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Endometriosis and adenomyosis: Similarities and differences

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ABSTRACT

Deep endometriosis and uterine adenomyosis are two frequently encountered conditions affecting approximately 200 million women worldwide. They are closely related, showing similar histological patterns and multiple common pathogenic features, and share the same symptoms. It is therefore not surprising that they are often thought to have a common developmental origin. Indeed, both deep endometriosis and adenomyosis appear to derive from estrogen-dependent overproliferation of endometrial tissue and its subsequent implantation in ectopic sites.

Although the scientific community has shown increasing interest in these diseases over recent years, neither pathogenesis has yet been elucidated, so there are currently no efficient treatment options. Understanding the mechanisms underlying disease development, as well as discerning their relationship, are key to improving clinical management for millions of patients.

The aims of this review are to summarize current knowledge on deep endometriosis and adenomyosis pathogeneses and discuss the possibility that these two entities are actually differential phenotypes of the same disease.

1. Introduction

Despite accumulating literature on uterine adenomyosis and deep endometriosis, these diseases remain poorly understood, with no definitive medical treatment as yet [1]. It is now estimated that uterine adenomyosis affects close to 20 % of gynecology patients, potentially accounting for more than 40 % of total hysterectomies performed [2–4]. Moreover, deep endometriosis, whose prevalence has clearly increased over recent decades, remains somewhat intriguing [5]. Adenomyosis and deep endometriosis are serious chronic conditions that markedly impair women's quality of life, placing a strain on healthcare systems worldwide. Since recent papers suggest that these two diseases are related, it is now vital to decipher the mechanisms underlying their pathogeneses and symptoms in order to explore novel, safer and more effective therapeutic options. The goal of this review is to summarize similarities and differences between adenomyosis and deep endometriosis.

1.1. Historical data

1.1.1. Uterine adenomyosis

The first description of lesions initially named adenomyomas was provided in 1860 by German pathologist Carl von Rokitansky,

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who identified endometrial glands in the myometrium and termed them 'cystosarcoma adenoids uterinum' [6]. The first systematic description of the disease emerged from the work of Cullen, who, in the 19th century, researched mucosal invasion previously observed in other pelvic organs [7]. He found that epithelial tissue invading the myometrium consisted of uterine mucosa. In 1925, two years before Sampson coined the term endometriosis, Frankl created a name for mucosal invasion of the myometrium, calling it adenomyosis uteri [8,9]. The current definition of adenomyosis provided by Bird in 1972 states: 'Adenomyosis may be defined as the benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic non-neoplastic endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium' [10].

1.1.2. Deep endometriosis

In the late 19th and early 20th centuries, Cullen and Sampson published descriptions of what is today called deep endometriosis. In 1922, Sampson defined cul-de-sac obliteration as 'extensive adhesions in the cul-de-sac, obliterating its lower portion and uniting the cervix or the lower portion of the uterus to the rectum, with adenoma of the endometrial type invading the cervical and the uterine tissue and probably also (but to a lesser degree) the anterior wall of the rectum' [8]. Later, Koninckx and Martin argued that rectovaginal endometriotic nodules resulted from the natural evolution of peritoneal endometriosis, turning into deep-infiltrating endometriosis [11].

In our opinion, nodules of the rectovaginal septum are distinct from peritoneal endometriosis with a different pathogenesis, corresponding more to adenomyotic nodules, as we strongly suggested in 1997 [12]. Indeed, as described by Donnez et al. [13], from a histological perspective, deep rectovaginal endometriotic nodules are 'adenomyomas consisting of smooth muscle hyperplasia with active glandular epithelium and scanty stroma'.

1.1.3. In fact …

In fact, histological patterns of deep endometriosis and uterine adenomyosis look very much alike. Similar characteristics were also found in case of bladder adenomyosis [14], as clearly reported in 2000 in the manuscript 'Bladder endometriosis must be considered as bladder adenomyosis'.

In 1996, the term RAD (retroperitoneal adenomyotic disease) was used by the first author of this paper during a lecture in Geneva in front of skeptical endometriosis experts, still convinced that deep endometriosis was the consequence of infiltration of endometriosis from the peritoneal cavity. In reality, the definition of deep-infiltrating endometriosis as lesions penetrating the retroperitoneal space to a depth of 4–5 mm [15] was erroneous. It was proposed by Cornillie, a pathologist, without any conclusive of evidence. Even Koninckx, one of the coauthors, later acknowledged that this theory was a mistake [16]. Inevitably, this definition has led many authors to consider the majority of peritoneal and uterosacral ligament lesions as deep-infiltrating endometriosis based on one flawed argument: that they descend to a depth of 4–5 mm. Recent studies indicate that both collective cell migration (CCM) and epithelial-mesenchymal transition (EMT) are implicated in the pathogenesis of both uterine adenomyosis and deep endometriosis, raising the question of whether these two pathologies are just different manifestations of the same disease [17].

