

# Annual Cervical Cancer Screening Revealed Early Stage Clear Cell Adenocarcinoma of the Uterine Cervix: A Case Report

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## Abstract

Clear cell adenocarcinoma of the uterine cervix (CCAC) is rare. We describe a case of CCAC, which was treated with complete resection without adjuvant therapy. The patient was a 42-year-old woman, who had no chief complaint. She had undergone annual cervical cancer screening, and no abnormalities had been detected in previous examinations. However, in a subsequent screening examination, cervical cytology produced negative results, but cervicovaginal erosion was observed at the uterine cervix. A detailed examination led to adenocarcinoma being suspected, and so conization was performed, resulting in a diagnosis of CCAC. A microscopic examination revealed atypical cells with clear-slightly basophilic cytoplasm, and immunohistochemical studies showed that they were positive for papsin A, p16, and AE1/3. Radical hysterectomy, pelvic lymph node dissection, and bilateral salpingo-oophorectomy were performed. Complete resection was achieved, and the postoperative diagnosis was CCAC, pT1b1N0M0, ly(-), v(-). The patient did not undergo adjuvant treatment. She is still alive and recurrence-free.

**Keywords:** Clear cell carcinoma; Cervical cancer; Screening

## Introduction

Clear cell adenocarcinoma of the cervix (CCAC) is a rare type of gynecological cancer, which accounts for about 0.48% of cervical carcinomas and 4-9% of cervical adenocarcinomas [1, 2]. Exposure to diethylstilbestrol (DES) *in utero* due to maternal

use of the drug is a risk factor for CCAC among young females [3]. CCAC often produces negative findings during routine vaginal cytology, so its early detection can be difficult. It has been reported that the prognosis of adenocarcinoma of the uterine cervix is worse than that of squamous cell carcinoma (SCC) of the uterine cervix, but there have not been any prospective studies about the postoperative adjuvant treatment of CCAC.

We experienced a case of CCAC, which was diagnosed after several years of normal cytological findings and was successfully treated via complete resection without adjuvant therapy. We report this case together with a brief review of the related literature.

## Case Report

The patient was a 42-year-old woman (gravida 0) without any coexisting disease. She had experienced sexual intercourse. She had no complaints related to gynecological disease. She had undergone cervical cancer screening every year at her own expense as part of health checkups conducted at a clinic, but no abnormalities had been found during previous examinations. However, during a subsequent cervical cancer screening examination, cervical cytology produced negative results for intraepithelial lesions or malignancy, but cervicovaginal erosion was observed at the uterine cervix. Therefore, she was referred to our hospital for consultation.

A vaginal examination showed cervicovaginal erosion, but no abnormalities were seen on a transvaginal ultrasonogram. However, atypical glandular cells were detected during cervical cytology, and so colposcopy was conducted, which revealed atypical blood vessels (Fig. 1a). A cervical biopsy of the region containing the atypical blood vessels resulted in a diagnosis of suspected adenocarcinoma. Endometrial cytology was negative for malignancy. The patient's serum levels of tumor markers were all within the normal range (carcinoembryonic antigen: 1.0 ng/mL, SCC antigen: 0.5 ng/mL, cancer antigen 125 (CA125): 18 U/mL, CA19-9: 9 U/mL). Pelvic magnetic resonance imaging (MRI) did not reveal a tumor (Fig. 1b), and no metastatic lesions were detected on thoracic or abdominal computed tomography. We performed conization for diagnostic purposes. A microscopic examination of the surgical specimen revealed atypical multiplying and infiltrating flattened and cuboidal cells

