Uterine pseudotumors

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Abstract
Pseudotumoral uterine lesions include benign reactive and artefactual changes, epithelial and mesenchymal, which occasionally are incorrectly interpreted as malignant or even premalignant lesions. Although some of these changes may have architectural or cytological abnormality, they are different from those observed in premalignant and malignant uterine lesions. The most common pseudotumoral lesions of the endometrium include various types of epithelial and stromal metaplasia, pseudolymphomas, inflammatory pseudotumor, adenomyosis, post-therapy surgical changes, artefactual changes, etc. Most of these changes may coexist with endometrial hyperplasia or endometrial carcinoma, and also with some benign conditions such as polyps or in combination with hormonal therapy or even in normal cyclic endometrium. These associated endometrial changes may raise important issues regarding the diagnosis and subsequent therapy.

Keywords: pseudotumors, epithelial metaplasia, adenomyosis, differential diagnosis.

Epithelium pseudotumors
Endometrial epithelial metaplasia

Endometrial epithelial metaplasia is a group of non-neoplastic lesions, often coexisting with endometrial hyperplasia or with endometrial carcinoma [1] and also in a number of benign diseases such as polyps or in combination with hormonal therapy [2, 3]. Endometrium with benign non-tumoral lesions associating changes metaplasia may be incorrectly interpreted if the pathologist is not aware of potential pitfalls, because the association of endometrial metaplasia complicates the histologic appearance of substance.

The changes in endometrial epithelial metaplasia may be the result of two phenomena [4, 5]:
- true metaplasia involving Müllerian differentiation processes, in which the cylindrical endometrial epithelium is replaced with mucosecretor epithelium, squamous or ciliotubar, epithelia with common Müllerian origin;
- degenerative or regenerative/reparative in which occur changes more frequently in the epithelium and/or surface glands, such as eosinophilic syncytial changes [6].

Squamous metaplasia (SM) can be found in all forms of hyperplasia and endometrial carcinoma [7, 8]. Banyameen M et al. [9] found an incidence of 3.2% relative to the lesion, while Moritani S et al. [10] communicated in their study a frequency of 7%.

The term SM is recommended to be used for benign lesions, while the term squamous differentiation should be used preferentially for carcinomas [11, 12].

A particular aspect is the relationship between the morulas and SM. Although SM originates de novo from glands, in a fifth of the cases it coexists with morules, situation in which transitions are observed between the two types of metaplasia [11–14].

Histopathologically, squamous metaplasia cells are usually benign, but when it is currently a degree of atypical nuclear grade, this often follows the grade of atypical glandular cells. Most often they take the form of localized (LSM) that develop intraglandular and rarely a diffuse form (DSM) which affects diffuse the surface of the endometrium and subjacent glands.

LSM is usually an immature squamous metaplasia. Metaplasia cells contain a moderate quantity of eosinophilic cytoplasm and present different cytoplasmic boundaries (Figure 1a). They can build up round-oval formations previously named squamous morulas. Nowadays is used the term of squamoid morula or simply morular metaplasia (MM) [13, 14].

A rare variety of SM is DSM or uterine ichthyosis, in which the surface epithelium of the endometrium is replaced by stratified squamous epithelium (Figure 1b). Metaplasia cells are mature, often glycogenated and frequently keratinised. Occasionally, it may pair up with koilocytosis modifications and dysplasia, the infection with HPV 6 and 11 being involved too [15, 16].

Immunohistochemically, many studies have highlighted differences between SM and MM. So, if MM is variable positive for cytokeratins, SM is constantly positive for 34βE12 [13], AE1/AE3, CK5/6 and LP34 [12]. Also, SM is positive for a series of other epithelial markers like p63, EMA and involucrin [12, 14].

Differential diagnosis of SM is made with primitive squamous endometrial or cervical carcinoma, which invades the endometrium by extension, which are excluded by the absence of cytological atypia and stromal invasion. In difficult cases, the positive immunoreaction for epithelial markers and the negativity
of reaction for reticulin in morula makes the diagnosis easier [12–14].

• Morular metaplasia (MM) is a term recently proposed for replacing the one of metaplasia with squamous morula, because it has been noticed that metaplasia cells do not always have the properties of squamous differentiation [13, 14]. In addition, immunohistochemical and ultrastructural properties are not constantly showing for these structures evidently squamous differentiation and are not conclusive to establish if the morules have early or immature squamous features [14].

The morules are structures with immunohistochemical properties and genetic profiles which present marked differences from the normal endotelium or/and of endometrioid neoplasm [11, 17, 18]. They involve the mutation of β-catenin, but not mutations of PTEN, K-ras or microsatellite instability, observed in endometrioid neoplasm without morular component [18, 19]. More than that, no matter what structure they develop in, they present a model of nuclear immunostaining for β-catenin and a genetic profile which involves mutations of β-catenin [20, 21].

The morules are almost invariable associated with complex glandular architecture of premalignant and malignant glandular injuries of low grade, [6, 13], and in benign injuries, they are almost every time associated with focal complex glandular lesions [11, 13, 14].