1.2. Magnetic resonance imaging (MRI) analysis: coexistence of both diseases

Although some reports in the 2000s revealed a high incidence of uterine adenomyosis in women with confirmed endometriosis,

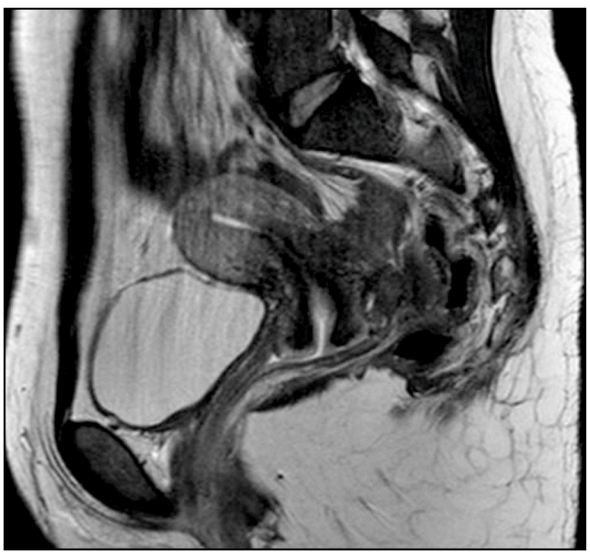

Fig. 1. Magnetic resonance imaging (T2 sagittal view) showing external uterocervical adenomyosis with involvement and hyperplasia of the bowel muscularis. Arrows clearly show the presence of cervical adenomyosis infiltrating the rectal muscularis (reprinted from 17).

accurate data were not available to assess its true prevalence or the extent of comorbidity between the two diseases (Fig. 1). Chapron et al. [18] documented the rate of MRI-detected adenomyosis according to the surgical phenotype of endometriosis. What they termed 'focal adenomyosis', was significantly associated with deep endometriosis.

To have a better idea of the prevalence of coexisting deep endometriosis and uterine adenomyosis, a retrospective analysis was conducted in a series of 100 women with clinically confirmed deep posterior endometriotic nodules of ≥3 cm in size, who had all undergone MRI before surgery [17]. Bazot and Darai's [19] MRI classification of uterine adenomyosis was applied. In this series of 100 patients (mean age 35.4 years), external uterine adenomyosis was observed in more than 97 % of subjects, strongly suggesting that uterine adenomyosis and deep endometriotic nodules are indeed linked. External posterior uterine adenomyosis was detected in the posterior part of the uterus in 39 cases and the posterior part of the cervix in 40 cases. In 20 cases, the adenomyotic lesions were situated in the lowest part of the cervix involving the posterior vaginal fornix. In two of these women, external adenomyosis involved the posterior part of both the uterus and the cervix.

The incidence of external posterior adenomyosis (97 %) was significantly higher in our study than in Chapron et al.'s series (66 %) [18]. This difference may be explained by more severe disease in our series, as we only included nodules of >3 cm in size.

MRI analysis confirms increasing evidence that these two diseases are associated. It is time to reconsider the pathogenesis of deep nodules, which might not be the result of deep-infiltrating endometriosis, but rather the consequence of some form of cervical or uterine adenomyosis.

As previously suggested by Nisolle and Donnez [12], Donnez et al. [20] and Adamyan et al. [21], these lesions may originate from the posterior uterine wall or cervical wall (uterine or uterocervical adenomyosis) and invade the rectovaginal space and digestive tract. Uterocervical adenomyosis could therefore be the cause of deep endometriotic nodules, as is the case for deep anterior endometriosis, also known as bladder adenomyosis (adenomyotic nodules) [14].

1.3. Mechanisms of action implicated in adenomyosis and deep endometriosis

The exact mechanism by which endometrial cells become invasive has yet to be determined. Two main mechanisms of pathologic cell invasion, namely EMT and CCM, have been described in the literature [22,23]. The former is characterized by destabilization of strong E-cadherin-positive cell-cell junctions. It is then replaced with N-cadherin, before eventually disassembling and allowing single cells to change their polarity and shape to mesenchymal cells with motile capacity [22]. Conversely, over the course of CCM, cells maintain intact junctions and collaborate to form invasive cell clusters with the ability to progress, attach and rearrange the surrounding extracellular matrix (ECM) [23]. Indeed, both EMT and CCM have previously been implicated in the pathogeneses of endometriosis and adenomyosis [24–27], but there is still a lack of firm evidence, especially on the initial steps of invasion.

1.3.1. Which molecular mechanisms are involved in uterine adenomyosis and what is known so far?

Like eutopic endometrium, ectopic endometrium in adenomyosis is likely to undergo cyclic bleeding. It inevitably initiates a process of tissue injury and repair (TIAR), inducing fibrosis. In uterine adenomyosis, high levels of estrogen stimulate muscle fiber peristalsis in the myometrium, generating stress in the endometrial-myometrial junctional zone (JZ) [28,29]. Hence, the combination of hyperestrogenism and hyperperistalsis leads to tissue self-trauma in the JZ, and has been speculated to aid translocation of basal endometrium to the myometrium.

