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CASE REPORT

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Vaginal clear cell carcinoma in a young patient with ectopic termination of the left ureter in the vagina

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Abstract The association of clear cell adenocarcinoma of the vagina and vaginal adenosis with prenatal exposure to diethylstilbestrol (DES) is well-documented in the United States. In Europe, however, DES was never used in the therapy of threatened abortion and, therefore, clear cell adenocarcinoma and vaginal adenosis remained rare diseases. We report on the clinical and pathological features of a case of clear cell adenocarcinoma of the upper vagina in a 17-year-old German girl, who had a history of hypoplasia of the left kidney with an ectopic termination of the ureter in the upper vagina, removed surgically 2 years before. No previous report of a similar coincidence of vaginal clear cell carcinoma and a congenital disorder of the genitourinary tract exists. Congenital anomaly of the ureter interfering with the development and the differentiation of the distal Müllerian tract and its epithelium might have provided a similar histological basis for carcinogenesis in our patient to that in those provided exposed to DES.

Key words Clear cell adenocarcinoma · Vaginal Ureteral ectopia

Introduction

Clear cell carcinoma of the vagina is a rare tumour occuring in the upper vagina of children and young adults. In about two-thirds of all cases reported, a history of intrauterine exposure to diethylstilbestrol (DES) was confirmed in the United States (8), pointing to the possible role of DES in the pathogenesis of this rare neoplasm. In Europe where DES had seldom been used in pregnant women, clear cell carcinoma of the vagina as well as vaginal adenosis are extremely rare. While the hypothesis of DES-related oncogenesis in the USA was strengthened by the findings in animal models (10, 11), the histogenesis of vaginal clear cell carcinoma without prenatal exposure to DES remains obscure, though there are no differences regarding morphology nor the clinical aspects of these tumours.

We report on a case of vaginal clear cell carcinoma in a patient without preceding exposure to DES, but with a history of a hypoplastic left kidney and ectopic termination of the ureter in the upper vagina.

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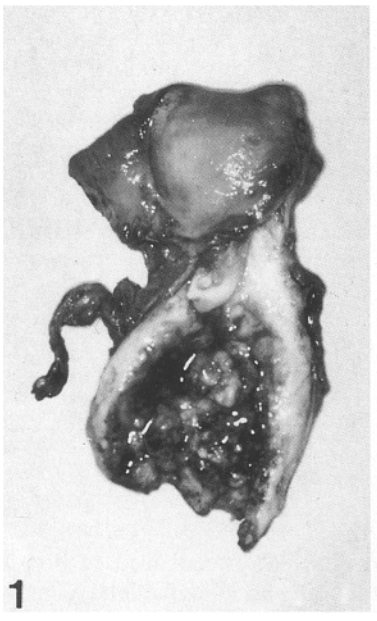
Clinical history

A 17-year-old nulliparous woman presented with continous vaginal bleeding. She was diagnosed as having an ectopic ostium of the left ureter into the left lateral fornix of the vagina at the age of 6. The ureter and a hypoplastic left kidney had been surgically removed in 1991 when the patient was 15. No vaginal tumour had been found and there was no history of intrauterine exposure to hormones by maternal intake of DES of treatment with agents known to be oestrogen modulators such as tamoxifen or danazol.

On examination with the vaginoscope a polypoid mass was seen in the upper vagina and the right anterior wall. The cervix uteri could not be identified behind this tumour. Vaginal endosonography and CT scanning revealed a normal-sized uterus and ovaries, the tumour being restricted to the vagina without evidence of intrauterine or abdominal spread. The right kidney and ureter were of normal size and shape on intravenous pyelogram.

The patient was treated by radical hysterectomy, partial vaginectomy, and bilateral pelvic lymph node dissection with preservation of the ovaries. Following surgery, the patient received intensive intravaginal radiotherapy (40 Gy, 5 fractions) using high dose brachytherapy.



