Isolated vulvar metastasis after robot-assisted laparoscopic hysterectomy for low grade, early stage endometrial cancer: a case report and review of the literature

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Objectives: Our objective is to report a case of isolated vulvar metastasis after robot-assisted laparoscopic hysterectomy for early-stage endometrial adenocarcinoma and to conduct a systematic review of the related literature to determine the frequency of this rare metastasis.

Methods: We present a case-report of a rare vulvar metastasis and conduct a systematic review of the English literature. Results: A 74-year-old woman with suspected uterine malignancy underwent a total laparoscopic hysterectomy with specimen removal through the vagina. Pathology revealed endometrioid carcinoma (WHO-World Health Organization-categorization of endometrial cancer histology) stage IA, grade 1 (FIGO-International Federation of Gynecology and Obstetrics-categorization). Upon a 12-month clinical examination after surgery, an isolated metastasis of the initial endometrial carcinoma was observed in the vulva and required surgical excision. Two and a half years later, the patient remains disease-free. Eleven articles consisting of 22 cases of metastatic endometrial carcinoma to the vulva have been reported in the English literature. To our knowledge, this is only the second case of developing isolated vulvar metastasis after minimal invasive surgery for low risk gynecological cancer described in literature.

Conclusion: The hereby presented case report aims to raise awareness among surgeons, regarding lesions that can be developed in the vulva after minimally invasive surgery of even low-risk, well differentiated EAC, which may represent recurrence of the primary cancer.

Keywords
Endometrial cancer, Vulvar metastasis, Minimally invasive surgery, Hysterectomy, Robo-assisted

1. Introduction

Endometrial cancer is the most common among all gynecological malignancies in developed countries, second only to cervical cancer in developing countries and the sixth most common form of cancer among women worldwide [1].

Endometrial cancer has two pathogenic types: type I consists of endometrioid adenocarcinomas and type II cancers usually has serous or clear cell histology and a more aggressive clinical course [2]. Endometrioid adenocarcinoma is the most common type of endometrial cancer with approximately 80% of all new cases belonging to type I which has more favourable prognosis and tend to have localized disease confined to the uterus [3, 4]. Endometrial cancer commonly spreads, in order of frequency, by: direct extension to the myometrium, lymphatic metastasis, hematogenous dissemination and intraperitoneal exfoliation. The risk of lymphatic and vascular spread increases with deeper myometrial invasion, aggressive cell types and with lower histological differentiation [2].

Minimally invasive surgery has long been used for the treatment of many benign gynecologic conditions but has nowadays even become the standard surgical management of early-stage malignancies such as endometrial cancer [5].

We hereby present, a rare case of isolated vulvar metastasis after robotic surgery for an early-stage endometrioid adenocarcinoma of the uterus. Furthermore, we conduct a systematic review of the related literature to assess the incidence of vulvar metastasis after minimally invasive surgery for endometrial cancer.

2. Case report

A 74-year old Caucasian multiparous woman with BMI 26 and no hormone replacement therapy, was referred to our clinic for postmenopausal bleeding. The patient underwent surgery for breast cancer in 2008 at the age of 66 and received both adjuvant chemotherapy and radiotherapy, followed by Tamoxifen and aromatase inhibitor therapy for five years. Transvaginal sonography revealed an endometrium of 9mm however an endometrial biopsy was negative for malignancy. She thereby, underwent a dilatation and curettage that suggested an endometrioid adenocarcinoma (WHO-World Health Organization-categorization of endometrial cancer histology) grade 2 (FIGO-International Federation of Gynecology and Obstetrics-categorization) (Figs. 1, 2, 3). As a computed tomography (CT) scan of the abdomen and pelvis was performed, there were no local invasion and no enlarged lymph nodes. A CT scan of the thorax was also performed without any suspicion of metastasis.