Histopathologically, the morules are formed from rounded cells, polygonal, or sometimes spindly, which form rounded cell aggregates in the glandular lumen. Cell proliferation has as a result the protrusion of the proliferated cells in the glandular lumen leading to the replacement of it and the appearances of „stromal morules” (Figure 1c). When individual cell aggregates come to a certain dimension, central necrosis is produced, but atypia and mitotic activity are absent.

Immunohistochemically, recent studies highlight the main differences between the immunophenotype MM and SM [12, 14, 22]. Diffuse positivity of the membrane for CDX2 and CD10, and nuclear for β-catenin is constant in MM and is differentiated of SM [13, 14, 17, 23]. The morules are inert structures hormonally, with the absence of receptors for α-estrogen and progesterone and a very low proliferative index [8, 11, 13, 14, 20]. Similar aspects have been presented in our studies too, the morules being CDX2 positive and negative for hormonal receptors and p63 (Figure 1d).

Chiarelli S et al. [13] consider that CD10 may be a marker of MM in various endometrial lesions, which indicate the precocious morular transformation of the glandular epithelium.

An interesting characteristic of MM is the presence of an aberrant neuroectodermal phenotype represented by the positivity for ENS, synaptophysin, S-100, somatostatin and acetylcholinesterase [11, 12].

Houghton O et al. [14] reports the absence of p63 expression for the morules without obvious squamous differentiation, which along with the lack of ultrastructural evidence of squamous differentiation leads the authors to conclude that these have not actually defining features for squamous differentiation.

MM reactivity for cytokeratins is greatly variable in different studies [11–14]. Chiarelli S et al. [13] communicate positive expression for CK8, CK18 and CK19, weak positivity for CK5/6, CK13 and 34βE12 and its lack for CK7 and CK20. Houghton O et al. [14] find the positivity of morules for LP34. In contrast, other authors reported the negativity of morules for AE1/AE3, CK5/6 and LP34 [11, 12].

The differential diagnosis of MM is made with the stromal granulomatous lesions or smooth muscle lesions, and sometimes may be impossible to differentiate from the spindle cell endometrioid carcinoma.

• Often, ciliated (CM) and tubal (TM) metaplasia does not represent a real metaplasia because the ciliated epithelial cells is a normal aspect of the proliferative endometrium. Diagnosis of CM must be formulated only when one or more endometrial glands are lined predominantly by ciliated cells while TM requires the presence of three types of tubal epithelial cells: ciliated, secretory and interlacing. Usually, numerous ciliated cells occur due to light and unantagonized estrogen stimulation [24].

CTM is present in the normal endometrium, endometrial hyperplasia and carcinoma [1, 10] or occasionally in isolated glands from the atrophic or inactive endometrium; also, in polyps or the endometrium of women who have undergone hormone replacement therapy [3].

In their study, Banyameen M et al. [9] reports an incidence of CTM of 28.5%. Related studies show similar values, namely a relative incidence of 31 [10].

Histopathologically, ciliated cells may be present among the unciliated columnar cells interspersed, individually or in small groups, or they can be numerous and line most of the gland. They are slightly rounded shape and volume increased, with pale eosinophilic or clear cytoplasm, producing a look similar to the epithelium of fallopian tubes. nuclei may appear stratified, but the nuclear membranes are smooth and regular, chromatin is fine and evenly distributed and the mitoses are generally absent (Figure 1e).

Immunohistochemically, CTM shows aberrant expression of cell cycle proteins (αHIF-1, cyclin E, p21, cyclin A, p27), suggesting a possible potential pre-malignant lesion [25].

Comer MT et al. [26] consider that LhS28 can be a valuable marker for identifying CTM and therefore useful in differentiating it from morphologically similar lesions. Also, consistent expression of p16 in CTM, in a characteristic mosaic pattern, may be useful in identifying the lesion as an alternative to LhS28 [25] (Figure 1f). In addition, p53 has also expression but is weak and heterogeneous in CTM, unlike endometrial carcinomas [27, 28].

The differential diagnosis must take into account that sometimes, the glands with CTM may present cytological or architectural abnormality (atypical hyperplasia with ciliated cells), requiring differentiation of ciliated cells carcinoma [29].

• Mucinous metaplasia (McM) is characterized by the presence of cytoplasm containing abundant mucin, similar to the endocervical glands.
Figure 1 – (a) Focal squamous metaplasia, HE stain, ×100; (b) Diffuse squamous metaplasia, HE stain, ×100; (c) Stromal morule, HE stain, ×100; (d) Morular metaplasia, CDX2 stain, ×200; (e) Ciliated metaplasia, HE stain, ×200; (f) Tubal metaplasia – mosaic pattern, p16 stain, ×200; (g) Endocervical mucinous metaplasia, HE stain, ×100; (h) Endocervical mucinous metaplasia, MUC5AC stain, ×200.
McM can be seen both in benign and neoplastic endometrium [30, 31]. Simple McM [10, 32] is most often found at women in peri- or post-menopausal that receive hormone replacement therapy [2].

Hendrickson MR and Kempson RL [24] refer to McM as the common endometrial modification while Silverberg SG and Kurman RJ [29] consider it one of the rare forms of endometrial epithelial metaplasia changes. Recently, Banyameen M et al. [9] reported a relative incidence of endometrial McM around 25.5%, of which more than 60% at postmenopausal women.

