Relapse as Advanced Carcinosarcoma Following Uterus-Preserving Therapy in a Patient with Early-Staged and Grade 1 Endometrioid Adenocarcinoma: A Case Report and Review of the Literature

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Abstract

Fertility-sparing treatment with high-dose progestin is now used in many young patients with early stage, grade 1 endometrioid adenocarcinoma. The response rate of this therapy is quite good, but the relapse rate is relatively high. If the site of recurrence is limited to the uterus, this may be treated with additional hormone therapy or hysterectomy. We recently experienced a case of a 30-year-old primigravida patient in whom intraperitoneal dissemination of carcinosarcoma occurred during follow-up after apparent complete remission of early-stage grade 1 endometrioid adenocarcinoma. We report the case as an example of a rare high-grade histology tumor that relapsed in an extraterine site after primary remission had been achieved with high-dose progestin therapy. In a review of the literature through a MEDLINE search, we found 13 articles describing relapse in an extraterine site, including 6 ovarian metastases, 4 retroperitoneal lymph node metastases, and 3 metastases to organs other than the ovary. Early stage, well-differentiated endometrioid adenocarcinoma of the uterus is generally considered to have a good prognosis, but counseling of patients regarding life decisions is important, with provision of sufficient information on the possibility of extraterine progression or disseminated recurrence.

Keywords: Relapse in progestin-treated uterine cancer; Clinical review; Conservative therapy for endometrial adenocarcinoma; High-dose progestin therapy; Relapse in an extraterine site; Carcinosarcoma

Introduction

Preservation of the uterus by treatment with high-dose progestin in young patients with endometrial adenocarcinoma is an important therapy for fertility preservation. This therapy is indicated for patients with grade 1 endometrial histology and very early stage cancer. Good hormonal response rates between 57% and 75% have been achieved, but the relapse rates after remission are also high, varying between 47% in follow-up of 7 to 22 months and 89% after follow-up of over 30 months [1-3].

Relapse within the uterus can be treated relatively easily by radical treatment. However, relapse occurring outside the uterus has less chance for a complete cure and is likely to reduce survival. Progression to high-grade disease during therapy or follow-up has been reported, although this is rare. Here, we report a case that relapsed as advanced stage carcinosarcoma during follow-up after apparent complete remission in a patient with grade 1 endometrioid stage Ia endometrioid adenocarcinoma. We also review previous cases to emphasize the importance of caution in management of patients after fertility-sparing treatment.

Case

In October 2007, a 30-year-old 0-0-0-0 Japanese woman presented to Nippon Medical School Chiba Hokusoh Hospital with suspected endometrial carcinoma diagnosed at a local in vitro fertilization clinic. Her body height was 154 cm, body weight was 57.4 kg, and blood pressure was 117/70 mmHg. She had no anemia and normal biochemistry laboratory findings. Serum CEA was 0.5 ng/ml, CA19-9 was 18.5 U/ml, and CA125 was 29.2 U/ml. Endometrial thickness was 11.5 mm on transvaginal ultrasound. Diagnostic imaging with CT and MRI did not indicate myometrial invasion or metastasis to regional/distant lymph nodes or remote organs. Endometrial biopsy by multidirectional curettage showed grade 1 endometrioid adenocarcinoma (Figure 1a).

High-dose progestin fertility-sparing treatment was started for a presumptive clinical stage of FIGO Ia, according to our protocol (Table 1) and with informed consent. A daily dose of oral Medroxyprogesterone Acetate (MPA) 600 mg was given for 16 weeks until endometrial histology showed atrophic glands among predecidual stroma (Figure 1b), and CT and MRI showed normal findings (Figure 1c). A daily dose of MPA 200 mg was subsequently given for another 12 weeks, after which the patient returned to the local clinic for in vitro fertilization and embryo transfer.

