Gynecol Surg (2006) 3: 281–284
DOI 10.1007/s10397-006-0182-4

CASE REPORT

Kadir Güzin · Semra Kayataş Eser · Ayşe Yiğit · Ebru Zemheri

Primary clear cell carcinoma of the vagina that is not related to in utero diethylstilbestrol use

Received: 27 October 2005 / Accepted: 29 December 2005 / Published online: 15 July 2006
© Springer-Verlag Berlin / Heidelberg 2006

Abstract Vaginal clear cell adenocarcinoma (VCCA) is most commonly related to in utero diethylstilbestrol (DES) use. Primary VCCA is an extremely rare entity except for this well-known condition. In this paper, a 23-year old, virgin, unmarried woman who was diagnosed with VCCA is presented. The woman had suffered from weakness and fatigue, and there was no history of in utero DES use. Magnetic resonance imaging showed a huge mass (Stage IIA in the FIGO classification) in the vaginal cavity, and a biopsy under general anesthesia revealed that it was a VCCA. Because of the advanced stage, no resection was planned, and the patient was treated with radiation therapy followed by chemotherapy. After a 14-month follow-up, she was doing well.

Keywords Primary vaginal cell carcinoma · Diethylstilbestrol

Introduction

Only 1–2% of all genital cancers are vaginal cancer, which most commonly occurs as a squamous cell carcinoma (92.8% of all cases) over the age of 50 [1]. Vaginal clear cell adenocarcinomas (VCCA) amount to only 5–10% of all vaginal cancers, and is most commonly observed in young females affected by the in utero use of diethylstilbestrol (DES) [1]. The relationship between VCCA and in utero DES use is well-known, and many studies have revealed that the daughters of women who used a non-steroidal estrogen—DES—and other synthetic estrogens in order to prevent abortion during the first 18 weeks of gestation, are at a high risk of VCCA [1]. Nordqvist et al. suggested that DES interferes with the normal process of the differentiation and degeneration of the Mullerian epithelium in the fetal vagina. Thus, the persistence of Mullerian cells alters at the subcellular level, and this situation may cause the carcinoma [2]. Vaginal squamous cancer, the most commonly detected form of vaginal malignancy, is generally seen in women after the age of 30, and peaks between the 5th and 7th decades; however, VCCA is observed at a median age of 18 [1].

Vaginal clear cell adenocarcinoma is an uncommon malignancy; it is even very unusual in patients who do not have a history of maternal DES use at the time of pregnancy. Herbest and Scully reported 7 cases—the largest series in the literature—of primary VCCA between the ages of 15 and 22 [3]. In this paper, an unmarried, 23-year-old woman with a histologically proven VCCA but with no history of in utero DES use is presented.

Case Report

A 23-year-old, virgin, unmarried woman (gravida 0) suffered from weakness and fatigue. Routine laboratory showed iron deficiency anemia, and further evaluation with magnetic resonance imaging revealed a huge tumoral mass in the vaginal cavity. Thus, the patient was referred to the Obstetric and Gynecology Department. Further evaluation showed that the patient sometimes had groin pain, dysmenorrhea, dysuria, and leukorrhea. In addition, abnormal genital bleeding was observed. According to her medical history, menarche had started at the age of 11, and her menstrual periods thereafter were almost regular (every 28 days). The patient denied any kind of maternal DES use. Since the patient was a virgin, a rectal examination was carried out, which revealed a semisolid mass 8–9 cm in

This manuscript was presented as a poster at the 7th Uludag Obstetric and Gynecology Congress in Bursa, Turkey, 13–16 January 2004

K. Güzin · S. Kayataş Eser · A. Yiğit · E. Zemheri
Clinics of Obstetric and Gynecology, Goztepe Education and Research Hospital,
Istanbul, Turkey

S. Kayataş Eser (✉)
Kars'lý Ahmet cad. Ispirli Canip sok,
Palmiye apt. No:26/6, Içerenköy,
Kadıköy, Istanbul, Turkey
e-mail: semrakayatas@hotmail.com
Tel.: +90-216-5762082
Fax: +90-216-5654849

diameter, originating from the right vaginal wall and pushing the vagina to the left. The uterus is small and mobile and placed centrally. The adnexes were not palpable. Laboratory examination revealed that the hemoglobin level was 8.9 g/dl. Renal and liver functional tests, urinalysis, and chest X-ray were normal. Pelvic magnetic resonance imaging showed a huge mass measuring 10 cm in diameter located in the vagina and extending to the posterolateral vaginal wall and exerting pressure on the cervix. There was no sign of penetration of the mass to the cervix or the uterus (Figs. 1 and 2) and the uterus and salpinx were enlarged (hematometra and hydrosalpinx). Cystoscopy and intravenous pyelography showed no invasion of the tumor into the urinary tract.

