

# LBC Diagnosis of Clear Cell Adenocarcinoma of Vagina: An Interesting Case Report

**Running Title:** Liquid based cytology of vaginal clear cell Adenocarcinoma

**Dr. Preeti Agarwal<sup>1</sup>, Dr. Pooja Gupta<sup>2</sup>, Dr. Sameer Gupta<sup>3</sup>, Dr. Renu Singh<sup>4</sup>, Dr. Madhu Mati Goel<sup>5</sup>**

<sup>1</sup>MD, DNB Assistant Professor, Department of Pathology, KGMU, Lucknow 226003, UP, India

<sup>2</sup>MD, Assistant Professor, Department of Obstetrics and Gynaecology, KGMU, Lucknow 226003, UP, India

<sup>3</sup>MS, Mch, Assistant Professor, Department of Surgical Oncology, KGMU, Lucknow 226003, UP, India

<sup>4</sup>MD, Associate Professor, Department of Surgical Oncology, KGMU, Lucknow 226003, UP, India

<sup>5</sup>MD, MIAC, Professor, Department of Pathology, KGMU, Lucknow 226003, UP, India

**Abstract:** *Clear cell Adenocarcinoma (CCA) of vagina is a rare malignancy, reported at early ages in daughters of mothers exposed to diethylstilbestrol (DES) in utero. Histological features are well established, however cytological findings and moreover Liquid Based Cytology (LBC) morphology is not well characterized. We report a case of primary vaginal CCA first time picked up on LBC smear examination, confirmed by further histopathology and immunohistochemistry. In this case LBC smear from a 27-year-old lady (with no maternal history suggestive of DES exposure) displayed multiple three-dimensional groups of atypical cells with abundant foamy to vacuolated cytoplasm with focal acinar formations. Subsequent histologic features from the polypoidal lesion from vagina were consistent with CCA confirmed by immunohistochemistry. This case emphasizes the role of LBC in detection of the lesion and stresses on the unique features of CCA.*

**Keywords:** Clear cell Adenocarcinoma (CCA) of vagina; Cytology; Liquid Based Cytology

## 1. Introduction

Clear cell Adenocarcinoma of cervix and vagina is reported in post menopausal females; but it was discovered that the daughters of mothers exposed to diethylstilbestrol (DES) in utero were at increased risk for developing Clear Cell Adenocarcinoma (CCA) at early ages [1]. Pap smear screening is a principle method of screening and identification in gynecology. With advent of Liquid based cytology (LBC) a system of smear preparatory technique started in 1996 [2, 3] this has become preferable method in gynaecology cytology; however in many parts of developing nations gynaecologists are not accustomed for LBC sampling. We herewith report vaginal CCA diagnosed by LBC preparation in a young female with no maternal history suggestive of DES exposure and no live issues.

## 2. Case Report

Twenty seven year P1+1 presented with chief complaint of post coital bleeding for past three months. The patient had visited another gynaecologist nearby and carried a Pap smear report which was Negative for Intraepithelial Lesion or Malignancy (NILM). She had one previous spontaneous abortion at three months of gestational age followed by one preterm vaginal delivery of still birth one year back. Her previous menstrual history was normal. On examination her blood pressure was 100/ 70, pulse was 76 bpm and pallor was absent. Abdominal examination was unremarkable. Gynaecological examination revealed a slightly inflamed cervix with a small polyp of 1-2 cms adjacent to cervix on right lateral vaginal wall, abutting the right fornix (Figure

1a). Uterus was normal size and left fornix was clear. LBC sample was taken. The lady was kept on conservative management and was asked to report after two weeks.

LBC smear was prepared as per standard protocols (Surepath BD™). The smear was adequately cellular with dispersed population all superficial, intermediate and basal squamous cells (Figure 1b). No atypia was found in squamous cells. However three dimensional cell groups of abnormal cells were seen displaying high nucleo-cytoplasmic ratio, clumped chromatin and moderate micro vacuolated to feathery cytoplasm (Figure 1c, 1d). The cytoplasmic character was quite different from micro-vacuolation seen in endocervical cells. Abortive acinar formation was noted. Smear was reported as Adenocarcinoma (NOS) with possibility of clear cell carcinoma.

