REVIEW

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Clinicopathological significance and prognostic value of myoinvasive patterns in endometrial endometrioid carcinoma

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Abstract

Endometrioid endometrial carcinoma has an overall good prognosis. However, variable five-year survival rates (92%–42%) have been reported in FIGO stage I, suggesting the involvement of other factors related to tumor biological behavior. These may be related to the role played by epithelial–mesenchymal transition (EMT) and cancer stem cells in endometrial carcinogenesis. In this context, our review highlights the prognostic significance of several types of myoinvasion in low grade, low stage endometrioid endometrial carcinoma, as a reflection of these molecular changes at the invasive front. According to recently introduced myoinvasive patterns, the diffusely infiltrating and microcystic, elongated, and fragmented (MELF) patterns show loss of hormone receptors, along with EMT and high expression of cancer stem cell markers, being associated with a poor prognosis. Additionally, MELF pattern exhibits a high incidence of lymphovascular invasion and lymph node metastases. Conversely, the broad front pattern has a good prognosis and a low expression of EMT and stem cells markers. Similarly, the adenomyosis (AM)-like and adenoma malignum patterns of invasion are associated to a favorable prognosis, but nevertheless, they raise diagnostic challenges. AM-like pattern must be differentiated from carcinoma invasion of AM foci, while adenoma malignum pattern creates difficulties in appreciating the depth of myoinvasion and requires differential diagnosis with other conditions. Another pattern expecting its validation and prognostic significance value is the nodular fasciitis-like stroma and large cystic growth pattern. In practice, the knowledge of these patterns of myoinvasion may be valuable for the correct assessment of stage, may improve prognosis evaluation and may help identify molecules for future targeted therapies.

Keywords: endometrial carcinoma, invasive patterns, MELF, adenomyosis-like, adenoma malignum.

Introduction

Endometrial carcinoma is the most frequent gynecological neoplasia in women, which bears an overall good prognosis, with a relative five-year survival rate of 84.5% for all stages and histological types [1].

As classified for the first time by Bokhman, in 1983, there are two types of endometrial carcinoma, with distinct epidemiological, clinical and histopathological features [2]. Type 1 comprises the majority (70–80%) of cases. It frequently affects women at perimenopausal age and develops on a background of endometrial hyperplasia, initiated by estrogen stimulation unopposed by progesterone, in conditions such as obesity, anovulation, nulliparity or exogenous hormone use. Type 1 endometrial carcinoma has low grade, endometrioid histological type, it is usually early diagnosed, and has a favorable prognosis. Type 2 includes the rest of 20–30% of cases, it is more frequent in post-menopausal women, and appears on a background of atrophic endometrium, in the absence of estrogenic stimulation. The histological type in this category is high grade, non-endometrioid (mainly serous, mucinous, and clear cell). Commonly, it is diagnosed in an advanced stage and has an unfavorable prognosis [3, 4]. Immunohistochemical (IHC) and molecular profile of these two types of carcinomas is usually estrogen receptor (ER) positive, along with variable mutations of tumor protein 53 (*TP53*), *CTNNB1* (*β*-catenin), AT-rich interaction domain 1A (*ARID1A*), phosphatase and tensin homolog (*PTEN*), and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) genes, in type 1, *versus* p53 positive, p16 positive, along with variable mutations of *PIK3CA*, F-box and WD repeat domain containing 7 (*FBXW7*), and protein phosphatase 2 scaffold subunit alpha (*PPP2R1A*) genes in type 2 [5, 6].

The high survival rate is due to the predominance of endometrioid histological type (80%), correspondent to anatomoclinical type 1 endometrial carcinoma, which generally has a favorable evolution [1]. However, survival rates are variable among *International Federation of Gynecologists and Obstetricians* (FIGO – *Fédération Internationale de Gynécologie et d'Obstétrique*) stages [7], defined by the depth of myometrial invasion, cervical stromal invasion, loco-regional spread, regional lymph node metastasis, involvement of adjacent organs and distant metastases [8]. In FIGO stage I tumors (limited to the uterine body), five-year survival rates can vary between 92% and 42% [7], demonstrating the heterogeneity of this neoplasia and suggesting that there may be other factors affecting the tumor's biological behavior.