The values are consistent with studies conducted by Moritani S et al. [10] who found a frequency of McM in postmenopausal of 26%, while Nucci MR et al. [31] communicates also an incidence of 80% in postmenopausal.

Histopathologically, glands with McM have a morphology similar to the normal ones but occasionally can be crowded and sometimes with a complex architecture [31]. Mucinous metaplastic endocervical epithelium tends to be focal distributed and is composed of high columnar cells with benign nuclei, basal-oriented and clear cytoplasm, slightly granular which contains diastase-resistant intense PAS positive mucin and also stained with mucicarmine and alcian blue (Figure 1g). In some cases, the mucinous transformation is accompanied by a commentary that is a risk of a differential diagnosis” accompanied by a commentary that is a risk of a degenerative nature or the reparatory one of this process [35]. Some other authors render this as a degenerative phenomenon of ischemia, which appears during the endometrial bleeding [6, 36].

Histopathologically speaking, the cells with eosinophilic cytoplasm conflunce on the endometrial surface, in a typical syncytium, which can be plain or, more frequently, can form papillary structures, which have no sustaining connective tissue. Some basophilic stromal aggregates can surround the curettage fragments creating the aspect of “stromal balls”. The syncytial nucleuses are disorderly oriented, but in general, they are small and benign, although sometimes they can be round and vesicular with coarse chromatin because of the degenerative modifications, or they are reagent, enlarged, vesicular with plain cellular membrane and obvious nucleus (Figure 2a). The mitosis are rare or frequently absent.

Immunohistochemically speaking, ESM is intensively cytoplasm and nuclear positive for p16INK4A [37] (Figure 2b).

The differential diagnosis of ESM with serous carcinoma or with EIC is imposed when the metaplastic process is very extended. In these cases, a special attention needs to be attended to the entire aspect of the endometrium, in which usually the ESM has collapse properties. In some problematic cases, the immunohistochemical investigations for p53 are useful [28].

- Eosinophilic metaplasia (EM) is the most common cytoplasm modification, which can be considered to be more likely a reactive change then a true metaplasia [22]. A certain degree of cytoplasm eosinophilia is frequent in endometrial epithelial cells, but this does not justify the ME diagnosis. The eosinophilic cytoplasm can be present in ciliar cells, squamous cells, oncocytes, papillary and syncytial surface modifications [38]. Hendrickson MR and Kempson RL [24] consider ME the most frequent variety supra-diagnosed as adenocarcinoma.

Moritani S et al. [10] consider EM as one of the most common endometrial metaplasia, which appear in the non-neoplastic endometrium as much as in the neoplastic one [1, 39]. However, the endometrial hyperplasia is more frequently present in carcinoma compared to the benign non-hyperplastic endometrium. In their study, Banyameen M et al. [9] find a relative incidence of 25.5% of EM.

Histopathologically, the endometrial glands are partially or completely dusted with eosinophilic cells, which can have considerable form variations. Sometimes can be observed an atypical nucleus, which is not criteria of malignancy, but just degenerative phenomenon. Most often metaplastic cells are columnar or slightly rounded and have a moderate quantity of pale pink cytoplasm (Figure 2c). In hyperplasias, the eosinophilic cells appear most often like the papillary sprout or as intraluminal bridges simulating the aspect of a carcinoma. In atypical hyperplasia the metaplastic cells can be columnar or polygonal, with “pavement” aggregate aspect in the cases where the cells confluence and have a squamous...
differentiation. Sometimes, pear-shaped hobnail cells can show up and have a small prominence with a rounded top that contains a big nucleus with a weak to moderate atypical form.

A rare variety of EM is the oncocytic metaplasia, characterized by the presence of the cells arranged in one layer, with eosinophilic cytoplasm, fine granulated and with round nuclei centrally situated with pleomorphic and small mitotic activity [40] (Figure 2d).

Immunohistochemically speaking, Shimizu K et al. [41] find bigger values of p53 in EM comparing to G1 endometrial adenocarcinoma, while the proportion of immunoreactive cells for Ki-67 and cyclin A was bigger in G1 endometrial adenocarcinoma comparing to EM. Moritani S et al. [10] report that 88% of EM expresses MUC5AC.

The differential diagnosis is made with the ciliary metaplasia and atypical hyperplasia or adenocarcinoma. The deficiency of the cilia excludes a ciliary metaplasia, while the deficiency of the stratification and the preserving of the polarity exclude the atypical hyperplasia or carcinoma.

- The clear cell metaplasia (CCM) is a rare modification, usually with a focal type, which seems to evolve more frequently while administrating progestatines than associated with hyperplasia [5]. The modification can be a repairing phenomenon after a curettage or radiotherapy, or it can appear more diffusely in gestational endometrium [29]. Banyameen M et al. [9] report a 1.09% CCM incidence, similarly with the results of the study made by Moritani S et al. [10].

Histopathologically speaking, columnar cells with secretory modifications can confluence with the polygonal clear cells and squamous cells with profuse clear glycogen cytoplasm (Figure 2e). Rarely, clear cells can have nucleuses and hobnail aspect like in Arias–Stella reaction.

