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# Providing new insights into the endometriosis-associated cancer arising in episiotomy scars

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## ABSTRACT

Endometriosis-associated malignancy in an episiotomy scar is rare. The predictive factors are poorly understood as are the mechanisms and pathways associated with implantation and malignant transformation.

In this study we describe the cases reported in the literature of malignancies arising in endometriosis foci of an episiotomy scar. We identified five cases described between 1990 and 2016.

These cases represent recurrence of endometriotic lesions in an episiotomy scar after previous diagnosis of endometriosis, three to twenty-five months before. Histology revealed clear cell tumours in four cases and a serous papillary carcinoma. The approach encompassed surgical removal for diagnosis and as part of the therapeutic strategy. Adjuvant treatment was performed depending on classical prognostic factors. Mechanisms of endometriosis implantation in scars include the influence of oestrogens in the healing process and activation of COX-2, aromatase and matrix metalloproteinases. Nevertheless, for malignant transformation, other pathways seem to play a role, namely inflammation, immune response and oxidative stress, induced by iron deposits due to haemorrhage.

Further studies are needed to allow the establishment of a predictive model for malignant transformation of endometriosis in episiotomy scars.

**Key words:** endometriosis; episiotomy; malignancy; carcinogenesis

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## INTRODUCTION

Endometriosis is a chronic benign and oestrogen-dependent gynaecologic disease, with estimated frequency from 6% to 10%, among women of reproductive age [1]. Ectopic endometrium can be localized in the pelvic peritoneum, ovaries and rectovaginal septum, and infrequently in extra-pelvic structures including the diaphragm, pleura, and pericardium [1]. Although endometriosis is a benign disease, various scientific data support the notion that it represents the initial stage of a neoplastic process [2]. Furthermore, albeit a benign condition, endometriosis has the potential for malignant transformation, in less than 1%, particularly concerning ovarian implants [3]. An atypical endometriosis can be considered a transitional state from benign disease to invasive cancer [2, 4]. The first description of endometriosis in a postoperative scar was in 1903 [5]. The true aetiology is unknown, but scar endometriosis might be explained by iatrogenic transplantation of endometrial tissue to the wound edge during any surgical procedure [5, 6], with typical manifestations including an immobile lump in the scar or near it, with bulging and pain during menstruation. Accordingly, some authors reported a 0.03% to 1.08% incidence of endometriosis in abdominal surgical scar in women undergoing pelvic surgery; nevertheless, malignancy transformation is very rare [5]. Perineal endometriosis is a rare condition and usually involves the episiotomy scar (occurring in only 0.00007% of births) [7].

The risk of malignant transformation of endometriosis has been associated with malignancies of the reproductive tract, such as ovarian, cervical and endometrial cancer, and with

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other frequent malignant diseases such as breast and thyroid cancer. The influence of the hormonal environment could also explain its association with melanoma and colorectal cancer [8, 9]. Gandini et al. [8] conducted a systematic review and meta-analysis evaluating the relation between endometriosis and extra-ovarian malignancies. The authors found an increased risk of endometrial and thyroid cancer, an inverse relation with cervical cancer and no association with breast cancer [10].

The mechanisms of malignant transformation of endometriosis are not yet completely understood, and the impact of therapeutic strategies is poorly clarified. Endometriosis has various molecular similarities with invasive cancer, including inflammation, tissue invasion, angiogenesis, dysfunction of immune cells, increased local oestrogen production, apoptosis, stem cell-like dysregulation, and pro-survival features [2]. Also, several biological models have tried to explain malignant transformation of endometriosis as inflammation, oxidative stress induced by iron derived from menstrual bleeding and hyperestrogenism [2, 11, 12].

Therefore, endometriosis foci in scars are a recognized entity in clinical practice, but their accepted, though rare, malignant transformation needs a well-established approach. The aim of this study is to systematically report clinical cases of carcinoma arising in episiotomy scar endometriosis and to give an insight into the best clinical approach to these malignancies in our practice.