1.3.1.1. Platelet investigation: is there a role for platelets?. In 2016, Liu et al. [30] reported that platelets can be detected in adenomyotic lesions, but not in healthy endometrium, and suggested a potential role for activated platelets in the EMT process and subsequent fibrogenesis. In a recent study by Mosele et al. [31], however, the role of platelets was not confirmed in the pathogenesis of adenomyosis. Indeed, expression of CD41, which is a marker of platelet aggregation, was significantly higher in stroma from women with normal uteri than in stroma (eutopic or ectopic endometrium) from women with adenomyosis. Only minimal CD41 expression was observed in ectopic stroma, failing to confirm Liu et al.'s findings on a possible role for platelets [30]. These results were also confirmed

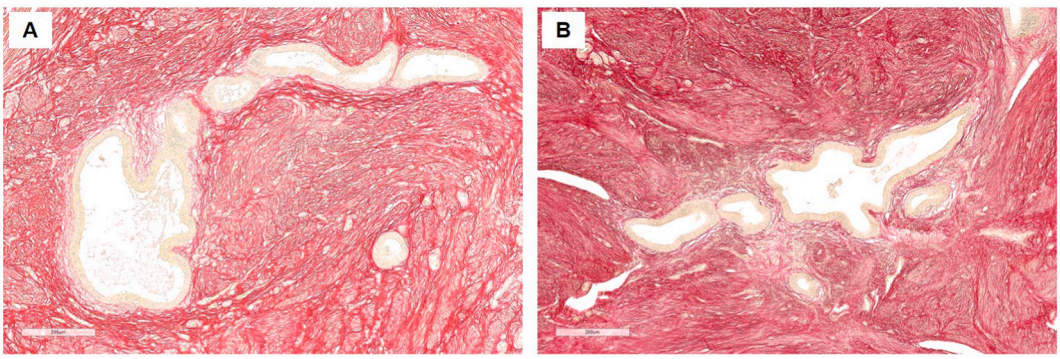

Fig. 2. Sirius red staining reveals the presence of dense collagen fibers (in red) around a deep endometriotic nodule of the rectovaginal septum (A) and an adenomyotic lesion (B).

in deep endometriosis, where platelet accumulation was shown to be significantly lower in ectopic lesions than in endometrium from healthy subjects [32].

1.3.1.2. Fibrogenesis: old evidence. Early evidence of fibrogenesis in adenomyosis dates back to 1930, and fibrosis is still considered an important aspect of the pathogenesis of the disease [33,34]. In one of our studies [27], staining for fibrosis in control uteri produced very weak results, but adenomyotic lesions contained fairly large numbers of collagen fibers [27]. In the same study, we observed fibrosis to be present in deep rectovaginal endometriosis as well. Indeed, smooth muscle tissue can be often recognized around ectopic endometriotic glands, suggesting a role of fibrosis in disease pathophysiology. It is now argued that fibrogenesis may be a 'molecular hallmark of endometriosis pathophysiology' and should be taken into account when defining and describing the condition [35,36].

Fibrosis results from activation of ECM-producing myofibroblasts and subsequent accumulation of collagen fibers [37]. We and others have previously found fibrosis to be a key element in the pathophysiology of both endometriosis and adenomyosis [31,32,38]