Epithelial–mesenchymal transition (EMT) is a key

process in embryo development, which is reactivated during neoplastic progression, having a crucial role in tumor invasion and metastasis [9]. EMT refers to the switch from an epithelial cell phenotype to a mesenchymal one, by losing cell polarity, changing the cell's shape to fusiform and acquiring motility. These features reflect in a change of cell markers expression, respectively, loss of apical and basolateral junction proteins (E-cadherin), simultaneously with the expression of mesenchymal markers, such as smooth muscle actin (SMA), vimentin, fibronectin, and the increase in matrix metalloproteinases (MMP2, MMP3 and MMP9) activity. EMT is induced by various extracellular impulses, that activate signaling pathways common with carcinogenesis pathways, and it is regulated by transcription factors, such as TWIST, SNAIL, SLUG, and ZEB1. A significant hallmark of EMT is the process called "cadherin switch", that assumes the progressive loss of E-cadherin expression, because of intercellular junction disassembly, and its replacement by mesenchymal-type cadherins, such as N-cadherin and cadherin-11 [10]. Estrogen and progesterone receptors (ER, PR) status is reversely correlated with EMT status, such that progressive loss of ER and PR is associated with EMT markers expression in high-grade endometrioid endometrial carcinoma. Concomitantly, in low-grade endometrioid endometrial carcinoma and in premalignant lesions, hormone expression is preserved, showing that EMT is a late event during carcinogenesis [11]. EMT-mediated tumor progression and invasion is associated with activation of Ras/rapidly accelerated fibrosarcoma (Raf)/mitogen-activated protein kinase (MEK)/ mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signaling pathway in low-grade endometrioid endometrial carcinoma, demonstrated by a high expression of phosphorylated ERK (p-ERK) and EMT regulatory factors [SLUG, zinc finger E-box-binding homeobox 1 (ZEB1), at high-mobility group AT-hook 2 (HMGA2)] at the myoinvasive front [12].

It was proven that EMT is reversible during carcinogenesis, so that the inverse process, of mesenchymal–epithelial transition (MET) is essential for the growth of distant metastasis. MET could be triggered by the absence of EMT inducing-signals, but also by additional signals from the metastatic niche. More studies could further elucidate the molecular regulators of MET [13].

Recent research has identified a particular type of stem cells, which has been considered as responsible for invasion, metastasis, and the development of resistance to conventional therapy, called cancer stem cells (CSCs) [14], having its counterpart in endometrium. Moreover, tumor milieu has reciprocal interactions with malignant cells. Therefore, stromal matrix is inducing CSCs proliferation, while a specific epithelial cells phenotype induces EMT, followed by invasion, metastasis, along with hormonal, chemo-, and radiotherapy resistance acquisition in different tumors, including endometrial carcinoma [14].

Several markers have emerged as useful for identification of CSCs, such as CD133 (human prominin-1), CD44, Nanog1, Sal-like protein 4 (Sall4) [14], along with CXC motif chemokine receptor 4 (CXCR4), c-Myc, sex determining region Y-box 2 (Sox-2), octamer-binding transcription factor 4A (Oct4A), ATP-binding cassette subfamily G member 2 (ABCG2), B lymphoma Mo-MLV insertion region 1 homolog (BMI1), cytokeratin (CK) 18, Nestin, and β-actin [15]. Moreover, CD133, CD44, Sall4, CXCR4 may be associated with a higher aggressiveness of endometrial cancers [15]. The downregulation of hormone receptors expression in endometrial cancers may be significant for invasion and metastasis and, added to the expression of CSCs markers and loss of E-cadherin expression, led to the hypothesis that CSCs possess the capability of EMT [16]. However, if the markers of EMT are permanently expressed, a correlation with the development of carcinosarcomas has been demonstrated [17].

Prognostic factors proven to have an impact on evolution and tumor recurrence are age, histological type, depth of myometrial invasion, histological grade, lympho-vascular tumor emboli, tumor size (>2 cm) and metastasis in pelvic and lumbo-aortic lymph nodes [7]. Among the most important is regional lymph node involvement, which represents an indication for adjuvant therapy [8, 18].

Recent evidence highlights the pattern of myoinvasion in low-grade, low-stage endometrioid endometrial carcinoma, as a possible predictor for tumor evolution [19]. There have been described five myoinvasive patterns, respectively diffusely infiltrating, broad front, adenomyosis (AM)-like, microcystic, elongated, and fragmented (MELF) glands and adenoma malignum [20], each having morphological and prognostic particularities. Also, a new pattern of myoinvasion has been identified, respectively the nodular fasciitis-like stroma and large cystic growth pattern, adding to the diagnostic challenge [21].

Frequently, more than one pattern of myoinvasion may coexist, with a predominant type which associates a minor component of other pattern. In these cases, the prognosis is given by the most aggressive pattern [19, 22].

In the following sections, we will discuss each of these patterns of myoinvasion in endometrial endometrioid carcinoma, aiming to emphasize the importance of their recognition, in relation to the existing proof on their prognostic significance.

Diffusely infiltrating

The diffusely infiltrating or single gland pattern [20] is the most common morphological aspect at the myo-invasive front in endometrioid endometrial carcinoma, observed with a frequency of 49–89% [14, 19, 23]. It is defined as scattered neoplastic glands within the myometrium, arranged individually or in small groups (less than three), having irregular contours and possibly, but not necessarily accompanied by desmoplastic stromal response [19] (Figure 1, a and b).

The infiltrative pattern is indicative of a poor prognosis, since it was associated with a higher FIGO grade, lymphovascular invasion and tumor recurrence [19, 24]. These findings could be justified by the molecular alterations identified in these areas. Respectively, in these zones, it was shown a high expression of cancer stem cell markers (CD44, CD133) and the loss of hormone receptors (ER, PR) [14]. Both of these changes in the molecular phenotype contribute to the induction of EMT

(marked by the loss of E-cadherin and the aberrant expression of β-catenin), a phenomenon highly involved in tumor invasion and metastasis [14].

