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PMS2 was absent in 9 MELF (32,14%) and in 37 NON MELF tumors (36.63%).
MLH1 and PMS2 were both negative in 6 MELF (21,34%) and in 30 NON MELF tumors (29,7%)
MSH6 was lost in 2 MELF (7,14%) and in 7 NON MELF tumors (6,93%)
MSH2 was lost in 2 MELF (7.14%) and in 4 NON MELF tumors (3.96 %)
MSH2 and MSH6 were both negative in 2 MELF (7,14%) and in 3 NON MELF tumors (2,97%).

Discussion. MELF pattern is a particular pattern of myoinvasion by EEC, characterized by the presence of micro-cystic and elongated glands, composed of flat cells with eosinophilic cytoplasm, invading the myometrium with associated fibromyxoid stromal reaction and more frequently associated to low-intermediate grade EEC. According to the recent literature, this particular pattern of invasion seems to be associated with lympho-vascular invasion and lymph node metastasis, despite the low grade of this tumors. However the prognostic role of MELF pattern of invasion remains unclear since the presence of discording data in the literature.
Our data confirmed the low-moderate grade of MELF tumors (94.94% MELF case were G1 or G2 FIGO) compared to NON MELF population.
Moreover, in our data MELF pattern resulted associated with a higher incidence of low-volume nodal metastases compared to NON MELF tumors (p=0.001). The presence of higher incidence of low-volume nodal metastases is also associated with absence of LVI (p=0.037)
Finally, the multi-parametric logistic regression analysis revealed that in NON MELF population the risk of lymph-node metastasis is higher with the increase of tumoral maximum diameter and the entity of LVI; in MELF population, this synergic association in determining node metastasis has not been observed.
This data may support the fact that MELF pattern is an independent prognostic factor in the risk to develop lymph-node metastasis, since the particular stromal reaction that can predispose to epithelial-mesenchymal transition (EMT).
Concerning molecular features, in our case-series there was a higher frequency of mutation of MLH1 in NON MELF endometrial pattern of invasion (32.67% of NON MELF cases *vs* 21.43% of MELF cases) but a higher prevalence of MSH2 loss in MELF pattern (7.14% in MELF population *vs* 3.96% of NON MELF population).
This preliminary data could support the hypothesis of a specific pattern of mutation among MSI in MELF pattern and probably in these group of EEC with worse prognosis an interesting role could be assumed by MSI mutation.
Further studies and larger population are requested to confirm these data.

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THE WIDE MORPHOLOGICAL SPECTRUM OF PRIMARY AND RECURRENT AGGRESSIVE ANGIOMYXOMA: A SERIES OF 36 CASES

G. Angelico[1], GF Zannoni[1,2], S. Spadola[1], L. Salvatorelli[3], M. Michal[4], G. Magro[3]

[1] Dipartimento Scienze della Salute della Donna, del Bambino e di Sanità Pubblica, Unità di Gineco-patologia e Patologia Mammaria, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; [2] Istituto di Anatomia Patologica, Università Cattolica del Sacro Cuore, Rome, Italy; [3] Department of Medical, Surgical Sciences and Advanced Technologies and Biotechnological Sciences G.F. Ingrassia, Anatomic Pathology, University of Catania, Italy; [4] Sikl's Department of Pathology, Charles University Medical Faculty Hospital, Czech Republic.

Background. Aggressive angiomyxoma (AAM) is a rare locally infiltrative, non-metastasizing mesenchymal neoplasm arising primarily in the soft tissues of the vulvo-vaginal region, perineum and pelvis of adult women (1). AAM is most commonly found in women of the reproductive age, however sporadic cases have been reported in males, occurring almost exclusively in the genital area (scrotum, spermatic cord, inguinal region, perianal region and pelvic soft tissues) (2). The reported age at presentation is 6-77 years, with the peak incidence occurring during the reproductive years. The female-to-male ratio is 6.6:1. The tumor usually presents as a slow-growing large multilobular or polypoid mass with finger-like projections infiltrating the surrounding soft tissues. On gross examination, it is rubbery and white or soft and gelatinous (1). Histologically, it is a hypocellular tumor composed of neoplastic spindle-shaped cells set in a loose myxoid stroma containing small to medium-sized thick-walled vessels. Despite the bland-looking cytology, AAM is a locally aggressive tumor, with infiltrative growth and high rate of local recurrence (1,2). Wide local excision is the therapy of choice. However, this is difficult at times as the tumour is non-encapsulated and has the same consistency as that of surrounding connective tissue.
In the present study, we present the clinico-pathologic features of a series of 36 cases of AAM, with emphasis on unusual morphological features in both primary and recurrent tumors.

Materials and methods. A series of 36 cases of surgically resected, vulvo-vaginal AAMs was retrospectively collected from the files of the University of Catania, University of Pilsen and Catholic University of Sacred Hearth (Rome). All patients were females, ranging in age from 43 to 65 years. Immunohistochemical studies were performed with the labeled streptavidin-biotin peroxidase detection system using the Ventana automated immunostainer (Ventana Medical Systems, Tucson, AZ). The following antibodies were applied: vimentin, CD34, alpha-smooth muscle actin, desmin, estrogen, progesteron and KI-67.

