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Short Communication

The Indigenous Transmutation-Adenocarcinoma *in situ* Cervix

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Adenocarcinoma *in situ* is designated as a cervical intraepithelial lesion constituted of glandular epithelium with a malignant countenance. Adenocarcinoma *in situ* manifests as a neoplastic glandular precursor of invasive endocervical adenocarcinoma. Untreated lesions display significant possible metamorphosis into invasive adenocarcinoma of uterine cervix. Employment of human papilloma virus (HPV) vaccine is associated with decimated disease incidence, especially in young females.

Contingent to diverse subtypes, lesion represents with variable histological features. Majority of lesions of adenocarcinoma *in situ* are associated with high risk variants of human papillomavirus (HPV), especially HPV16. Nevertheless, non reactive immunohistochemistry pertaining to p16 appears indicative of non human papilloma virus (HPV) subtype of adenocarcinoma *in situ*.

Adenocarcinoma *in situ* is additionally designated as high grade cervical glandular intraepithelial neoplasia (HG-CGIN). Besides, neoplasm may be denominated as endocervical adenocarcinoma *in situ* and atypical endocervical cells(neoplastic) or atypical endocervical cells not otherwise specified (NOS).

The uncommonly encountered adenocarcinoma *in situ* of uterine cervix configures ~1% of non invasive cervical lesions, in contrast to high grade squamous intraepithelial lesion (HSIL) configuring ~99% of lesions. An estimated 50% instances of adenocarcinoma *in situ* concur with high grade squamous intraepithelial lesion (HSIL).

Generally, adenocarcinoma *in situ* arises adjacent to or incriminates transformation zone of uterine cervix. Adenocarcinoma *in situ* arises from reserve cells demonstrating a potential for columnar differentiation. Alternatively, lesion may arise from columnar epithelium [1,2].

Mean age of disease emergence is 38 years wherein lesion may progress into invasive endocervical adenocarcinoma in up to 15 years.

Average age of representation of adenocarcinoma *in situ* appears at 39 years whereas average age of emergence of invasive adenocarcinoma appears at 52 years. In contrast to squamous cervical lesions, adenocarcinoma *in situ* may rapidly progress into invasive adenocarcinoma. Generally, high risk variants 16 and 18 of human papilloma virus (HPV) are associated with occurrence of adenocarcinoma *in situ* of uterine cervix [1,2].

Characteristically, lesions are asymptomatic. Commonly, abnormal cervical cytological features are associated with exfoliation of atypical endocervical glandular epithelial cells. Exceptionally, vaginal bleeding may ensue.

Cytoplasmic characteristics are variable and pertain to subtype of adenocarcinoma *in situ* and staining characteristics [2,3].

Cytological examination of adenocarcinoma *in situ* demonstrates smears of variable cellularity. Tumour cells are permeated with eosinophilic or cyanophilic cytoplasm and crowded, overlapping, polarized nuclei lying perpendicular to circumferential or luminal axis. Atypical cells may display peripheral feathering on account of

cellular polarization and existing wisps of cytoplasm. Tumour cell nuclei may bulge from centric cytoplasmic zone thereby delineating a 'snake egg' like appearance.

Goblet cells are encountered. Tumour cells are admixed with intact red blood cells.

Tumour cell nuclei appear elongated to ovoid, hyperchromatic and mildly pleomorphic with uniform nuclear chromatin. Enhanced nucleo- cytoplasmic ratio is observed. Cytological ascertainment of mitotic figures or apoptotic bodies may be challenging [2,3].

Neoplastic cells configure crowded sheets, strips and disrupted glandular articulations. Rosette-like cellular structures may ensue. Smears obtained with liquid based cytology exhibit a clean background admixed with sheets of miniature, atypical glandular epithelial cells.

Singular cells and cellular strips with 'fish tail' or 'bird tail' appearance are encountered. Subtle strips of cells or miniature cells devoid of cytoplasmic mucin may simulate endometrial cells.

Peripheral feathering may be challenging to discern as it manifests as 'peripheral knuckles'. Besides, it may be difficult to ascertain rosette-like structures [2,3].

Gastric subtype of adenocarcinoma *in situ* demonstrates smears with a clean background and disseminated singular cells or crowded clusters of neoplastic cells pervaded with pale, foamy or vacuolated cytoplasm and well defined cytoplasmic perimeter.