This pattern of invasion was observed in many other types of malignancies. Its direct association with EMT markers and poor prognosis was so far proven in squamous cell carcinoma of the head and neck [25], of the vulva [26], in endocervical adenocarcinoma [27] and urothelial carcinoma of the bladder [28], serving as an evidence of how molecular changes associated with tumor progression imprint on the tumor's histology, including in endometrial carcinomas.

Additionally, another issue, which arises in practice, is represented by the difficulty of delimitation between the invasion of the basal endometrium from the superficial myometrium invasion in endometrioid endometrial tumors.

However, it is considered that there is no difference of survival rates between superficial invasive endometrial carcinoma and that which invades less than 1/2 of the myometrium thickness (90% *versus* 91%) [29].

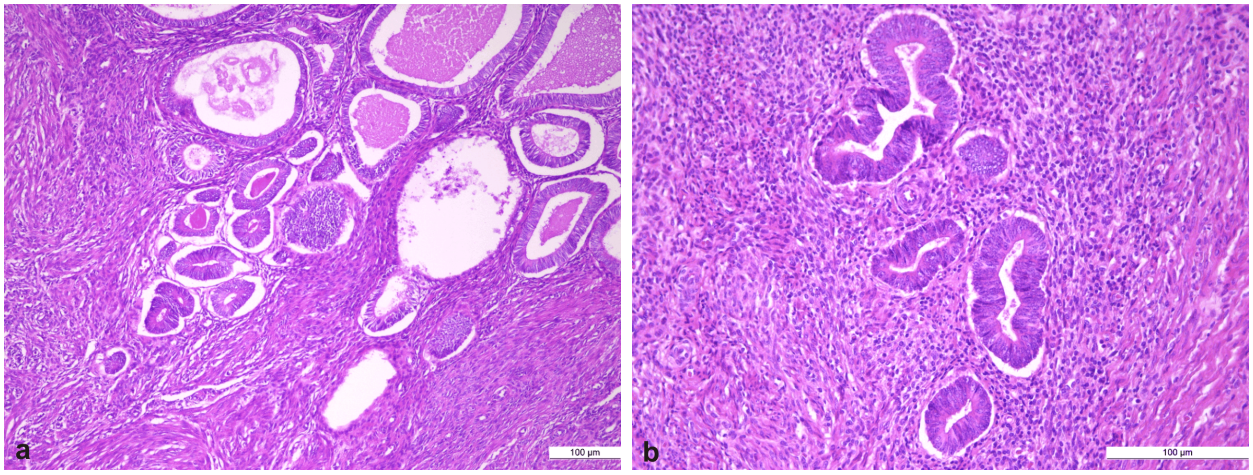

Figure 1 – ***(a and b) Diffusely infiltrating pattern of myoinvasion in endometrioid endometrial carcinoma. HE staining: (a) ×100; (b) ×200.***

Broad front (expansile, pushing border)

The broad front pattern of invasion is reported with variable frequencies. In some series, it was the second most common after the diffusely infiltrative type, with a frequency of 21% [19], while in others, it was detected with a lower incidence, varying between 2.8% and 9.6% [14, 23, 30]. Histologically, it is defined as a large mass of neoplastic glands, with well-defined margins, that seems to compress into the underlying myometrium, with or without an associated desmoplastic response [19] (Figure 2, a and b).

As opposite to the diffusely infiltrative pattern, it is associated with a good prognosis. There is no statistically significant association between this pattern of invasion and a high FIGO or histological grade, lymphovascular invasion or tumor recurrence [14]. Also, markers of EMT transition and stem cells markers have a low frequency of expression in these areas [14], further suggesting the low aggressiveness of the neoplastic process with this architectural feature.

A pushing border pattern of invasion has also been recognized in other types of cancers, likewise with a good prognosis. In the vulvar squamous cell carcinoma, it is associated with a lower recurrence rate and a lower expression of EMT transition markers, compared to the infiltrative pattern [26]. Also, in advanced colorectal carcinoma this pattern is linked to a lower rate of lymph node and distant metastases, a lower recurrence rate and a high 5-year survival rate [31].

