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The Cystic Procreant-Uterine Adenosarcoma

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Abstract

Uterine Adenosarcoma is an infrequent, malignant, biphasic, lobulated neoplasm with polyp-like lesions comprised of benign glandular epithelial component admixed with sarcoma component or heterologous elements as skeletal muscle, cartilage, foci of rhabdomyosarcoma or ovarian sex cord-like differentiation. Uterine Adenosarcoma commonly exhibits JAZF1-BCORL1 genetic rearrangement, EP300-BCORL1 or internal BCORL1 genomic rearrangement, inactivating BCORL1 chromosomal mutation and homozygous BCORL1 genomic deletion. A dense proliferation of uniform, spindle shaped cells configuring fascicles, a distinct herringbone pattern or focal areas of leaf-like architecture with intra-glandular polyploidy stromal projections is observed with superimposed benign endometrial glandular epithelium. Subjacent cellular stroma is composed of miniature spherical cells pervaded with moderate, pale cytoplasm and spherical to elliptical, vesicular nuclei with prominent nucleoli. Benign epithelial component is immune reactive to cytokeratin whereas neoplastic mesenchyme component is immune reactive to CD10, WT1, oestrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), smooth muscle actin (SMA), vimentin or desmin. Uterine Adenosarcoma requires segregation from conditions such as uterine adenofibroma, endometrial stromal sarcoma or uterine Carcinosarcoma. Next generation sequencing (NGS) exhibits amplification of E3 ubiquitin protein ligase (MDM2) and cyclin dependent kinase 4 (CDK4) along with alterations within phosphatidylinositol 4,5-bisphosphate 3 kinase (PIK3CA/AKT/PTEN) pathway. Uterine Adenosarcoma can be appropriately treated with surgical procedures as hysterectomy with bilateral salpingo-oophorectomy. Tumours of advanced grade, vascular invasion, occurrence of heterologous elements, differentiation into rhabdomyosarcomas, appearance of rhabdoid cells and tumour overgrowth within sarcoma component are accompanied by inferior prognostic outcomes.

Keywords: Epithelium; Stroma; Malignant

Abbreviations: PR: Progesterone Receptor; ER: Estrogen Receptor; AR: Androgen Receptor; SMA: Smooth Muscle Actin; NGS: Next Generation Sequencing; CDK4: Cyclin Dependent Kinase 4; CGP: Comprehensive Genomic Profiling.

Introduction

Uterine Adenosarcoma is an exceptionally discerned, malignant, biphasic, lobulated neoplasm configuring polyp-like lesions. Tumefaction is comprised of benign glandular epithelial component admixed with sarcoma component of mesenchymal origin. Uterine Adenosarcoma may exhibit overgrowth of sarcoma component, defined as a neoplasm comprised of >25% sarcomatous component. Overgrowth of pure sarcoma component within uterine Adenosarcoma comprises nearly 25% to 80% of tumour parenchyma and is associated with an aggressive clinical course. Homologous sarcomatous component is commonly incorporated within the neoplasm although heterologous elements as skeletal muscle, cartilage, foci of rhabdomyosarcoma or ovarian sex

cord-like differentiation may been countered. Malignant uterine Adenosarcoma exemplifying variable quantities of rhabdoid cells is commonly associated with an aggressive biological course.

Extra-uterine Adenosarcoma incriminates younger women and exhibits an aggressive clinical course, in contrast to uterine Adenosarcoma. Up to 50% of extra-uterine lesions manifest sarcomatous overgrowth with consequently inferior prognostic outcomes and enhanced proportionate tumour reoccurrence. Besides, tumefaction may demonstrate heterologous elements as foci of rhabdomyosarcoma or leiomyosarcoma. Uterine Adenosarcoma comprises of ~8% of uterine sarcomas. Generally, postmenopausal women are incriminated. Disease emergence is commonly encountered within 14 years to 89 years with median age of disease onset at 58 years [1,2]. Uterine Adenosarcoma frequently arises within the endometrium. Besides, sites such as cervix, fallopian tube, ovary or para-ovarian tissue may exemplify the neoplasm [1,2].

Factors such as obesity, diabetes, endometriosis, adenomyosis, history of pelvic irradiation, excessive levels of serum oestrogen or therapy with tamoxifen may contribute to emergence of uterine Adenosarcoma.

Uterine Adenosarcoma demonstrates an intense nuclear immune reactivity to BCOR with expression of JAZF1-BCORL1 fusion gene. Uterine Adenosarcoma commonly exhibits JAZF1-BCORL1 genetic rearrangement along with EP300-BCORL1 or internal BCORL1 genomic rearrangement, inactivating BCORL1 chromosomal mutation and homozygous BCORL1 genomic deletion, features which are associated with aggressive clinical behaviour. Nearly 50% of uterine sarcomas with BCORL1 genetic mutation delineate CDK4 genomic amplification or deficiency of CDKN2A [1,2]. Upon gross examination, resected neoplasm appears as solid, submucosal, well defined, greyish white and haemorrhagic with focal mucinous degeneration. Tumour magnitude is variable.