Grossly, adenocarcinoma *in situ* is an incidentally discovered lesion devoid of distinctive macroscopic appearance.

Upon colposcopy, erythematous mucosa may exceptionally be encountered. Besides, multifocal lesions may be enunciated [2,3].

Upon microscopy, normal superficial endocervical epithelium and epithelium confined to pre-existing endocervical glands appear substituted. However, normal endocervical architecture is preserved. Foci of abrupt transformation from normal endocervical epithelium into atypical epithelium within diverse glands and within individual glands are encountered. Frequently, skip lesions may be discerned.

Commonly, partial incrimination of glandular articulations or surface epithelium is observed. A desmoplastic stromal reaction is absent [3,4]. Encompassing stroma is infiltrated by minimal inflammatory infiltrate.

Additionally, histological features may variably emerge as

Human papilloma virus (HPV) related conventional subtype of adenocarcinoma *in situ* delineates

- Exceptionally encountered cribriform pattern or papillary intra-glandular structures
- Variable quantities of apical, eosinophilic to mucinous cytoplasm
- Enlarged, fusiform, hyperchromatic and pseudostratified nuclei pervaded with irregular, coarse nuclear chromatin and occasional, prominent nucleoli
- Frequent occurrence of mitotic figures appearing as apical or 'floating' mitosis
- Apoptotic bodies [3,4].

Superficial variant of HPV induced adenocarcinoma *in situ* demonstrates epithelial cells with minimal nuclear enlargement or nuclear stratification and few apoptotic bodies. Generally, tumefaction appears within younger females with mean age of disease emergence at 27 years.

- Intestinal subtype of adenocarcinoma *in situ* is commonly commingled with foci of conventional subtype and exemplifies frequently discerned goblet cells with appearance of Paneth cells and entero-endocrine cells. Few mitotic figures or apoptotic bodies may be encountered. Infrequently, pancreato-biliary subtype of epithelium is observed.
- Tubal subtype of adenocarcinoma *in situ* exhibits ciliated cuboidal or columnar epithelial cells permeated with apical, eosinophilic cytoplasm delineating variable cytological atypia. Mitotic figures may be discerned. Foci of tubal metaplasia require exclusion.
- Stratified mucin producing intraepithelial lesion (SMILE) demonstrates glandular articulations layered by variably pseudostratified epithelium. Epithelial cells appear as polyhedral to columnar cells pervaded with eosinophilic to mucinous cytoplasm [3,4].

Upon low power examination, lesion recapitulates high grade squamous intraepithelial lesion (HSIL). However, stratified neoplastic cells are pervaded with intracellular mucin configuring discrete vacuoles. Alternatively, cytoplasmic clearing within comprehensive cellular layers may be discerned. The lesion may appear singularly or in concordance with high grade squamous intraepithelial lesion (HSIL) or conventional adenocarcinoma *in situ*. Lesion may represent a variant of adenosquamous carcinoma *in situ* [3,4].

Human papilloma virus (HPV) independent adenocarcinoma *in situ* configures distinct variants as gastric subtype composed of columnar epithelial cells permeated with pale, foamy to mucinous cytoplasm with prominent cytoplasmic boundaries and basal nuclei

- Foci of intestinal differentiation are frequently enunciated
- Mitotic figures and apoptotic bodies are minimal, in contrast to HPV related adenocarcinoma *in situ* [3,4].

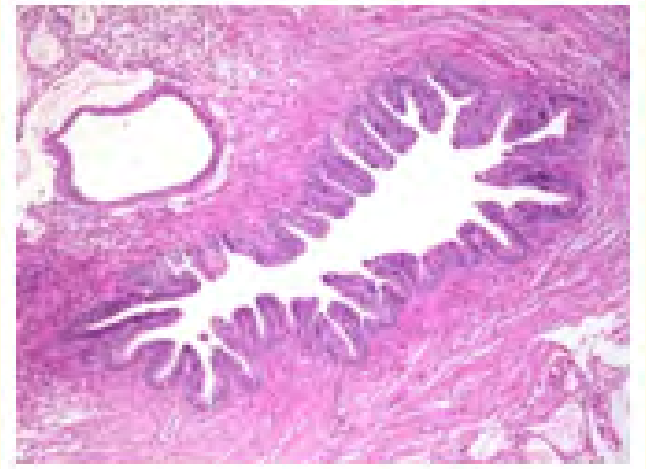

Figure 1: Adenocarcinoma *in situ* demonstrating glandular articulations lined by tall, columnar epithelial cells imbued with apical, eosinophilic cytoplasm and elongated, hyperchromatic nuclei with prominent nucleoli. Several mitotic figures are observed. Desmoplasia of surrounding stroma is minimal [6].