In hyperplasia, the secretory diffuse modifications, vacuolar cytoplasm and luminal secretions give the aspect of secretory hyperplasia, which is present to the patients in perimenopause with sporadic ovulation or treated with progestatines [42, 43]. A particular aspect is represented by the recognition of the cytological atypia due to the cytoplasm secretory processing, which modifies the aspect of the glandular cells and may highlight the tortuosity of the glands. Most of the times in this cases is necessary the repetition of the biopsy and the reevaluation of the endometrium [44].

Immunohistochemically, the most CCM are ER positive and they present a weak positive and heterogeneous pattern for p53 [45].

The differential diagnosis regards neoplastic proliferation, such as carcinoma with clear cells or the secretory type of endometrioid carcinoma is based on the lack of architectural complexity, matrix invasion, cellular pleomorphism and mitotic activity.

- The hobnail cells metaplasia (HCM) it might look idiopathic, but more often it represents a reactive postabortion change or it may show on the surface of a polyp. Hobnail cells can often be related to pregnancy, progesterone therapy, or a part of the Aria–Stella reaction. Other situations associated with HCM are chronic endometritis, DIU and radiation [46, 47].

Speaking from a point of view related to histopathology, the cells are usually stratified; they have prominent nucleus with the shape of an upholsterer’s nail in the gland’s lumen and may contain cytoplasm invaginations (Figure 2f). The plasmatic membrane is downsized, eosinophilic or clear.

The differential diagnosis of HCM includes carcinoma with clear cells, but the absence of the invasion and mitotic activity, next to predisposing factors direct the diagnosis to a benign lesion.

Endometrial papillary proliferation

Endometrial papillary proliferation can take complex aspects, being over diagnosed in the sense of a glandular endometrial adenoma. The changes appear usually postmenopausal, in 2/3 of the cases along with polyps. Some of these patients have a history of substituting hormonal therapy [47].

Histopathology shows us that the papilla has a fibrovascular matrix’s ax, with varying grades of ramification. Lehman MB et al. [47] describe two types of architectural patterns:

- the simple papillary pattern, including the implication of a small number of glands and reduced epithelial proliferation, omnipresent;
- the complex papillary pattern with extended implication of the endometrial glands, with a higher degree of ramification of the papilla and the presence of the cellular buds. The epithelial cells can present low degrees of atypia and occasional mitotic activity.

What’s more, authors find that the papillary proliferations can associate with mucinous metaplastic endocervical changes (90%) with eosinophilic cells (89%), with ciliate cells (70%) or exfoliating (22%) and with hobnail cells (22%).

Stromal pseudotumors

Mesenchymal metaplasia

Mesenchymal metaplasia represents examples of the pluripotent capacity of differentiating the endometrial matrix. The endometrial stem/progenitor cells are the best possible candidates for developing a pluripotent differentiation capacity, including mesenchymal type [22].

- Bone metaplasia is a rare entity, often under-diagnosed, which affects the uterus and may be associated with secondary infertility [48]. Cayuela E et al. [49] confirm the metaplastic nature of such a change, by comparing the DNA genotypes, which indicate the genetic origin for the patient’s bone tissue and the uterine bone material.
- Smooth muscular metaplasia is sometimes observed under the form of small focus outbreaks in the endometrium, which they were named, and intra endometrial leiomyoma [22]. Pathogenic – this lesion is connected to the capacity of the endometrial matrix to differentiate itself in smooth muscle [50].
Figure 2 – (a) Eosinophilic papillary syncytial modification – degenerative atypia, HE stain, ×100; (b) Eosinophilic papillary syncytial modification, p16 stain, ×100; (c) Eosinophilic metaplasia, HE stain, ×200; (d) Oncocytic metaplasia, HE stain, ×100; (e) Clear cell metaplasia – complex hyperplasia without atypia, HE stain, ×100; (f) Hobnail cell metaplasia – complex hyperplasia without atypia, HE stain, ×100; (g) Inflammatory pseudotumor, HE stain, ×100; (h) Non-tumoral stromal cells with "signet ring" pattern, HE stain, ×200.
Adipose metaplasia is seen like small focus points of mature adipose cells in the endometrial matrix. Mature fat is also occasionally found in myometrium [51]. In an abortion, the adipose cells they should be completely surrounded by the endometrium normally or by the myometrium, along with an easy inflammatory reaction.

The differential diagnosis is made by using the adipose tissue obtained because of the uterine perforation and also with lipoma and uterine lipoleiomyoma [52].

Gliarial tissue from the uterus represents the most controversial non-epithelial metaplastic change, because the metaplastic capacities of the endometrial matrix, it should limit itself only to mesodermal tissues. This way, most of the cases reported were considered to come from a previous abortion [53].

The differential diagnosis is made mainly with a glioma in which there are some cellular atypical, or a teratoma in which we can find tissue from other layer of the Germinal cells.

Extramedullary hematopoiesis is extremely rare in the absence of hematological disorders or of the systemic disease and there are few reports about this conditions from the uterine mucosa level. Sirgi KE et al. [54] underlined focal centers isolated by the extramedullary hematopoiesis composed from one or more lines of precursors of sanguine cells, immunohistochemically confirmed with antibodies for von Willebrand factor, CD34 and CD15.