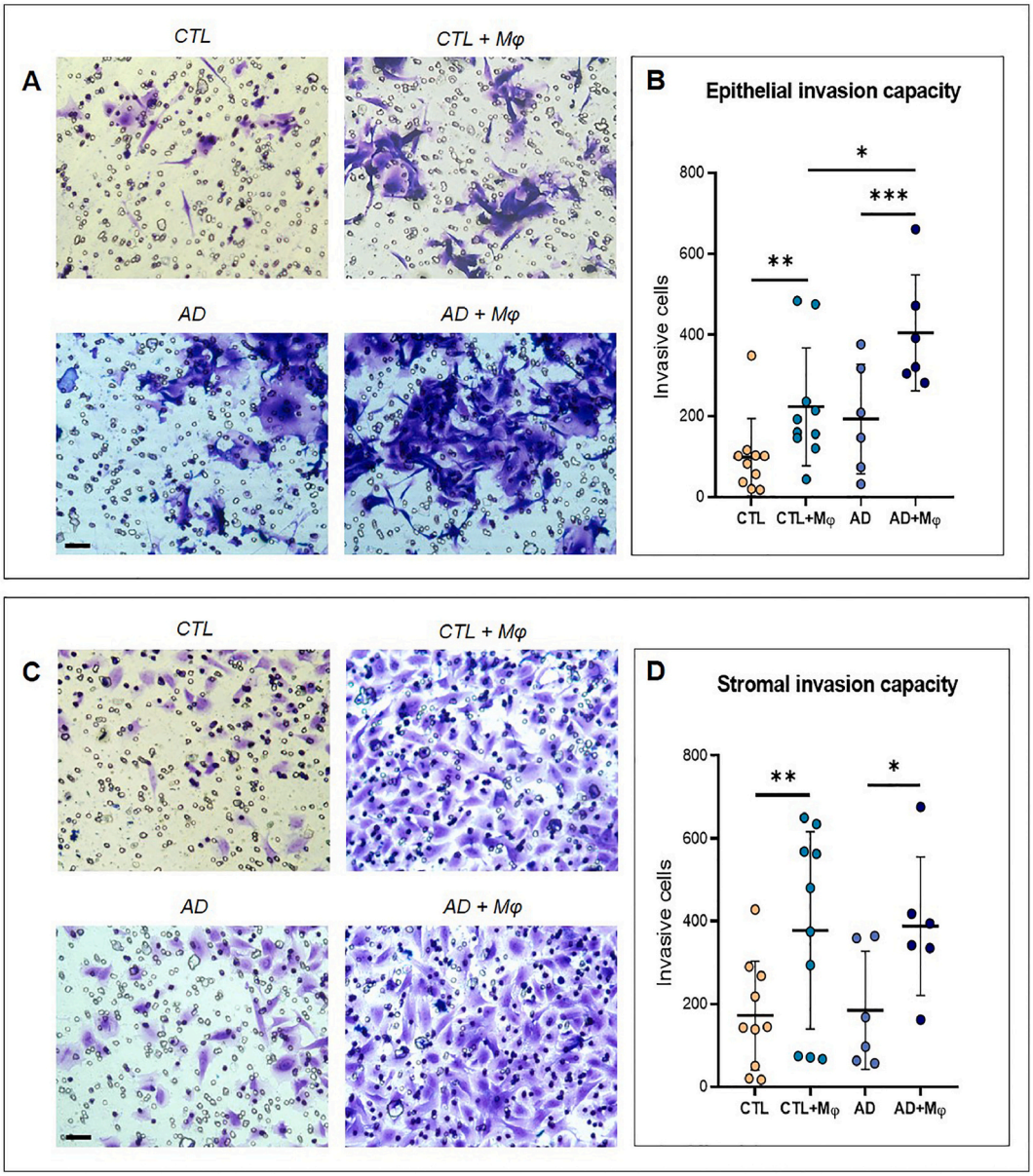

Fig. 3. Evaluation of endometrial epithelial and stromal cell invasiveness in the presence of M2 macrophages. (A) Epithelial cell invasiveness. Scatterplots showing numbers of invasive cells (**p = 0.002; ***p = 0.0002; *p = 0.0312). Results are presented as mean ± SD. (B) Stromal cell invasiveness. Scatterplots showing numbers of invasive cells (**p = 0.0047; *p = 0.0469). Results are presented as mean ± SD. Scale bars represent 50 μm. CTL: cells from healthy controls; CTL + Mφ: cells from healthy controls co-cultured with macrophages; AD: cells from adenomyosis patients; AD + Mφ: cells from adenomyosis patients co-cultured with macrophages (reprinted from 43).

(Fig. 2). In our investigations, however, aberrant accumulation of collagen was only detected in ectopic lesions, while eutopic endometrium from the same subjects did not differ much from healthy tissue [31,32]. We therefore believe that fibrogenesis may be triggered at some later stage upon lesion establishment. The exact impact of macrophages on this process in ectopic lesions must be further explored, because the inflammatory activity of these cells often causes fibrosis [38,39].

1.3.1.3. Role of M2 macrophages: M2 macrophages enhance endometrial cell invasiveness by promoting CCM in uterine adenomyosis. Macrophages are potent mediators of tumor progression, inducing ECM remodeling, enhancing cell motility and promoting angiogenesis via a range of pro- and anti-inflammatory molecules they secrete [40]. They also show differential properties during disease evolution, as they are capable of reversibly shifting their phenotype between M1 and M2 with distinct capacities [41].

Ample data confirm the role of immunological dysregulation in case of adenomyosis, primarily altered macrophage infiltration and function [3,42]. Indeed, numerous studies have reported greater accumulation of these cells in endometrium and lesions from adenomyosis subjects, implicating them in disease invasiveness, pain and infertility [42]. Since excess macrophage infiltration has also been confirmed in adenomyosis [32], we conducted an in vitro study to investigate if and how these cells trigger endometrial invasiveness during disease onset [43]. In our study, specifically M2 macrophages were detected in both in endometrium and lesions from adenomyosis patients, suggesting that they play a crucial role in disease development and/or progression. When co-cultured with endometrial cells from both adenomyosis patients and healthy subjects, M2 macrophages induced a more invasive phenotype, confirming their important role during disease progression [43] (Fig. 3). Moreover, preliminary data suggest that endometrium from both endometriosis and adenomyosis have the capacity to drive macrophage polarization toward the M2 phenotype, whose accumulation may indeed trigger disease initiation and lead to progression and fibrosis [43–45].

1.3.1.4. EMT or CCM?. EMT has previously been blamed for epithelial cell invasiveness in adenomyotic lesions [24], but our previous research failed to confirm this hypothesis, having observed higher epithelial N-cadherin levels in ectopic lesions but no significant decrease in E-cadherin. These findings were consistent with previous reports on deep endometriosis, where E-cadherin expression was retained in evolving ectopic glands [25,26].

Our studies also revealed that CCM may be the mechanism behind endometrial invasiveness [43]. The hallmarks of CCM include maintenance of tight intercellular junctions and, concurrently, motility and capacity to rearrange the surrounding ECM [23]. E− and N-cadherin-positive cell junctions look to be maintained in endometrium from adenomyosis subjects, and are especially pronounced in glands adjacent to the JZ, pointing to movement of entire clusters of cells rather than single cells individually (Fig. 4). It has also been demonstrated that endometrial cells do possess invasion capacity in vitro, despite undergoing EMT and losing their cohesion molecules [43].

