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# Tralucent and Pellucid-Clear Cell Adenocarcinoma Uterine Cervix

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## Abstract

Clear cell adenocarcinoma of uterine cervix is predominantly comprised of clear cells or hobnail cells articulating distinct architectural patterns as solid, tubulocystic or papillary. Tumour cell cytoplasm is clear, eosinophilic with intracytoplasmic hyaline globules and enhanced nuclear grade. A historic association with intrauterine diethylstilbestrol (DES) exposure is enunciated. Sporadic overexpression of p53 tumour suppressor gene may be observed. Neoplasm manifests with vaginal bleeding, postcoital bleeding or abnormal vaginal discharge. Cytological smears exhibit sheets, clusters or papillae of tumour cells permeated with delicate, vacuolated, glycogen rich or finely granular cytoplasm, enlarged, pale, spherical nuclei with prominent nucleoli or naked nuclei with tigroid background composed of granular, reticulated substance. Clear cell adenocarcinoma appears immune reactive to pan-cytokeratin as AE1 / AE3, CAM5.2, CK7, CK8, CK18, CK19, HNF1β, Napsin A, Ki67 or epithelial membrane antigen (EMA). Tumefaction requires segregation from neoplasms such as microglandular hyperplasia, Arias-Stella reaction, primary alveolar soft part sarcoma, mesonephric adenocarcinoma, metastatic clear cell renal cell carcinoma, endometrioid carcinoma, serous carcinoma, squamous cell carcinoma, urothelial carcinoma, adenosis, endometrioid adenocarcinoma with clear cell or secretory change, gastric subtype of endocervical adenocarcinoma or yolk sac tumours of uterine cervix. Neoplasm may be preliminarily subjected to radical hysterectomy with pelvic lymphadenectomy or fertility sparing radical trachelectomy.

**Keywords:** Diethystilbestrol; Clear Cells; Architectural Diversity

**Abbreviations:** EMA: Epithelial Membrane Antigen; ER: Oestrogen Receptor; PR: Progesterone Receptor SMA: Smooth Muscle Action; NSE: Neuron Specific Enolase; CEA: Carcinoembryonic Antigen; DES: Diethylstilbestrol; HPV: Human Papilloma Virus; WT: Wilms Tumour; PFS: Progression Free Survival; OS: Overall Survival.

## Introduction

Clear cell adenocarcinoma of uterine cervix is predominantly comprised of clear cells or hobnail cells which configure distinct architectural patterns as solid, tubulocystic or papillary. Neoplasm depicts a bimodal age distribution and emerges in women between 17 years to 37 years followed in frequency by women between 44 years to 88 years. Tumefaction exhibits multiple architectural patterns with occurrence of hobnail cells and hyalinised stroma. Tumour cell cytoplasm appears clear or eosinophilic and intracytoplasmic hyaline globules may be discerned. Nuclear grade is enhanced within focal areas whereas neoplasm depicts minimal mitotic count and mildly elevated Ki67 proliferative index. Neoplastic cells appear immune reactive to HNF1β, napsin A, oestrogen receptor (ER) or progesterone receptor (PR) and immune non-reactive to p16. Majority of neoplasms delineate unaltered expression of p53. Clear cell adenocarcinoma of uterine cervix represents an estimated 4% of adenocarcinomas of uterine cervix. A historic association with intrauterine diethylstilbestrol (DES)

exposure is enunciated. Conditions such as endometriosis of uterine cervix may contribute to neoplastic emergence in the absence of diethylstilbestrol (DES) exposure. Neoplasm is non-concordant with infection by high risk variants of human papilloma virus (HPV). Median age of diethylstilbestrol (DES) related clear cell adenocarcinoma appears at 18.9 years whereas median age of non-diethylstilbestrol (DES) associated clear cell adenocarcinoma of uterine cervix is 53 years [1,2].

Clear cell adenocarcinoma appears devoid of genetic mutations within KRAS or HRAS proto-oncogenes, Wilms tumour (WT1) suppressor gene or oestrogen receptor gene. Sporadic overexpression of p53 tumour suppressor gene may be observed upon immunohistochemistry, in the absence of discernible p53 genetic mutation. Genetic instability, as encountered with somatic mutation within microsatellite repeats may appear in diethylstilbestrol (DES) associated tumours and in ~50% of diethylstilbestrol (DES) unrelated tumours. Aforesaid genetic instability appears indicative of initiation of genomic instability which significantly contributes to genesis of diethylstilbestrol (DES) induced carcinogenesis [1,2].