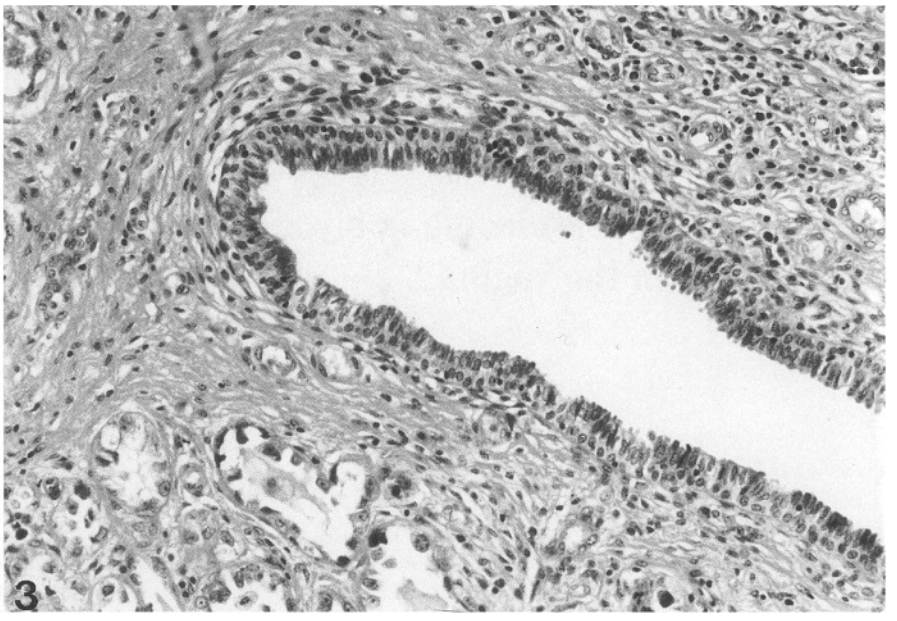


Fig. 1 Surgical specimen of hysterectomy and partial vaginectomy showing polypoid tumour masses in the vagina

Fig. 3 Remnants of Gartner's duct in the lateral vaginal wall, showing no relation to the surrounding tumour infiltrate

Materials and methods

The tumour was investigated using H&E, Di-PAS and Gordon-and-Sweet stains. Immunohistochemistry was performed on paraffin and fresh frozen sections using antibodies against cytokeratins, vimentin, carcinoembryonic antigen (CEA) (DAKO), oestrogen receptor, progesterone receptor (Abbott) and the proliferation associated antigen Ki-67.

Pathological findings

A polypoid large tumour with central ulceration and a maximal diameter of 5.5 cm was found in the vagina in the surgical specimen (Fig. 1). The main tumour mass was located in the upper vagina, resulting in the destruction of the lower cervix and portio uteri with smaller parts of the tumour extending to the lower vagina. Since parts of the tumour reached the margins of surgical resection, a further part of the vagina was removed, also showing small polypoid tumour masses.

The tumour showed a mixed growth pattern with papillary, tubular, cystic, and solid areas. It was largely composed of polygonal and hobnail cells with large and irregular nuclei. An abundant clear cytoplasm with negative PAS-staining could be seen in most of the tumour cells, preferably in areas with a solid growth pattern (Fig. 2). The tumour infiltrated deeply into the smooth muscle layer of the vagina, and no vascular invasion was observed. In the lateral vaginal wall small residues of Gartner's duct were detectable (Fig. 3). However, no obvious relationship of these structures to the carcinoma was seen. In small areas inconspicious fragments of intact squamous epithelium were found mainly in the additional tissue removed from the lower vagina. Adenosis was not evident in these structures. All lymph nodes were found to be free from tumour infiltrates.

Immunohistochemistry revealed positive reactions of tumour cells with antibodies for cytokeratins 13/14 and 8/18, but negativity for vimentin and CEA. No expression of oestrogen or progesterone receptors could be detected. The proliferation associated antigen Ki-67 was positive in up to 60% of the tumour cells.

