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著者名	NAGANO Hiroaki, FURUKAWA Yuri, UENO Mariko, TAKAGI Koichiro
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Case Report

Advanced Endometrial Cancer Arising in Adenomyosis: A Case Report

Hiroaki NAGANO, Yuri FURUKAWA, Mariko UENO, and **Koichiro TAKAGI**

Department of Obstetrics and Gynecology, Tokyo Women's Medical University Medical Center East, Tokyo, Japan

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Endometrial cancer arising in adenomyosis (EC-AIA) is a rare form of uterine cancer. A 53-year-old Japanese postmenopausal female was referred to our outpatient clinic for adenomyosis. After the 4-year follow-up, she presented with an increased vaginal discharge. Endometrial curettage demonstrated either atypical endometrial hyperplasia or well-differentiated endometrioid carcinoma. Positron emission tomography/computed tomography revealed multiple pulmonary metastases, pelvic bone metastases, para-aortic node metastases, and uterine tumor as the primary lesion. She was clinically diagnosed with stage IVB endometrial cancer. Accordingly, total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. Macroscopic findings of the resected uterus were difficult to distinguish from ordinal adenomyosis. Microscopically, diffuse endometrioid carcinoma (grade 2) occupied the entire uterine body, coexisting with adenomyosis. Postoperatively, chemotherapy and zoledronic acid administration were initiated, which are ongoing till date. The case highlights that EC-AIA, a rare but aggressive disease, should be considered when managing patients with adenomyosis.

Key Words: endometrial carcinoma, adenomyosis, malignant transformation

Introduction

Adenomyosis is one of the most common benign diseases of the uterus and is defined as ectopic endometriosis invading the uterine myometrium. While endometrial cancer coexisting with adenomyosis (EC-A) is a frequent occurrence, the malignant transformation of adenomyosis, that is, endometrial cancer arising in adenomyosis (EC-AIA), is considered to be a rare event. Here, we report a case of an advanced EC-AIA based on the clinical features of the patient, although it did not fulfill the classical histological criteria.

Case

A 53-year-old Japanese postmenopausal female was referred to our outpatient clinic for adenomyosis. She had been diagnosed with adenomyosis by occasional magnetic resonance imaging (MRI) at an internal department. Without any interval change, the patient was followed-up at either 6-month or 1-year interval to monitor for any changes in status. After the 4-year follow-up, she presented with an increased vaginal discharge since 10 days. Endometrial cytology raised a suspicion of adenocarcinoma. Total curettage of the endometrium under anesthesia revealed either atypical endometrial hyperplasia or well-differentiated endometrioid carcinoma. However,

Corresponding Author: Hiroaki Nagano, Department of Obstetrics and Gynecology, Tokyo Women's Medical University Medical Center East, 2-1-10, Nishiogu, Arakawa-ku, Tokyo 116-8567, Japan

E-mail: nagano.hiroaki@twmu.ac.jp

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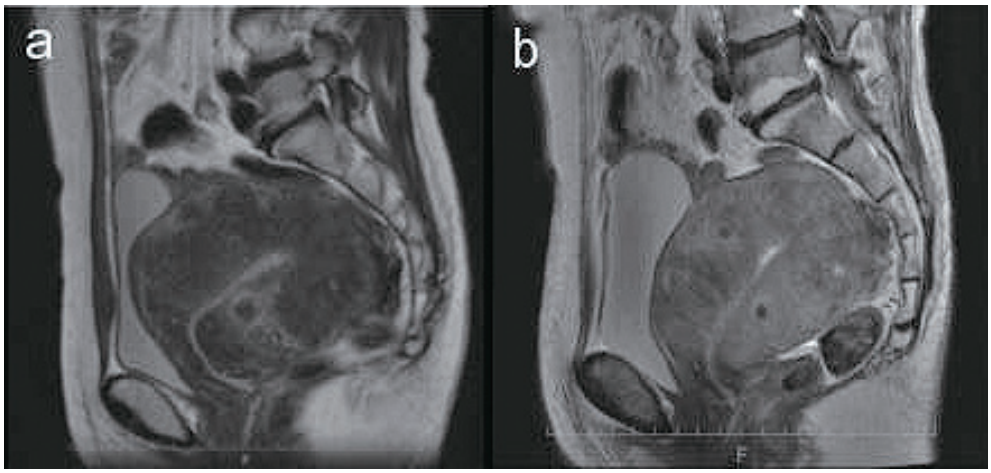

Fig. 1 (a) Magnetic resonance imaging (MRI; T2-weighted image) in the sagittal view when the patient was initially referred to the institute; diffusely thickened myometrium with low signal intensity indicates the presence of adenomyosis. (b) MRI under the same condition when the patient was diagnosed with endometrial cancer. Although uterus size does not show considerable change, the signal intensity in (b) appears higher than that in (a).

