that CCAs can also occur without exposure to DES.[3] Since then, only few cases of CCAs not associated with DES have been reported in the literature. Though mostly sporadic, some cases of CCAs of vagina in association with vaginal endometriosis.[4] and some cases associated with congenital anomalies of the genitourinary tract have been reported.[5,6] The age of diagnosis among DES exposed patients are usually between 14 to 22 years (median age of 19 years). Among non-DES exposed patients, age distribution is bimodal comprising of young females mostly with congenital genitourinary anomalies[5,6] and postmenopausal women mostly with endometriosis.[4]

2. Case Report

A 16-year-old female presented to the Gynaecology OPD with complaints of heavy bleeding per vaginum for the past 2 months. On per vaginal examination a polypoidal mass was seen on posterior wall of vagina. Ultrasonography revealed additionally presence of a uterus didelphys in

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the patient. Complete blood count revealed severe anaemia. Rest of the haematological parameters were normal. Polypectomy was done and mass was sent for histopathological examination. On microscopy, sections showed a cellular mass composed of tumour cells arranged in a lobular pattern. Within the lobules, tumour cells were showing back to back arrangement of glands with mild variation in size and with few mucin filled vacuoles. The intervening stroma showed dense desmoplasia and mild inflammatory infiltrate. These tumour cells were moderately pleomorphic, with high N :C ratio, vesicular chromatin, prominent nucleoli and predominantly clear cytoplasm. Mitotic activity was not high. Some areas of necrosis were seen. [Figures 1, 2, 3 and 4] A diagnosis of clear cell adenocarcinoma was made and IHC was advised for confirmation. Tumour cells showed positivity for CK 7 and PAX 8 thus confirming our diagnosis of clear cell adenocarcinoma.[Figures 5,6] Further clinical history ruled out any DES medication in mother. No details of post – op treatment and response could be obtained as the patient was lost to follow up.

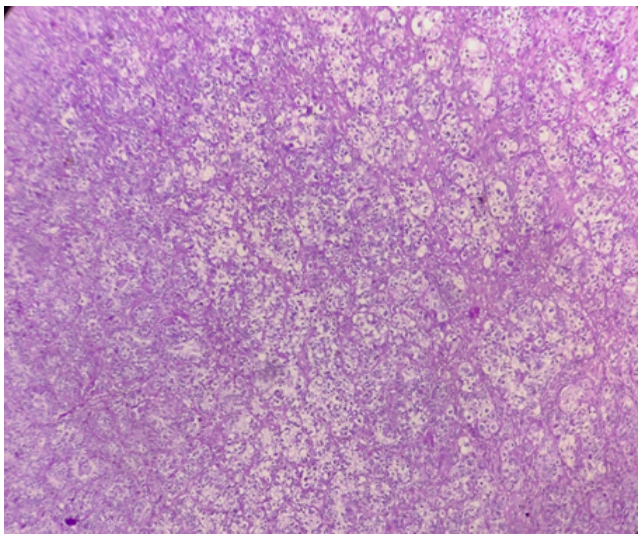

Fig. 1: Low power view of the tumor (H&E, 4X)

3. Discussion

Primary adenocarcinomas accounts for 6-14% of vaginal tumours which in turn account for 2% of all gynaecological malignancies.[1] Clear cell adenocarcinomas, also known as Mesonephroid carcinomas or Mesonephric carcinomas are rare tumours accounting for 2-9% of adenocarcinoma s of the female genital tract.[2] Ovary, cervix and urinary tract are the most commonly involved areas.[7] with rare occurrences in vagina (5-10%).[8] In vagina, their most common location is anterior vaginal wall,[9] but it can also occur elsewhere.