A DaVinci robot-assisted hysterectomy with bilateral salpingo-oophorectomy was subsequently performed according to the low-grade endometrial cancer protocol treat-
Intraoperatively, there was no suspicion of metastasis after the examination of the entire abdominal cavity including omentum, diaphragm, liver, intestinal package and peritoneum as well as the careful assessment of the lymph node stations on the pelvic walls. The surgical specimen, consisting of uterus, fallopian tubes and ovaries, a bit of infundibulopelvic ligament as well as a smaller vaginal cuff was vaginally extracted en bloc using an Axtrocare-Blue endo MyTube uterine manipulator. The histological examination after surgery showed an endometrioid carcinoma (WHO categorization) grade 1 (FIGO categorization), in opposition on the preoperative grading assessment (Figs. 4,5,6). Invasion of the myometrium was less than 50% and there was no local invasion to cervix, vagina or fallopian tubes either. Peritoneal cytology was negative for malignant cells. The final stage after surgery was FIGO stage IA, grade 1.

The patient was also complaining about pruritus in the anogenital area and white, atrophic lichen-like papules were observed in labia majora, at the posterior fourchette and over perineum during gynecological examination. For this reason, biopsies from labia majora and perineum were taken before the insertion of the uterine manipulator and confirmed the presence of lichen sclerosus.

The patient was evaluated one month postoperatively, with no signs of recurrence and she was at that point prescribed corticosteroid cream for the treatment of lichen sclerosus. Follow-up was also performed without any sign of recurrence at six months after surgery. Clinical examination at 12 months after surgery revealed an easy-bleeding, palpable, tender nodule in the posterior fourchette with a diameter of approximately one cm that was believed to be a benign polyp. A surgical excision of the lesion was performed as outpatient surgery. Nevertheless, surprisingly enough, pathology revealed a suspected metastasis of endometrioid adenocarcinoma from the endometrium, therefore a “second opinion” has been asked to our reference university hospital (Figs. 7,8,9). At the time the original suspicion was confirmed a medical appointment was arranged hardly 4 months after the
surgical excision. Upon clinical examination an eight mm nodule was seen, in the same place and with the same aspect as the one previously removed (Fig. 10). No deep invasion was suspected upon digital palpation and there were no signs of metastasis or cancer recurrence at a CT scan of the abdomen and thorax. Magnetic resonance imaging (MRI) did not raise any suspicion of metastasis or recurrence of primary cancer either. Notably, the nodule could not be seen in the MRI exam of pelvis. A local excision of the lesion was performed again, this time under general anaesthesia. Pathologic examination showed positive immunostaining for estrogen’s receptors and cytokeratin 7 while negative for vimentin, p53, p16 and progesterone receptors as well as intermediate-high expression of Ki67 and PAX8, consistent with recurrence of the primary endometrial cancer (Figs. 11,12,13). The margins of the surgical specimen were free of tumor. To date, 31 months after the excision of the isolated metastasis and 48 months after primary surgery, the patient has been free of disease.
3. Discussion

The hereby, reported case is interesting because vulva is not a common site for metastatic tumors, accounting only for 5-8% of all vulvar cancers [6, 7] of which endometrial cancer was the primary tumor in an estimated 9% [8] to 18% [6, 9]. Given the histopathologic features of endometrial carcinoma in our case, a low incidence of metastasis to the vulva would be expected. The literature search that we conducted, confirmed indeed, the rarity of the above-mentioned phenomenon.