The surgical specimen of the hypoplastic left kidney was small (approximately 2 cm maximal length) with regular glomeruli and normal vessels. Small suburothelial infiltrates of lymphocytes and plasma cells were seen in the pelvic system. A regularly differentiated transitional epithelium was found in the ureter accompanied by a scanty round cell infiltrate and slight fibrosis. No atypical cells were observed.

Discussion

Glandular lesions of the vagina are rare, the organ is normally devoid of glands and lined by squamous epithelium. The incidence of benign glandular changes (adenosis) as well as adenocarcinomas of clear cell type rose significantly in the USA in 1970 and following years, related to prenatal DES-exposure during the 1940s through the 1960s (1, 9). In countries where DES was not used during pregnancy, vaginal adenosis is only rarely observed; sporadic cases of malignant epithelial tumours with glandular differentiation are mainly found to be endometrioid type, mucinous and mesonephric carcinomas. In contrast, clear cell carcinomas are even rarer with a striking morphological and clinical similarity to the DES-related cases reported in the USA, as observed in our 17-year-old patient (7).

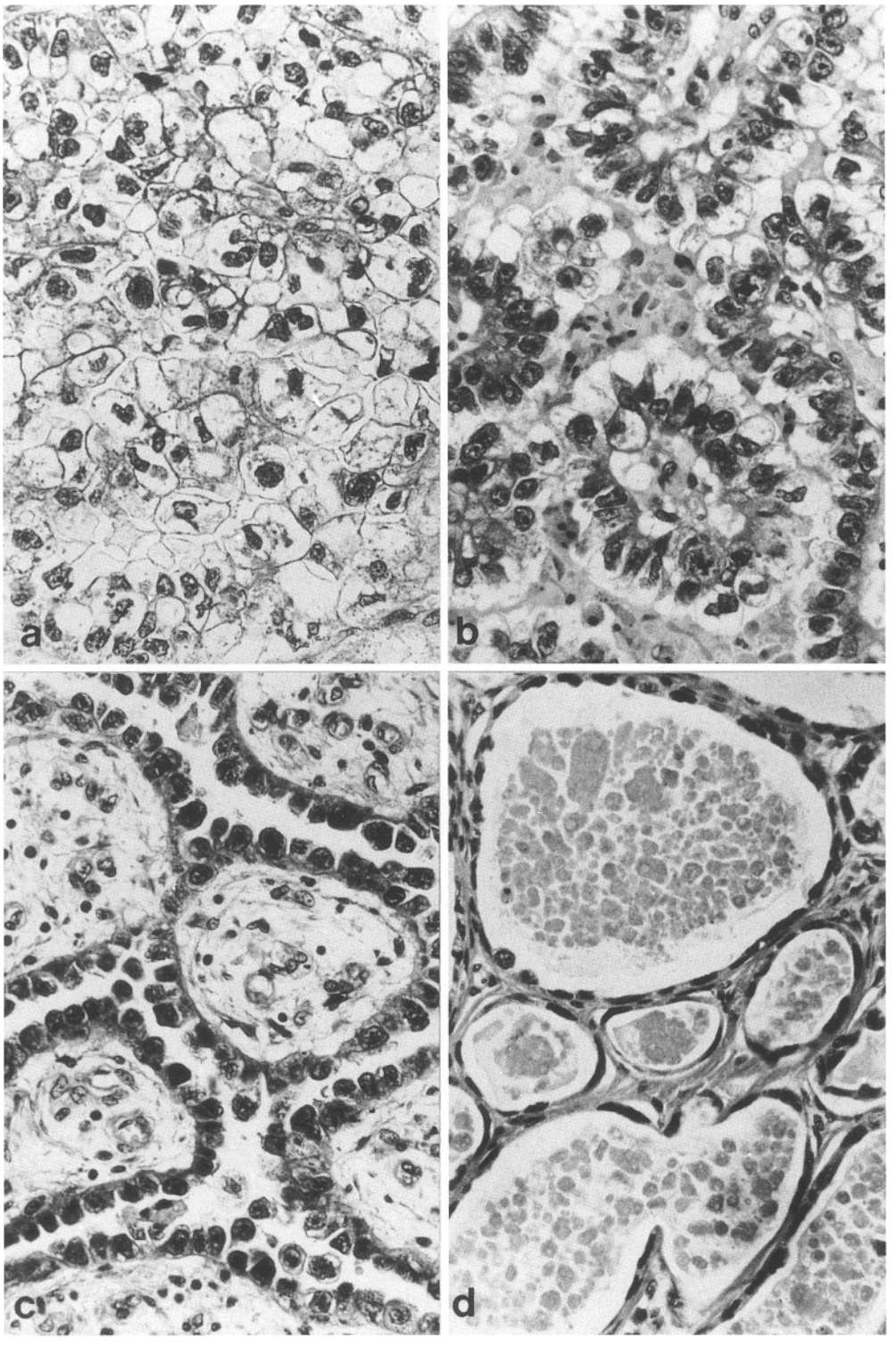


Fig. 2 Histological findings with solid (**a**), papillary (**b, c**) and cystic (**d**) growth patterns. Note characteristic clear cells (**a, b**) and hobnail cells (**c**)

There is substantial experimental evidence that DES is a teratogen leading to congenital abnormalities of the upper and lower female genital tract. Obviously, DES inhibits the normal up-growth of squamous epithelium derived from the urogenital sinus and interferes with the replacement of Müllerian-derived columnar epithelium in the upper vagina (11). According to the leading hypothesis of a stroma-induced differentiation in the female genital tract, the contact of the persisting Müllerian epithelium with the stroma of the upper vagina results in the induction of tuboendometrial-type glandular lesions, preferably presenting as tuboendometrial-type adenosis (5, 11). In patients without DES-exposure, similar development of adenosis is postulated with an hypothetical addi-

tional effect of steroid hormones after the menarche (4, 5). In this context it should be of interest that the median age at the time of diagnosis is 19 years in patients with DES-related clear cell carcinoma (2).