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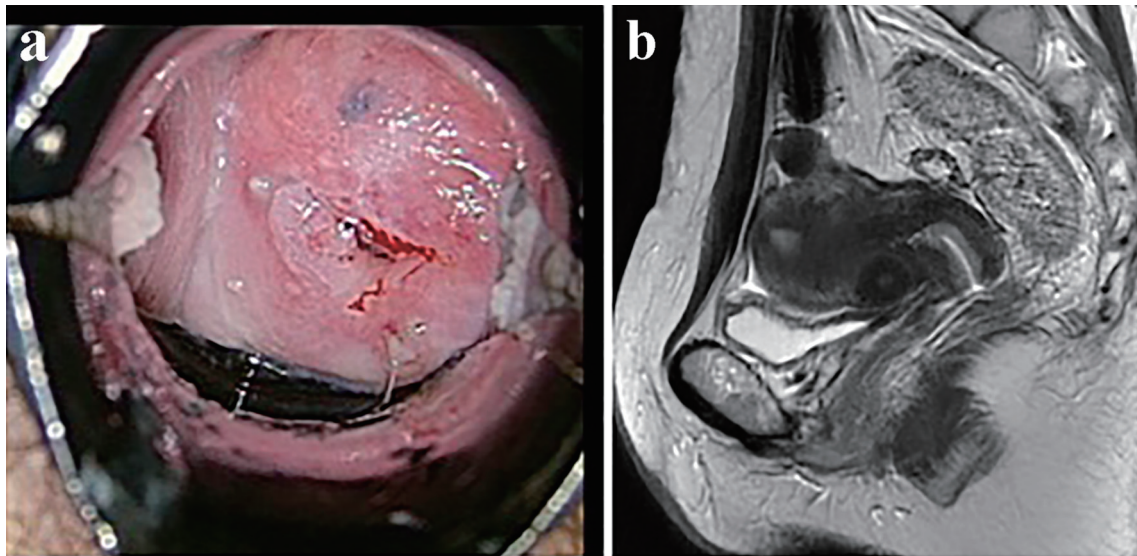
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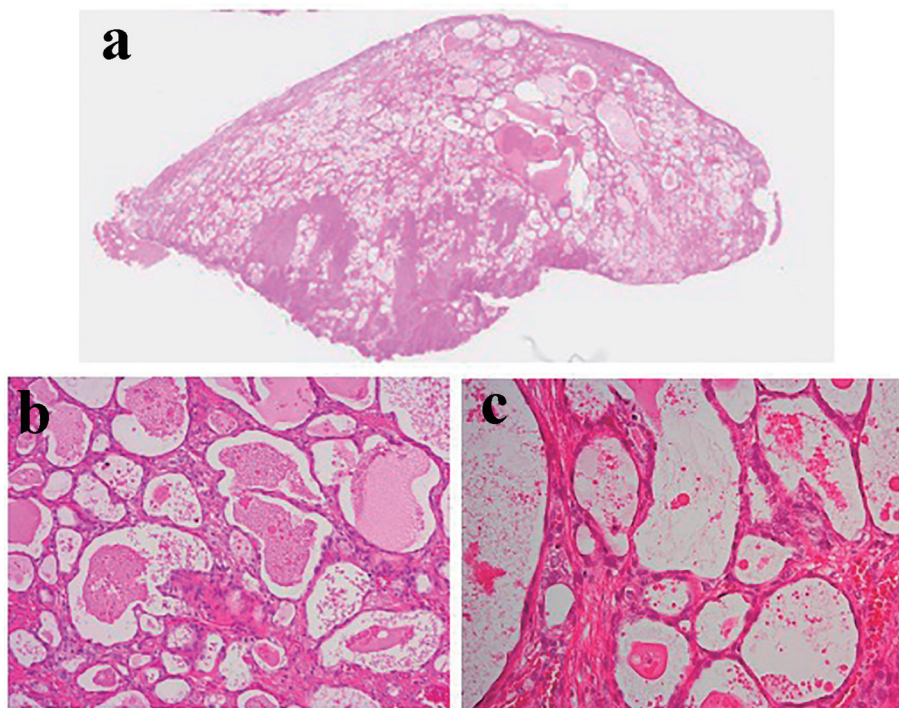
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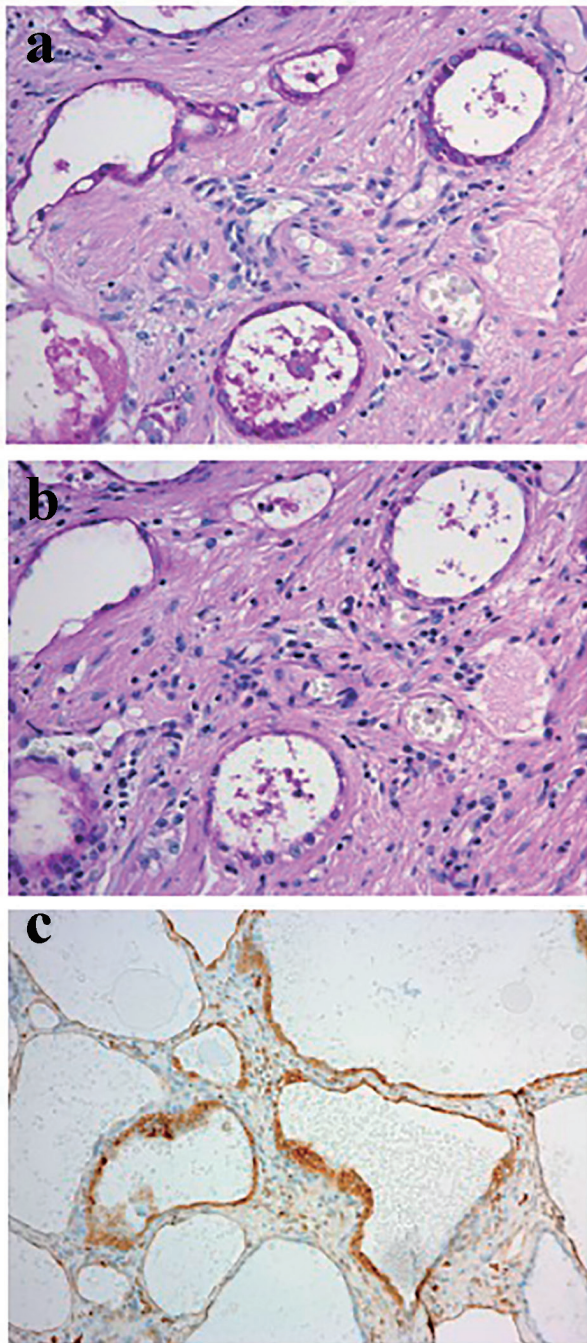
**Figure 1.** The results of imaging examinations. (a) Colposcopic findings. Atypical vessels were detected on colposcopy. (b) T2-weighted pelvic MRI images. No tumor was detected.