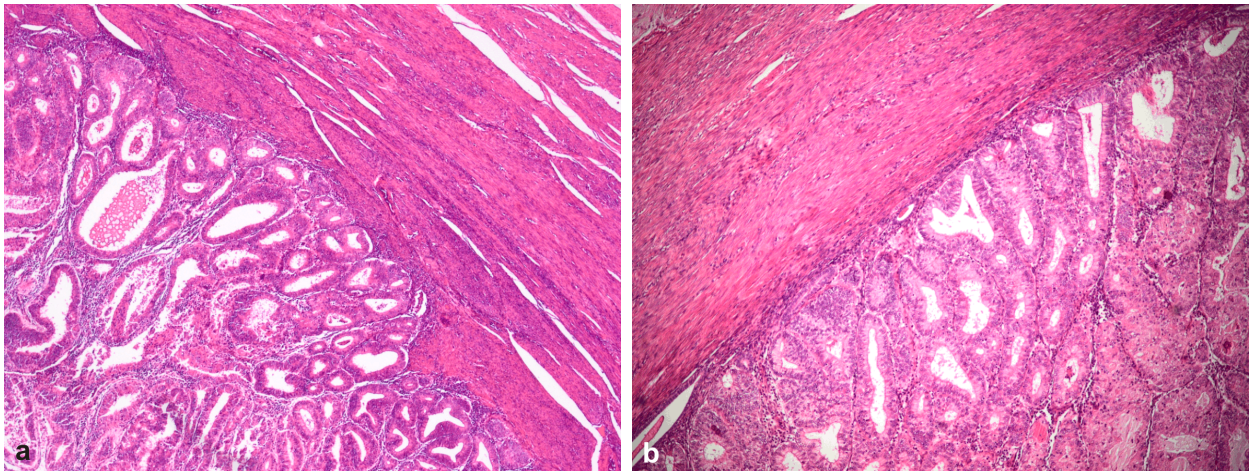

Figure 2 – ***(a and b) Broad front (pushing border) pattern of myoinvasion in endometrioid endometrial carcinoma. HE staining: (a) ×25; (b) ×40.***

From our experience, endometrial endometrioid carcinomas exhibiting a broad invasive front are usually associated with a well-differentiated pattern, are less invasive, infiltrating less than 1/2 of the myometrium. These features correspond to the favorable prognosis reported in literature in broad invasive front tumors, including endometrioid endometrial carcinomas.

Microcystic, elongated, and fragmented (MELF) glands

MELF pattern of invasion is reported with variable frequencies, ranging between 7% and 48% [14, 19, 23, 30, 32–37]. It was first defined by Murray *et al.*, in a study focusing on epithelial and stromal alterations in myoinvasive endometrioid endometrial carcinoma [38]. Two types of stromal reaction were identified, respectively lymphocytic and fibromyxoid, the latter being associated with a distinctive type of invasive glands. The histological appearance of these glands, as cystic-dilated or slit-like, lined by flattened, endothelial-like epithelium or squamoid tumor cells, with eosinophilic cytoplasm, often with intraluminal tufts or fragmented, alongside with small groups or isolated tumor cells, led to their denomination as "microcystic, elongated and fragmented glands" (Figure 3, a and b).

Frequently, these glands show a dense neutrophilic infiltrate in their lumen and are situated deepest in the myometrium [38]. Their subtle appearance can create difficulties in assessing the depth of myoinvasion, but the associated fibromyxoid surrounding stroma and neutrophilic infiltrate, visible at low power can be helpful in their identification [20] (Figure 3, a and b).

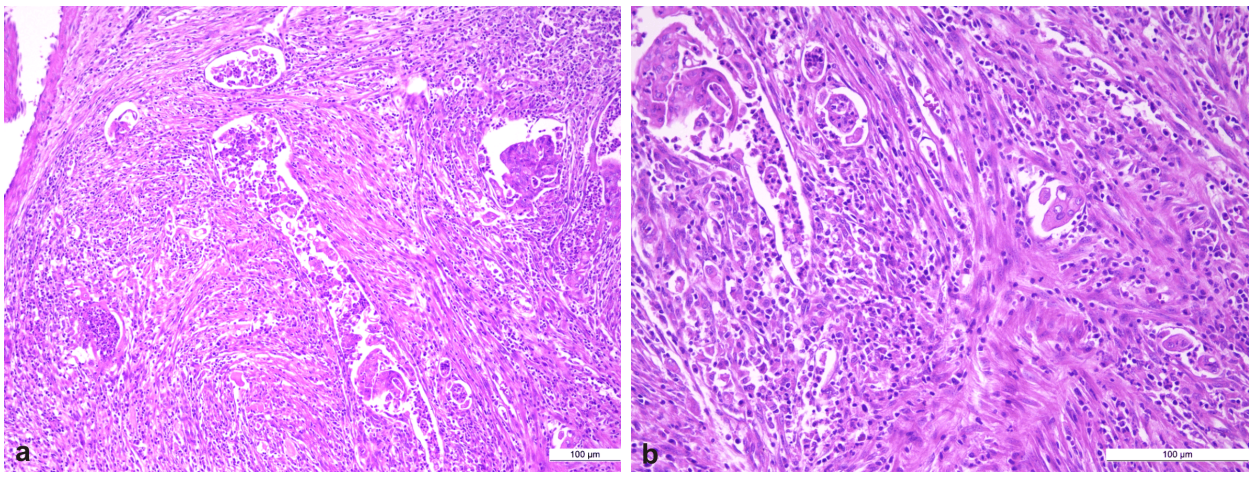

Figure 3 – ***(a and b) MELF pattern of myoinvasion in endometrioid endometrial carcinoma. HE staining: (a) ×100; (b – detail) ×200. MELF: Microcystic, elongated and fragmented.***

Given their histological aspect, these areas were initially thought to represent degenerative changes of tumor glands [38], but later studies suggested that they rather represent areas of intense tumor activity. The resemblance between MELF pattern of invasion and areas of EMT identified at advancing margins of other neoplasia, such as budding glands in colorectal cancer [32] led to the investigation of this phenomenon in the MELF-type glands. Several studies have shown a distinct immunophenotype of these glands, compared to those with conventional morphology. Intense expression of CK7 [33], CK19 [27] and molecular markers of EMT, such as reduced expression of E-cadherin, aberrant expression of β-catenin, loss of hormone receptors, overexpression of cyclin D1, p16, galectin-3 and fascin and low Ki-67 reactivity were detected [33, 39–41]. Furthermore, a high expression of stem cell markers (CD44, CD133, Nanog1, Sall4), known to have the ability to induce EMT, was shown in MELF glands [14].

