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Interceding and Metamorphosed- Endometrial Stromal Sarcoma

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Editorial

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Abbreviations: ITD: Internal Tandem Duplication; FIGO: International Federation Of Gynaecology And Obstetrics; PR: Progesterone Receptor; ER: Estrogen Receptor; SMA: Smooth Muscle Actin; EMA: Epithelial Membrane Antigen; MRI: Magnetic Resonance Imaging.

Editorial

Endometrial stromal sarcoma manifests as an infrequently discerned, malignant, high grade uterine mesenchymal neoplasm originating from endometrial stroma and composed of spherical or spindle shaped cells. Additionally designated as undifferentiated endometrial sarcoma, uniform subtype or high grade endometrial stromal sarcoma with YWHAE-FAM22 genetic fusion; the cellular tumefaction may occasionally be associated with a low grade component. Contingent to specific molecular alterations, tumour cells appear variably immune reactive to BCOR, cyclin D1 or CD10. Smooth muscle markers and hormone receptors may be focally immune reactive or non-reactive. Endometrial stromal sarcoma manifests subtypes as ~sarcoma demonstrating YWHAE-NUTM2A/NUTM2B genetic fusion ~BCOR rearranged endometrial stromal sarcoma ~endometrial stromal sarcoma exemplifying BCOR internal tandem duplication (ITD). Exceptionally encountered, endometrial stromal sarcoma manifests with wide age range of disease emergence. YWHAE-NUTM2A / NUTM2B genetic fusion may appear within third decade to seventh decade with mean age of disease emergence at 50 years. BCOR rearranged endometrial stromal sarcoma emerges within third decade to seventh decade with median age of disease occurrence at 54 years. Endometrial stromal sarcoma with BCOR ITD emerges within second decade to sixth decade with median age of disease occurrence at 42 years [1,2]. Commonly, endometrial stromal sarcoma undergoes high grade metamorphosis within fifth decade to eighth decade with median age of disease occurrence at 54 years. Endometrial stromal sarcoma commonly incriminates uterine corpus. The vagina is infrequently implicated [1,2]. Of obscure aetiology, endometrial stromal sarcoma exhibits numerous genetic alterations denominated as YWHAE-NUTM2A/NUTM2B genetic fusion, BCOR genetic fusion or BCOR ITD.

Besides, low grade endometrial stromal sarcoma may delineate metamorphosis into high grade endometrial stromal sarcoma. Endometrial stromal sarcoma exhibiting YWHAE-NUTM2A /NUTM2B genetic fusion enunciates chromosomal translocation t (10;17)(q22;p13). Genesis of oncoprotein 14-3-3 may ensue. BCOR rearranged endometrial stromal sarcoma demonstrates ZC3H7B as a frequently associated genetic partner along with chromosomal translocation t(X;22) (p11;q13) [2,3]. Infrequently, genetic partners as L3MBTL2, EP300, NUTM2G, RALGPS1, MAP7D2, RGAG1, ING3, NUGGC, KMT2D or CREBBP may be encountered. Tumefaction exhibits amplification of MDM2, FRS2 or CDK4. Besides, homozygous deletion within CDKN2A or CDKN2B gene may be discerned. Endometrial stromal sarcoma with BCOR ITD exemplifies internal tandem duplications of variable lengths involving exon 15. Homozygous deletion within CDKN2A/ CDKN2B gene may ensue. Besides, MDM2 or CDK4 genetic amplification is absent. Low grade endometrial stromal sarcoma depicting high grade metamorphosis commonly displays JAZF1-SUZ12 genetic fusion. Exceptionally, JAZF1-PHF1, EPC1-PHF1 or BRD8-PHF1 genetic fusions may be encountered. Generally, YWHAE and BCOR genomic alterations appear absent. Endometrial stromal sarcoma delineates cogent clinical symptoms as pelvic pain, pelvic tumefaction or anomalous uterine haemorrhage [2,3]. Upon gross examination, endometrial stromal sarcoma depicting

