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Inmixed and Bellicose-Adenosquamous Carcinoma-Uterine Cervix

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Abstract

Adenosquamous carcinoma of uterine cervix is a preponderantly high grade neoplasm configured of admixed glandular articulations and squamous epithelium wherein glassy cell carcinoma emerges as an exceptional, aggressive variant. Adenosquamous carcinoma is posited to arise from sub-columnar reserve cells confined to endocervical basal epithelium. Cytological smears depict papillary articulations admixed with bland columnar epithelial cells and high grade squamous intraepithelial lesion. The biphasic tumour is composed of well defined, malignant components of glandular articulations and poorly differentiated squamous epithelium. Glassy cell carcinoma demonstrates solid cell nests comprised of pleomorphic, polygonal tumour cells pervaded with glassy, eosinophilic cytoplasm, enlarged, eosinophilic nuclei, prominent nucleoli and distinct cytoplasmic membrane. Neoplastic cells appear enmeshed within an intense inflammatory cell infiltrate with significant eosinophils. Glassy cell carcinoma appears immune reactive to MUC1, MUC2, epithelial membrane antigen (EMA), CAM5.2 or p63 with focal immune reactivity to carcinoembryonic antigen (CEA). Adenosquamous carcinoma requires segregation from neoplasms such as adenocarcinoma with coexisting squamous intraepithelial lesion (SIL), adenoid basal carcinoma, cervical extension of endometrial adenocarcinoma, and squamous cell carcinoma with focal mucin droplets, large cell non keratinizing squamous cell carcinoma or lymphoepithelioma-like carcinoma. Tumefaction may be appropriately treated by radical abdominal hysterectomy followed by adjuvant chemotherapy and radiation therapy.

Keywords: Glandular; Squamous; Glassy

Abbreviations: EMA: Epithelial Membrane Antigen; SIL: Squamous Intraepithelial Lesion; HPV: Human Papilloma Virus; HMB: Human Melanoma Black; PAS: Periodic Acid Schiff's.

Introduction

Adenosquamous carcinoma of uterine cervix represents as a neoplasm configured of an admixture of glandular articulations and squamous epithelial components. Tumefaction configures an estimated ~10% of carcinomas afflicting uterine cervix. Glassy cell carcinoma of uterine cervix manifests as an exceptionally discerned, aggressive variant of adenosquamous carcinoma. The poorly differentiated neoplasm is accompanied by rapid tumour progression, an aggressive clinical course, antecedent tumour metastases and inferior prognostic outcomes.

Glassy cell carcinoma commonly incriminates young female subjects with peak age of disease incidence within

third decade to fourth decade. Mean age of disease emergence appears at 41 years. Additionally, neoplasm is associated with gestation and tumour cells pervaded with high risk variants of human papilloma virus 16 and 18 (HPV 16, 18) [1,2].

Glassy cell carcinoma, concurrent with high risk variant of human papilloma virus 18(HPV 18), is postulated to stimulate biphasic tumour cell differentiation into squamous epithelial cells and glandular articulations. Additionally, expression of cytokeratin recapitulates the expression encountered within reserve cells or immature squamous cells of uterine cervix.

Adenosquamous carcinoma of uterine cervix is posited to arise from sub-columnar reserve cells confined to basal epithelial cell layer of endocervix. Tumefaction is commonly encountered within gestation period. Generally, neoplasm is associated with high risk variant of human papilloma virus 18(HPV 18). Besides, absence of ARID1A protein expression is frequently observed [1,2].

Adenosquamous carcinoma exemplifies prognostic outcomes identical to diverse carcinomas incriminating uterine cervix, especially concurrent with tumour grade and tumour stage. Majority of neoplasms emerge as high grade tumour. Glassy cell carcinoma configures ~2% of carcinomas of uterine cervix. The neoplasm is associated with an aggressive clinical course and unfavourable prognostic outcomes, in contrast to conventional adenosquamous carcinoma or adenocarcinoma. Neoplasm is accompanied by peripheral blood eosinophilia [1,2].