MRI indicated a suspicious image of the pelvic bone metastasis (bilateral pubic and sacral bone) despite no considerable change in the uterine size (**Fig. 1**). After confirmation using positron emission tomography/computed tomography (PET/CT), which revealed multiple pulmonary metastases, pelvic bone (bilateral pubic and sacral bone) metastases, para-aortic node metastases, and uterine tumor as primary lesions, she was clinically diagnosed with stage IVB endometrial cancer (**Fig. 2**). Accordingly, total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. The surgical findings revealed small amount of serous ascites, over newborn-head-sized enlarged uterus with smooth surface without adhesion, normal appearance of the ovaries and tubes, and no apparent peritoneal dissemination. Macroscopically, the resected uterus exhibited a diffuse-thickness myometrium (4-5 cm in thickness), which was difficult to distinguish from ordinal adenomyosis, and a minimal endometrial lesion at the fundus of the uterus (5 mm) (**Fig. 3**). Histologically, the resected specimens revealed that diffuse-type endometrioid carcinoma occupied the entire uterine body (depth of the invasion, 45 mm/45 mm). The endometrium appears thin and inconspicuous and is mostly replaced by intraepithelial carcinoma, except for the lesion observed at the fundus wherein aberrant glands with eosinophilic papillary nest in the lumen were predominantly observed, along with small foci of the solid growth component with eosinophilic cytoplasm and milder nuclear atypia (**Fig. 4**). Myometrial lesions were diffuse and primarily comprised two patterns: in situ lesions that replaced the glands of adenomyosis and invasive lesions with microcystic, elongated, and fragmented pattern (accompanied with psammoma bodies). The depth of myometrial invasion was mostly just beneath the serosa, although partly exposed microscopically. Further, small parts of benign adenomyosis coexisted (**Fig. 5**). Furthermore, the cervical invasion and lymphatic spread in the adnexa were observed. The immnohistochemical staining for vimentin was focally positive, whereas it was negative for p53 (wild-type), estrogen receptor, and progesterone receptor.

The patient's postoperative course was uneventful. Chemotherapy with paclitaxel plus carboplatin was initiated on postoperative day 13 at the 3-week interval for six cycles; no major adverse events were observed during the chemotherapy. In addition, she was administered zoledronic acid (4 mg/body) every 4 weeks. After six cycles of chemotherapy, PET/CT revealed a reduced size of pulmonary metastases (partial response). Subsequently, three additional cycles of the same regimen were administered. Chest CT for reevaluation revealed small residual lesions of pulmonary metastases. Finally, the chemotherapy regimen was changed to doxorubicin combined with cisplatin, and the treatment is ongoing till date.