MELF together with infiltrating pattern are associated with hormone receptors loss due to EMT induction and tumor progression [33, 42–45]. Furthermore, the expression of E-cadherin is lost in MELF tumors, in association with an aberrant β-catenin expression, downregulation of ER and PR expressions, along with lymphovascular invasion and, consequently, poor prognosis [38].

The molecular changes identified in these areas reflect in clinicopathological parameters with prognostic significance in endometrial carcinoma. MELF pattern is most frequently found in low-grade endometrial endometrioid carcinoma, in association with a high depth of myometrial invasion, lymphovascular invasion, lymph node metastases, and a high FIGO grade [32].

The association between MELF pattern of invasion, lymphovascular invasion and lymph node metastases was proven by several studies [14, 18, 19, 32, 34–36, 46, 47]. Recently, Joehlin-Price *et al.* have further confirmed this correlation by standardizing their study group, which included only FIGO I endometrial endometrioid carcinoma, eliminating other variables that could favor lymph node metastases. They defined three morphological types of lymph node metastases, respectively sinusal, histiocyte-like, solid and glandular and claimed that, in contrast to breast carcinoma, isolated tumor cells and micrometastases are not proven clinically relevant in endometrioid carcinoma [30], even though they have been recently reported in literature [18, 48].

The high probability of lymph node metastases in endometrioid endometrial carcinoma with MELF pattern can lead to a better therapeutic management in low-grade tumors, where lymphadenectomy indication remains controversial. Given the favorable evolution in most cases

of low-grade endometrial carcinoma, lymphadenectomy is generally avoided because of its possible complications (lower limb lymphedema, vascular or nerve injury, symptomatic lymphocysts, and chylous ascites) [18, 49]. In this context, identification of MELF pattern could represent an indication for subsequent lymphadenectomy. Furthermore, sentinel lymph node mapping techniques are beginning to be recommended in endometrial cancer [50].

Some researchers regard MELF pattern as a specialized variant of the infiltrative pattern of invasion, given their frequent concomitancy and the similar molecular changes regarding EMT and stem cell phenotype [14]. The pattern of invasive front may be significant for a poor prognosis, in MELF and infiltrating pattern, along with lympho-vascular invasion, lymph node metastasis, and CSCs markers expression [14], and may select a group of patients requiring an aggressive therapy [14]. In this view, MELF-type glands could appear because of stromal alterations and inflammation [19]. MELF pattern has also been associated with papillary architecture and mucinous differentiation [37].

Even though it is highly associated with lympho-vascular spread and extravaginal recurrences [51, 52], MELF pattern was correlated with an enhanced overall survival [47]. In this perspective, Kihara *et al.* argue that MELF pattern could have any implications on prognosis, proving a high expression of cellular growth arrest and senescence markers (p16, p21), together with low Ki-67 expression in these areas. Also, in their study, no statistically significant association between MELF pattern and recurrence-free survival or disease-specific survival was found [37]. These researchers question the causal relation between MELF pattern and lymph node metastases, which, in their opinion, can be determined by other associated factors such as tumor size, myometrial invasion, and lymphovascular invasion. In this view, MELF glands could only represent a morphological change in senescent glands, having no impact on prognosis [37]. However, decreased cellular division has been demonstrated during tumor progression and local invasion in other neoplasia, especially during EMT [40]. This observation could continue to support the theory of MELF being a morphological manifestation of EMF at the advancing margins. Further studies are needed to elucidate the clinico-pathological implications of this pattern.

Recently, new molecular markers associated to MELF pattern have been identified. High expression of S100A4 was correlated to myometrial and lymphatic invasion, demonstrating an aggressive phenotype, with strong and diffuse staining in MELF type glands [53]. Also, increased microvessel density in the neoplastic stroma and high expression of vascular endothelial growth factor (VEGF) in tumor cells, correlated with the presence of MELF pattern, could be predictors of unfavorable outcome [54].

In cases where the criteria for MELF diagnosis are incomplete, it is helpful to consider this pattern when at least two features are accomplished.

A practical application of the identification of this type of myoinvasion emerges from the large spectrum of histological features characteristic for MELF, which create heterogeneous tumoral areas. These areas raise the issue of the differential diagnosis with other types of invasion or with other types of tumors.

Moreover, the effect of autolysis should be eliminated when evaluating MELF pattern and an optimum preparation of specimens for grossing should be mandatory.

MELF-type features have also been observed in other cancers. In intraductal papillary mucinous neoplasm of the pancreas, they were frequently detected in association with high-grade dysplasia, deleted in pancreatic cancer 4 (DPC4) loss, and p53 overexpression, possibly suggesting stromal invasion [55]. In ovarian endometrioid carcinoma, MELF pattern was seen with similar frequencies as in uterine endometrial carcinoma, but without impact on prognostic features. However, it was associated with clear cell features and mismatch repair protein loss, hence it could be an indicator for surgical staging and Lynch syndrome screening [56].