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Figure 1: **a:** Histological diagnosis of endometrioid adenocarcinoma of grade 1 was obtained through multidirectional endometrial curettage. This procedure demonstrated confluent glands with a cribriform bridging arrangement in most areas (H&E, low power magnification). **b:** Microscopic findings for the endometrial curetted specimen after 16 weeks of progestin treatment showed small atrophic glands scattered in the background of predecidualstroma (H&E, low power magnification). This finding indicates complete remission. **c:** T2-weighted MRI (sagittal section) showed no abnormal findings and a thin endometrium. **d:** T2-weighted MRI (sagittal section) showed no endometrial abnormality, but a 3 cm abnormal mass (white arrowheads) was observed between the cervical wall and rectum, with a moderate amount of ascites. **e:** T2-weighted MRI (coronal section) indicated a suspected metastasis at the surface of the right hepatic lobe (white arrow). **f:** In laparotomy, a cul-de-sac tumor was found to have invaded the rectal wall. The cervical wall of the uterus and both ovaries looked normal. **g:** Microscopic observation (H&E, low power magnification) revealed foci of carcinomatous elements with strong epithelial connections, and sarcomatous elements with atypical cells losing epithelial arrangement and osseous formation. In other areas, various levels of differentiations of endometrioid, squamous, and clear cell carcinomas were observed with immature cartilaginous formation. **h, i:** Low power magnification of the ovarian cortex showed multiple (independent) foci of carcinoma. This finding suggests that the ovarian malignancy was more metastatic than the primary origin.
For nulliparous women wishing to preserve the uterus
MRI, CT and D&C at week 0
If presumptive FIGO stage Ia& grade 1 endometrioid adenocarcinoma
- No myometrial invasion on T2-weighted pelvic MRI
- No swelling of pelvic and paraaortic lymph nodes on CT scan
- No space occupying lesion on CT scan
- Grade 1 endometrioid adenocarcinoma on HE-stained slides
  → Start MPA* at 600 mg/day
Otherwise
  → Surgical treatment including hysterectomy
D&C at 4, 8 and 12 weeks
If worse histology than before
  → Surgical treatment including hysterectomy
Otherwise
  → Continue MPA at 600 mg/day
D&C at 16 weeks
If any residual carcinomatous focus
  → Surgical treatment including hysterectomy
Otherwise
  → Continue MPA at 200-400 mg/day for another 4 months
then MPA at 10 mg/day until expecting pregnancy
*MPA-medroxyprogesterone acetate

Table 1: Treatment regimen of high-dose progestin therapy for uterine preservation at the Nippon Medical School Chiba Hokusoh Hospital.

In January 2009, she returned to our hospital for infusion therapy for emesis; however, her pregnancy was terminated at gestational age 14 weeks due to intrauterine fetal death. Two months later, she came to our hospital complaining of dull but intolerable pain around the perianal area. Rectovaginal examination revealed a palpable hard nodule. The patient was treated by proton irradiation. At the end of 2013, one month after completion of irradiation, the size of the new lesion had decreased. The lesion was treated by partial resection of the liver in April 2012. In histology, well-differentiated endometrioid adenocarcinoma was detected again. One year later, a new lesion appeared in the liver near the great vessels and was treated by proton irradiation. At the end of 2013, one month after completion of irradiation, the size of the new lesion had decreased. The patient still requires careful follow-up.

Recurrence of endometrial adenocarcinoma after fertility-sparing treatment has been widely reported. The site of recurrence is usually limited to the endometrium and histology typically shows the same well-differentiated endometrioid type. In contrast, endometrioid carcinoma recurring as carcinosarcoma (as in our case) is rare, with only four reported cases, three of which occurred in older patients who were diagnosed with high-grade carcinoma at an advanced stage [4]. Only one case has been described in a younger patient after fertility-sparing treatment, with Fujiwara et al. [5] describing a patient who was initially presumed to have early stage endometrial adenocarcinoma and was finally diagnosed with heterologous carcinosarcoma of the uterus following hysterectomy after 16 weeks of unsuccessful conservative therapy. Our case differs from this case because recurrence occurred as multiple intra-abdominal disseminations after apparent complete remission.

Recurrence restricted to the uterus and with a well-differentiated endometrioid histology is more likely to respond to additional hormonal therapy [6]. However, recurrence outside the uterus may result in serious life-threatening complications. We performed a MEDLINE search for cases of extraterine metastasis or recurrence after temporal cure for early stage low-grade endometrioid type endometrial adenocarcinoma or endometrial hyperplasia. Kempton and Pokorny used uterus-conserving therapy with hydroxyprogesterone caproate and found one ovarian recurrence in a patient under 40 years of age among 22 cases treated between 1930 and 1967 [7]. Only four cases were treated hormonally and none of these cases had ovarian recurrence; therefore, they were excluded from our list of cases. Cases in which extraterine metastasis occurred during conservative therapy, such as those reported by Imai et al. and Ota et al., were also excluded because such cases can be treated by standard surgery. Thus, 13 cases of extrauterine recurrence after temporary remission are listed in Table 2 [3,8-14]. Six of these cases had ovarian lesions as the extrauterine site. These cases were mostly thought to be independent primary or concurrent ovarian endometrioid adenocarcinoma based on histological findings showing that both lesions were very early stage and were rarely confirmed by a heterogeneous pattern at the human androgen receptor gene locus. It is of note that Huang et al. found similar microscopic patterns, immunohistochemical profiles, and DNA ploidy in a small ovarian lesion of 2x2 mm² compared to a primary endometrial lesion [9,11,14-16].