An exploration of the tumor under general anesthesia in the lithotomy position was decided upon. The tumor was explored with a right Schuchardt perineal incision via the vagina; however, the complete removal of the tumor was impossible and therefore it was biopsied. The pathological examination of the material showed tubules and cysts lined with clear cells alternating with solid areas (Fig. 3) and papillary formations (Fig. 4). Tumor cells were composed of clear cells with giant clear cytoplasms and hobnail-shaped cells protruding into the glandular lumen. Mitotic figures were variable but scanty. There was no necrosis or hemorrhage. Finally, VCCA was diagnosed through the histopathological examination.

The stage of the tumor was considered to be IIA (according to the FIGO classification). Radiotherapy and then cisplatin-based chemotherapy was prescribed. The course of therapy lasted for 3 months, which were uneventful, and the patient is still alive 14 months after the completion of the treatment.

Discussion

Clear cell carcinomas are rarely observed. Ovary, cervix, and urinary tract are the most common locations for this

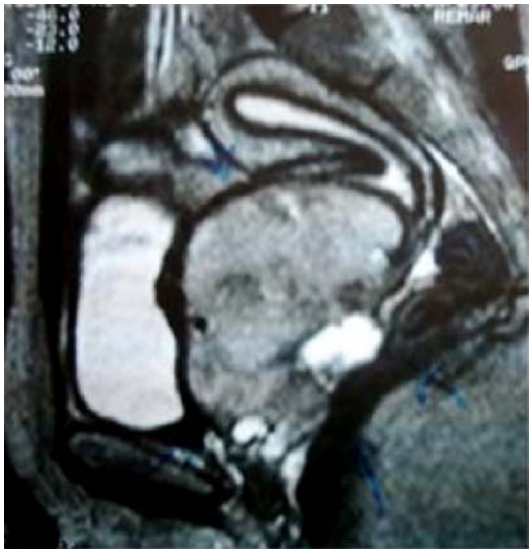

Fig. 1 Pelvic MRI, sagittal T2-weighted section

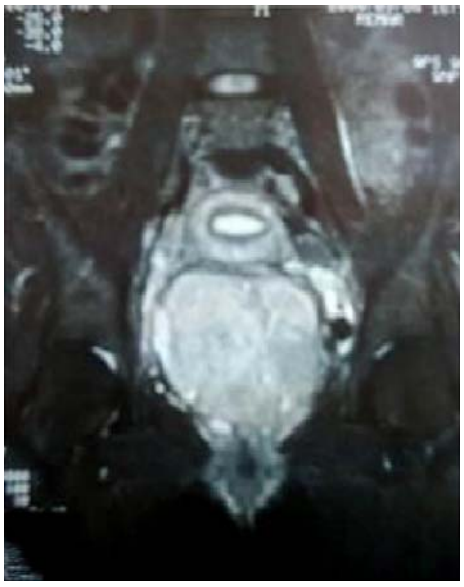

Fig. 2 Pelvic MRI, coronal short-time inversion recovery (STIR) section

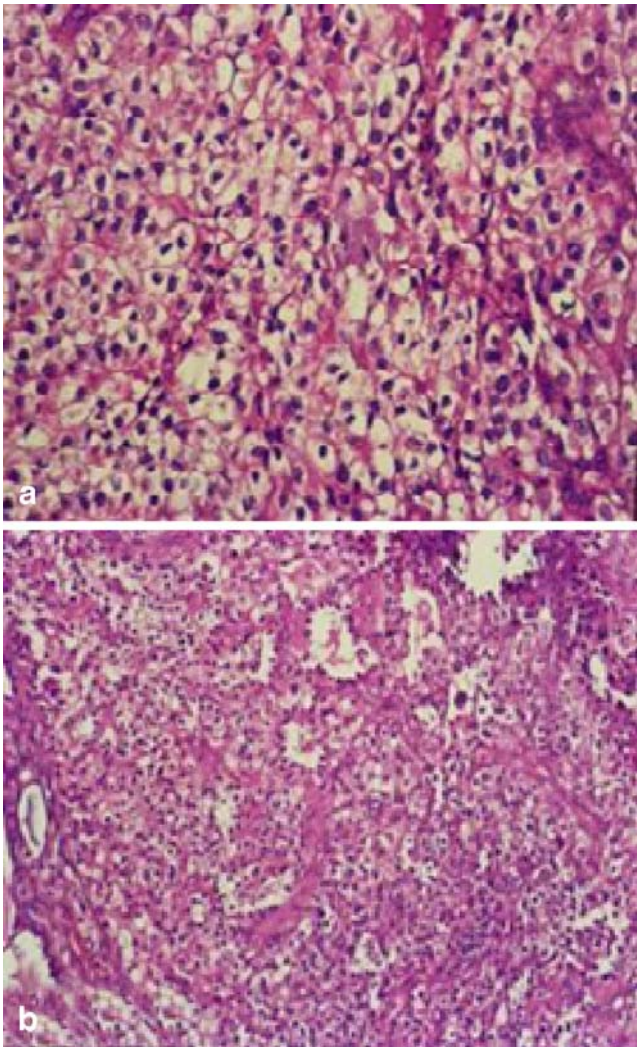

Fig. 3 Clear cell carcinoma. **a** Tubular pattern. **b** Solid pattern with prominent clear cells

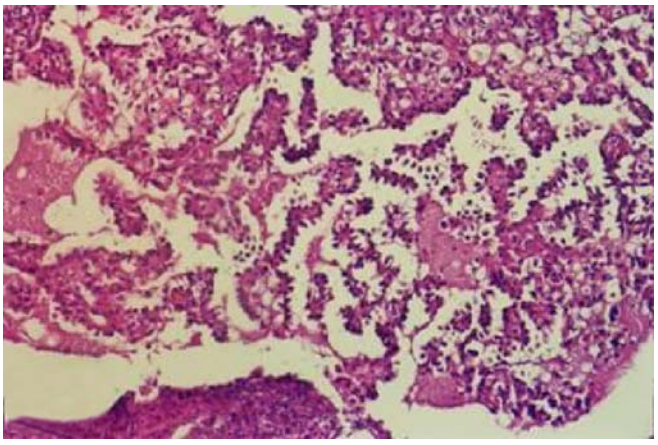

Fig. 4 Papillary pattern with prominent hobnail cells

malignancy. Hughes presented 46 patients with metastatic clear cell carcinoma, 27 of which originated from the kidney [4]. The size of clear cell carcinomas may vary from a few centimeters to large masses. Larger cancers are generally presented as polypoidal and nodular or sometimes as flat and ulcerated tumors. Dissolution of glycogen is the main cause of the clear appearance of the cytoplasm. The tubulocystic pattern is common, which is characterized by hobnail, flat or Mullerian-type cells. A bulbous nucleus is the main sign of the hobnail