## MATERIAL AND METHODS

We performed a search in PubMed and Embase using the combination of "endometriosis" and "AND" Boolean operators to combine with MeSH terms and text words "episiotomy", "episiotomy scar", "malignancy", "clear cell carcinoma" and "neoplasm", from January 1980 to March 2019. English abstracts were analysed, and one case was excluded as it was reported in Hungarian without access to the full text and it was not possible to contact the corresponding author. All the other corresponding authors were contacted by email to obtain further information considering the follow-up of patients and there were no responses. So, it was not possible to determine survival rates and disease-free survival for all the cases. Also, the sample size limited the statistical analyses. We describe clinical cases of malignant transformation of endometriosis in episiotomy scars, considering clinical outcomes, namely survival and prognostic factors as well as treatment options.

## RESULTS

We included five patients in our review analysis, all reporting endometriosis-associated malignant transformation in an episiotomy scar [11, 13–16]. The patients' characteristics are shown in Table 1. The median age at the time of diagnosis was 45 years (range 36–50 years). Two patients were perimenopausal [13, 16], and for the remaining patients the menopausal state was not reported. No previous history of endometriosis was diagnosed.

**Table 1. Characteristics of the patients with endometriosis-associated malignant transformation in an episiotomy scar**

| | |
|---|---|
| **Age at diagnosis, years (median, range)** | **45 (36–50)** |
| Interval since surgery for benign endometriosis in episiotomy scar, month (median, range) | 9 (3–25) |
| Interval since last vaginal delivery to diagnosis of malignancy, month (median, range) | 19 (15–30) |
| Histological type (%, n)<br>Clear cell carcinoma<br>Serous papillary cystadenocarcinoma | <br>4<br>1 |

The median time from the diagnosis of endometriosis in the episiotomy scar and the diagnosis of malignancy at the same site was 9 months (range 3 to 25 months). All patients underwent wide excision of the mass in the episiotomy scar; histology of the removed tissue revealed endometriosis. Furthermore, three patients had additional treatment options: gonadotropin-releasing hormone agonist leuprorelin acetate for 6 months [15]; danazol and laser vaporization of superficial endometriosis at pouch of Douglas by laparoscopy [13]; and medroxyprogesterone acetate injectable suspension for one year followed by mifepristone for half a year, in addition to traditional Chinese medicine [11].

All the patients presented clinical recurrence of a perineal mass after previous diagnosis of endometriosis in an episiotomy scar. The symptomatic description was a solid vaginal mass associated with cyclic perineal pain in two cases; or a painless pruritic perineal nodule with gradual increased dimensions in two other cases; and as an ulcerated lesion with bilateral lymphadenopathies in the remaining case [14].

Considering the available data, the median period from last vaginal delivery and episiotomy carcinoma was 19 months (range 15 to 30 months) [11, 13–15]. Two spontaneous vaginal deliveries and two forceps and in one case there is no data. Perineal pain was described several months after delivery in three cases, one of them associated with slow recovery of perineal wound and swelling.

The imagological studies performed included pelvic and abdominal ultrasound and/or computerized tomography and/or magnetic resonance imaging. Tumour marker analysis was carried out in two patients and results were negative, including CA 125 [13, 14].

Tumour dimensions ranged from 3 cm to 10 cm and all were submitted to biopsy. The most common histological type was clear cell carcinoma in four cases [11, 14–16]; the remaining case was a serous papillary cystadenocarcinoma, diagnosed after surgical resection, as a previous biopsy revealed endometriosis but was negative for malignancy [13]. There is no additional data regarding molecular characterization.