In our case, we were unable to identify the exact date of recurrence; therefore, the tumor might have already recurred at the time of IVF-ET treatment. It is generally thought that a high serum progesterone level during pregnancy suppresses the growth of well-differentiated endometrioid adenocarcinoma, but Mitsuhashi et al. reported that recurrence can occur before pregnancy [17] and speculated that carcinoma may remain during pregnancy and delivery after conservative therapy. If this is so, implantation of carcinoma cells could occur via the needle from the cul-de-sac tumor to the bilateral ovaries or from the ovary to the cul-de-sac tumor during ovum assembly in IVF-ET.

Egarter et al. described a retrograde intraperitoneal spread of endometrial cancer cells through tubal reflux during hysteroscopy [18]. Rose et al. reported complete response with conservative treatment with repeated D&C, hysteroscopic resection and oral progestin in a patient with endometrial cancer who developed pelvic peritoneal implants involving the sigmoid colon at 24 months after diagnosis [19]. However, a literature search over two decades by Revel provided...
or from a new malignant ovarian neoplasm that, by chance, occurred disseminated carcinosarcoma is a recurrence from endometrial cancer in most cases.

well-differentiated histology could have survived and recurred, as seen eliminated by chemotherapy; whereas a clone with chemo-resistant (i.e., well-differentiated endometrioid adenocarcinoma with squamous recurrence had the same histology as the primary endometrial cancer carcinoma. Furthermore, since the metastatic liver lesion in the latest histology (including clear, squamous cells from G1 to G3 endometrioid ovum sampling.

Secondary lesions through implantation by repeated punctures for the foci may have been the primary lesion and others could have been observed of the lesion showed multiple foci in the cortical area. Nevertheless, in our case, the lesions may not be detected until a microscopic study is performed cases have an endometrioid type histology [21,22].

Another possible explanation in our patient may be that carcinosarcoma arose as a recurrence from grade 1 endometrioid adenocarcinoma and that the epithelial components of the carcinosarcoma showed various histology (including clear, squamous cells from G1 to G3 endometrioid histology) because carcinosarcoma can be thought of as a metaplastic carcinoma. Furthermore, since the metastatic liver lesion in the latest recurrence had the same histology as the primary endometrial cancer (i.e., well-differentiated endometrioid adenocarcinoma with squamous differentiation), a clone with worse histology could have been eliminated by chemotherapy; whereas a clone with chemo-resistant well-differentiated histology could have survived and recurred, as seen in most cases.

In conclusion, we cannot say with certainty that our case of disseminated carcinosarcoma is a recurrence from endometrial cancer or from a new malignant ovarian neoplasm that, by chance, occurred independently. However, it is clear that carcinosarcoma was present and extraterine recurrence occurred after fertility-sparing treatment. Early stage, well-differentiated endometrioid adenocarcinoma of the uterine corpus is generally considered to have a good prognosis, but counseling of patients in life decisions is important, with provision of sufficient information about the possibility of extraterine progression or disseminated recurrence.

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**References**


**Table 2:** Cases with extrauterine recurrence after temporary remission of endometrioid adenocarcinoma or atypical endometrial hyperplasia.