YWHAE-NUTM2A/NUTM2B genetic fusion appears as an apparent tumefaction associated with infiltration and permeation into circumscribing myometrium. Tumour magnitude varies from one centimetre to 12 centimetres. BCOR rearranged endometrial stromal sarcoma configures a polypoid neoplasm with endometrial extension. The soft, fleshy tumour with rubbery consistency appears tan, pink or yellow. Tumour diameter varies from 1.5 centimetres to12 centimetres with median diameter of 9.7 centimetres. Myometrial tissue is exceptionally involved. Endometrial stromal sarcoma with BCOR ITD appears as a polypoid lesion associated with intramural tumour nodules. Tumour dimension varies from 2.5 centimetres to 14.5 centimetres with median diameter of 7 centimetres [2,3]. Upon frozen section, high grade endometrial stromal sarcoma is constituted of spindle shaped and epithelioid cells. Appropriate characterization may be obtained with permanent histological sections and ancillary studies as precise immunohistochemistry and molecular evaluation [2,3]. Upon microscopy, endometrial stromal sarcoma with YWHAE-NUTM2A/NUTM2B genetic fusion exemplifies tongue-like foci of tumour permeation and infiltration into surrounding endometrium and myometrium with ill defined, nested pattern of tumour evolution. Tumefaction is comprised of spherical cells incorporated with scanty to moderate, eosinophilic cytoplasm and uniform nuclear atypia. Neoplasm appears reminiscent of small round blue cellular tumours. Tumour parenchyma is traversed by delicate network of arborizing or curvilinear vascular articulations. Mitotic activity is significant and exceeds > 10 mitosis per 10 high power fields. Tumour cell necrosis and lymphoid or vascular invasion is commonly encountered [3,4]. Around 50% neoplasms demonstrate a low grade, spindle shaped cellular component simulating low grade endometrial stromal sarcoma. Monomorphic, bland spindle shaped cells appear admixed or occasionally manifest well demarcated foci. Overt nuclear pleomorphism is exceptionally observed. Surrounding stroma appears fibrous or may be constituted of fibromyxoid matrix. Morphological features such as pseudo-glandular or pseudo-papillary countenance, sex cord-like cellular differentiation or rosette-like formations may be variably encountered. Mitotic activity is minimal and appears at ≤3 mitosis per 10 high power fields. Typically, tumour necrosis is absent [3,4]. BCOR rearranged endometrial stromal sarcoma frequently incriminates endometrium or myometrium and manifests with tongue-like invasive segments or broad structures of infiltrative tumour perimeter. Neoplasm represents with haphazard fascicles of uniformly atypical, spindle shaped cells permeated with scanty to moderate, eosinophilic cytoplasm or abundant, blue/grey cytoplasm. Overt nuclear pleomorphism is exceptional. Tumour cells appear enmeshed within an extensively myxoid stroma. Nearly 50% neoplasms display collagen plaques or lymphatic and vascular tumour invasion. Mitotic activity is significant and appears as ≥10 mitosis per 10 high power fields. Tumour parenchyma is pervaded with miniature arterioles devoid of perivascular whorling of neoplastic cells. Infarct type necrosis is commonly observed, in contrast to tumour cell necrosis. Low grade component of endometrial stromal sarcoma appears absent [3,4].

Endometrial stromal sarcoma with BCOR ITD exemplifies tongue-like architecture of tumour invasion. The high grade neoplasm composed of round cells or spindle shaped cells represents with uniform cellular and nuclear atypia. Overt nuclear pleomorphism is infrequently encountered. Low grade fibromyxoid, spindle shaped cellular component may be delineated. Circumscribing stroma is myxoid. Mitotic activity is significant and represents with ≥ 10 mitosis per10 high power fields. Lymphoid and vascular invasion with tumour cell necrosis may be discerned [3,4]. Low grade endometrial stromal sarcoma delineating high grade metamorphosis may occur within primary, metastatic or reoccurring tumour. High grade component may be appropriately demarcated from low grade component upon microscopy with low power magnification. Infrequently, discernible transition between dual components may be gradual. High grade component comprises of an estimated 10% to 90% of the neoplasm and manifests with well-defined tumour nodules surrounded by sclerotic or infrequently, myxoid stroma [3,4]. Tumefaction is composed of spherical or epithelioid cells demonstrating uniformly increased cellular or nuclear atypia. Significant mitotic activity exemplifies a median of 16 mitosis per 10 high power fields. Surrounding stroma is pervaded with delicate vascular articulations in the absence of perivascular dissemination of tumour cell whorls. Tumour cell necrosis is uncommonly encountered. Low grade component of endometrial stromal cell sarcoma may represent as conventional low grade endometrial stromal sarcoma. Neoplasm may manifest with variant morphology as fibroblastic, smooth muscle differentiation, sex cord-like differentiation or myxoid matrix (Figures 1 & 2) [5].

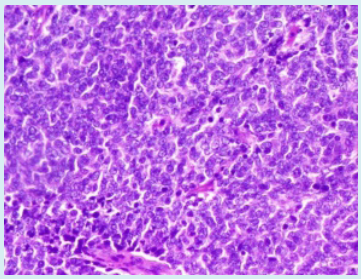

Figure 1: Endometrial stromal sarcoma depicting spherical cells with moderate eosinophilic cytoplasm and atypical nuclei. Surrounding stroma is permeated with vascular articulations. Mitotic figures and tumour necrosis is observed [6].

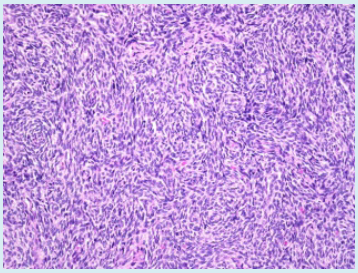

Figure 2: Endometrial stromal sarcoma exemplifying spherical cells pervaded with eosinophilic cytoplasm and atypical nuclei. Surrounding stroma is fibromyxoid and imbued with vascular articulations. Mitotic figures are observed [7].