**Inflammatory pseudotumor**

Inflammatory pseudotumor (IPT) is a rare pseudotumor proliferation, with unknown etiology, that might appear in some structures simulating a neoplasm. The long time controversial nature of IPT and the great variety of microscopic aspects are reflected in the multiple terms used as synonyms: inflammatory myofibroblastic tumor, spindle cell granuloma or plasma cell granuloma. Currently, IPT term is no longer used as synonyms: inflammatory myofibroblastic tumor (IMT), considering that there are sufficient data on long time controversial nature of IPT and the great variety of microscopic aspects are reflected in the multiple terms used as synonyms: inflammatory myofibroblastic tumor (IMT), considering that there are sufficient data on differentiation, decidual and histiocytic.

**Histopathologically**, SRST appear under the form of aggregates in the endometrial stroma. They have a characteristic nucleus placed at the periphery, small, uniform with indistinct nucleoli and without mitotic activity (Figure 2h). There cytoplasm presents some cytoplasmic vacuoles which are unique, being negative for PAS, mucicarmine and Alcian Blue [61].

**Immunohistochemically** are reactive in most of the cases for vimentin and negative for EMA and cytokeratins [61]. Guerrero-Medrano J et al. [62] communicate reactivity at most of the histiocytic markers, including CD68, HAM 56, lysozyme, LN5 and cathepsin D.

**Differential diagnosis**. The morphological aspect of SRST can be confused with those from a metastatic adenocarcinoma with therapeutic and prognostic implications. This pitfall can be avoided if the cells are recognized as histiocyte [62].

**Non-neoplastic stromal cells with symplastic atypia**

Non-neoplastic stromal cells with symplastic atypia (NNSCSA) has rarely been described in normal endometrium as benign when it involves a non-neoplastic endometrial stroma [63]. Symplastic atypical nuclei are similar to those of various female genital tract diseases (polypys, leioyomatis) [64].

**Histopathologically**, are present focal changes characterized by nuclei with worrying aspect, because of greatly increased volume, hyperchromatic, atypical forms, segmented nuclei, but without mitotic activity.

The differential diagnosis is made with benign or malignant endometrial tumors, which contain atypical mesenchymal cells such as endometrial polyps with atypical stromal cells, carcinomas, adenocarcinoma.  

**Histioytic nodule**

Histiocytic nodule (HN) or nodular histiocytic hyperplasia is a reactive histiocytic proliferation with nodular arrangement [65, 66]. This type of histiocyte is
often associated with hyperestrogenism, being observed in endometrial hyperplasia and xanthogranulomatous endometritis, but also in adenocarcinoma [65].

Histopathologically, HN has the aspect of a nod formed from aggregates of round or polygonal histiocytes, with pale and foamy cytoplasm and in a moderate quantity, and which contains unique or multiple cytoplasmic vacuoles, negative for PAS and mucicarmine [65]. The nuclei are vesicular or kidney-shaped, lobulated or ovoid with small nucleoli. Next to these, we can also find cells that resemble with the Langerhans’ cells with incised nucleus, lobulated and reniform, and granular cytoplasm (Figure 3a). The endometrial glands are observed in both in or outside of HN. In the nod’s structure there are not present vascular structures. Mitosis is rarely frequent [65].

Immunohistochemically, histiocytic cells are intensively positive for vimentin, CD68 and lysozyme (Figure 3b). The immunoreaction for ER and PR are positive for S-100 protein and cytokeratins and CD10 [65, 66].

The differential diagnosis is made with a series of neoplastic, inflammatory and reactive conditions such as xanthogranulomatous endometritis, malakoplakia, histiocytic granuloma, hormonal changes of the endometrial stroma, Langerhans’ cell histiocytosis, morular metaplasia, extravillous trophoblast and exaggerated placental situs.

Pseudolymphomas

Pseudolymphomas (PL) have pathological and clinical characteristics which suggest that their apparition are the result of a focal florid lymphoid proliferation in association with cervicitis and chronic endometritis or it may be a generalized disorder of the lymphoid cells, such as infectious mononucleosis [67, 68].

Histopathologically, it may also involve the endometrium and the myometrium, where we can observe an abundant infiltration with big cleaved or no cleaved lymphoid cells with mitotic activity, immunoblastic and centrofollicular cell, sometimes with the aspect of “starry sky”. Plasmocytes, polymorphonuclear cells and small lymphocytes can also be present in the infiltration.

Immunohistochemically, the reactions indicate polymorph lymphoid infiltrations with predominating T-cells [68, 69].

The differential diagnosis with lymphomas, which rarely occurs in this location it, might be difficult [68]. The surface ulcerations and the presence of acute inflammatory cells and plasmocytes are rarely observed in lymphomas, while the lesions with big dimensions with cellular monomorphism, deep invasion and sclerosis are not observed in PL.

Intravascular endometrial tissue

The intravascular endometrial tissue is rarely observed on hysterectomy specimens, frequently associated with extended endometriosis [70].

Histopathologically, they can be observed in parametrium blood vessels or uterine menstrual debris, consisting in small epithelial or fusiform stromal cells [70, 71].

Immunohistochemically, intravascular stromal cells are positive for vimentin, and the epithelial one for epithelial markers [71].