with clear-slightly basophilic cytoplasm, arranged in irregular tubular structures (Fig. 2a-c). Microscopically, the tumor cells had invaded the cervix to a depth of 9 mm. The cytoplasm of the tumor cells was positively stained with periodic acid-Schiff (PAS) stain, whereas it was not stained with diastase-digested-PAS (di-PAS) (Fig. 3a, b). Thus, the cytoplasm was shown to contain glycogen. Immunohistochemical studies demonstrat-

ed that the tumor cells were positive for napsin A, p16, and AE1/3 and negative for CD10, calretinin, the estrogen receptor, the progesterone receptor, and D2-40. The Ki-67 index of the tumor cells was almost 5% (Fig. 3c). Thus, the conization resulted in a pathological diagnosis of clear cell adenocarcinoma. The cut end of the pathological sample was positive. A histological examination of a tissue sample obtained via endometrial



**Figure 2.** The histological findings of the conization specimen. Atypical flattened and cuboidal cells filled with eosinophilic secretions had formed dilated and irregular lumens. The tumor cells had invaded the cervix to a depth of 9 mm. (a) Magnification:  $\times 1$ . (b) Magnification:  $\times 4$ . (c) Magnification:  $\times 20$ .



**Figure 3.** The results of PAS staining and the immunohistochemical staining of napsin A. (a) PAS staining. The tumor cells were positively stained with PAS (magnification:  $\times 20$ ). (b) The di-PAS staining (magnification:  $\times 20$ ). The tumor cells produced negative results during di-PAS staining, which indicated that they contained glycogen. (c) Immunohistochemical staining of napsin A (magnification:  $\times 10$ ). The tumor cells were positive for napsin A.

curettage did not show any evidence of malignancy.

The patient was preoperatively diagnosed with CCAC (International Federation of Gynecology and Obstetrics (FIGO) stage IB1 cervical cancer). Radical abdominal hysterectomy

combined with bilateral salpingo-oophorectomy and systemic pelvic lymphadenectomy were performed as primary treatments for the cervical cancer. The microscopic findings of the surgical specimen included invasion into the muscular layer, while atypical cuboidal cells with oval swollen nuclei had formed irregular tubular structures. The surgical stump was negative, and there was no metastasis in the ovaries or lymph nodes. There was a small amount of aberrant endometrial tissue in the connective tissue of the cervix.