1.3.1.5. A role for MMP9?. Matrix metalloproteinases (MMPs) are proteolytic enzymes expressed in the endometrium during the menstrual cycle to induce ECM breakdown, leading to menstruation and ultimately tissue regeneration [46,47]. MMP9 has been identified as one of the most crucial factors to endometrial function, since its expression markedly increases in stromal, epithelial and inflammatory cells throughout the cycle in response to ovarian steroids [48–50].

In adenomyosis patients, we observed increased MMP9 levels in eutopic endometrium, in line with previous reports on the involvement of this protein in the endometrial invasion process [51]. Indeed, Zhai et al. also found MMP9 expression to be substantially higher in adenomyosis patients, along with a variety of genes involved in cellular cohesion and coupling [52]. Elevated MMP9 levels in eutopic endometrium from adenomyosis patients would drive adenomyotic tissue to remodel the stroma and invade surrounding uterine muscle, allowing lesions to implant in ectopic zones. Collectively, these data provide further proof that CCM may be the main mechanism behind endometrial invasiveness in adenomyosis.

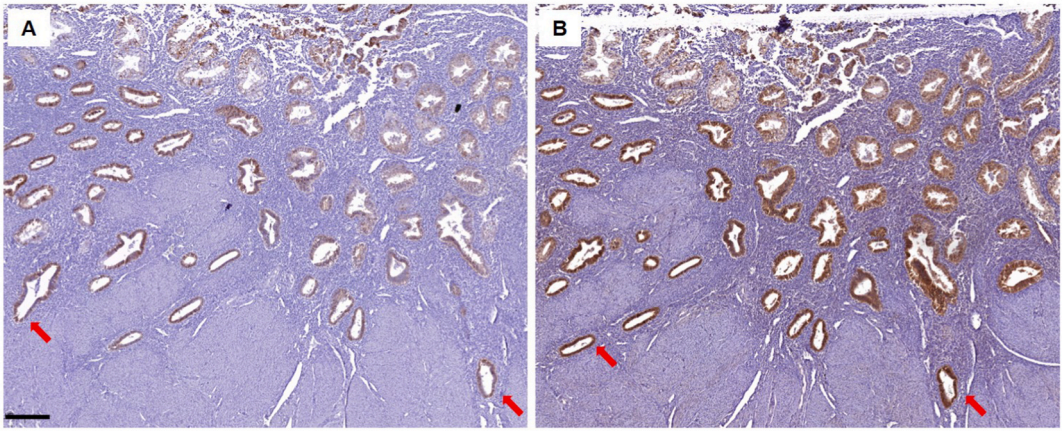

Fig. 4. E− (A) and N-cadherin (B) expression is maintained in basal glands in adenomyosis. Red arrows point to positive invasive glands. Scale bar represents 200 μm.

1.3.2. Identifying common pathogenic features in deep endometriotic nodules and uterine adenomyosis

1.3.2.1. Are we able to identify common pathogenic features in both diseases?. Previous research has already proved that CCM is an essential component of the invasion process in deep endometriotic nodules, which acquire an invasive phenotype and ECM rearrangement properties. At the same time, they maintain their epithelial phenotype and some cell-cell junctions, even along the most progressive front edge of the disease [25,26,32].

By making a direct comparison between deep endometriotic nodules and adenomyosis, we were able to identify pathogenic features common to both diseases, including decreased platelet numbers, greater macrophage accumulation, fibrosis and irregular angiogenesis [32].

In a very recent study, Stratopoulou et al. clearly demonstrated that platelet aggregation was significantly curtailed in deep endometriotic nodules, similar to observations in adenomyotic lesions. There was significantly more macrophage accumulation in deep endometriotic and adenomyotic lesions than in their corresponding endometrium or healthy controls. As it is widely known that excessive macrophage accumulation and associated inflammation can induce disease invasion and fibrosis, it is reasonable to assume that they also mediate these processes in both diseases [39,53]. Indeed, it could be argued that macrophages are the root cause of endometriosis, mistaking ectopic endometrial tissue for a wound that they constantly try to repair. The sheer abundance of macrophage-secreted cytokines and growth factors could therefore promote lesion invasiveness and fibrosis [39]. Like the increase observed in adenomyotic lesions, collagen accumulation was clearly present at significantly higher levels in deep endometriotic lesions than in corresponding endometrium.

MMP9 has also been described in the context of deep nodular endometriosis, where it is believed to participate in CCM during disease development and progression [25,52,54]. Other studies have previously reported elevated MMP9 activity in the endometrium of both adenomyotic and endometriotic tissues, where this enzyme is thought to contribute to metastasis of lesions and ensuing angiogenesis [32,52,54].

The role of estrogen should also be highlighted, as it is implicated in both diseases and may trigger their development and associated symptoms [3,5,55,56]. In fact, new treatment options that reduce estrogen levels do appear to alleviate symptoms in severe cases of both endometriosis and adenomyosis [5,55,57–59], but it is abundantly clear that many other factors are involved in their pathogeneses.