The differential diagnosis is made with carcinomatous tumoral emboli, excluded by the benign aspect of the intravascular cells and ultimately by immunohistochemical reactions [70].

Psammoma bodies

Psammoma bodies are occasionally observed at the endometrium or myometrium of postmenopausal women. They can be seen in non-neoplastic conditions, such as old endometritis, Asherman’s syndrome or prolonged usage of intrauterine device (IUD) in association with hormonal substitution therapy [72–74].

Histopathologically, the aspect is similar with the one from other carcinomas. You can observe spherical, well shaped and intensively hematoxylinophilic structures (Figure 3c).

Endometrial decidual reaction at post-menopause women

The endometrial decidual reaction at post-menopause women in absence of endogenic or exogenic progesterone stimuli is a rare change of course [75, 76]. Such modifications are described at patients who followed tamoxifen and progesterone therapy for breast cancer [77].

Histopathologically, can be observed a decidual transformation of the endometrial stroma, necrosis, cellular pleomorphism and in some cases hyperplastic glands with focal atypia.

Immunohistochemically, endometrial tissues are negative, both cytoplasmatic and nuclear for ER and positive for PR and CBG [75].

Amyloidosis

Amyloidosis with endometrial localization is rarely mentioned in literature, more frequently presented as an affection of endometrium in the systemic form of the disease, or following some lesions (endometrioid carcinoma, leiomyosarcoma) [78–80].

Histopathologically, in systemic amyloidosis, eosinophilic deposits may interest endometrial stroma, myometrium and the walls of blood vessels, unlike the one associated with endometrial neoplasias in which can occur nodular homogeneous, eosinophilic deposits. Amyloid deposits are positive with “Congo red” and have a greenish birefringence in polarized light.

Myxoid modifications

Myxoid modifications of endometrial stroma, unassociated with other lesions, are considered pseudoneoplasic degenerative modifications, wrongly diagnosed as myxoid leiomyomas [81]. Veras E et al. [82] described myometrial myxoidosis, present in patients diagnosed with systemic lupus erythematosus.

Histopathologically, it can be observed a hypocellular stromal material with myxoid aspect, which contains fusiform cells and small blood vessels.
Figure 3 – (a) Histiocyte nodule, HE stain, ×100; (b) Histiocyte nodule, CD68 stain, ×100; (c) Myometrium psammoma body, HE stain, ×200; (d) Adenomyosis, HE stain, ×100; (e) Stromal adenomyosis, HE stain, ×100; (f) Adenomyosis, ER stain, ×200; (g) Adenomyosis, Vimentin stain, ×200; (h) Adenomyosis, Ki67 stain, ×200.
Adenomyosis

Adenomyosis (AM) is characterized by the presence of ectopic endometrial tissue in myometrium, where it can grow.

In spite of numerous publications, it still exists a disagreement regarding incidence, theories concerning the origin of AM, the symptomatology and pathology associated with it. “Syndrome of dislocated basal endometrium” (SDBE) refers to the physiopathological continuous spectrum which contains endometriosis, endometriosis associated with AM, AM and pre-menopause and consequently seems to be a common phenomena [83].

It has been suggested that uterine dysfunction at women with endometriosis and AM is the result of the action of hyperestrogenism on the paleomyometrium [83–85]. Both endometriosis and AM can be integrated in the new physiological and oncological concept of “agression and reparation of tissues” (ARTI), in this context representing a far end of a physiological principle regarding the extreme sensibility of the gonads at estrogens, amplified by the estrogen-sensitive environment normally controlled by the ovary [86].

Recently, it has been proved that adenomyosis is correlated with abnormal quantities of a variety of substances. Recently, Huang HY et al. [87] found a significant increase in IL-18 mRNA receptors and in the ratio between 18BP/IL-18 at patients with adenomyosis and stated that these modifications could be responsible of the appearing lesions.

Histopathologically, the diagnose criteria vary a lot, but accepted by the majority is the separation of the lesion from the surface endometrium through at least a field with a large zooming capability. Around the lesion can be observed the hypertrophy of myometrial musculature. Recently it was proposed as a more reliable diagnose criteria an equal or bigger distance of 3 mm from the endomyometrial intersection, and the presence of myometrial concentric hyperplasia [88]. It can be see glands and endometrial stroma which respond variable at the ovarian hormones, similar with the medium proliferative phase or inactive endometrium, cystic dilated glands all the way to the aspect of non atypical simple hyperplasia (Figure 3d) [89], rarely secretory modifications, with the exception of pregnancy and progestine treatment. The endometrial tissue can penetrate the myometrial vessels, simulating invasion like in the case of a neoplasm [90].

Sometimes, at postmenopausal women, the glands can be missing and the AM area only contains only endometrial stroma, with the aspect of stromal AM (Figure 3e) [91]. A peculiar aspect consists in the aspect of the lesion, which appeared in the case of tamoxifen therapy. In these cases, there were noticed more frequently aspects of marked cystic dilatation of the glands, stromal fibrosis and various epithelial metaplasias [92].

Immunohistochemically, the lesions has characteristic immunophenotype with strong and diffuse posititivity for CD34 and CD10, and its absence for smooth muscle markers [81].