Cytological examination enunciates an absence of appropriate tumour discernment upon Papanicolaou smears. Thin layer cytology can be employed to detect papillary subtype of adenosquamous carcinoma of uterine cervix. The extensively cellular lesion is comprised of multiple, miniature, papillary clusters of basaloid or columnar epithelial cells impregnated upon a distinct, fibrovascular core [2,3]. Papillary articulations appear admixed with disseminated population of bland columnar epithelial cells and cellular components of high grade squamous intraepithelial lesion. Additionally, a smattering of scattered epithelial cells pervaded with intracytoplasmic vacuoles configuring an adenocarcinoma may be delineated [2,3]. Glassy cell carcinoma is constituted of sheets or clusters of neoplastic cells incorporated with moderate to abundant, finely granular, ground glass-like cytoplasm, intracytoplasmic vacuoles, enlarged, spherical to elliptical, vesicular nuclei, finely dispersed or coarse, irregular nuclear chromatin with singular or multiple, prominent nucleoli and distinct cellular margins. Foci of bizarre cells or multinucleated tumour cells are discerned. Mitotic figures are frequently encountered. Neoplastic cellular constituents appear admixed with an inflammatory infiltrate comprised of neutrophils, plasma cells, lymphocytes and innumerable eosinophils. Foci of tumour necrosis, abortive production of keratin, squamous epithelial cells or glandular differentiation may be exemplified. Besides, focal clear cell differentiation may ensue [2,3]. Grossly, glassy cell carcinoma represents as a bulky tumefaction with exophytic pattern of evolution. Besides, a barrel shaped cervix may be enunciated.

Upon microscopy, a biphasic tumour configuration is exemplified. Neoplasm is composed of well defined, malignant components of glandular articulations and squamous epithelial cells. Aforesaid constituents appear distinct and may be appropriately identified with the absence of special stains. Generally, glandular component appears poorly differentiated and is comprised of endocervical glands layered with epithelial cells permeated with cytoplasmic mucin vacuoles or luminal aggregates of intracytoplasmic mucin. Additionally, squamous cellular component appears is poorly differentiated [3,4]. Besides, foci of endometrioid carcinoma with squamous epithelial cell differentiation may be exemplified. Glassy cell carcinoma demonstrates solid cellular nests comprised of prominently pleomorphic, polygonal tumour cells pervaded with glassy, eosinophilic cytoplasm, enlarged, eosinophilic nuclei, prominent nucleoli and a distinctive cellular membrane. Neoplastic cell clusters are encompassed within an intense inflammatory cell infiltrate along with significant, quantifiable eosinophils. Mitotic activity is preponderant. Tumefaction appears minimally invasive. 'Pure' glassy cell carcinoma appears devoid of morphological evidence of glandular epithelial or squamous cell differentiation [3,4]. Upon ultrastructural examination, features such as intracellular bridges, dyskeratosis or intracellular glycogen accumulation appear absent. Ultrastructural examination of neoplastic cells depicts features of glandular differentiation as mucous secretory vacuoles, configuration of 'true' lumen and scattered intracytoplasmic glycogen. Besides, tonofilaments and secretory products may be observed. Upon ultrastructural assessment, glassy cell carcinoma demonstrates features of glassy cells as denominated by cytoplasmic polyribosomes, innumerable tonofilaments and abundant, dilated rough endoplasmic reticulum. Features of adenosquamous differentiation emerge as well developed desmosomal complexes and microvilli. Intracellular lumens are occasionally observed. Majority of undifferentiated carcinomas incriminating uterine cervix display ultrastructural features of squamous epithelial or glandular differentiation [3,4].