Clear cell adenocarcinomas (CCAs) arising due to in-utero exposure to Diethylstilbestrol (DES) is well

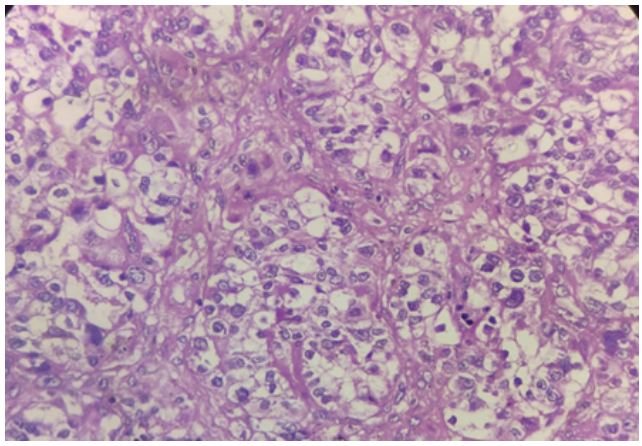

Fig. 2: Tumour cells in a lobular pattern separated by fibrovascular septa (H&E, 10X)

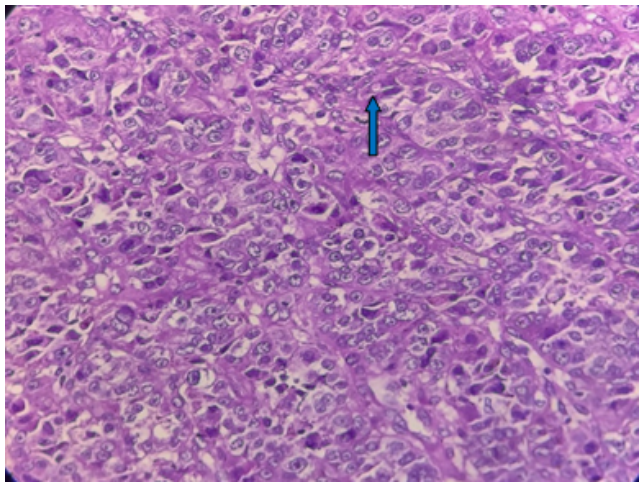

Fig. 3: Back to back arrangement of glands within the lobules with mild variation in size. Occasional intracellular mucin vacuoles were seen (↑) (H&E, 40X)

documented, however, only few cases of Primary Vaginal Clear Cell Carcinoma (PVCC) not associated with DES have been reported in the literature. Amongst the latter, PVCC in association with vaginal endometriosis[4] and congenital anomalies of the genitourinary tract have been reported.[5,6] Few sporadic cases not associated with any other anomaly/pathology have also been mentioned[2,7] The age of diagnosis among DES exposed patients is usually between 14 to 22 years (median age of 19 years). Among non-DES exposed patients, age distribution is bimodal comprising of young females mostly with some congenital genitourinary anomalies[6] and postmenopausal women mostly with co-existent endometriosis[4]

Diethylstilbestrol (DES), a synthetic oestrogen was prescribed off-label from the early 1940's through 1975 in women with a history of miscarriage to prevent adverse pregnancy outcomes. DES is a teratogen and inhibits

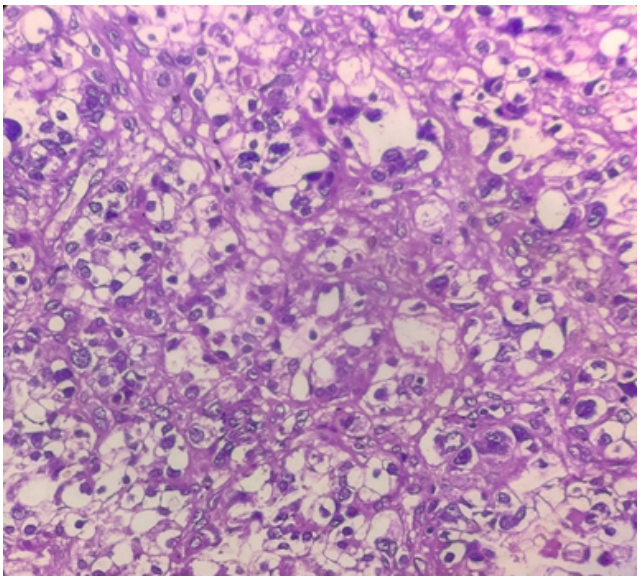

Fig. 4: Moderately pleomorphic tumor cells with high N :C ratio, vesicular chromatin, prominent nucleoli and predominantly clear cytoplasm. The intervening stroma showed dense desmoplasia and mild inflammatory infiltrate. (H&E, 40X)