Clear cell adenocarcinoma commonly manifests with vaginal bleeding, postcoital bleeding or abnormal vaginal discharge. Upon per vaginal examination, an endocervical lesion, barrel shaped cervix or normal uterine cervix may be exemplified. Exceptionally, a pelvic mass is enunciated [2,3]. Cytological smears stained with Papanicolaou stain exhibit sheets, clusters or papillae of tumour cells permeated with delicate, vacuolated, glycogen rich or finely granular cytoplasm and enlarged, pale, spherical nuclei with prominent nucleoli. Naked nuclei and tigroid background with characteristic granular, reticulated substance disseminated as 'foamy' or 'tiger-striped' material are observed [2,3]. Grossly, neoplasms devoid of diethylstilbestrol exposure preponderantly emerge within ectocervix or endocervix. Tumefaction concordant with diethylstilbestrol exposure commonly arises within the ectocervix. Median tumour magnitude appears at 3.3 centimetres. Neoplasm is associated with variable gross representation as everting, nodular, reddish lesions, miniature punctate ulcers, exophytic tumour mass or normal uterine cervix [3,4]. Upon microscopy, predominantly discerned configurations are denominated as

- Tubulocystic pattern is commonly observed and is comprised of tubules layered by singular layer of bland epithelial cells. Besides, prominent hyper chromatic nuclei may project into apical cytoplasm, thus manifesting a 'hobnail' cellular appearance.
- Papillary pattern is infrequently discerned and comprised of papillae incorporated with centric, hyaline fibrous tissue core and a layer of hobnail cells pervaded with hyper chromatic nuclei.
- Solid pattern is constituted of cellular nests of tumour cells permeated with clear to pale eosinophilic cytoplasm and cytoplasmic vacuoles of variable magnitude, thereby simulating signet ring cells, which are common in clear cell adenocarcinoma of uterine cervix. Nuclear atypia is significant. Focal gland formation is observed. Intracytoplasmic hyaline globules may be enunciated, especially within solid pattern (3,4). Morphologic spectrum of the neoplasm appears reminiscent of clear cell adenocarcinoma of endometrium or ovaries. Mitotic index is minimal at 0 to 5 mitosis per 10 high power fields. Tumour necrosis or psammoma bodies appear absent within neoplasms confined to the endocervix [3,4]. Ultra structural examination exhibits a contiguous lamina densa, several mitochondria, rough endoplasmic reticulum, abundant glycogen and blunt microvilli. Besides, vesicular aggregates within the nucleoplasm, perinuclear cytoplasm or between membranes of nuclear envelope may be observed [3,4]. FIGO staging of carcinoma cervix [3,4].

- stage I: carcinoma confined to cervix with absent extension to uterine corpus
- ~stage IA: carcinoma discernible upon microscopy with depth of invasion ≤5 millimetres
- ~stage IA1: depth of stromal invasion≤ 3 millimetres
- ~stage IA 2: depth of stromal invasion > 3 millimetres and ≤5 millimetres
- stage IB: stromal invasion > 5 millimetres with tumour confined to the cervix
- ~stage IB1: tumour > 5 millimetres in depth and ≤ 2 centimetres in greatest dimension
- ~stage 1B2: tumour > 5 millimetres in depth and > 2 centimetres and ≤4 centimetres in greatest dimension
- ~stage IB3: tumour > 5 millimetres in depth and > 4 centimetres in greatest dimension
- stage II: tumour extension beyond the uterus with absent invasion of pelvic wall or lower 1/3rd of vagina
- ~stage IIA: tumour confined to upper 2/3rd of vagina with absent extension to parametrium
- ~stage IIA1: tumour ≤ 4 centimetres in greatest dimension ~stage IIA2: tumour > 4 centimetres in greatest dimension
- ~stage IIB: tumour extension into parametrium with sparing of pelvic wall
- stage III: tumour extension into pelvic wall and/or incrimination of lower 1/3rd of vagina and/or occurrence of hydronephrosis or non-functioning kidney and/ or incrimination of pelvic or para-aortic lymph nodes
- ~stage IIIA: tumour extension to lower 1/3rd of vagina with absent extension to pelvic wall
- ~stage IIIB: tumour extension into pelvic wall and/or occurrence of hydronephrosis or non-functioning kidney



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- ~stage IIIC: tumour extension into pelvic or para-aortic lymph nodes irrespective of tumour extent or magnitude
- ~stage IIIC1: tumour metastasis into pelvic lymph nodes
- ~stage IIIC2: tumour metastasis into para-aortic lymph nodes
- stage IV: tumour extension beyond true pelvis or histological evidence of incrimination of urinary bladder or rectal mucosa
- ~stage IVA: tumour extension into adjacent pelvic organs
- ~stage IV B: tumour extension into distant organs

Clear cell adenocarcinoma of uterine cervix appears immune reactive to pan-cytokeratin as AE1 / AE3 or CAM5.2. Immune reactivity to CK7, CK8, CK18, CK19, HNF1β, Napsin A, Ki67 or epithelial membrane antigen (EMA) is observed. Exceptionally, tumour cells exhibit diffuse nuclear expression of p53 associated with TP53 genetic mutation. Neoplastic cells appear immune non reactive to CK20, high molecular weight CK 34βE12, oestrogen receptor (ER), progesterone receptor (PR), vimentin, smooth muscle actin (SMA), desmin, chromogranin, synaptophysin, CD56, neuron specific enolase (NSE) or carcinoembryonic antigen(CEA) [4,5].