**Table 2.** Therapeutic strategies and survival described for malignancies arising in endometriosis in episiotomy scar

| Case | Author | Year | Surgery | Chemotherapy | Radiotherapy | Disease-free survival | Global survival |
|---|---|---|---|---|---|---|---|
| 1 | Hitti et al. | 1990 | No | Yes | Yes | 12 months | 30 months |
| 2 | Todd et al. | 2000 | Partial vaginectomy + bilateral salpingo-oophorectomy + Hartmann's procedure | No | Neoadjuvant 19 fractions discontinued due to severe skin reaction | 6 months | Unknown |
| 3 | Chene et al. | 2007 | Complete resection by perineal surgery | Adjuvant weekly carboplatin + interstitial application of iridium | Adjuvant 45 Gy in 5 weeks perineal area and inguinal lymph node chain discontinued at 4 weeks due to urethritis and vulvovaginal inflammation | > 10 years | Unknown |
| 4 | Kwon et al. | 2008 | Radical vaginectomy + wide vulvar excision with partial skin graft + total abdominal hysterectomy + pelvic lymphadenectomy + right inguinal lymphadenectomy | No | No | 10 months | Unknown |
| 5 | Han et al. | 2016 | Radical vulvectomy with skin graft + inguinal lymphadenectomy | Neoadjuvant (1 cycle) Adjuvant (10 cycles) paclitaxel + cisplatin | No | 6 months | Unknown |

The treatments performed are described in Table 2. Surgery was part of the primary treatment in the majority of the cases [11, 13–15]. In the case reported by Hitti at al. [14], case 1, the patient did not accept radical surgery and was submitted to chemotherapy and radiotherapy [14]. In case 2, described by Todd et al. [16], radiotherapy was followed by radical and complete surgery that included partial vaginectomy, bilateral salpingo-oophorectomy and Hartmann's procedure, as the patient was submitted to total abdominal hysterectomy seven years before. Chene et al. [13] reported case 3, with primary surgical treatment that was radical and complete, followed by adjuvant radiotherapy of 45Gy in five weeks, followed by chemotherapy with weekly carboplatin and interstitial application of iridium. Concerning case 4, by Kwon et al. [15], surgical treatment consisted of radical vaginectomy and a wide vulvar excision with partial skin graft, total abdominal hysterectomy, pelvic lymphadenectomy and right inguinal lymphadenectomy. Concerning case 5, neoadjuvant chemotherapy was followed by surgery and chemotherapy. The surgical procedure consisted on radical vulvectomy with skin graft and inguinal lymphadenectomy, followed by chemotherapy with paclitaxel and cisplatin (1 cycle before surgery and 10 cycles after) [11]. One patient (case 1) died 30 months after the diagnosis of malignancy [14].

## DISCUSSION

The most probable pathogenic mechanism for endometriosis in an episiotomy scar is a transplantation theory, which involves iatrogenic implantation of the endometrium to the surgical wound [11]. This is more commonly diagnosed in situations of vaginal delivery followed by uterine curettage [6, 17]. Indeed, this hypothesis can justify the transport of endometrial tissue to the vulva during delivery [11]. Recently, many arguments in the literature suggest a well-established causal relationship between trauma and the endometriotic lesions diagnosed in surgical scars [18]. Various traumas namely delivery, uterine curettage or episiotomy may explain atypical locations of the disease. Growth factors released in the traumatized area and the associated oestrogen production that is essential in wound healing and tissue repair, may enable the implantation and growth of endometriotic cells [18]. Activated platelets involved in the mechanisms of initial tissue repair may induce COX-2 (cyclo-oxygenase 2) production by monocytes, endothelial and stromal cells and oestrogen receptor-β expression in endometriotic stromal cells. Elevated COX-2 expression results in augmented prostaglandin E2 (PGE2) production. PGE2 activates EP2/EP4 receptors, resulting in stimulation of COX-2, aromatase and matrix metalloproteinases (MMP)-2/MMP9 expression. Increased oestradiol supports motility in ectopic endometrial cells and elevated MMP activity pro-

motes their invasiveness [19]. A possible genetic predisposition and exposure to endocrine disruptors could explain why some patients develop the disease whereas others do not, despite being exposed to the same event. A better understanding of the mechanisms favouring the onset of the disease after trauma, for example obstetric, is fundamental to establish future preventive strategies. However, in the same series, some women had pre-existing endometriosis before their gynaecological procedure, indicating that endometriosis foci in scars may originate from lymphatic or haematogenic dissemination or anomalous differentiation of extrauterine cells into endometrial cells [20]. Hormonal or immunological factors may explain the metaplastic theory.

Specific tumour markers have not yet been identified to predict malignant transformation of endometriotic extraovarian lesions [11]. The results of the five cases reported here point out the importance of a close follow-up due to the absence of specific markers for malignant transformation and unpredictable course of this disease.