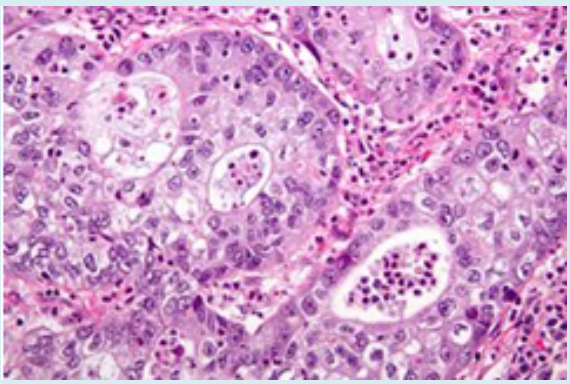

Figure 1: Adenosquamous carcinoma demonstrating glandular articulations layered with mucin secreting columnar epithelial cells imbued with eosinophilic cytoplasm, apical mucin and basal, hyperchromatic nuclei. Commingled are foci of squamous cell carcinoma with polygonal cells devoid of intercellular bridges [6].

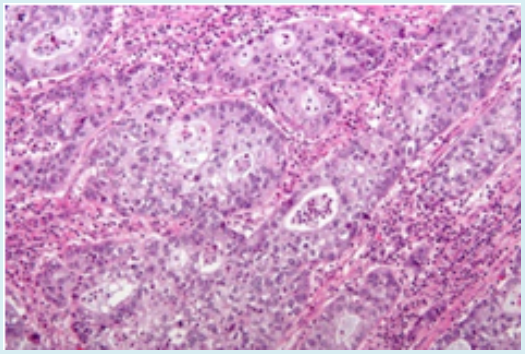

Figure 2: Adenosquamous carcinoma delineating glandular configurations layered by mucin secreting columnar epithelium incorporated with eosinophilic cytoplasm, apical mucin and basal, hyperchromatic nuclei admixed with foci of squamous cell carcinoma constituted of polygonal cells lacking intercellular bridges [7].

FIGO Staging of Carcinoma Cervix

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 [3,4].
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 nonfunctioning kidney.
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 IVB: Tumour extension into distant organs.

Squamous cellular component of adenosquamous carcinoma appears immune reactive to p63 or CK7. Glassy cell carcinoma appears immune reactive to MUC1, MUC2, epithelial membrane antigen (EMA), CAM5.2 or p63 with focal immune reactivity to carcinoembryonic antigen (CEA). Cell wall can be highlighted with Periodic acid Schiff's (PAS) stain. Tumour cells appear immune reactive to vimentin and demonstrate a focal reaction to mucin. Neoplastic cells configuring glassy cell carcinoma appear immune non reactive to human melanoma black 45(HMB45) antigen or oestrogen receptors(ER) [4,5]. Adenosquamous carcinoma of uterine cervix requires segregation from neoplasms such as adenocarcinoma with coexisting squamous intraepithelial lesion(SIL), adenoid basal carcinoma, cervical extension of endometrial adenocarcinoma, squamous cell carcinoma with focal mucin droplets, large cell non keratinizing squamous cell carcinoma or lymphoepithelioma-like carcinoma [4,5]. Adenosquamous carcinoma of uterine cervix may be appropriately treated by radical abdominal hysterectomy followed by adjuvant chemotherapy and radiation therapy. Adoption of cisplatin based chemoradiation delineates an overall survival identical to squamous cell carcinoma of uterine cervix. Nevertheless, prognostic outcomes are inferior [4,5]. Singular adoption of radiation therapy is accompanied by adverse prognostic outcomes. Glassy cell carcinoma of uterine cervix delineates unfavourable prognostic outcomes.

Factors contributing to inferior prognostic outcomes appear as
Angiolymphatic tumour invasion
Deep seated stromal invasion
Enlarged tumour magnitude

Besides, overexpression of HER2 appears concordant with aggressive biological behavior and adverse clinical outcomes [4,5].

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6. Image 1 Courtesy: Libre Pathology.

7. Image 2 Courtesy: Pathology Apps.