Immediately colposcopy was done, no suspicious are was found on cervix so biopsy was taken from vaginal polyp. Biopsy tissue was received as multiple gray white tissue pieces measuring 1x0.6x0.8 in aggregation. All the tissue pieces were processed and H&E stained sections showed an epithelial neoplasm disposed in acinar and papillary pattern lined by atypical cells with high nucleo-cytoplasmic ratio (Figure 2b), hyperchromatic nuclei and moderate clear cytoplasm (Figure 2c). Hob-nailing of tumor nuclei was also evident (Figure 2d). The case was provisionally diagnosed as Clear Cell Adenocarcinoma and further immunohistochemistry was performed to rule out metastasis form renal cell carcinoma, ovarian clear cell carcinoma and cervical carcinoma. IHC for WT1, CD10 (Figure 3a), CEA (Figure 3b) and CK20 (Figure 3c) were negative. There was

diffuse strong immunoeexpression for CK7 (Figure 3d). So histopathology with IHC was reported as Clear Cell Adenocarcinoma with suspicion of primary vagina.

Further investigation including chest X-ray, CT –whole abdomen and pelvis with cystoscopy were performed to rule out primary from other site and also access the spread of disease. All the investigations were unremarkable. Hence a diagnosis of primary vaginal CCA- FIGO stage I was made.

As the lady had no live issue she was further managed by wide local excision of vaginal tumor (Figure 2a). Six week follow up gynaecological examination was unremarkable.

### 3. Discussion and Conclusion

Primary vaginal CCA accounts for about 5–10% of all vaginal cancers [4]. Average age of presentation is post menopausal, but there is strong association of early development of cervical or vaginal CCA in young daughters of DES exposed mothers with absolute risk of 1 in 1000 [5]. In the present case, mother of the lady had no past history of in utero exposure to DES. This is the second case we have seen of vaginal CCA in a young female not associated with DES exposure [6]. Non DES exposure related CCA of vagina have poor prognosis and significantly worse outcomes than those seen in patients with other primary carcinomas of the vagina [7].

Clinical presentation of was also unusual as vaginal lesions usually present with abnormal vaginal discharge, pain and bleeding moreover in a latest series on cervical CCA by *Jiang et al* 55% (16/29) of patients presented with abnormal vaginal bleed and post coital bleed was seen only in six cases (20%) [8].

This malignancy is said to originate from vaginal epithelium with possible association with preliminary adenosis. However it can attain any size, our tumor was polypoidal with size of 1.2x1.5x0.6cms.

Most interesting and unique feature of the present case was that the patient came to us with a Conventional Pap cytology report of NILM. However LBC smear prepared at our side displayed malignant cells. This led to Colposcopy examination and detailed evaluation of the lady. Although cervix was hyperaemic but only suspicious lesion was the vaginal polyp (Figure 1a). Though LBC is gaining popularity in various centres of India but still gynaecologists prefer Conventional method of smear preparation at their centres. Hence present case stands out to be an excellent example of efficacy of LBC. Almost complete transfer of cellular material to fixative fluid, smaller screening area clear background leads to identification of even a single atypical cell cluster. Good morphological preservation leads to precise identification of cells.

Though a definite diagnosis of CCA was not made on cytology smear initially, even then the cytoplasmic character of tumor cells was of classical endocervical Adenocarcinoma. The present LBC smear displayed only two suspicious hyperchromatic crowded groups. The nuclei were almost round to oval. Kidney shaped small nuclei were

not seen so the possibility of endometrial cancer was also not considered morphologically. Cytoplasm of the cells as seen in (figure 2d) was abundant and feathery; bi-nucleation was also noted. These features made it unique. Retrospective examination after definite histopathology revealed further supportive features like round nuclei with prominent nucleoli and well defined cytoplasmic borders in some cells.

On histopathology morphological differential of CCA is Areias stella reaction, which does not form a localized lesion and has low Ki67 labelling index low immunoeexpression for p53. Immunohistochemistry for CD10 was done to rule out metastasis from Renal cell carcinoma. CEA immunoeexpression is seen in ovarian and cervical clear cell carcinoma [9]; however its expression may be seen in some cases; but in our case CEA immunoeexpression was not seen. Moreover there was no mass lesion in her abdominal and pelvic USG and CT. Thus definite diagnosis of primary vaginal CCA was made.