The ovary is the most frequent site of endometriosis-associated malignancy, in 80% of cases and extraovarian endometriosis accounts for one quarter to one fifth of these cases [13]. The most common histological malignancies described in endometriosis-associated ovarian cancer are endometrioid and clear cell carcinoma; endometriosis was detected in 30–55% of clear cell and 30–40% of endometrioid ovarian cancers [21, 22]. In extraovarian sites, endometrioid tumours represent 69.1% to 75.9% and clear cell carcinoma 4.5% to 13.5% of the malignancies [11]. However, in abdominal surgical scars, clear cell carcinoma represented 66.7% of cases, followed by endometroid carcinoma in 14.6% [5]. These endometrioid adenocarcinomas express mainly positive oestrogen receptors, but clear cell carcinoma exhibits lower oestrogen receptor expression [2]; the development of these type of tumour is considered to be connected to oxidative stress derived from free iron from endometriomas [22]. Indeed, iron-induced oxidative stress resulting of frequent menstrual bleeding was thought to be a main pathway in the malignant transformation of the disease [1, 2]. Not only stress factors (as lactose dehydrogenase, lipid peroxidase and 8-hydroxy-2--deoxyguanosine) increase oxidative stress and consequent DNA damage [12], but also both endometriosis and cancer are linked to inflammation [2]. It has been also hypothesized that alterations in the expression of tumour suppressor genes and oncogenes happening in normal endometrial tissue originate the overgrowth of endometrial foci external to the uterine cavity [2]. Moreover, a various of genetic changes, including loss of heterozygosity (LOH), PTEN, ARID1A and p53 mutations were already described in endometriosis and also endometriosis-associated malignancies [23].

Likewise, alterations in immunological response, either cell-mediated and humoral, contribute to the pathogenesis of endometriosis and relevant alterations associated with cellular immunity originate an inadequate removal of ectopic endometrial cells from the peritoneal cavity. Considering the immunological mechanisms, either iron-induced oxidative stress, inflammation and hyperestrogenism have been advocated as important associations between endometriosis and cancer [2]. Undeniably, hyperestrogenism has been suggested as a major contributor for the development of endometrioid cancer and clear cell carcinoma [11]. The levels of oestradiol and aromatase activity inside endometriosis stimulate cyclooxygenase-2 and prostaglandin E2 production, also described as driving factors for tumour progression [12]. Furthermore, local inflammatory reactions in endometriosis originate a response that includes cytokine release [11]. The endometriosis-associated inflammatory responses are dependent on increased activated macrophages and their secreted cytokines in peritoneal fluid; this local inflammatory microenvironment will allow the growth and maintenance of endometriosis through endometrial-peritoneal adhesion, invasion, angiogenesis, and proliferation [24]. The levels of pro-inflammatory cytokines are increased in tissue/intercellular fluid of ovarian endometrioma, such as interleukin (IL)-1, IL-6, IL-8, tumour necrosis factor-$\alpha$, and tumour necrosis factor-$\beta$. These mediators are involved in angiogenesis, cell proliferation and production of oxygen reactive species (superoxide; hydrogen peroxide; hydroxyl radical; hydroxyl ion; and nitric oxide) [25, 26]. These cytokines within the endometriosis microenvironment lead to the increasing synthesis of PGE2, which leads to angiogenesis, proliferation, and inhibition of apoptosis, also described in carcinogenesis [11]. The aberrant expression of fibroblast growth factor receptor-2 (FGFR2) gene has been linked to the carcinogenesis of endometriosis and has been referred to as a targeted intervention in this process [12].

Part of the mechanisms of malignant transformation were studied in endometriomas, but extragonadal endometriosis, namely rectosigmoid, colon, rectovaginal septum and pelvic peritoneum and surgical scars, point to an overlapped phenomena, as previously emphasized [23]. The presence of a transitional dysplastic region between benign endometriosis and cancer is an important histological aspect in carcinoma arising from endometriotic foci, reinforced by the fact that 36% to 42% of endometriosis-associated cancers exhibit endometrial glandular dysplasia [11].