Grossly, the tan, friable tumour mass may arise from fundus and expand into the cervix [2,3]. Upon microscopy, tumour exemplifies a dense proliferation of uniform, spindle shaped cells configuring fascicles, a distinct herringbone pattern or focal areas of leaf-like architecture with intra-glandular polypoid projections of the stroma. The biphasic neoplasm exemplifies alternating sparsely cellular and densely cellular areas intermingled within an oedematous stroma [2,3].

Densely proliferating, uniform stromal spindle shaped cells congregate beneath the benign glandular epithelium and appear circumscribed by an oedematous stroma. Atypical stromal cells appear permeated with irregular, oval to elliptical nuclei [2,3].

Commonly, polypoid uterine tumefaction is superimposed with benign endometrial glandular epithelium. Subjacent cellular stroma is composed of miniature spherical cells pervaded with moderate, pale cytoplasm and spherical to elliptical, vesicular nuclei with prominent nucleoli. Focal, sub epithelial condensation of sarcomatous component may ensue. Mitotic activity is significant and figures of up to 40 mitosis per 10 high powerfields may be obtained. Tumour necrosis is frequently observed. Nuclear atypia is absent [2,3]. Uterine Adenosarcoma with rhabdoid cells emerges as a distinct subtype and predominantly exemplifies cytoskeletal inclusions composed of intermediate filaments appearing as an eccentric, eosinophilic cell body displacing the atypical nucleus. Stromal cellular component may display disseminated sheets of rhabdoid cells permeated with abundant cytoplasm and eosinophilic inclusion bodies with laminated architecture exemplifying eccentric displacement of nuclei [2,3]. SMARCA4 deficient uterine sarcoma devoid of the genetic mutation may demonstrate a focal leaf-like architecture with cellular infiltration into adjoining benign endometrial glands and an admixture of sheets of rhabdoid cells [3,4]. TNM staging of uterine Adenosarcoma as per American Joint Committee on Cancer 8th edition and International Federation of Gynaecology and Obstetrics (FIGO) [3,4].

Primary Tumour

- TX: primary tumour cannot be assessed
- T0: no evidence of primary tumour
- T1 (I): tumour confined to the uterus
- ~T1a (IA): tumour confined to the endometrium or endocervix
- ~T1b (IB): tumour infiltrates < 50% of myometrium
- ~T1c (IC): tumour infiltrates ≥ 50% of myometrium
- T2 (II): tumour extends beyond the uterus and appears confined within the pelvis ~T2a (IIA): tumour incriminates uterine adnexa
- ~T2b (IIB): tumour incriminates diverse pelvic tissues
- T3 (III): tumour infiltrates abdominal tissues or viscera
- ~T3a (IIIA): tumour infiltrates abdominal tissues within a singular site
- ~T3b (IIIB): tumour infiltrates abdominal tissues in > singular site
- T4 (IVA): tumour infiltrates urinary bladder or rectum

Regional Lymph Nodes

- NX: regional lymph nodes cannot be assessed
- N0: regional lymph node metastasis absent
- N0(i+): isolated tumour cells within regional lymph

node(s) ≤ 0.2 millimetre diameter N1 (IIIC): regional lymph node metastasis present

Distant Metastasis

- M0: distant metastasis absent
- M1 (IVB): distant metastasis present with the exclusion of tumour extension into uterine adnexa, pelvic soft tissues or abdominal soft tissues International Federation of Gynaecology and Obstetrics(FIGO) staging and grouping of uterine Adenosarcoma [3,4].
- stage I: T1, N0, M0
- stage IA: T1a, N0,M0
- stage IB: T1b, N0,M0
- stage IC: T1c, N0,M0
- stage II: T2, N0, M0
- stage IIIA: T3a, N0, M0
- stage IIIB: T3b, N0, M0
- stage IIIC: T1, T2, or T3, N1, M0
- stage IVA: T4, any N, M0
- stage IVB: any T, any N, M1