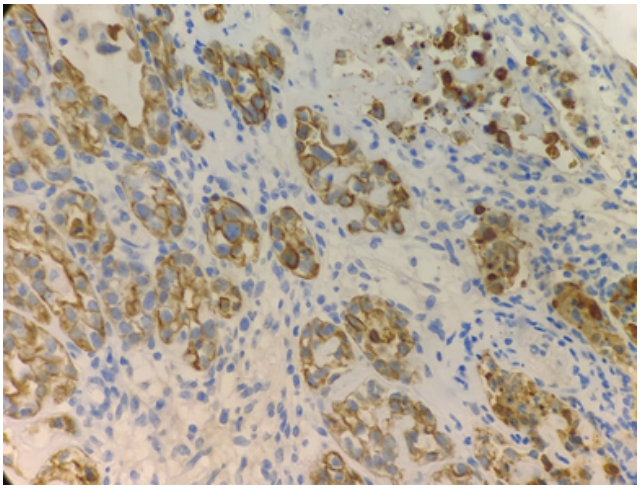

Fig. 5: Tumour cells showing cytoplasmic positivity for CK7

the replacement of the Müllerian duct-derived glandular epithelium. The risk of developing CCA among the exposed was 1 in 1,000 as rarely the ectopic glandular epithelium underwent malignant transformation.[10]The rarity of this tumour among exposed women and its presence even in non - exposed suggested that diethylstilbestrol may not be the only carcinogen responsible. Other factors such as obesity, genitourinary malformation and unopposed oestrogens may also be involved in the pathogenesis.[4]

Female genital tract congenital malformations result from aberrant embryonic development. They have a prevalence of 4 – 7% and an incidence of 0.2 – 0.4%

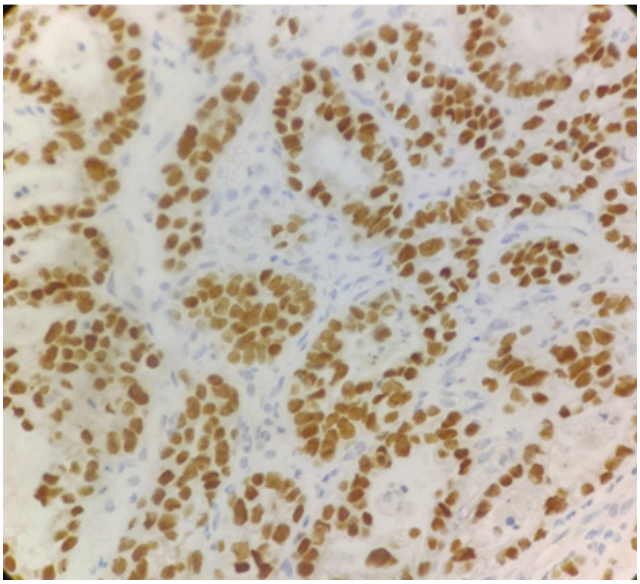

Fig. 6: Tumour cells showing nuclear positivity for PAX8

in the general population. Zong et al. suggested that genitourinary anomalies, especially uterus didelphys, are linked to an increased risk of adenocarcinoma Kusunoki et al too had reported a case of cervical clear cell carcinoma with OHVIRA syndrome. Similarly, Satou et al. had also documented the relationship between the malformations of the uterus or vagina and PVCC.[5]Tanaka et al. described a 17-year-old patient with PVCC who had a chromosomal abnormality (47XX+) and a bicornuate uterus.[11] In our case too, the patient had a didelphys uterus.

Although rare, endometriosis associated clear cell adenocarcinoma remains a well-documented phenomenon in ovary though rarely seen in vagina. Sampson et al. first described origin of adenocarcinoma in the setting of endometriosis in 1925 . The frequency of vaginal tumours arising in endometriosis ranges from 4% - 11%.[4]

PVCC usually presents as abnormal vaginal bleeding or discharge[4]although 16 - 25% are asymptomatic.[9] Zong et al. documented that clinical presentation is often atypical in PVCC patients with a congenital malformation. Intermenstrual vaginal bleeding was the most common presenting symptom (54.8%) in their study.[5] In this case also, the patient presented with heavy bleeding per vaginum.