Recent studies show the fact that in case of the association of AM with an endometrioid carcinoma, not only that they are more likely to invade the myometrium, but are more likely to invade the external half of the myometrium.

Immunohistochemically, the lesions are positive for ER, vimentin, Ber-EP-4 and cytokeratins, as well as for CA125 [93–95] (Figure 3, f–h). CD10, marker for the neoplastic and non-neoplastic endometrial stroma, is useful in differentiating AM areas from invasive endometrioid adenocarcinoma areas [96].

Endometriosis post therapy surgical changes

The progress in the field of therapeutic, surgical and non-surgery fields can significantly modify the microscopic appearance and can lead to diagnosis problems for the pathologist. Widespread use of increasingly large new diagnostic modalities and therapies need pathologists to be familiarized with a broad spectrum of tissue changes that can be observed in samples taken from their application. Some of these changes can significantly alter the appearance of tissues leading to a real iatrogenic pathology [97].

Postoperative spindle cell nodule

Postoperative spindle cell nodule (PSCN) or post-operative tumor with spindle cells of genitor-urinary tract is an exuberant reparative proliferation in response to local injury.

Histopathologically, there is a dense proliferation of spindle cells with uniform appearance, arranged in short bundles or bands which intersect and are separated from each other in areas of edema. Proliferated cells have nuclei with small pleomorphism, oval or spindle, pale, with prominent nucleoli and insignificant mitotic activity in general reduced by typical mitosis. The presence of neutrophils and erythrocytes is typical; it gives the lesion the appearance of a granulation tissue. Plasma cells are small in number compared to inflammatory pseudotumor. The change was compared with nodular fascitis, peripheral areas of lesions being able to develop infiltratively or together with granulation tissue.

Immunohistochemically, PSCN cells are widely positive for low molecular weight cytokeratins, actin, vimentin, and desmin, and negative for EMA [98].

The differential diagnosis is made by stromal sarcoma with fibrosarcoma or leiomyosarcoma, which are excluded by the absence of nuclear atypia, the atypical mitosis, the absence of invasion of adjacent structures and the operator history as well.

Endometrial adhesions

Endometrial adhesions (EA) or uterine synechiae (Asherman syndrome) correspond to fibrous bands of scar tissue, with its bridges partially or fully occupying the endometrial cavity [99, 100]. This fibrous tissue is formed because of inflammation most often associated with endometrial trauma, because of the procedures of surgical curettage, which in recent years is added to...
myoma surgery, and bicornuate and septate uterus. Whatever the cause, the mechanism is common, because of damage of the basal layer of the endometrium.

Histopathologically, fibrous bands are made of conjunctive tissue of variable density, sometimes hyalinized, and may contain glandular tissue (Figure 4a). The most common are fibromuscular bands of tissue, sometimes padded with endometrium. The endometrium can be largely replaced by a proliferation of fibroblast cell type. Outstanding endometrium obtained by curettage at the time of treatment, may have secretory aspect in 80% of cases, proliferative in 12% of cases, atrophic in 5% of cases and hyperplasia in 3% of cases [101, 102]. Mazur M and Kurman RJ [103] described another type of EA, a band composed of endometrial tissue with dense stroma and non-reactive small glands.

Postelectroresection endometrial changes

Postelectroresection endometrial changes are most likely a response to its healing, which is expressed by a distinct pattern of regeneration, which should be recognized so as not to be confused with damage due to other etiologies.

Histopathologically, the most important and frequent changes postablation, which can be attributed to thermal effects is granulomatous non-necrotizing endometritis with a similar appearance to that of rheumatoid arthritis [104–106]. Extensive coagulation necrosis can be seen in both endometrium and superficial myometrium, accompanied by variable inflammatory infiltrate. Also, hyalinosis and fibrosis were observed, with the formation of scars.

The differential diagnosis is primarily made with other disorders manifested by necrotizing granulomas, such as those caused by other agents, allergic or infectious.

Postablation thermal endometrial changes

Postablation thermal endometrial changes may be useful for understanding the failure of the procedure related to its direct mechanisms and complications of the procedure [104].

Histopathologically, fragments collected by hysteroscopy, at different time postablation intervals, indicate varied changes [107]. In the first three months after ablation variable necrotic areas are present both in the endometrium and superficial myometrium. At six months postablation, granulomatous reactions and fibrosis are described, while one-year postablation fibrous scar tissues are developed. At two months and after two years postablation intrauterine adhesions occur in over half the patients (52.8%). Similar studies have shown complete endometrial atrophy and fibrosis, followed by partial adhesions appearance and even the disappearance of the cavity [108].

Postradiation endometrial changes

Postradiation endometrial changes for cervix cancer were proved that destroy ovarian function and may cause endometrial ablation.

Histopathologically, on endometrial fragments collected from the patients there is a wide variety of issues depending on the dose, application method and time from radiotherapy until hysterectomy. Most histopathological observations made at 1–2 months after irradiation indicate nuclear reactive atypia in the surface epithelium and glands (Figure 4b) or papillary eosinophilic metaplasia [109] and the presence of hobnail cells [110]. The stroma also contains cells with increased volume, with bizarre nuclei and infiltrated with polymorphonuclear neutrophils and histiocytes and at approximately six weeks post irradiation sclerosis and hyalinosis [109, 111]. Sometimes vascular changes may be similar to those observed in peripheral endarteritis menopause [109, 111].