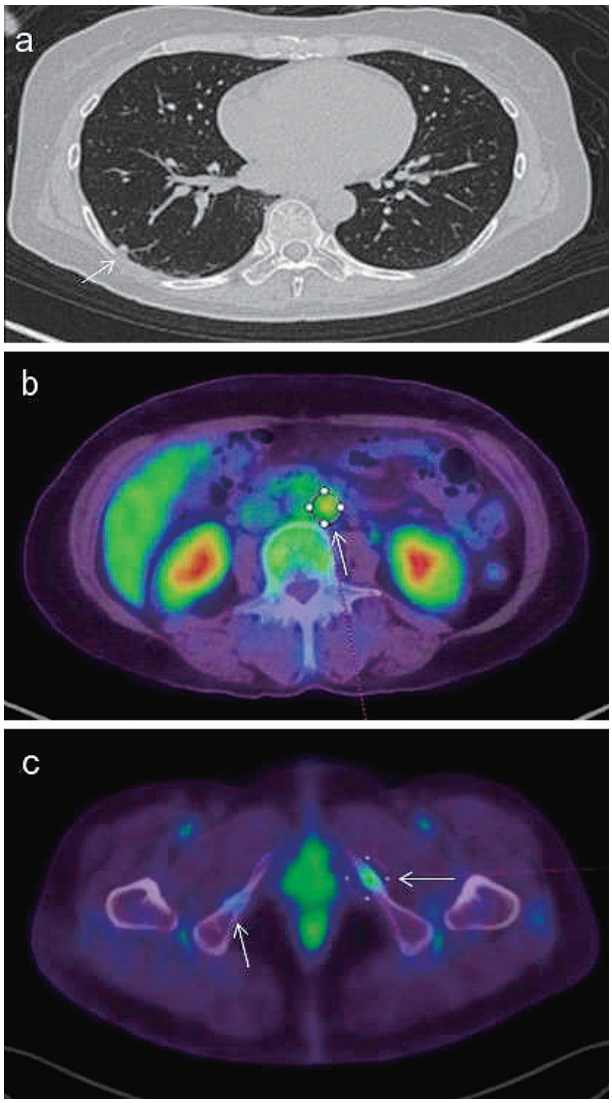

Fig. 2 Positron emission tomography/computed tomography demonstrates multiple pulmonary metastases (a), para-aortic node metastases (b), and pelvic bone metastases (c). Arrows: each lesion.

Discussion

The malignant transformation of endometriosis is well-established carcinogenesis in ovarian cancer, especially for clear cell and endometrioid types. Reportedly, the malignant transformation occurs in approximately ≤1 % of ovarian endometriosis cases[1]. However, the malignant transformation of adenomyosis into endometrial carcinoma is considered to be an extremely rare occurrence. Till date, only a limited number of case reports have been documented sporadically. In 1959, Colman proposed a diagnostic criteria for EC-AIA, which was a modification of that for the malignant transformation of endometriosis, as follows: (1) cancer must not be located in the endometrium or any other place in the pelvis, (2) cancer

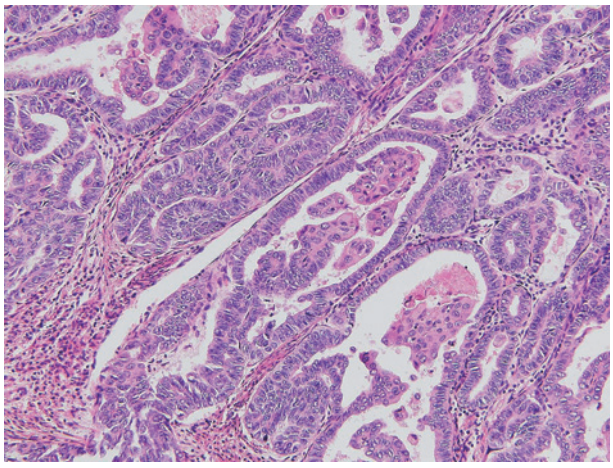

Fig. 4 A high power view of the neoplastic glands show floating eosinophilic cancer nests (H&E; magnification, ×100).

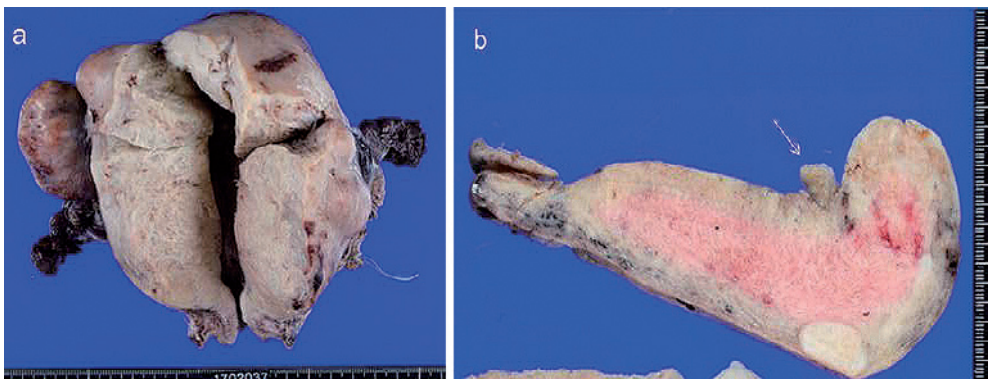

Fig. 3 The macroscopic view of the resected uterus (a) and its sagittal section (b). The uterus shows the diffuse-thickness myometrium, which is difficult to distinguish from ordinal adenomyosis. The endometrium was thin, except for a minimal lesion observed at the fundus (arrow).

