Pathogenesis of Adenomyosis

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Cancer arising from adenomyosis is very rare, with transformation occurring in only 1% of cases and in older individuals. Adenomyosis, endometriosis and cancers may share a common pathogenic mechanism that includes hormonal factors, genetic predisposition, growth factors, inflammation, immune system dysregulation, environmental factors and oxidative stress. Endometriosis and adenomyosis both exhibit malignant behaviour. The most common risk factor for malignant transformation is prolonged exposure to oestrogens. The golden standard for diagnosis is histopathology. Colman and Rosenthal emphasised the most important characteristics in adenomyosis-associated cancer.

adenomyosis cancer endometriosis

1. Introduction

Adenomyosis is a common, benign gynaecological disease characterised by the extension of endometrial tissue into the myometrium [1]. It affects mostly women of late reproductive age, including women in menopause [2][3]. Pelvic endometriosis is a common disease affecting 7–15% of women of reproductive age [4][5], and it is expected to disappear with advancing age as it is oestrogen-dependent [6]. However, it has a prevalence of 2–4% in postmenopausal women, and in these cases, it can be associated with adenomyosis with a rare possibility of malignancy [6].

Adenomyosis is characterised by the presence of aberrant endometrial tissue outside of the uterine cavity in intra- and extra-abdominal sites [4][5][7]. It can also occur in the cervix, round ligament, abdominal scars [4][7], pararectal space, paraovarian region, parametrium, liver, appendix and mesentery [8]. It is often associated with endometriosis [7].

Cancer arising from adenomyosis is very rare, with transformation occurring in only 1% of cases [4][5][9] and in older individuals [10]. The first case of clear cell and endometrioid carcinoma arising from adenomyosis was described in 1897 [3]. Adenomyosis is more commonly associated with endometrioid carcinoma, but clear cell carcinoma is also observed [3][4]. Certain cell types are involved, such as epithelial and mullerian types, with sarcomas described as well [11][12].

Even if endometriosis, adenomyosis and cancers have common manifestations, the pathogenic mechanism of malignant transformation remains unknown. A better knowledge of pathogenesis aids in diagnostic and therapeutic

management [11][12]. The histological description is important for standardising the description of cancers developed from adenomyosis and to differentiate them from those that appear simultaneously with adenomyosis without knowing the exact relationship between them [13][14]. These concomitants are important because they modify the therapeutic strategy [14].

As cancer arising from adenomyosis is very rare, adenomyosis, endometriosis and cancers may share a common pathogenic pathway, though the pathogenic mechanism still remains to be established. There is also a need to have a standardised treatment.

2. Pathogenesis

The pathogenesis of a malignant transformation in adenomyosis appears to involve inflammation and elevated levels of IL1 and IL6 [4]. The underlying mechanisms may involve genetic mutations, epigenetic changes, and tumour suppressor gene alterations in adenomyosis [11]. IL-37 is also involved in adenomyosis. IL-37 was discovered through a bioinformatics analysis in 2000 and is a member of the IL-1 family. Oestrogen and progesterone do not have an effect on the IL-37 protein in cancer cells. While IL-37 does not affect the proliferation and colonisation of cancer cells, it suppresses the migration and invasion ability of endometrial cancer cells. Furthermore, a decreased expression of MMP2 via the Rac/NF-kB signalling pathway in cancers is also observed [12].

Adenomyosis, endometriosis and cancers may share a common pathogenic mechanism that includes hormonal factors, genetic predisposition, growth factors, inflammation, immune system dysregulation, environmental factors and oxidative stress [11] (**Table 1**). Endometriosis and adenomyosis both exhibit malignant behaviour [4][5][11][12].

Table 1. Common pathogenic mechanisms between adenomyosis, endometriosis and cancers.

Pathogenesis	Genetics	Inflamation and Immunology	Hormones	Oxidative Stress
Adenomyosis with a similar role in malignancy	K-RAS mutation (V-Ki-RAS 2 Kirsten rat) CTNNB1 encoding B-cathenin ARID1A (A-rich interactive domain-containing protein 1A) p53 JAZF1-SuZ12 EPC1-PHF1 PTEN loss	COX2 TNF-*α* Toll-like receptors (TLR1) Nuclear factor Kappa (NF-KB) Macrophage IL-6 IL-10	Oestrogen Poor response to progesteron	ROS Annexin ANXA2 EMT MMP2 and 9 (metalloproteinase)

COX2—cyclooxygenase-2; TNF-*α*—tumour necrosis factor alpha; IL-6—interleukin-6; IL-10—interleukin-10; ROS —oxygen-containing reactive species.

The pathogenic mechanisms of transformation still remain unclear [11].

Annexin ANXA2, a protein that is increased in angiogenesis, metastasis, endometrial growth and the epithelial–mesenchymal transition, is implicated in pathogenesis. Similarly, invasion, metastasis and tissue growth occur in oxidative stress and inflammation. A KRAS mutation in the V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog is responsible for increased growth factors and hinders the tumour response to progesterone, interfering with treatment [10][11][12][13][14].

This condition may be associated with genetic mutations at the CTNNB1-encoding B-catenin (cadherin-associated protein) level [12]. The ARID1A (A-rich interactive domain-containing protein 1A) is a tumour suppressor gene that is disrupted and interacts with p53 [12][14][15]. It is associated with heterozygosity loss in adenosarcomas, and other mutations such as JAZF1-SuZ12, EPC1-PHF1 or PTEN loss have also been reported [15][16]. Reactive oxygen species (ROS) can cause DNA damage, and various inflammatory factors, including cyclooxygenase 2 (COX-2), TNF-alpha, toll-like receptors (TLRs), nuclear factor kappa B (NF-κB) and macrophages, as well as IL-6 and IL-10, are implicated in pathogenesis. Ceasing and reversing the epithelial–mesenchymal transformation may function as a therapeutic strategy [10][11]

Tamoxifen may be implicated in the malignancy of adenomyosis, which is a risk factor for the development of genital cancers but has a good prognosis [6][10][11][12]. While direct malignancy occurs in less than 1% of cases and is associated with a poor prognosis, the potential for transformation is poorly understood, even though it shares pathogenic pathways. Further studies are needed [11].

Risk factors include pelvic irradiation, and the laparoscopic morcellation of benign uterine tumours can lead to unexpected malignancies [9][15][17]. However, endobag morcellation can be used with minimal risks. Other risk factors associated with endometrial cancer include BMI, hypertension, hyperinsulinemia and prolonged exposure to oestrogens [3]. Hormone replacement therapy is the most common risk factor, although ectopic endometrial tissue can produce oestrogens through autocrine and paracrine effects, which may explain the persistence and recurrence of tumours in menopause [6].

Metalloproteinases 2 and 9 appear to be involved in tumour invasion, while PCNA is a marker of proliferation [18]. They can be used in an immunoreactive score which has been previously used in colorectal endometriosis and endometriotic invasion [18]. However, MMP2 and MMP9 increase during a malignant transformation, so they can be used as indicators of malignancy [18].

Regarding the theories of adenomyosis, there are two main hypotheses: the first is that tissue injury and repair in the endometrium lead to stromal invagination into the layer of myometrium, which is associated with environmental factors; the second is based on the metaplasia of displaced embryonic pluripotent Mullerian remnants or stem cells. An essential involvement in adenomyosis is the epithelial–mesenchymal transition, as previously mentioned [16].

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