Reported incidence of malignant transformation in surgical scars is 0.3% to 1% [13]. The rarity of the pathology stresses the difficulty in stratifying risk factors to predict the clinical progression or to establish the best treatment approaches. Moreover, these reports highlight the need to closely follow up all patients with previous removal of nodules in episiotomy scars. Routine imaging and tumour markers are still not defined and need further studies.

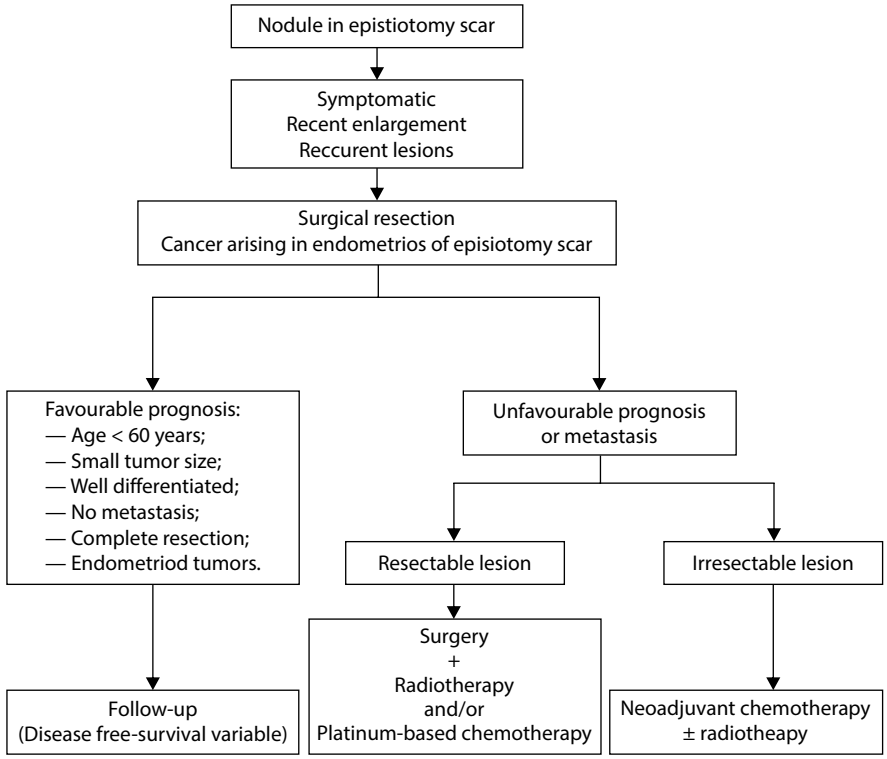


**Figure 1.** Proposed algorithm for diagnosis and treatment of episiotomy scar nodule

Therapeutic options were diverse, but surgical removal was mainly performed as a diagnostic and therapeutic procedure. The 5 mm free edges were defined by some authors to consider a complete excision [13]. Adjuvant treatment can be planned according to prognostic factors such as tumour size, histological differentiation, local or systemic spread, age of the patient and patient-informed decision. Nevertheless, endometrioid sub-types have better prognosis than clear cell tumours [15]. Patients with an unfavourable prognosis can be offered adjuvant treatment with radiation or platinum-derived chemotherapy [15]. Large tumours probably benefit from neoadjuvant radiotherapy to reduce size, followed by less invasive surgery due to the associated downstaging, which is probably is the best method [16].

Malignant transformation of endometriosis in an episiotomy scar is rarely reported in clinical practice. To systematize the approach of a nodule in episiotomy scar and therapeutic options of malignant lesions arising in endometriosis, we propose an algorithm described in Figure 1. Clinical suspicion should arise when a recurrent lesion is detected after endometriosis removal in an episiotomy scar. The mechanisms of transplantation in episiotomy scars have recently been highlighted, namely encompassing trauma, growth factors and hormonal influence. Also, the malignant transformation was associated with hyperestrogenism, inflammation, immunological and oxidative stress induced by iron from menstrual bleeding. The clinical approach must be individualized due to limited data and consequences for patient's quality of life.

### *Conflict of interest*

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