After intracavitary brachytherapy, injuries are more severe, the endometrium and superficial myometrium are replaced with areas of necrosis followed by fibrosis and hyalinisation, like a scar (Figure 4c).

Curettage samples contamination

Curettage samples contamination with other tissue on the fragments obtained should be identified and evaluated to rule out some major problems of pathology [45].

The most common are normal cervical tissues, they are readily identifiable and generally do not create diagnostic problems (Figure 4d). Also, squamous epithelia bands can be seen in the cervix and rarely in the vagina; they may occasionally even be diagnosed as CIN lesions or squamous cell carcinoma. Microglandular hyperplasia with or without squamous metaplasia give a complex pattern witch, however, is not always easily recognizable due to confusing similarity with hyperplasia or endometrial carcinoma with microglandular pattern (Figure 4e). Smooth muscle fragments can be present, representing myometrial beams or fragments from a submucous leiomyoma. The presence of adipose tissue may signify uterine perforation or may be fragments from a leiomyolipoma or lipoma, or may be an artefactual change [45, 103].

Endometrial changes associated with IUDs

Endometrial changes associated with IUDs are very varied, depending on device type and duration of use. Regardless of type, all IUDs cause some degree of foreign body reaction, and trauma at the contact of IUD with endometrium surface.

Histopathologically, among the changes induced by IUD there can be included nonspecific chronic or actinomyocotic endometritis, squamous metaplasia and with hobnail cells, interglandular and glandulo-stromal dissincronism. Pseudoactinomyocotic grains appearance is also cited [112, 113].

Artefactual changes of endometrium on biopsy fragments

Artefactual changes of endometrium on biopsy fragments if they are not recognized can be mis-interpreted as endometrial hyperplasia or endometrial carcinoma [45].
Figure 4 – (a) Endometrial adhesion – fibrous hyalinised bands and endometrial functional area, HE stain, ×40; (b) Post-irradiation endometrium – reactive atypical glandular epithelium, HE stain, ×100; (c) Post-brachytherapy endometrium – necrosis, cholesterol deposits and infiltrate with xanthomatous cells, HE stain, ×200; (d) Contamination of curettage samples with endocervical epithelia, HE stain, ×100; (e) Contamination of curettage samples with squamous cervical epithelia and microglandular hyperplasia, HE stain, ×100; (f) Glandular telescoping, HE stain, ×100; (g) Overcrowding and artefactual compression, HE stain, ×100; (h) Pseudolipomatosis, HE stain, ×100.
Glandular telescoping is an artifact frequently observed that refers to the presence of gland-looking as “lumen in lumen” (“gland in gland”) or as “double lumen” (Figure 4f). Change may be the consequence of glands intussusceptions during curettage [114] or of mechanical distortion of the glands during fixation and cutting [103] and may be confused with complex hyperplasia or even an endometrial carcinoma. 

Artifact agglomeration is characterized by adjacent glands due to cleavage of the tissue around them, which is a clue to the artifact nature of the amendment (Figure 4g).

The presence of glandular pseudopolyps corresponds to some thin fragments of superficial endometrium with a pseudopapillary architecture coming from atrophic endometrium, and requires sometimes the differentiation from benign or malign polypoid lesions of endometrium.

Post-curettage epithelial atypia is a change limited to surface epithelium and superficial glands. Reactive epithelial cells have large, hyperchromatic nuclei with obvious nucleoli, and sometimes they appear nuclei with a hobnail aspect.

Endometrial stromal compaction may be an aspect often seen in the menstrual endometrium. It can be observed densely cellular islands of degenerated stromal spindle cells, with reduced cytoplasm and hyperchrome nuclei.

**Pseudolipomatosis**

Pseudolipomatosis is a relatively common artefactual change present on endometrium fragments collected during histeroscopy, refers to the existence of clear optical vacuoles similar to fatty infiltration. Optically empty spaces represent air or gas bubbles, which penetrate the mucosa through microscopic fragmentation secondary to gaseous insufflation [115].

Histopathologic changes are characterized by optical empty vacuoles, round or oval, like adipocytes, with mild or marked variation in size, which can be misinterpreted when it is well represented (Figure 4h). Vacuoles are distributed in groups or may be isolated, lonely and occasionally are seen in vascular spaces [115].

Immunohistochemically, reactions for adipocytes and endothelial markers are negative. 

Endometrial pseudolipomatosis is easily mistaken and wrongly diagnosed as uterine perforation.

**Vascular pseudoinvasion**

Vascular pseudoinvasion is an artifact described on total hysterectomy specimens obtained by abdominal laparoscopy, and is probably due to closed pressure system generated by the surgical technique [116]. The importance of this artifact is to avoid diagnosis overestimation and misinterpretation as vascular invasion, with corresponding therapeutic and prognostic implications. 

Histopathologically, in tumors with vascular pseudo-invasion it is obviously the tumor separation from vessels walls without around inflammatory infiltrate, which usually is present in a real lymphovascular invasion [117].

**References**