<table>
<thead>
<tr>
<th>Case</th>
<th>1st Author</th>
<th>Pt. Age (yr)</th>
<th>Histology &amp; Stage</th>
<th>Primary Lesion</th>
<th>Treatment</th>
<th>Extra-uterine Recurrence or progression</th>
<th>Site</th>
<th>Time</th>
<th>Histology</th>
<th>Prognosis after Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Duska [1]</td>
<td>31</td>
<td>EA G1. stage Ia</td>
<td>Progestins</td>
<td>Ovary</td>
<td>At least after term pregnancy</td>
<td>EA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Kaku [2]</td>
<td>36</td>
<td>EA G1. stage Ia</td>
<td>MPA 600 mg/day</td>
<td>ITOblator LN</td>
<td>22 mo</td>
<td>EA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Yasuda [3]</td>
<td>31</td>
<td>AEH MPA 600 mg/day</td>
<td>2 mo+r LA 3.75 mg/mo, 2 mo</td>
<td>Retropitoneal LN</td>
<td>Multiple Organ Metastasis</td>
<td>36 mo</td>
<td>EAG3 with partly cell differentiation</td>
<td>DOD 7 mo</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Huang [4]</td>
<td>36</td>
<td>EA G1. stage Ia</td>
<td>MA 160 mg/day, 1 mo+TMX20 mg/day, 2 mo</td>
<td>rt Ovary</td>
<td>2 more mo of TMX+BLA</td>
<td>EA</td>
<td>G1</td>
<td>NED</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Rubatt [5]</td>
<td>40</td>
<td>AEH MA 80 mg2W+LNG/EE for 3mo and until recurrence</td>
<td>Light pelvic LN Positive peritoneal cytology</td>
<td>30 mo</td>
<td>EA</td>
<td>G2</td>
<td>12 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Yang [6]</td>
<td>30</td>
<td>EA G1. stage Ia</td>
<td>MA 160 MPA 400 mg/day, 5mo</td>
<td>Ovary</td>
<td>5 mo</td>
<td>EA</td>
<td>NED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Yang [6]</td>
<td>37</td>
<td>EA G1. stage Ia</td>
<td>MA 160 MPA 400 mg/day, 2mo</td>
<td>Ovary</td>
<td>4 mo</td>
<td>EA</td>
<td>NED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Ferrandina [7]</td>
<td>30</td>
<td>EA G1. stage Ia</td>
<td>Cyclic DG 20 MPA 400 mg/day, 3 mo</td>
<td>Lung/Liver/Bone Retropitoneal LN</td>
<td>14 mo (9 mo after C/S)</td>
<td>EA</td>
<td>G3</td>
<td>DOD 10 mo</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Cormio [8]</td>
<td>30</td>
<td>EA G1. stage Ia</td>
<td>MA320 mg/day MPA 400 mg/day</td>
<td>rt Ovary</td>
<td>36 mo</td>
<td>EA</td>
<td>G1</td>
<td>DOD 7 mo</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Yamazawa [9]</td>
<td>33</td>
<td>EA G1. stage Ia</td>
<td>MPA 400 mg/day, 6 mo</td>
<td>rt Ovary</td>
<td>10 mo</td>
<td>EA</td>
<td>G1</td>
<td>NED 69 mo</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Yamazawa [9]</td>
<td>38</td>
<td>EA G1. stage Ia</td>
<td>MPA 400 mg/day, 6M</td>
<td>rt Ovary</td>
<td>22 mo</td>
<td>EA</td>
<td>G1</td>
<td>NED 39 mo</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Ushijima [10]</td>
<td>20-39</td>
<td>EA G1. stage Ia</td>
<td>MPA 600 mg/day</td>
<td>Peritoneal Calcification</td>
<td>24 mo</td>
<td>EA</td>
<td>G2</td>
<td>DOD 4 mo</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Kohtan [11]</td>
<td>14</td>
<td>EA G2. stage Ia</td>
<td>MA160 mg/day, 6 mo+LNG/IUD</td>
<td>Pelvic Implants</td>
<td>21+6 mo</td>
<td>EA</td>
<td>G1</td>
<td>NED 24 mo</td>
<td></td>
</tr>
</tbody>
</table>

Pt: Patient; EA: Endometrioid Adenocarcinoma, G1-3: Grade 1-3; AEH: Atypical Endometrial Hyperplasia; LN: Lymph Node; HP: Hydroxyprogesterone; MPA: Medroxyprogesterone Acetate; MA: Megesterol Acetate; DG: Dihydrogesterone; LNG: Levonorgestrel; EE: EthinylEstradiol ;TMX: Tamoxifen; dLA: depot Leuprolide Acetate; rt: right; lt: left; IUD: Intrauterine Device; DOD: Died of Disease; NED: No Evidence of Disease; NA: Not Available; C/S: Cesarean Section.