Due to the proven poor prognosis in these types of tumors, the histopathological report should contain a special mention about the possible identification of MELF myoinvasive pattern. Clinicians should be aware of MELF significance as a more aggressive tumor subtype, possible in association with other factors, in order to adjust the therapy to an appropriate approach, by different therapeutic means association.

Adenomysis (AM)-like invasion

Adenomyosis is defined as the presence of endometrial glands and stroma within the myometrium, surrounded by hypertrophic and hyperplastic smooth muscle [57]. The condition is determined by alterations of the endometrium–myometrium interface, also called "junctional zone", with different embryological origins, structure, and functions than the outer myometrium [58]. Diagnostic criteria for AM presume the presence of endometrial glands deeper than 2.5 mm or than one quarter of the junctional zone thickness. AM can exhibit a diffuse pattern, in which the uterus is globally enlarged, or various focal patterns, such as the "pseudowidening" form, the cystic form, and adenomyoma. The "pseudowidening" form refers to the involvement limited to a single uterine wall, usually the posterior one. In the cystic form, there is accumulation of coagulated blood into dilated glands. Adenomyoma presents as a nodular mass of endometrial glands, stroma and smooth muscle [57].

The AM-like pattern of invasion is characterized by groups of at least three malignant glands invading the myometrium in scattered islands [19]. In large study groups, it was reported with variable frequencies, of 7% and 26.3%, respectively [14, 19] (Figure 4).

It was shown that this pattern was associated with favorable histology, low depth of myoinvasion, low incidence of lymphovascular invasion and lymph node metastases, and therefore it has a good prognosis [14]. Also, AM-like invasive areas showed reduced expression of stem cell markers (CD44, CD133, Nanog1) and maintained immunoreactivity for E-cadherin and hormone receptors (estrogen and progesterone) [14].

The challenge of this pattern of invasion lies in differentiating it from AM foci involved by carcinoma, which cannot be considered when evaluating depth of

myoinvasion [20]. Histological features in favor of AM are the presence of residual endometrial stroma or normal endometrial glands, smooth, round borders, and the existence of adjacent foci of AM. Instead, AM-like invasion is characterized by desmoplastic stroma, possibly with edema and inflammation, visible at low power examination, irregular, pointed outlines, and identification of similar foci of invasion within the adjacent myometrium [20].

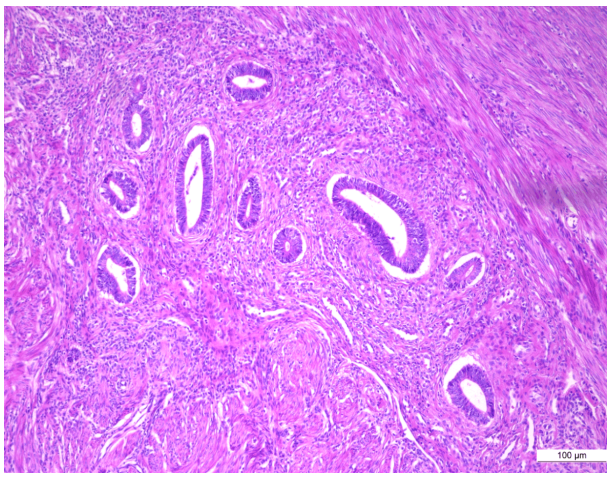

Figure 4 – ***Adenomyosis-like pattern of myoinvasion in endometrioid endometrial carcinoma (HE staining, ×100).***

In difficult cases, trichrome staining may be helpful, by optimally highlighting the desmoplastic peritumoral reaction.

The current reporting of this pattern is limited by the practical possibility of its overdiagnosis. Therefore, an algorithm of histological criteria, along with special stains, supplemented, if necessary, by a panel of selected IHC markers, could avoid therapeutic approach and monitorization errors.

Adenoma malignum (minimal deviation endometrial adenocarcinoma)

Adenoma malignum or minimal deviation adenocarcinoma is typically described as an extremely well differentiated variant of gastric type adenocarcinoma of the uterine cervix. This type of cervical neoplasia is unrelated to human papilloma virus (HPV) infection. Its histogenesis resembles more to gastric carcinogenesis, possibly with lobular endocervical glandular hyperplasia, as its precursor lesion. Histologically, it is composed of glands with mucinous epithelium, with cells having abundant, clear pale eosinophilic cytoplasm, pleomorphic nuclei, and mitotic figures. The glands show an irregular outline, are dilated, fused or cribriform, disposed within a various amount of desmoplastic stroma [59].

Adenoma malignum consists in regular, round, often widely spaced glands, with minimal nuclear atypia, lacking a desmoplastic or inflammatory stromal response [19, 60]. It has rarely been described at the invasive front of endometrial carcinoma, as a distinct pattern of myoinvasion, with frequencies of 1% [23] or 1.33% [19] (Figure 5, a and b).