This suggestion may be strengthened by the findings in our patient. The history of the ectopic termination of the ureter in the upper vagina points to a congenital failure in the development of the urogenital system. Ectopic ureters are the result of an anomalous outgrowth of the metanephric duct (the future ureter) from the distal mesonephric duct as it is absorbed into the lateral urogenital sinus. During this phase, an abnormal juxtaposition to the Müllerian system and especially its lower part, contacting the vaginal anlage with cephalad growth from the sinus urogenitalis, may lead to an ectopic termination of the ureter. This abnormal structure may have prevented the homogeneous replacement of Müllerian epithelium by the upgrowing squamous epithelium. It is possible that Müllerian epithelium persisted in the upper vagina and remained throughout childhood and to the time of the surgical removement of kidney and ureter. The high percentage of Ki-67 positively staining cells in the clear cell carcinoma points to a rapid growth of the tumour in the years after surgical correction. The onset of menarche might have had a similar influence on tumour development to that postulated for DES-related carcinomas. However, no residual foci of Müllerian epithelium nor of adenosis were observed within the tumour free parts of the vagina. It is possible that such foci had been obliterated by the large tumour masses.

The association of a malformation and a vaginal clear cell carcinoma might also be fortuitous and other possible mechanisms of oncogenesis should be considered. Clear cell carcinomas of identical morphology are occasionally observed in the bladder and the urethra (13). These tumours, however, occur at an age of 35 to 78 years, whereas in our case, the patient showed all the clinical features of a DES related tumour including presentation at young age. The remnants of Gartner's duct were not found to be related to the carcinoma, so that a mesonephric tumour is less probable. Endometriosis was also absent.

In patients with urinary diversion operations, including ureterosigmoid placement, an increased risk of the development of adenocarcinomas has been observed (3, 6, 12). In these cases, carcinogenesis is thought to be related to exposure to carcinogens in urine or to chronic inflammation. Although no signs of chronic vaginal inflammation had been observed since the first examinations in childhood in our patient, this possibility cannot be ruled out.

The constellation of findings in our case seems to give useful hints for the histogenesis of this genital neoplasm.

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