cells, and protrudes into the lumen beyond the apparent cytoplasmic limits of the cells. The papillary and tubular patterns, which are more common in endometrial carcinomas, may also be observed [5]. Since many characteristic patterns occur in clear cell carcinomas, it is generally easy to differentiate it microscopically from other malignancies. In our patient, the histopathological examination revealed a classical pattern of VCCA including tubular and solid structures with clear cells and a bulbous nucleus with hobnail cells (Figs. 3 and 4).

Vaginal clear cell adenocarcinomas are rare vaginal malignancies. Trimble et al. analyzed the incidence of VCCA in the United States from the data of the registry of the National Cancer Institute. Only 33 new cases of vaginal clear cell carcinoma and 11 recurrent cases were reported in 1990 and 23 new cases and 8 recurrent cases were reported in 1991 in the USA [6]. VCCA is more commonly observed on the anterior wall of the upper vagina. Senekjian et al. reported that the upper vagina was invaded in 42% of the cases [7]. In their series, only 10% of cancers filled the whole vagina. Even though the vagina was fully invaded with the tumor in our case, it was interesting that the patient had only minor complaints related to this problem.

Since VCCA is extremely rare in patients who did not have a history of in utero maternal DES use, only a few case reports are present in the medical literature. Goodman et al. presented vaginal adenosis and VCCA after 5-fluorouracyl treatment for a condyloma [8]. Satou and Takasu reported the relationship between the malformations of the uterus or vagina and VCCA [9]. Similarly, Tanaka et al. described a 17-year-old patient with VCCA who had a chromosomal abnormality (47XX+) and a bicornuate uterus [1]. In our patient, no malformation was observed. In addition, the patient denied any kind of 5-fluorouracyl treatment. Most importantly, no history of any maternal use of DES was defined during the pregnancy. Thus, we believe that it was a very unusual presentation of VCCA that was not associated with any of the conditions mentioned above.