Results. Our series included 31 primitive tumors and 5 local recurrences of surgically resected AAMs. On gross examination, the majority of tumors presented as unencapsulated, poorly or vaguely circumscribed masses with a gelatinous, myxoid or fibrous cut surface. Tumor size was highly variable, ranging from 1.5 cm to 20 cm in greatest dimension. Histologically, all the selected tumors exhibited the following common basic theme: proliferation of bland-looking small-sized cells set in a myxoid, fibro-myxoid or collagenous stroma,

containing numerous small- to medium-sized blood vessels. The neoplastic cells exhibited spindled, round to ovoid or stellated morphology, with palely eosinophilic cytoplasm. Nuclei were round-to-ovoid in shape, with dispersed chromatin. Mitotic figures and nuclear pleomorphism were rare or absent. All cases exhibited infiltrative borders, often with entrapment of adipose tissue, nerve and skeletal muscle at the periphery. Cellularity was low to moderate, with focal areas displaying a mild hypercellularity, especially around large vessels at the periphery of the tumor. An interesting finding, observed in 11 cases, was the presence of small bundles of spindle-shaped smooth muscle cells with eosinophilic cytoplasm, scattered within the stroma, often around blood vessels. Immunohistochemical findings confirmed the considerable overlap of AAM with that of many other mesenchymal tumors of the lower female genital tract. All cases showed diffuse immunoreactivity for vimentin and desmin, while alpha-smooth muscle actin and CD34 were variably expressed. The majority of cases (70%) exhibited strong nuclear staining for estrogen and progesterone receptors in most of the tumor cells. Labeling for Ki-67 demonstrated a low proliferative index (<1% of tumor cells).

The following unusual morphological features were seen: i) 5 cases (2 primary and 3 recurrent tumors) were extensively hypercellular with a moderate amount of fibro-myxoid stroma; ii) 3 primary and 2 recurrent tumors showed areas of neoplastic spindle-shaped cells with a concentric layered, perivascular "onion skin-like" arrangement; usually the blood vessels had hyalinized walls; iii) 4 primary tumors showed focal areas with microvascular proliferation, as typically seen in glioblastoma; iv) 3 primary tumors showed focal hypercellular areas due to a perivascular condensation of neoplastic cells (most of them with round morphology), closely packed and set in a fibrous stroma; v) two cases showed areas with a leyomioma-like morphology, consisting of spindle cells with moderate eosinophilic cytoplasm and elongated nuclei with small evident nucleoli; vi) two recurrent cases were composed of a hypocellular proliferation of bland-looking spindle cells with wavy nuclei set in abundant fibro-sclerotic stroma, closely reminiscent of neurofibroma; vii) two recurrent cases with extensive stromal hyalinization showed small- to medium-sized blood vessel replaced by fibrous tissue, with complete obliteration of their lumen; these vascular changes resulted into confluent fibrotic nodular structures of variable sizes, closely resembling ovarian corpora albicantia.

Conclusions. AAM is currently included in the category of the "*specific stromal tumors of the lower female genital tract*", together with angiomyofibroblastoma, cellular angiofibroma, and myofibroblastoma (3). Although some overlapping features between these entities do exist, an accurate evaluation of their clinico-pathologic features allows their distinction in most cases. Among these tumors, it is crucial to separate AAM from others for its high rate of local recurrences. Although diagnosis of AAM is usually straightforward if typical morphology is encountered, diagnostic problems may arise when pathologist is dealing with unusual morphological features, especially in recurrent tumors exhibiting hypercellularity or extensive sclerosis and/or neurofibroma-like appearance.

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ATYPICAL ENDOMETRIAL HYPERPLASIA, LOW-GRADE: "MUCH ADO ABOUT NOTHING"

E. D'Angelo[1], I. Espinosa[2], J. Szafranska[2], V. Cipriani[3], M. Barbareschi[4], J. Prat, F.R.C Path[2]

[1] Department of Life, Health & Environmental Sciences, University of L'Aquila, Coppito-L'Aquila, Italy; [2] Department of Pathology, Hospital de la Santa Creu i Sant Pau. Institute of Biomedical Research (IIB Sant Pau). Autonomous University of Barcelona, Barcelona, Spain; [3] William Harvey Research Institute, Queen Mary University of London, London, United Kingdom; [4] Department of Pathology, Hospital Santa Chiara, Trento, Italy

Background. Atypical endometrial hyperplasia (AEH) is considered a precursor of endometrioid carcinoma. The 2014 World Health Organization (WHO) classification divides endometrial hyperplasia into two categories: hyperplasia without atypia and atypical hyperplasia/endometrioid intraepithelial neoplasia (EIN). However, this classification disregards the degree of nuclear atypia. The Aim. of this study is to show the importance of grading nuclear atypia and estimate the risk of developing endometrial carcinoma following a diagnosis of low-grade or high-grade AEH. In addition, we investigated the potential role of genes known to be involved in endometrial carcinogenesis such as *ARID1A, PIK3CA, PTEN, KRAS, CTNNB1* and mismatch repair genes.

Methods. We reviewed 91 biopsies of AEH from 91 patients who subsequently underwent hysterectomy within 1-year interval. The association between the grade of nuclear atypia at biopsy and the findings at hysterectomy was assessed via a Fisher's exact test. Targeted sequencing was performed in 26 cases of AEH and 4 samples of simple hyperplasia.

Results. The degree of nuclear atypia at biopsy was highly predictive of the findings at hysterectomy ($P=5.0x10^{-25}$). None of the patients with low-grade AEH had a diagnosis of high-grade AEH or carcinoma at hysterectomy; whereas 9 (29%) patients with high-grade AEH in the biopsy also had high-grade AEH in the uterus and 22 (71%) patients had FIGO grade-1 carcinoma. None of the genes tested showed a mutational load significantly associated with the degree of nuclear atypia.

Conclusions. We conclude that in AEH is crucial to assess the degree of nuclear atypia. Our data strongly support that low-grade AEH is inconsequential and question the need of hysterectomy for such patients.

Key words: atypical hyperplasia, low-grade nuclear atypia, high-grade nuclear atypia, endometrial metaplasia, well differentiated (G1) endometrial carcinoma, risk of progression to carcinoma.