Eleven articles consisting of 22 cases of metastatic endometrial carcinoma to the vulva has been reported in the English literature. Table 1 summarizes their clinical and pathological features. The average age of patients at the time of vulvar metastases was 66 years and the average time of recurrence after primary treatment was 25 months (range 4 to 84 months). In one case the primary tumor and the vulvar metastasis were diagnosed simultaneously. In most cases (18/22) vulvar metastases are accompanied by metastases involving other organs and are mostly associated to a more advanced cancer stage (> Stage IA) and/ or aggressive type (histologic grade G2 or G3) of primary cancer. Isolated vulvar metastasis after endometrial cancer is reported in only four cases. Neto et al. [8] provide no further information regarding the characteristics of the primary tumor. In Wimmer et al. [10] a very rare tumor-to-tumor metastasis is reported where an advanced stage II endometrioid adenocarcinoma (EAC) found to have metastasized to a squamous cell carcinoma upon examination of an excised vulvar lesion. In Fakor et al. [11] a clitoris metastasis occurred after treatment for stage IB poorly differential EAC. The surgical treatment of
Table 1. Characteristics of cases of metastatic endometrial carcinoma to the vulva.

| Author                  | No | Age | Histological type | FIGO stage | Surgery                  | Adjuvant therapy | Time from primary treatment (mo.) | Site of metastasis        | Isolated metastasis | Treatment                      |
|-------------------------|----|-----|-------------------|------------|--------------------------|------------------|----------------------------------|---------------------------|---------------------|--------------------------------|
| Dehner, 1973            | 4  | 56  | AC                | I          | None                     | None             | 12                               | Labium major             | NO                  | RT                             |
|                         | 78 | AC  | None              | III        | None                     | None             | 0                                | Labium major             | NO                  | RT                             |
|                         | 69 | AC  | None              | I          | None                     | None             | 4                                | Labium major             | NO                  | RT                             |
|                         | 71 | AC  | TAH + BSO         | I          | None                     | None             | 5                                | Labium major             | NO                  | RT                             |
| Mazur, 1984             | 3  | NR  | NR                | NR         | NR                       | NR               | NR                               | NR                        | NR                  | RT + CT                       |
| Neto, 2003              | 6  | 62  | AC                | NR         | NR                       | NR               | 24                               | Labium minus             | NO                  | wide local excision + RT      |
|                         | 63 | AC  | NR                | NR         | NR                       | NR               | 84                               | Right labium major       | YES                 | RT                             |
|                         | 54 | AC  | NR                | NR         | NR                       | NR               | 24                               | Bilateral labia major    | NO                  | RT                             |
|                         | 68 | AC  | NR                | NR         | NR                       | NR               | 10                               | NR                       | NO                  | RT + CT                       |
|                         | 51 | AC  | NR                | NR         | NR                       | NR               | 9                                | Right labium minus + clitoris | NO            | CT                             |
|                         | 73 | AC  | NR                | NR         | NR                       | NR               | 38                               | Introitus                | NO                  | RT + CT                       |
| Giordano, 2005          | 1  | 66  | G3, EAC           | IIIC        | TAH + BSO + PL + PAL     | No               | 7                                | Posterior vulvar commissure | NO                  | local excision + HT           |
| Ray, 2006               | 1  | 53  | G1, EAC           | IB         | TAH + BSO + PAL          | No               | 10                               | Right Bartholin’s gland | NO                  | local excision               |
| Temkin, 2007            | 2  | 63  | PAC               | IB         | TAH + BSO + PAL          | BT               | 84                               | Left labium              | NO                  | Radical vulvar resection + RT + CT |
|                         | 83 | G1, EAC | II               | TAH        | EBRT + BT                | NR               | 5                                | Right labium             | NO                  | wide local excision           |
| Wimmer, 2013            | 1  | 79  | G2, EAC           | II         | TAH + BSO                | RT               | 5                                | Right vulva              | YES                 | partial vulvectomy            |
| Fakor, 2013             | 1  | 52  | G3, EAC           | IB         | TAH + BSO + PAL          | BT               | 18                               | clitoris                 | YES                 | wide local excision + EBRT    |
| Abdullah, 2014          | 1  | 87  | G1, EAC           | IB         | LAH + BSO + PAL          | BT               | 8                                | Posterior commissure     | YES                 | partial vulvectomy            |
| Heller, 2016            | 1  | 65  | G2, EAC           | IB         | Supracerv. AH            | No               | 12                               | Bilateral labia major    | NO                  | CT + RT                       |
| Rottenstreich, 2019     | 1  | 60  | G2, EAC           | IIIA       | TAH + BSO + PL           | CT               | 72                               | Bilateral labia major,m.pubis, lower abdomen | NO                  | CT                             |