Due to its rare occurrence, different treatment protocols for VCCA are recommended. Thus, the therapy should be individualized, mainly based on the factors such as the general condition of the patient, stage of the tumor, and the severity of the vaginal involvement. Although the role of surgery in the treatment of vaginal malignancies is limited, satisfactory results can be achieved in selected patients. Herbst et al. reported a large series consisting of 346 cases of VCCA. In his series stage I tumors were the most common presentation (51% of all cases), and extended resections were performed in these patients including radical hysterectomy, limited or complete vaginectomy, pelvic lymph node dissection, and vaginal replacement with a split-thickness skin graft. In most cases ovarian preservation could be achieved [10]. However, radiation therapy is the treatment of for stage II VCCA. Surgery may be reserved for small lesions at this stage [10]. More advanced tumors can be treated with radiation therapy. The radiation planes should include pelvic lymph nodes and parametrial tissues in this situation. Radical pelvic surgery such as pelvic exenteration may be effective for cancers that were unresponsive to radiation therapy and for those invading the lower two-thirds of the vagina [11]. Since the case presented here was of a huge mass, the stage of the tumor was considered as being IIA according to the criteria of the International Foundation of Gynecology and Obstetrics (FIGO). Thus, although the biopsy was obtained with a small perineal incision, no further surgery, including extended resection, is thought to be necessary for the completion of the treatment.

Chemotherapy, including alkylating agents, progestational compounds, 5-fluorouracil, actinomycin D, adriamycin, and vinca alkaloids, has been performed. The results of chemotherapy have been frustrating. Some responses have been observed in isolated cases, but no response to progestogen agents was seen.

Tanaka et al. concluded that the 5-year survival rates were 91%, 80%, 37%, and 0% for stages 1, 2, 3, and 4 tumors in VCCA respectively [1]. The patient in the case presented here is still alive after a follow-up of 12 months after completion of the therapy.

Conclusion

In conclusion, in this paper, a 23-year-old woman with VCCA, which was not related to in utero DES use, is presented. The diagnosis was performed with biopsy under general anesthesia. Because of the advanced disease, no further surgery was indicated, and radiation therapy followed by single agent chemotherapy was given to the patient. After a follow-up of 14 months, the patient is still alive.

References

1. Tanaka H, Tabata T, Yanase H, Nishiyama M, Yamawaki T (1994) Clear cell adenocarcinoma of the vagina in a young female, treated by combination chemotherapy (local and systemic chemotherapy), complicated with chromosomal abnormality. Gynecol Oncol 55:259–264
2. Nordqvist SRB, Fidler WJ, Woodruff JM, Lewis JL (1976) Clear cell adenocarcinoma of the cervix and vagina—a clinicopathologic study of 21 cases with and without a history of maternal investigation of estrogens. Cancer 37:858–871
3. Herbst AL, Scully RE (1970) Adenocarcinoma of vagina in adolescence: a report of 7 cases including 6 clear cell carcinomas (so-called mesonephromas). Cancer 25:745–748
4. Hughes JH, Jensen CS, Donelly AD, Cohen MB (1999) The role of fine needle aspiration cytology in evaluation of metastatic clear cell tumors. Cancer 87:380–389
5. Kurman RJ (2002) Blaustein's pathology of the female genital tract, 5th edn. Springer, Berlin New York Heidelberg, pp 185–187
6. Trimble EL, Rubinstein LV, Menck HR, Hankey BF, Kosary C, Giusti RM (1996) Vaginal clear cell adenocarcinoma in the United States. Gynecol Oncol 61:113–115
7. Senekjian EK, Frey KW, Anderson D, Herbest AL (1987) Local therapy in stage I clear cell adenocarcinoma of the vagina. Cancer 60:1319–1324
8. Goodman A, Zukerberg LR, Nikuri NN, Scully RE (1991) Vaginal adenosis and clear cell carcinoma after 5-fluorouracil treatment for condyloma. Cancer 68:1628–1632
9. Satou Y, Takasu K (1990) Clear cell adenocarcinoma in duplicated and imperforated vagina with didelphys uterus—a case report. J Kyoto Pref Univ Med 99:725–738
10. Herbst AL, Norusis MJ, Rosennow PJ, Welch WR, Scully RE (1979) An analysis of 346 cases of clear cell adenocarcinoma of the vagina and cervix with emphasis on recurrence and survival. Gynecol Oncol 7:111–115
11. Ayhan A (2003) Klinik Jinekolojik Onkoloji, 6th edn [in Turkish]. Güneþ Kitapevi, Ankara, pp 250–258