1.3.3. Are apoptosis, autophagy and progesterone resistance also implicated in both diseases? Apoptosis

Human endometrium is a dynamic tissue, periodically undergoing shedding and regeneration in response to the local hormone

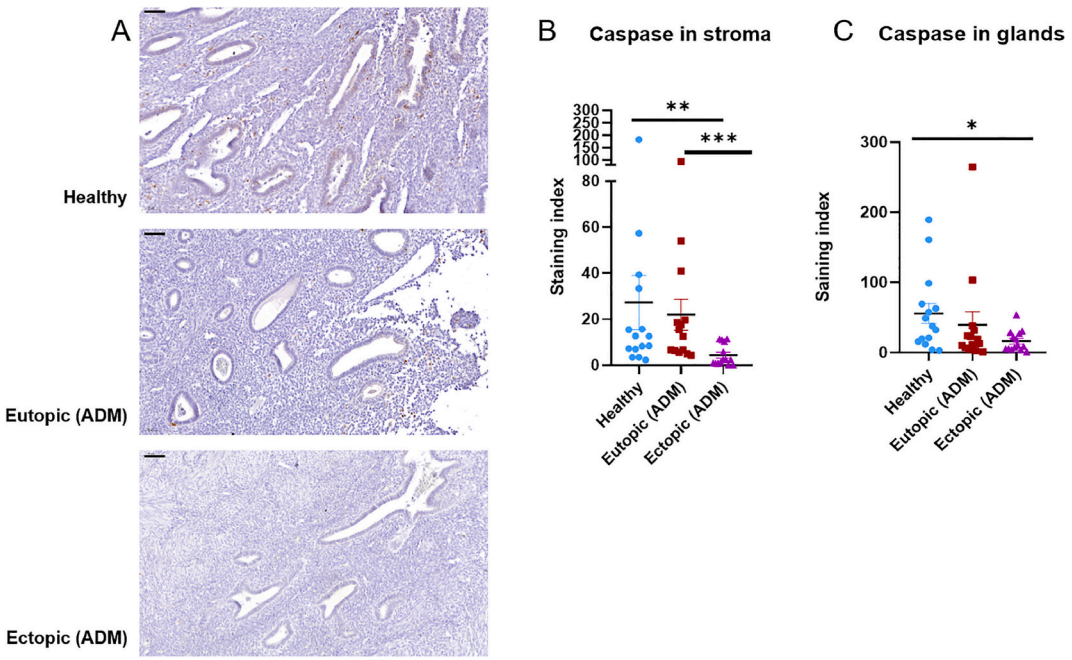

Fig. 5. Evaluation of caspase 3 expression. (A) Immunoreactivity staining results for caspase 3 in healthy endometrium, eutopic adenomyotic endometrium and matched ectopic adenomyotic endometrium. Phase: menstrual. (B) Staining index for caspase 3 in endometrial stroma. Caspase 3 expression was found to be significantly stronger in healthy and eutopic adenomyotic stroma than in matched ectopic adenomyotic stroma (**p = 0.0013, ***p = 0.0006). Results are presented as mean ± SD. (C) Staining index for caspase 3 in endometrial glands. Caspase 3 expression was found to be significantly stronger in healthy endometrial glands than in ectopic adenomyotic glands (*p = 0.0157). Results are presented as mean ± SD. Scale bar represents 50 μm. ADM, adenomyosis (reprinted from 64).

milieu [46,60]. Apoptosis therefore occurs physiologically in endometrium when circulating progesterone levels drop, prompting transition from the secretory to the menstrual phase [61]. This process is essential to endometrial regeneration and function maintenance [60,61]. Dysregulation of apoptotic mechanisms, on the other hand, has been found to contribute to endometriosis development by inhibiting physiological cell death and promoting aberrant cell survival and invasion [62,63].

To assess apoptosis in adenomyosis, we previously analyzed caspase 3 expression, which was found to be significantly less intense in ectopic adenomyotic stroma than in healthy endometrial stroma, also demonstrating dysregulation of apoptotic mechanisms in uterine adenomyosis [64] (Fig. 5).

1.3.3.1. Autophagy. Autophagy is another important biological cellular process that removes unnecessary or dysfunctional cell components in compromising conditions, such as hypoxia, starvation, lack of nutrition, or extreme pH values [65]. Autophagy is involved in physiological processes occurring in endometrium, such as menstruation, decidualization and successful establishment of pregnancy. Its dysregulation has been implicated in endometrium-associated diseases and disorders, such as endometriosis, endometrial carcinoma and infertility [66]. In peritoneal endometriotic lesions, levels of autophagy are decreased compared to normal endometrium [67,68]. Similarly, in adenomyosis, we previously demonstrated that ectopic lesions resist to autophagic signals, as stromal expression of microtubule-associated proteins 1A/1B light chain 3B (LC3B) was significantly diminished in ectopic endometrium, which could in turn lead to ectopic implantation and survival of lesions. Moreover, decreased expression of autophagy-related genes has been observed in eutopic endometrium from adenomyosis patients compared to that of healthy women, pointing to aberrant cell survival in these cells as well [69].

All in all, our results point to resistance to cellular autophagy and death in ectopic adenomyotic sites, allowing adenomyotic cells to survive and proliferate in a disorganized way, deviating from normal patterns of the menstrual cycle [64].