#### 3.1 Conclusion

Though well established but LBC is not the regular method of sampling the female genital tract in developing countries. This case stands out to be an excellent example where LBC proved to be superior to conventional smear in terms of detection of malignancy even of adjoining areas.

#### 4. Source(s) of support: None

#### 5. Presentation at a meeting: None

#### 6. Conflicting Interest: NIL References

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HCG; 1c and 1d: High power view shows cytoplasmic character of tumor cells (long arrow). Acinar formation is marked by smaller arrow in 1c.

Figure 2: 2a- Shows the gross specimen of wide local excision of tumor with solid grey white areas on cut surface (inset). 2b Low power view shows tumor disposed in acinar formations (H&E x 100). High power view shows tumor cells with clear cytoplasm 2c along with tumor cell hob nailing 2d.

Figure 3: Immunohistochemistry shows tumor cells are negative for CD10 (3a), CEA (3b) and CK20 (3c). There was diffuse strong immunorexpression for CK7 (3d)

### Figure Legends

Figure1: 1a- Per-speculum examination showed hyperaemic anterior cervical lip (long arrow) with a polypoidal lesion in right lateral vaginal wall (small arrow); 1b- Low power view of LBC smear displaying unremarkable squamous cells with

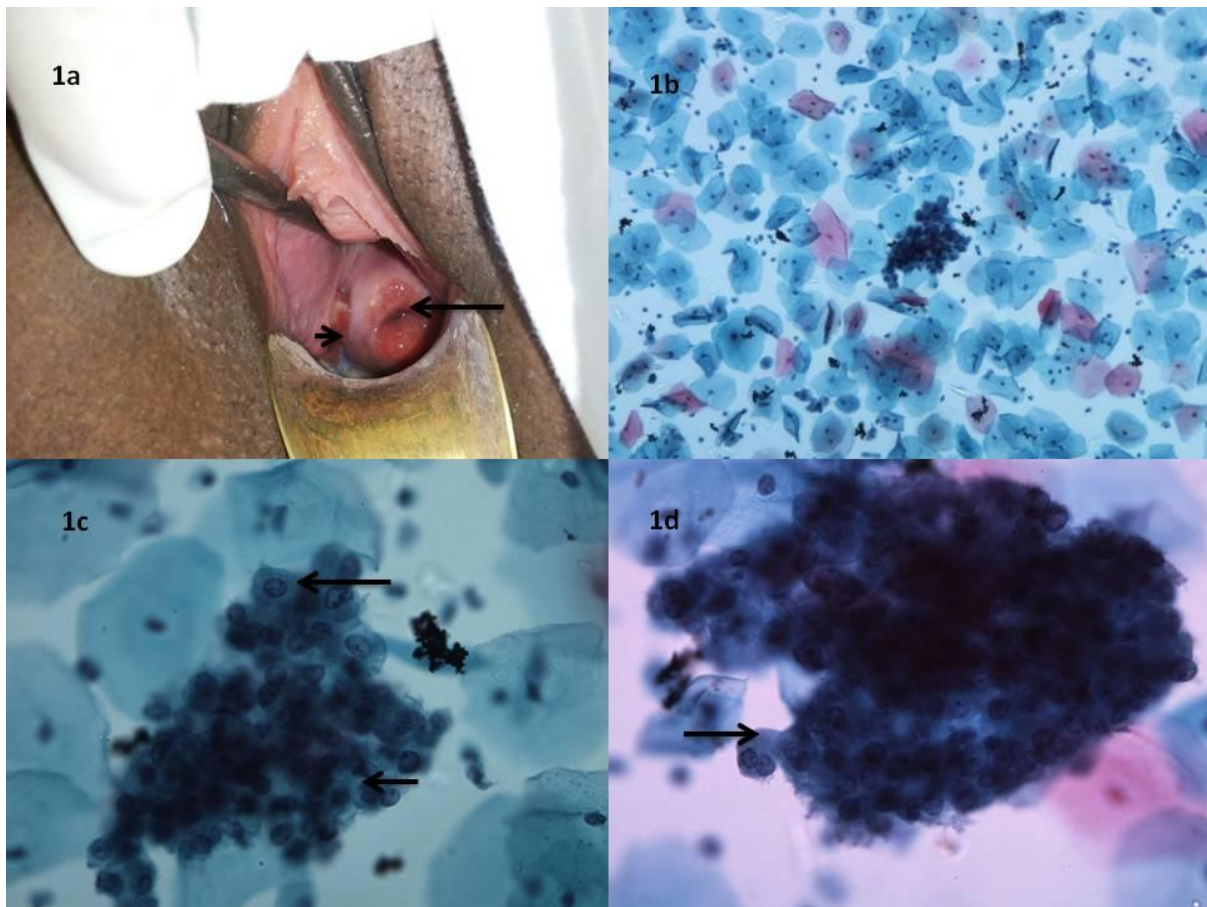


Figure 1

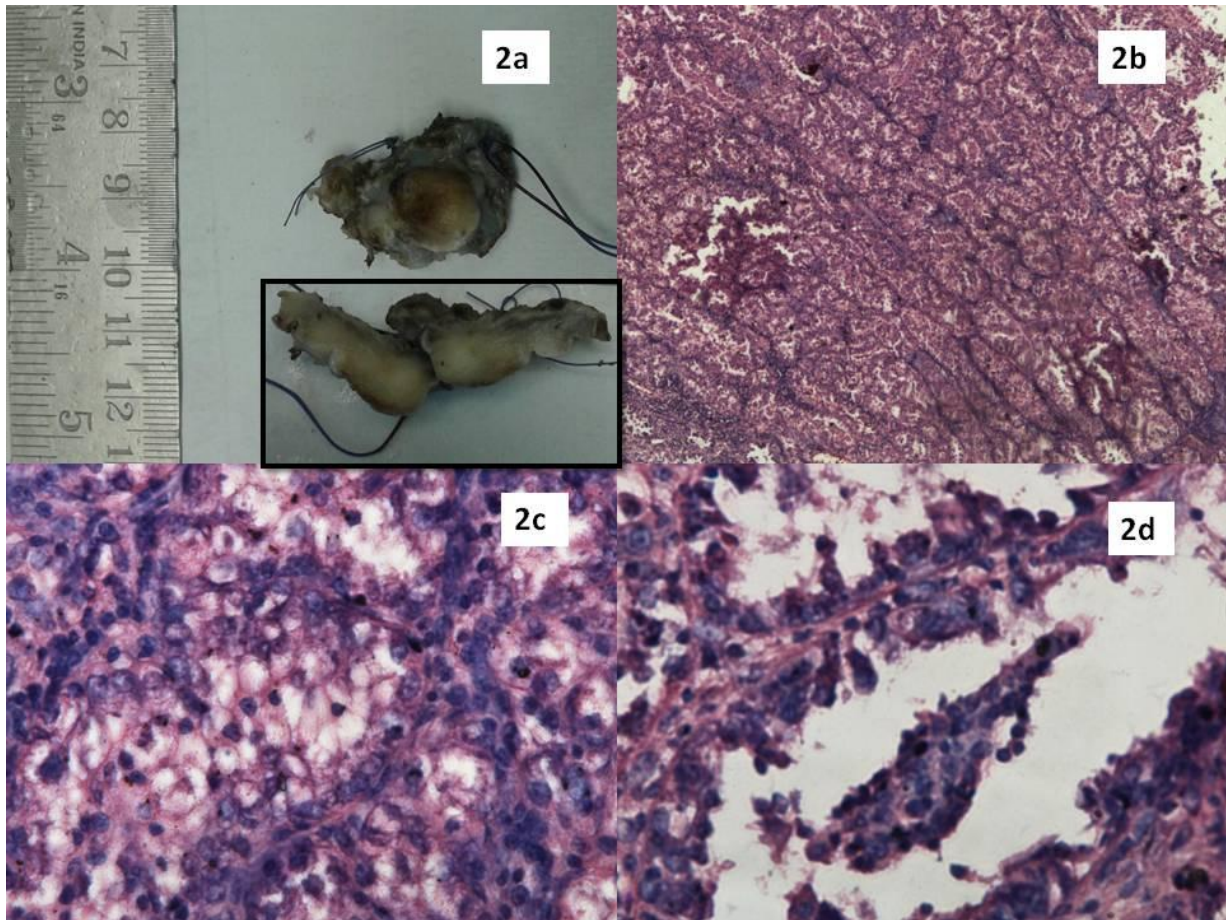


Figure 2

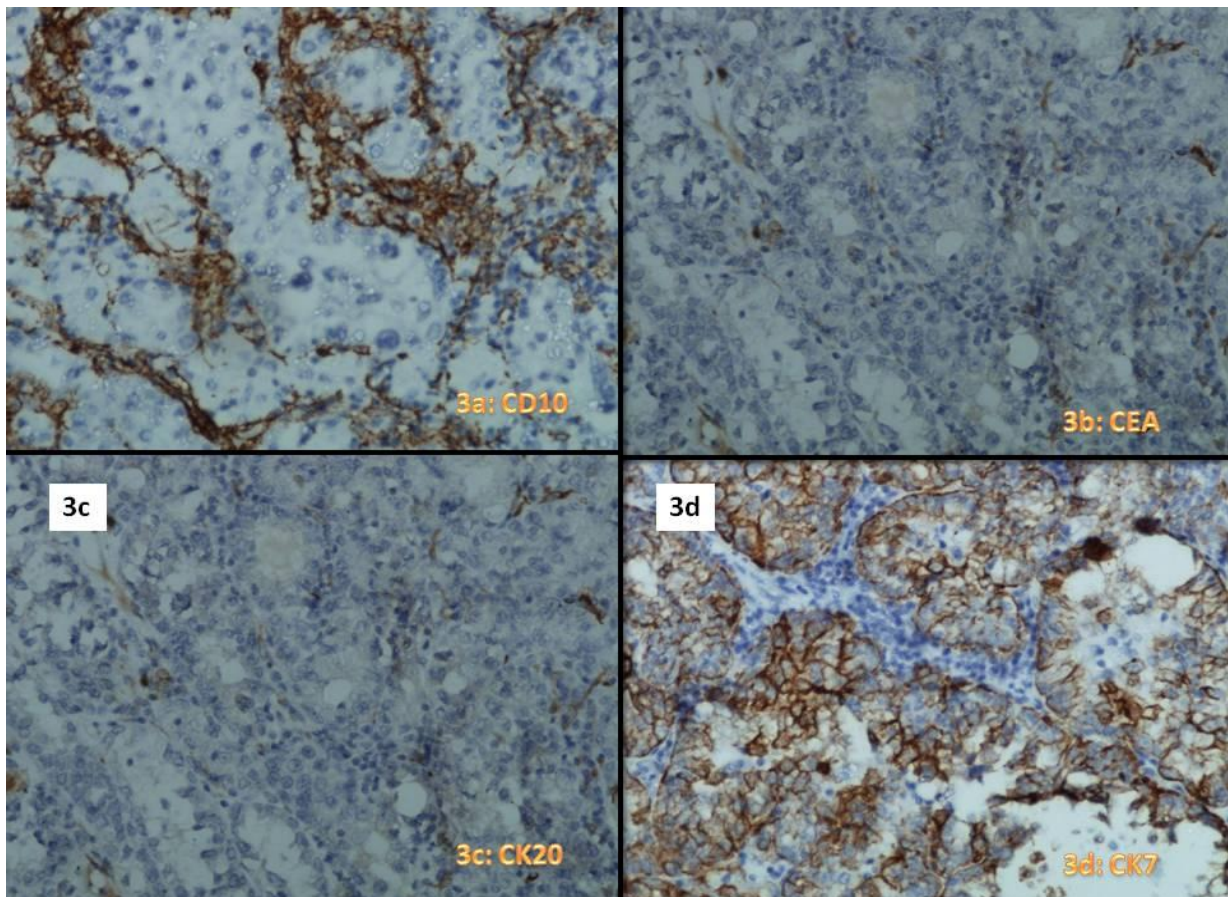


Figure 3