Abbreviations: NR, not reported; AC, adenocarcinoma; EAC, endometrioid adenocarcinoma; SPAC, serous papillary adenocarcinoma; TAH, total abdominal hysterectomy; LAH, laparoscopic assisted hysterectomy; BSO, bilateral salpingo-oophorectomy; PL, pelvic lymphadenectomy; PAL, pelvic and paraaortic lymphadenectomy; CT, chemotherapy; RT, radiotherapy; BT, brachytherapy; EBRT, external beam radiotherapy; HT, hormone therapy; Treatment by only radiotherapy as the guidelines in the late 60’s recommended. In case 4, neoadjuvant radiotherapy.
the primary tumor was abdominal hysterectomy in 21/22 of cases. There is only one case described in the literature, whereas ours is the second one occurred, with an isolated vulvar metastasis after treatment of well-differentiated early-stage endometrioid adenocarcinoma where minimally invasive surgery was used.

Given the overall rarity of vulvar metastasis from a primary endometrial cancer and the even rarer incidence of the up to now described isolated metastasis, no safe conclusions can be drawn on the patterns of spread. However, we try hereby to find the most plausible pattern of spread of a well-differentiated early-stage endometrioid cancer treated by robot-assisted total laparoscopic hysterectomy to an isolated vulvar metastasis.

Endometrial cancer most commonly spreads in order of frequency by direct extension, lymphatic metastasis, hematogenous dissemination and intraperitoneal exfoliation. This concerns particularly Type I endometrioid tumors and its variants whereas Type II serous and clear-cell carcinomas have a particular and early propensity for extraterine disease. Thus, the risk of spread is related to histologic type but even to other factors such as depth of invasion into the myometrium (more or less than 50%) and tumor grade (G1-3). For stage I endometrioid carcinoma, the depth of invasion of the endometrial stroma is the most important prognostic factor.

In the case report presented hereby, the primary tumor was of endometrioid type and histologic grade 1. The surgical stage after robot-assisted laparoscopic hysterectomy was FIGO IA since tumor invasion of myometrium was less than 50% and cervical stroma as well as vagina were not involved; therefore, metastasis by direct extension can be excluded.

Lymphatic drainage of the uterus is primarily to the obturator, internal and external iliac nodes and secondarily to the para-aortic nodes. The frequency of pelvic and para-aortic nodal metastases increases as the depth of invasion, the tumor grade and the surgical stage increase but this is possible even if only superficial myometrial invasion occurs. The estimated risk for pelvic lymph node metastases for endometrial carcinoma grade 1 with myometrial invasion less than 50%, is approximately 3% [2, 4]. Some lymphatic channels from the uterine corpus may pass along the round ligaments to the superficial inguinal nodes which are, at the same time, the main afferent lymph nodes of the vulva. Thus, endometrial carcinoma could hypothetically spread to the vulva via this bilateral course. In our case, however, there was neither pelvic nor inguinal lymph node involvement by imaging at the time of staging for endometrial cancer, which would, in any case, indicate distant metastasis. Nevertheless, Fakor et al. [11] speculated that lymphatic spread could still be possible after extensive radical pelvic surgery (Type III) or radiation therapy, by retrograde spread to the vulvar lymphatic due to the newly formed lymphatic stasis. In our case though, a simple hysterectomy (Type I) was performed and no radiation therapy was given thereby even this pattern of lymphatic spread can be ruled out.