1.3.3.2. Progesterone resistance. Progesterone signaling is vital to physiological endometrial function, as its upregulation during the secretory phase leads to proliferation arrest, differentiation of cells to a receptive phenotype, and eventually activation of the apoptotic mechanism with a view to menstruation [61]. The theory of progesterone resistance is now well established in patients suffering from endometriosis [70–73] and particularly deep endometriosis [73,74]. In adenomyotic lesions, both eutopic and ectopic sites show decreased progesterone receptor (PR) expression, confirming that progesterone resistance is also involved in this disease. Due to the multifaceted role of progesterone in endometrium, it is likely that inadequate progesterone signaling in adenomyosis both impairs endometrial receptivity and blocks apoptosis, promoting overproliferation and thereby facilitating disease progression. Bulun et al. [74] recently corroborated one of our papers reporting that endometrial cell populations possess survival and growth capabilities [3,43].

According to Bulun et al., KRAS-activating mutations are the most commonly found genetic variants in endometriotic epithelial cells, while adenomyotic epithelial cells almost always carry KRAS mutations. In endometriotic and adenomyotic stromal cells, epigenetic abnormalities are very similar and involve abnormal expression patterns of nuclear receptors, including steroid receptors. Deficient PR expression results in progesterone resistance in both endometriosis and adenomyosis.

Interestingly, MMP9 has been shown to be downregulated by progesterone [75,76], so progesterone resistance itself may be to blame for endometrial cell invasiveness in deep endometriosis and adenomyosis. This also explains why a considerable proportion of patients (approximately 1/3) do not respond to progestogen treatment, highlighting the need for alternative therapies [77].

1.4. Experimental models

In 1950, Te Linde and Scott [78] reported the first nonhuman primate (rhesus monkey) model of endometriosis, involving autologous transplantation of surgically excised fragments of endometrium inside the pelvis. Unfortunately, we do not know if just endometrium or endometrium associated with myometrium was grafted. What we do know, from several reports, is that nonhuman primates present with spontaneous endometriosis: 36 % of female rhesus monkeys [79], 27 % of baboons [80], and 28.7 % of cynomolgus monkeys [81]. In our baboon study, we only observed a 4.8 % rate of spontaneous endometriosis among 41 baboons originating from the wild, while endocervical canal resection revealed a 27.6 % rate of induced endometriosis [82].

The presence of 'iatrogenic' endometriotic (adenomyotic) tumors was also demonstrated in women after laparoscopic subtotal hysterectomy for fibroids or adenomyosis and subsequent uterine morcellation, when pieces of myometrium and endometrium were inadvertently left behind in the peritoneal cavity [83]. This suggests that retained fragments containing of endometrial glands and myometrium are able to survive and grow inside the peritoneal cavity by generating neovascularization from the peritoneum. It results in tumors composed of smooth muscle hyperplasia, endometrial glands and stroma with exactly the same histopathological profile as adenomyosis and similar to nodular endometriosis [83].

Based on these observations of iatrogenic adenomyosis in women, Donnez et al. developed an experimental model to investigate nodular endometriosis in baboons [84,85]. Using grafted specimens containing endometrium including the JZ and superficial/deep layers of myometrium, they were able to induce nodular endometriotic/adenomyotic lesions within 6 months. To our knowledge, this was the first time that an experimental animal model was able to replicate adenomyotic lesions with the same histological aspect as uterine adenomyosis and deep endometriotic nodules. These induced nodular endometriotic/adenomyotic lesions were significantly larger and showed greater glandular density when tissue specimens containing the JZ were grafted, indicating that the JZ may well be a key component that clearly merits further scrutiny [84,85]. Already back in 1998, Leyendecker et al. [86] suggested that abnormal functioning of the human JZ could constitute a common pathogenic factor for endometriosis and adenomyosis development. These

investigators postulated that disruption to the basal endometrium may explain structural and functional abnormalities of the JZ (hyperperistalsis, dysperistalsis) and smooth muscle proliferation associated with endometriosis and adenomyosis [87]. A possible relationship between adenomyosis and deep nodular endometriosis could be a consequence of this infiltrating growth pattern. Although endometriosis is considered a benign condition, some investigators have pointed out certain characteristics of malignancy, such as distant foci and invasion of other tissue, with subsequent damage [88,89]. Friedl and Alexander [90] described invasion processes in cancer in some detail and, according to O. Donnez, there are number of similarities with endometriosis. First of all, endometriosis and cancer appear to share the same proinflammatory paracrine environment, including common cytokines, growth factors and nuclear factor kappa B. The theory of collective invasion posited by Friedl et al. [91] and Ilina and Friedl [92] requires cell-cell adhesion and multicellular coordination to occur simultaneously with migration. As in most cases of collective cancer cell invasion [93], Donnez et al. observed in their baboon model that several leader cells with mesenchymal characteristics generated traction and pericellular proteolysis toward the invaded tissue structure [25]. Morphological similarities can also be found with the invasive behavior of deep nodular endometriosis in humans, which is known to sometimes invade the anterior rectal muscularis [94]. In lesions induced after grafting, we found sigmoid wall invasion to be morphologically indicative of CCM, with native nodular tumors and secondary groups of cells able to infiltrate surrounding organs and even colonize the sigmoid mucosa. This demonstrates that the theory of CCM could be applied to the invasion patterns in deep endometriosis as well as adenomyosis [3,5].