TNM Staging of Endometrial Stromal Sarcoma 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(IA): tumour confined to the uterus ~T1a (IA): tumour magnitude ≤ 5 centimetres in greatest dimension ~T1b (IB): tumour magnitude > 5 centimetres in greatest dimension.
- T2 (II): tumour extends beyond uterine cavity and appears confined within the pelvis ~T2a (IIA): tumour incriminates adjoining uterine adnexa ~T2b (IIB): tumour incriminates diverse pelvic anatomical tissues.
- T3 (III): tumour infiltrates various abdominal soft tissues and visceral structures ~T3a (IIIA): tumour infiltrates adjoining abdominal soft tissues confined to singular site ~T3b (IIIB): tumour infiltrates adjoining abdominal soft tissues within > singular site.
- T4 (IVA): tumour infiltrates adjoining viscera as 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 disseminated within regional lymph node(s) ≤ 0.2 millimetre magnitude.
- N1 (IIIC): regional lymph node metastasis present.

Distant Metastasis

- M0: distant metastasis absent.
- M1 (IVB): distant metastasis present excluding sites such as uterine adnexa, pelvic soft tissue or abdominal soft tissues.

International Federation of Gynaecology and Obstetrics (FIGO) Staging and Grouping of Endometrial Stromal Sarcoma [3,4]

- stage I: T1,N0, M0
- stage IA:T1a, N0,M0
- stage IB: T1b, 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

High grade component of endometrial stromal sarcoma with YWHAE-NUTM2A/NUTM2B genetic fusion appears immune reactive to cyclinD1, BCOR, CD117, pan-TRK, CD56 or CD99. Low grade component of endometrial stromal sarcoma appears immune reactive to CD10, oestrogen receptor (ER) or progesterone receptor (PR). BCOR rearranged endometrial stromal sarcoma appears immune reactive to CD10, cyclin D1, pan-TRK or BCOR. Neoplasms with BCOR ITD appear immune reactive to BCOR, cyclin D1 or pan-TRK [4,5]. Low grade endometrial stromal sarcoma may metamorphose into high grade sarcoma. High grade component appears immune reactive to CD10, oestrogen receptor(ER) or progesterone receptor.

High grade component of endometrial stromal sarcoma with YWHAE-NUTM2A/NUTM2B genetic fusion appears immune non-reactive to CD10, oestrogen receptor (ER) or progesterone receptor(PR). Low grade component of endometrial stromal sarcoma appears immune non-reactive to cyclin D1 or CD117. Low grade and high grade components of endometrial stromal sarcoma appear immune non-reactive to desmin, smooth muscle actin(SMA), caldesmon, DOG1, pankeratin, epithelial membrane antigen (EMA), S100 protein, human melanoma black 45 (HMB45) antigen and wildtype of p53 [4,5]. BCOR rearranged endometrial stromal sarcoma appears immune non-reactive to oestrogen receptor (ER), progesterone receptor (PR), smooth muscle actin (SMA), caldesmon, desmin or wildtype of p53. Endometrial stromal sarcoma with BCOR ITD appears immune non-reactive to CD10, desmin, oestrogen receptor (ER), smooth muscle actin (SMA) or caldesmon. Low grade endometrial stromal sarcoma may undergo metamorphosis into high grade sarcoma which appears immune non-reactive to BCOR, cyclin D1 or wildtype of p53 [4,5].

High grade endometrial stromal sarcoma delineating YWHAE-NUTM2A/NUTM2B genetic mutation requires

segregation from neoplasms such as undifferentiated carcinoma, myxoid leiomyosarcoma, inflammatory myofibroblastic tumour, low grade endometrial stromal sarcoma, conventional leiomyosarcoma, spindle cell variant of leiomyosarcoma or undifferentiated uterine sarcoma [4,5]. Endometrial stromal sarcoma may be appropriately discerned with surgical procedures as hysterectomy. Exceptionally, tumefaction may be diagnosed upon endometrial tissue sampling or endometrial curettage. Upon magnetic resonance imaging (MRI), solid or occasionally cystic tumefaction may be encountered. Feather-like image enhancement and foci of haemorrhage or necrosis may be discerned. Endometrial stromal sarcoma may be appropriately treated with cyto-reductive surgical intervention. Besides, multimodal therapeutic strategies may be adopted [4,5]. Endometrial stromal sarcoma with YWHAE-NUTM2A/NUTM2B genetic mutations may be treated with anthracycline based chemotherapy. BCOR rearranged endometrial stromal sarcoma may be managed with MDM2 or CDK4 inhibitors as the neoplasm manifests with MDM2 genetic amplification or alterations within genes of cyclin D1/ CDK4 kinase pathway [4,5]. Anti-hormonal therapy appears inefficacious as majority of neoplasms appear devoid of or demonstrate restricted expression of oestrogen receptors (ER) or progesterone receptors (PR). Endometrial stromal sarcoma exemplifies prognostic outcomes intermediate between low grade endometrial stromal sarcoma and undifferentiated uterine sarcoma [4,5]. As inadequate information is documented on disease monitoring of the exceptionally discerned neoplasm, favourable or unfavourable factors contributing to prognostic outcomes may be challenging to ascertain [4,5].

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6. Image 1 Courtesy: Springer link.

7. Image 2 Courtesy: Web pathology.