Hematogenic dissemination of endometrial carcinoma is usually related to advanced cancer stage. In fact, deep myometrial invasion is the strongest predictor of this pattern of spread [2]. In all cases of non-isolated vulvar metastases described in Table 1, the primary endometrial cancer was of a more advanced cancer stage (> Stage IA) and/or aggressive type (histologic grade G2 or G3). Thus, metastases could theoretically be explained by an hematogenic spread. In Wimmer et al. [10] case report, an isolated vulvar metastasis located within a well-differentiated squamous carcinoma (tumor-to-tumor metastasis) is described. In that case, the stage of the primary cancer (Stage II, G2) and the very rare tumor-to-tumor metastasis may suggest hematogenic spread. However, in both Abdullah et al. [12] and our case report, the primary cancer was well differentiated and in early stage, making this pattern of spread highly implausible.

Intraperitoneal exfoliation is another mechanism by which malignant cells reach the peritoneal cavity but a metastasis to the vulva is impossible by this pattern since the latter is an extraperitoneal organ. Finally, a direct neoplasm seeding during surgery must be taken into consideration.

During minimally invasive surgery with transvaginal specimen removal, cancer cells can theoretically adhere and then multiply, to the vulva or other sites giving isolated metastasis. Furthermore, adhesion and multiplication could hypothetically be favored by seeding on an already damaged or altered tissue (e.g., presence of VIN III as in Wimmer et al. [10] lichen sclerosus in our case). This theory is speculative and cannot be proved given the limited number of cases reported up to now where a minimally invasive surgery was applied for treatment of Stage I endometrioid endometrial cancer.

Furthermore, the same theory has been speculated upon the more well-described port-site metastasis (PSM) following minimally invasive surgery for endometrial cancer.

The etiology of PSM remains unknown but multiple factors seem to be associated to this rare complication. The most common etiologies proposed for PSM are hematogenous spread, multiple effects of pneumoperitoneum, the effects of the gases used for insufflation, the aerosolization of tumor cells, local immune reactions, and surgical technique, direct wound contamination and implantation as well as the “chimney effect” [13]. Most of these theories appear to be less plausible in cases of isolated PSM after an early stage, well differentiated endometrioid endometrial cancer. The direct wound contamination and implantation may though be implicated in our case of vulvar metastasis, given the common characteristics of the primary cancer. The surgical specimen being the uterus, fallopian tubes and ovaries or the uterine manipulator itself could have been contaminated with malignant cells and then, in their turn, contaminated the vulva during extraction. The “Chimney Effect” (increase in the number of tumor cells at the port sites caused by leakage of gas along the trocars) could also be implicated in our case, with tu-
umor cells coming along with leakage of gas following the extraction of the surgical specimen and contaminating thereby the vulva. In both theories, direct wound implantation and pneumoperitoneum’s Chimney effect, the vulva contamination could theoretically be facilitated by the presence of areas of already altered-damaged tissue in the vulva such as in lichen sclerosus, that would enable adherence of cancer cells if seeding occurs.

However, the endeavor to describe the patterns of spread of the primary cancer to the vulva still remains speculative due to limited data, the complex interrelation of the different factors in the theories described above, the conflicting reports and even the only few cases of vulvar metastases after minimally invasive surgery for uterine cancer.

In order to prevent a vulvar metastasis after minimally invasive surgery for endometrial cancer, a specimen bag could be a possible solution. Nevertheless, the very low incidence of such metastases with only two cases described up to now, the technical difficulties of such an implementation as well as the cost-effective perspective, render this solution non-indicated at present. It might though be considered in the cases where altered-damaged vulva tissue either exists already such as in lichen sclerosus, VIN, or it is expected to have been developed during over manipulation/complicated transvaginal extraction of the specimen.

The hereby presented case report aims to raise awareness, among surgeons, regarding lesions that can be developed in the vulva after minimally invasive surgery of even low-risk, well differentiated EAC, which may represent recurrence of the primary cancer.

Author contributions
NG authored this manuscript. IV and MK supervised and approved the final manuscript.

Ethics approval and consent to participate
Oral and written informed consent was obtained from the patient.

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Conflict of interest
The authors declare no competing interests.

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