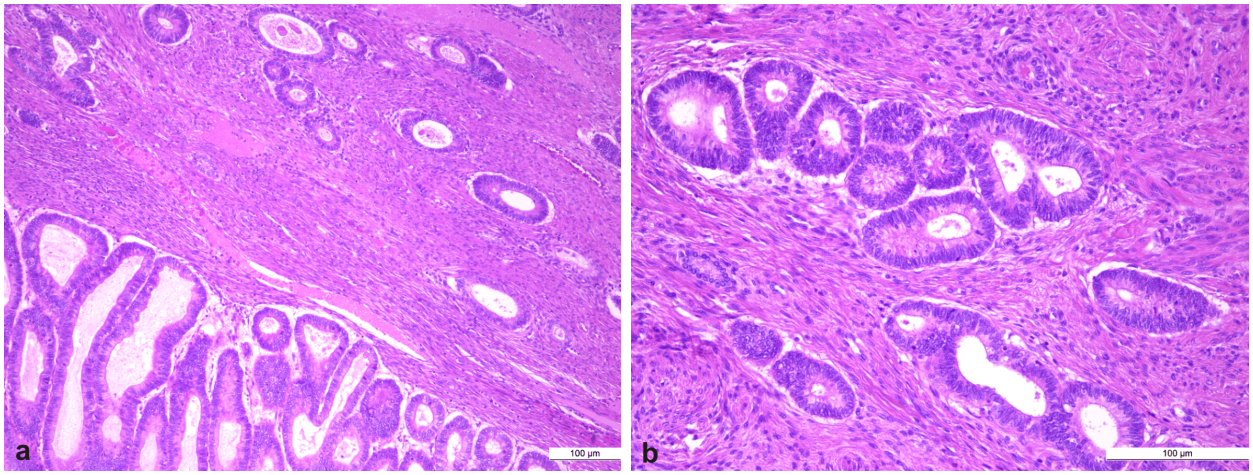

Figure 5 – ***(a and b) Adenoma malignum pattern of myoinvasion in endometrioid endometrial carcinoma. HE staining: (a) ×100; (b – detail) ×200.***

In endometrial carcinoma, adenoma malignum pattern brings difficulties in assessing the tumor, grossly and microscopic. The diffuse, infiltrative spread of the glands, without an associated stromal reaction, can be misleading when appreciating the depth of myoinvasion [61], also causing an unobvious gross appearance, as a thickened, firm, grey-white myometrium [60] that can render the neoplasia undetectable at high-precision imagistic examinations [62]. The complexity of the diagnosis increases, as this pattern of invasion can extend beyond the uterine body, with a frequent involvement of the cervix, or possibly, of the ovaries. Mainly, adenoma malignum areas must be distinguished from adenomyosis, synchronous adenocarcinoma of the cervix, deeply located endocervical glands, mesonephric remnants, cervical tubo-endometrioid metaplasia, cervical or ovarian endometriosis or cortical inclusion cysts of the ovary.

Adenomyosis can be excluded in the absence of endometrial stroma, the presence of mitotic activity, identification of carcinoma in the surface endometrium, with possible association of conventional invasion areas, and the absence of AM foci elsewhere in the myometrium.

In case of cervical involvement, synchronous adenocarcinoma of the cervix can be excluded in the presence

of benign surface endocervical glands and also by distinctive IHC profile.

Deeply located endocervical glands can be ruled out given the location in the uterine body and the absence of mucinous overlying epithelium, respectively.

The lack of a lobular architecture and the presence of mitotic activity help distinguishing adenoma malignum from mesonephric remnants.

Tubo-endometrioid metaplasia and endometriosis can be excluded by the absence of endometrial stroma and ciliated cells, or hemosiderin-laden macrophages.

Ovarian cortical inclusion cysts can be ruled out in the absence of ciliated cells and the presence of minimal cellular atypia and mitotic activity [61].

The frequent association of uterine corpus adenoma malignum with endometrioid endometrial carcinoma [61], as well as the IHC profile supports its histogenesis from endometrial carcinoma, as a differentiated variant [63]. Uterine corpus adenoma malignum areas are positive for ER, PR, CK7, vimentin and negative for CK20, carcinoembryonic antigen (CEA) and p16. Immunohistochemistry is useful in cases of cervical involvement, for excluding a synchronous cervical adenocarcinoma, which is positive for CEA and p16 and negative for vimentin and ER [61, 63].

Even though in the cervix, adenoma malignum is associated with a dismal prognosis [59], a study showed that endometrial carcinomas with this pattern of invasion do not have a worse evolution compared to those with a conventional tumor front. Similar recurrence and survival rates were detected in both categories [22]. This observation is supported by Quick *et al.*, which report a favorable evolution of one patient with adenoma malignum pattern of invasion in their study group [19].

However, a small number of cases of mucinous, gastric-type adenocarcinoma of the uterine corpus, associated with chemoresistance and poor prognosis have been reported [64, 65]. They were often found in combination with endometrioid carcinoma and endometrial hyperplasia. These tumors are composed of cells with pale eosinophilic cytoplasm and well-defined borders, suggestive of gastric differentiation. Immunohistochemistry confirmed the histological appearance, showing positivity for markers of pyloric glands mucin (HIK1083 and/or MUC6), partial positivity for p53, and negativity for p16 [65]. These findings suggest that this neoplasia could arise on areas of gastric metaplasia [64]. As opposed to the extremely well differentiated variant, respectively, adenoma malignum, these tumors showed desmoplastic stroma and presented grossly as well defined tumor masses within the myometrium [64, 65].