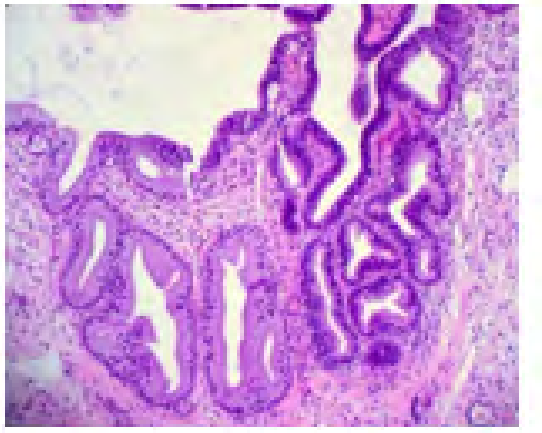

Figure 2: Adenocarcinoma *in situ* delineating glandular articulations lined by tall, columnar epithelial cells permeated with apical, eosinophilic cytoplasm and elongated, hyperchromatic nuclei with distinct nucleoli. Several mitotic figures are discerned. Circumscribing stroma is minimally desmoplastic [7].

Human papilloma virus (HPV) related adenocarcinoma *in situ* appears intensely and diffusely immune reactive to p16,ProExTMC, carcinoembryonic antigen(CEA), p63, CDX2, HIK1083 or mucicarmine.

Ki67 proliferation index is elevated and exceeds > 75% within conventional subtype of adenocarcinoma *in situ*.

Tumour cells appear immune non reactive to oestrogen receptor(ER), progesterone receptor(PR), vimentin, PAX2 or BCL2 [4,5].

On histological grounds, adenocarcinoma *in situ* of uterine cervix requires segregation from cervical endometriosis, benign reactive endocervical glands, mesonephric remnants, microglandular hyperplasia, tubal metaplasia, effects of radiation and cautery, invasive adenocarcinoma, high grade squamous intraepithelial lesion (HSIL) or Arias-Stella reaction of the cervix.

Cytological demarcation of adenocarcinoma *in situ* is required from conditions such as Arias-Stella reaction of the cervix, endometriosis, benign reactive endocervical glands, tubal metaplasia, radiation atypia, invasive adenocarcinoma or high grade squamous intraepithelial lesion (HSIL) [4,5].

Adenocarcinoma *in situ* of uterine cervix may be precisely discerned with cytological or histological examination of surgically obtained endocervical tissue samples.

Majority of lesions of adenocarcinoma *in situ* demonstrate infecting human papillomavirus (HPV) which may be appropriately discerned with polymerase chain reaction (PCR) or *in situ* hybridization. Nevertheless, gastric or intestinal subtypes appear devoid of infection with HPV [4,5].

Cogent cytological discernment may be followed by appropriate management of adenocarcinoma *in situ*. Specific monitoring with colposcopy and endocervical tissue sampling is comprehensively recommended within female subjects. Endometrial tissue sampling is recommended in women ≥ 35 years or subjects with possible emergence of concurrent endometrial neoplasia [4,5].

Subsequent to precise histological discernment of adenocarcinoma *in situ*, lesions may be subjected to cold knife conisation or total abdominal hysterectomy.

Majority of lesions can be optimally alleviated with conisation. Besides, close monitoring with colposcopy, assessment of cytological features and evaluation of human papilloma virus(HPV) infection, especially within endocervical lesions devoid of adenocarcinoma *in situ* is recommended [4,5].

Total abdominal hysterectomy may be beneficially adopted in women demonstrating malignant metamorphosis of lesion confined within endocervical tissue perimeter or women with undesired fertility.

Adenocarcinoma *in situ* is associated with superior prognostic outcomes. Following conisation, lesions confined to endocervical surgical margins may augment possible occurrence of residual or reoccurring adenocarcinoma *in situ* and subsequent emergence of invasive adenocarcinoma of uterine cervix. Exceptionally, lesions may incriminate endometrium or uterine adnexa with pagetoid pattern of disease dissemination [4,5].

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6. Image 1 Courtesy: Pathology outlines.

7. Image 2 Courtesy: Wikimedia commons.