Clear cell adenocarcinoma of uterine cervix requires segregation from neoplasms such as microglandular hyperplasia, Arias-Stella reaction, primary alveolar soft part sarcoma, mesonephric adenocarcinoma, metastatic clear cell renal cell carcinoma, endometrioid carcinoma, serous carcinoma, squamous cell carcinoma, urothelial carcinoma, adenosis, endometrioid adenocarcinoma with clear cell or secretory change, gastric subtype of endocervical adenocarcinoma or yolk sac tumours of uterine cervix [4,5].

Clear cell adenocarcinoma of uterine cervix may be preliminarily subjected to radical hysterectomy with pelvic lymphadenectomy or fertility sparing radical trachelectomy. Aforesaid manoeuvers are recommended for treating early stage disease or stage IA to stage IB1 disease demonstrating an absence of distant metastasis. Adoption of adjuvant therapy is associated with limited contribution to disease alleviation [4,5]. Direct therapeutic strategies for treating advanced stage disease upon initial representation or neoplastic reoccurrence may be achieved with surgical intervention, adjuvant chemotherapy or radiation therapy, although benefits remain undocumented. Prognostic outcomes are contingent to FIGO staging, especially concurrent with status of regional lymph nodes

- incrimination of parametrium
- ~> one third involvement of cervical stroma
- surgical margins pervaded with disseminated tumour cells
- tumour magnitude exceeding > 4 centimetres
- incrimination of lymphatic and vascular spaces

In contrast to clear cell carcinoma of the ovary delineating unfavourable prognostic outcomes, clear cell adenocarcinoma of uterine cervix demonstrates prognostic outcomes identical to squamous cell carcinoma incriminating uterine cervix [4,5]. Median duration to tumour reoccurrence is 12 months whereas stage I or stage II tumours may reappear within 8 months. Tumour reoccurrence is commonly enunciated within pelvis, para-aortic lymph nodes or diverse distant sites. However, neoplastic dissemination within the peritoneum is minimal [4,5].

Stage I and stage II tumours depict a 3 year overall survival of 91% whereas advanced stage neoplasms exemplify 3 year overall survival of 22%. 5 year progression free survival (PFS) emerges at 85% for stage I to stage IIA neoplasms and 42% for stage IIB to stage IV neoplasms. 5 year overall survival (OS) for stage I to stage IIA tumours appears at 90% and 63% for stage IIB to stage IV tumours [4,5].

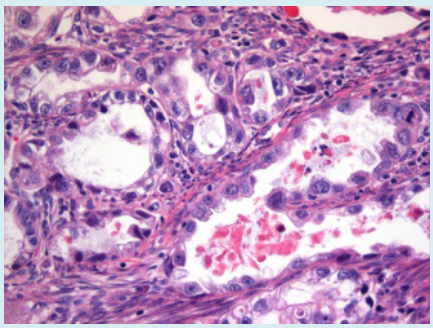

**Figure 1:** Clear cell adenocarcinoma demonstrating glandular articulations layered by hobnail cells and clear cells pervaded with clear cytoplasm, hyaline globules, nuclear atypia and elevated nucleocytoplasmic ratio. Few mitotic figures are seen. Intervening stroma is fibrotic [6].

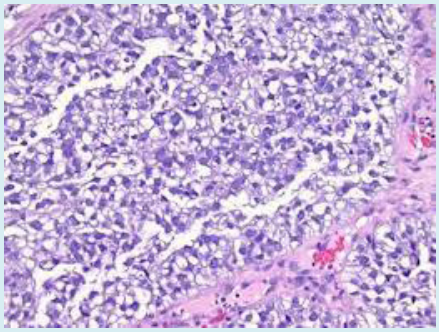

**Figure 2:** Clear cell adenocarcinoma delineating glandular structures lined by hobnail cells and clear cells permeated with clear cytoplasm, hyaline globules, nuclear atypia and enhanced nucleocytoplasmic ratio. Mitosis is minimal, Intervening stroma is scanty [7].



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6. Image 1 Courtesy: Sunny brook Hospital.

7. Image 2 Courtesy: Cureus.com.



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