Benign epithelial component of uterine Adenosarcoma appears immune reactive to cytokeratin. Neoplastic mesenchymal component, reminiscent of endometrial stromal sarcoma, appears immune reactive to CD10, WT1, oestrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), smooth muscle actin (SMA), vimentin or desmin. Peri-glandular zones appear intensely immune reactive to aforesaid markers. Proliferating, stromal spindle shaped tumour cells appear immune reactive to CD99 and may express nuclear integrase interactor-1 (INI-1). Weak immune reactivity to cyclinD1 may ensue. Foci of rhabdomyosarcomatous differentiation appear immune reactive to MyoD1 or myogenin. Foci of sarcoma overgrowth appear immune reactive to p53 [4,5]. Benign epithelial component of uterine Adenosarcoma appears immune non-reactive to oestrogen receptor (ER) or progesterone receptor (PR). Tumour cells appear immune non-reactive to cytokeratin AE1/AE3, CAM5.2, epithelial membrane antigen(EMA), CDK4, MDM2, DOG1, CD31, CD34, smooth muscle actin (SMA), desmin, myogenin, Myo D1, S100 protein, synaptophysin, STAT6 or MUC4. Rhabdoid variant of uterine Adenosarcoma is consistently immune non-reactive to nuclear chromatin remodelling factor (SRF5/INI 1). Foci of sarcoma overgrowth appear immune non-reactive to CD 10, oestrogen receptor (ER) or progesterone receptor (PR). Ki67 proliferation index appears at up to 30% [4,5]. Uterine Adenosarcoma requires segregation from conditions such as uterine adenofibroma, endometrial stromal sarcoma or uterine Carcinosarcoma [4,5].

Next generation sequencing (NGS) exhibits amplification of E3 ubiquitin protein ligase (MDM2) and cyclin dependent kinase 4 (CDK4) along with alterations within phosphatidylinositol 4,5-bisphosphate 3 kinase (PIK3CA/AKT/PTEN) pathway. Generally, TP53 genetic mutations are uncommon within uterine Adenosarcoma although neoplasms with overgrowth of sarcoma component may enunciate the mutation. Comprehensive genomic profiling (CGP) can be adopted for evaluating neoplasms of advanced stage or exceptionally discerned tumours as uterine Adenosarcoma with distant metastasis [4,5]. Uterine Adenosarcoma can be appropriately treated with surgical procedures as hysterectomy with bilateral salpingo-oophorectomy. Adjuvant radiation therapy, chemotherapy or hormonal therapy necessitates additional evaluation as employable, cogent therapeutic strategy [4,5]. Extensive tumour infiltration within the myometrium or cervical stroma may occur. Regional lymph node metastasis is rarely encountered. Proportionate tumour reoccurrence is minimal [4,5]. Uterine Adenosarcoma devoid of overgrowth of sarcoma component exhibits 2 year progression free and overall survival at ~100%.

Prognostic outcomes of uterine Adenosarcoma are contingent to factors such as age of incriminated subject, tumour magnitude, occurrence of cellular atypia, sarcomatous overgrowth, myometrial invasion, mitotic activity, tumour necrosis, status of surgical resection, FIGO tumour stage and configuration of heterologous elements as rhabdomyosarcoma within the neoplasm [4,5].

Factors contributing to inferior prognostic outcomes emerge as tumours of advanced grade, vascular invasion, occurrence of heterologous elements, differentiation into rhabdomyosarcoma, appearance of rhabdoid cells and tumour overgrowth within sarcoma component [4,5].

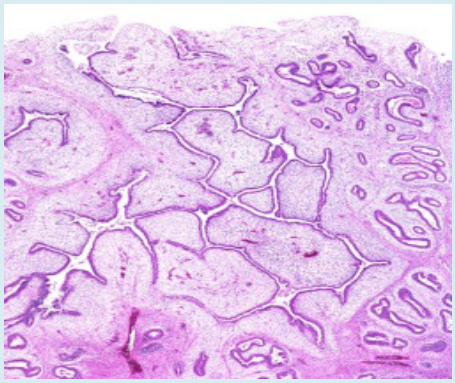

Figure 1: Uterine Adenosarcoma demonstrating fascicles of spherical to elliptical tumour cells imbued with moderate, pale cytoplasm, vesicular nuclei and prominent nucleoli surrounded by an oedematous stroma. The sarcoma component is superimposed with benign glandular epithelium. Mitotic figures are observed [6].

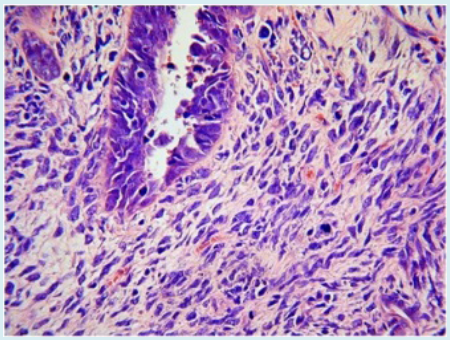

Figure 2: Uterine Adenosarcoma delineating sheets of spherical to ovoid tumour cells incorporated with moderate, pale cytoplasm, vesicular nuclei and prominent nucleoli encompassed within an oedematous stroma. Neoplastic sarcoma cells appear superimposed by benign glandular epithelium. Few mitotic figures may be discerned [7].

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6. Image 1 Courtesy: NCBI.

7. Image 2 Courtesy: Wikipedia.