The similar morphological features of adenoma malignum in both cervix and endometrium may suggest possible common cancer stem cells for both locations, along with possible epigenetic factors acting in female genital tract.

Adenoma malignum-like features were exceptionally described in other locations, such as in gallbladder adenocarcinoma [66] and urinary bladder adenocarcinoma [67], creating diagnostic difficulties, as they had to be distinguished from other benign conditions, such as Rokitansky–Aschoff sinus and adenomyomatosis of the gallbladder, or Müllerianosis of the urinary bladder, respectively.

Nodular fasciitis-like stroma and large cystic growth

Recently, Švajdler *et al.* have reported a new growth pattern at the invasive front of endometrioid endometrial carcinoma, in a 67-year-old woman, different from all other patterns of myoinvasion or morphological variations previously described in the literature. Its particularities consist in stromal and glandular architecture. In these areas, the stroma was vaguely nodular, with fibromyxoid change, variable cellularity, without nuclear atypia, pleomorphism or mitotic activity and collagen deposition, similar to nodular fasciitis. Neoplastic glands were elongated, slit-like or large and cystic, lined by flattened cells, with variable degrees of squamous differentiation. Large stromal nodules, alongside interconnected glandular spaces give resemblance to the phyllodes tumor of the breast [21].

This pattern is somewhat similar to MELF, but in the latter, there is only focal fibromyxoid change. As opposite to MELF pattern, in this case, the glands were interconnected, without fragmentations or single cells. Also, vascular invasion was not identified [21].

The appearance of the tumor in these areas produced diagnostic controversies, as it was considered, on a previous biopsy, a Müllerian adenofibroma, due to the benign-looking glands. This diagnostic was infirmed after examination of tissue samples following hysterectomy, in which there were found adjacent areas of well-differentiated endometrioid endometrial carcinoma, with pushing border pattern of myoinvasion. Differential diagnosis of the unusual growth pattern was made with carcinosarcoma (malignant mixed Müllerian tumor), that was invalidated by IHC tests showing keratin negativity in the stromal component [21].

Given that it is the single reported case of such pattern of invasion in endometrial carcinoma, its prognostic value cannot be appreciated, especially since the patient died of surgical complications and therefore, a response to oncological therapy could not be assessed [21].

Further studies are necessary to validate this newly described pattern of myoinvasion and to provide clinico-pathological correlations, mainly regarding the prognostic significance.

A similar growth pattern, with exuberant nodular fasciitis-like stroma was described in a variant of papillary thyroid carcinoma, requiring differential diagnosis with fibrous thyroiditis (fibrous variant of Hashimoto's thyroiditis and Riedel's thyroiditis), solitary fibrous tumor, anaplastic carcinoma secondary to dedifferentiation of a conventional papillary thyroid carcinoma, and carcinosarcomas [68].

Final remarks and conclusions

The review of the main myoinvasive patterns in endometrioid endometrial carcinoma highlights the difference between MELF, diffusely infiltrative, and, possible, nodular fasciitis-like stroma and large cystic growth patterns as the most aggressive tumor subtypes, compared to broad front, AM-like, and adenoma malignum patterns, which have a good prognosis.

Furthermore, these patterns may successfully complete the dual clinicopathological classification of the two types of endometrial tumors and may lead to new therapeutic approaches for each type.

The knowledge and accurate evaluation of the multiple patterns of myoinvasion in endometrioid endometrial carcinoma has a great practical value, as demonstrated in our experience, firstly for the correct assessment of the depth of myoinvasion, one of the main criteria in staging. Additionally, considering the results of numerous studies showing an association between patterns of myoinvasion and various features that influence the patient's evolution, we would like to highlight their possible prognostic value. The diversity of morphological aspects seen at the advancing margins of the tumor could be the result of a variable degree of molecular alterations, involved in carcinogenesis and tumor progression, explaining the higher aggressiveness of some patterns of myoinvasion.

In cases with mixed pattern of myoinvasion, a complex evaluation of the dominant pattern and the depth of myometrium invasion should be corroborated in order to obtain a good perspective about patients' prognosis.

Considering the possibility to identify specific molecular markers correlated to these patterns of myoinvasion, in correlation with EMT and cancer stem cells, future targeted therapies open promising perspectives in the treatment of endometrioid endometrial carcinomas.

The identification of invasion patterns known to be associated with more aggressive tumors, even in the presence of an initial low-grade morphology and corresponding stage, could raise the idea of some similarities in the gene profile of these endometrial carcinomas type 1 with those of type 2, being known that high-grade endometrioid endometrial carcinomas share a specific gene expression profile with serous-type endometrial carcinomas [69]. In this regard, the study of the characteristic molecular expression of type 2 endometrial carcinomas occurrence in low-grade endometrioid carcinomas with aggressive myoinvasion pattern could provide new insights into endometrial carcinogenesis and could also represent valuable predictive factors.

Conflict of interests

The authors declare that they have no conflict of interests.

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Received: January 20, 2018

Accepted: June 1, 2018