The postoperative diagnosis was clear cell adenocarcinoma of the uterine cervix, pT1b1N0M0, ly(-), v(-). As we achieved a complete surgical resection, and there was no residual disease, the patient did not receive any other adjuvant therapy, chemotherapy, or radiotherapy after the operation. Currently, two years have passed without recurrence.

## Discussion

CCAC of the cervix is a rare type of tumor, accounting for about 0.48% of cervical carcinomas and 4-9% of cervical adenocarcinomas [1, 2]. The risk factors for and pathogenesis of CCAC remain unclear. However, it is apparent that exposure to DES *in utero* due to maternal use of the drug is a risk factor for CCAC. DES was used to prevent miscarriages and other complications of pregnancy in the United States between 1938 and 1971. In 1971, the use of DES in pregnant women was prohibited because it was found to carry an increased risk of clear cell adenocarcinoma in female offspring [3]. During the period when DES was used in pregnant women, cases of CCAC involving younger ages at onset were seen, but in the post-DES era, DES is not used in pregnant women, and the frequency of CCAC is higher in the postmenopausal period [4]. There have not been any DES-related cases of CCAC in Japan. Instead, in Japan CCAC normally arises in middle-aged and elderly women.

The typical symptoms of CCAC include prolonged genital bleeding, as is the case with other histological types of cervical cancer [2, 5]. However, in the early stages of CCAC, there may be no symptoms. Also, CCAC frequently produces negative results during cervical cytology, and CCAC often cannot be palpated [6, 7]. Cytological examinations have been found to be less useful for diagnosing cervical adenocarcinoma than SCC [5, 8]. In our case, although the first cytological examination produced a negative result, the detection of cervicovaginal erosion resulted in a diagnosis of CCAC.

The pathological features of CCAC include the proliferation of cells with clear cytoplasm arranged in papillate, tubular, and/or solid growth patterns, and the appearance of hobnail cells, whose nuclei project into the lumen. These features are similar to those of ovarian clear cell carcinoma. As is the case in ovarian clear cell carcinoma, napsin A has been found to be a marker of CCAC [9]. In our case, the tumor was positive for napsin A.

The pathogenesis of CCAC is unclear, but a previous case report suggested that, as is found in ovarian clear cell carcinoma, endometriosis might be involved in the pathogenesis of CCAC [10]. In the current case, aberrant endometrial tissue was observed in the uterine cervix.

The prognostic factors for CCAC include a tumor size of > 4 cm, the presence of lymph node metastasis, and advanced stage carcinoma [2, 5, 8]. In a study by Thomas et al involving 34 facilities [5], although it was suggested that early stage CCAC patients might be at slightly higher risk of nodal spread, clear cell histology by itself did not appear to denote a worse prognosis than SCC of the cervix in the absence of traditional risk factors. In addition, the stage I or IIA patients (n = 26) demonstrated superior 3-year overall survival (OS) compared with the advanced stage (n = 8) patients (91% vs. 22%,  $P < 0.001$ ). Furthermore, the presence of positive lymph nodes had adverse effects on 5-year progression-free survival and 5-year OS among stage I and IIA CCAC patients.

The established treatment for early stage CCAC is surgery [6, 11]. As for postoperative adjuvant treatments, chemotherapy or concurrent chemoradiotherapy are used at some facilities [12, 13], but there have not been any prospective studies about the use of such adjuvant treatments for CCAC. Thomas et al suggested that patients with low-risk early stage CCAC that are not treated with adjuvant therapy exhibit good prognoses, so they can be managed with radical surgery alone [5, 13, 14].

In the current case, the disease was diagnosed at an early stage (after the gynecologist that conducted her cervical cancer screening noticed slight erosion) because the patient underwent annual cervical cancer screening examinations at her own expense (although there is governmental support for biennial cervical cancer screening in Japan).

## Conclusion

We experienced a rare case of CCAC. The patient had exhibited normal cytological findings for several years, but slight erosion of the cervix was subsequently observed, which resulted in a diagnosis of CCAC.

## Conflict of Interest

The authors declare no conflict of interest.

## Abbreviations

CA: cancer antigen; CCAC: clear cell adenocarcinoma of the uterine cervix; DES: diethylstilbestrol; di-PAS: diastase-digested PAS; FIGO: International Federation of Gynecology and Obstetrics; MRI: magnetic resonance imaging; PAS: periodic acid-Schiff; SCC: squamous cell carcinoma

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