Unfortunately, typical mouse models of adenomyosis remain insufficiently characterized. While a several of hormone-disrupting procedures have been reported to promote an adenomyosis-related phenotype, strain specificity and lack of consistency hamper our understanding of the disease pathogenesis, calling for more extensive studies to validate these models [95]. To overcome these limitations, our current research focuses on implementing primary endometrial organoids as an advanced in vitro model to more accurately mimick the pathogenesis of the disease. Using this approach, we aim to dig deeper into the mechanisms of impaired apoptosis and autophagy in adenomyosis and elucidate their underlying causes.

2. Conclusion

Over 20 years ago, it was asserted that superficial peritoneal endometriosis, ovarian endometriomas and deep endometriosis should be considered distinct entities from both a morphological and pathogenic perspective, with the latter closely resembling uterine adenomyotic lesions [12]. The present review reveals that deep endometriosis and adenomyosis are frequently associated. According to a recent review by Vercellini et al. [96], emerging evidence suggests that adverse reproductive and obstetric outcomes are due to their association.

Deep endometriosis and uterine adenomyosis development depend on a number of similar dysregulated mechanisms, including resistance to physiological cell death, aberrant ECM-degrading ability and inadequate responsiveness to progesterone [64,74]. Both apoptosis and autophagy are downregulated, potentially contributing to disease progression by ensuring cell survival and invasion. MMP9 is increased and therefore likely to promote invasion during disease initiation. Progesterone resistance appears to be a key component in the pathogenesis of adenomyosis and deep endometriosis, inhibiting cell death and promoting lesion invasion [64].

Hence, the idea that retrograde menstruation alone could account for deep endometriosis and adenomyosis development is highly unlikely. In our view, a more complex process plays out during lesion development. It is possible that certain endometrial cells acquire invasive capabilities and evade the JZ to generate adenomyotic as well as deep endometriotic lesions. Of course, Müllerian remnants displaced during embryonic development or adult progenitor cells could also participate in de novo generation of endometrial tissue in ectopic sites [2,3]. We, however, favor the hypothesis that adenomyotic lesions may actually trigger deep endometriosis by proliferating and spreading to extrauterine locations [17,97], thereby activating the TIAR mechanism. Tissue-repairing leukocytes like macrophages accumulate in the damaged location, then secrete various growth factors and cytokines in attempts to heal the trauma. This boosts cell proliferation and neoangiogenesis, facilitating and even promoting lesion progression by CCM and fibrotic tissue formation [39,64,98].

Practice points

- Progestins and COC's are usually effective in treating endometriosis-related pain, but one third of the patients fail to respond because of progesterone resistance.
- Severe adenomyosis fails to respond to COC's and progestins due to progesterone resistance.
- Oral gonadotropin-releasing hormone–antagonists constitute a new medical option showing potential in treating endometriosis- and adenomyosis-associated symptoms
- Presence of uterine adenomyosis in deep endometriosis patients is very common and should be considered when handling the diseases in a clinical context.

Research agenda

- The underlying causes of macrophage accumulation in endometriosis and adenomyosis
- The mechanisms via which endometrial cells in those diseases manage to resist physiological cell death mechanisms
- The molecular mechanisms responsible for progesterone resistance observed in endometriosis and adenomyosis patients
- The possibility of a common developmental origin of endometriosis and adenomyosis

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Summary

Although adenomyosis and deep endometriosis were first described more than a century ago, controversy still surrounds their pathogeneses. It is now known that the two diseases frequently coexist and share multiple pathogenic features, suggesting a link. Recent literature reveals involvement of CCM in endometrial tissue invasion and disease establishment. Macrophages but not platelets could trigger this process in deep endometriosis and adenomyosis, subsequently leading to lesion progression and fibrogenesis. Matrix metalloproteinases and especially MMP9 degrade the ECM to facilitate motility, and have been found to play a key role in the pathogenesis of both conditions. On the other hand, ectopic cells from endometriotic and adenomyotic tissue possess the capacity to resist apoptosis and autophagy, eventually surviving and proliferating aberrantly. Finally, the role of hormones should be emphasized, as hyperestrogenism and progesterone resistance are involved in both pathogeneses and related symptoms. There is much to learn about the origin of the two conditions and several animal models have attempted to address these knowledge gaps over the years. Nonhuman primates appear to mimic disease characteristics more accurately than smaller animals, including the processes of CCM and lesion invasion, while also demonstrating similarities between DENs and adenomyotic lesions. All in all, there are ample data supporting a link between deep endometriosis and adenomyosis. It is probable that adenomyotic lesions resist physiological cell death, overproliferate and progress to implant in extrauterine locations, hence generating DENs. Taking into account what we already know, future research is expected to elucidate the mechanisms underlying endometriosis and adenomyosis development, clarify their association, and eventually improve clinical management for millions of patients suffering worldwide.

Declaration of competing interest

The authors declare no competing interests.

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