The tumour can vary in size from microscopic to more than 10 cm in diameter. On histopathologic examination, this tumour shows cells with clear cytoplasm and hobnailing. About 60% of cervical and vaginal tumours show a predominantly tubulocystic growth pattern; 20% have a predominantly solid pattern of growth, and 12% are papillary. A mixture of growth patterns is usual. Nuclear pleomorphism is variable. Mitotic activity is usually low. In the present case, tumour cells were arranged in a lobular pattern and were showing back to back arrangement of

glands with mild variation in size and clearing of cytoplasm. Mitotic activity was not high. We however did not see much of hobnailing.

Though identifying a Clear cell adenocarcinoma under the microscope is usually simple, a few differentials have to be kept in mind especially in young females. Mesonephric remnants may mimic CCA at low magnification but at high magnification dilated tubules of cuboidal cells with eosinophilic secretions are seen without any nuclear atypia. Microglandular hyperplasia consists of tightly packed glands without intervening stroma and may be confused with glandular portions of clear cell carcinoma. These lesions however, typically lack the degree of nuclear atypia seen in clear cell carcinoma and contain mucin, often forming subnuclear / supranuclear vacuoles and often show presence of squamous metaplasia. Arias-Stella reaction is notable for nucleomegaly and bizarre nuclei, reactive clear or hobnail cells may be seen- features that can be mistaken for those of a CCA. However, a mass lesion is absent and the cells are not mitotically active and the nuclei show degenerative features with pseudoinclusions. The atypical looking areas are usually focal, are seen in the context of other reactive changes such as syncytial metaplasia, and are present within a spectrum of otherwise benign cellular alterations.[12] Alveolar soft part sarcoma is a well circumscribed tumor with a pseudoalveolar pattern and lacks the characteristic cytologic and architectural patterns seen in clear cell carcinoma. Tumour cells contain PAS+ diastase resistant intracytoplasmic crystals unlike CCAs where tumours cells may have focal PAS+ areas in cytoplasm, but are diastase sensitive. Hobnailing and clearer cytoplasm is seen in CCA[13] Metastatic tumour is a more important differential in elderly females.

Immunohistochemistry is mandatory for confirmation. Tumour cells show cytoplasmic positivity for CK 7, EMA and nuclear positivity for PAX- 8 and HNF β1 along with overexpression for P53 and Bcl-2.

Non-DES associated CCAs generally have a worse prognosis compared to DES associated ones that have a relatively good prognosis.[14] Atypical clinical presentation and difficult examination associated with congenital malformation(s) may partially be responsible for worse prognosis of anomalies associated clear cell carcinomas.

Depending upon the stage and grade of disease, most patients are treated with combination of radical surgery and radiation therapy.[9] Chemotherapy is infrequently used because of associated poor outcomes. 5 year survival in stage I PVCC is only 56 %.[6] The overall recurrence rate for clear cell carcinoma approaches 21%. Recurrence has been observed as long as 20 years after primary therapy emphasizing the importance of prolonged follow-up.[9]

CCAs are prone for widespread dissemination with the lungs, supraclavicular lymph nodes and pelvis being the most common sites of tumour metastasis.[9] Cerebral[9] and cardiac metastasis[15] has also been reported.

4. Conclusion

Due to the handful number of cases of Clear cell Adenocarcinomas reported in females with no DES exposure, the probable etiology and the most effective mode of treatment remains unknown. The rarity of this tumour among DES-exposed cases and its presence in non-exposed patients warrants a more thorough search for the underlying causes. It is essential to consider this tumour as a differential even in the setting of patients not exposed to DES owing to its aggressive nature and recurrence. CCAs in females with genital anomalies may go unnoticed for a longer period than in those without such malformations owing to atypical clinical presentations and difficult examination. Hence it is essential that such patients undergo a thorough gynaecological check up with regular follow ups so that more such cases can be brought to light and an effective treatment strategy can be planned.

5. Source of funding

None.

6. Conflict of interest

None.

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