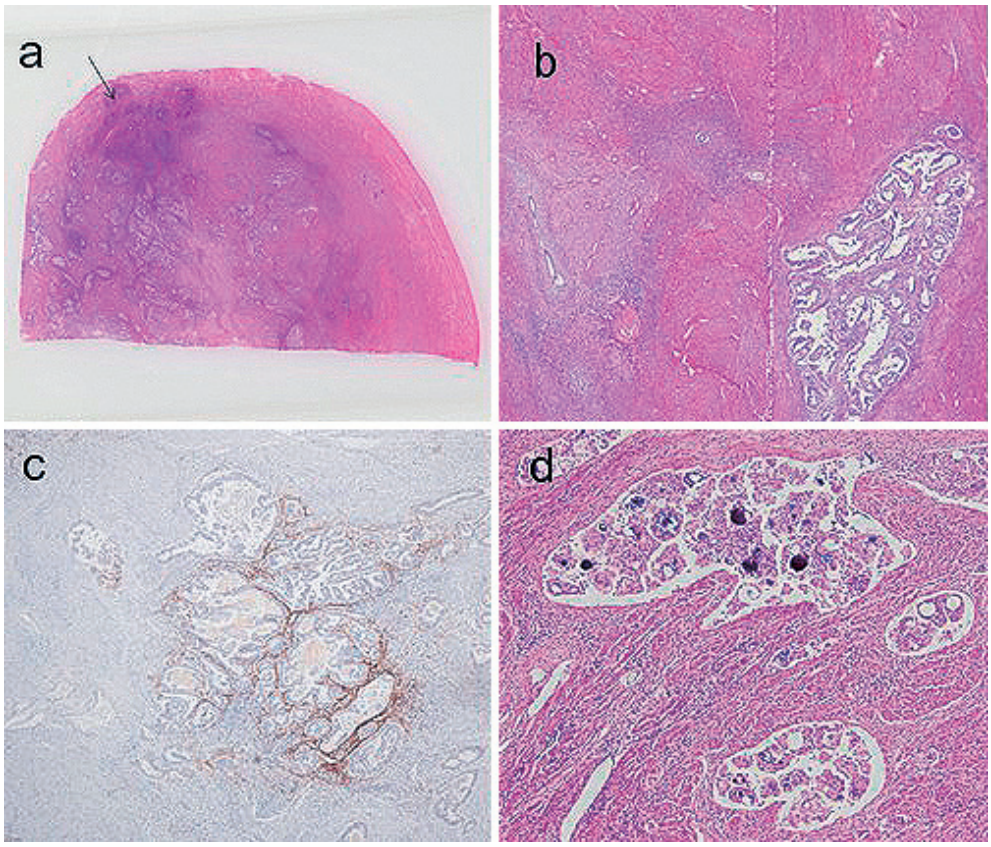

Fig. 5 Microscopic findings reveal that (a) diffuse-type carcinoma occupied the complete uterine body, partly coexisting with adenomyosis (arrow) in a loupe image; (b) a nest of cancer adjacent to adenomyosis in the left portion (H&E; magnification, ×40); (c) in situ lesion surrounded by the endometrial stromal cells that are stained with CD-10 (immunohistochemical staining for CD-10; magnification, ×40); and (d) invasive lesion with microcystic, elongated, and fragmented pattern accompanied with a psammoma body (H&E; magnification, ×100).

arises from the epithelium of adenomyosis and should not invade from another source, and (3) endometrial stromal cells surround the aberrant glands to support the diagnosis of adenomyosis[2]. Since then, most case series have referred these criteria. Nevertheless, the first criterion "cancer must not be located in the endometrium or other place in the pelvis" seems to inconsistently correspond to the relatively aggressive nature of EC-AIA. It has been pointed out that the prevalence of EC-AIA has possibly been underestimated because to fulfill all the aforementioned criteria, advanced cases of adenomyosis have to be excluded.

Machida et al. examined 46 patients with EC-AIA in 24 studies, which were extracted from the systematic English literature searched through web-based search engines[3]. They adapted the modified criteria supported by the immunostaining results based on previous reports, although the details were not explained. EC-AIA-involved-endometrium was defined as a continuous transition from the adenomyotic epithelium in the myometrium to adenocarcinoma, which extended to the endometrium. They compared 16 patients with EC-AIA with tumors extending into the endometrium with the remaining 28 patients with EC-AIA with tumors confined to the myometrium (excluded 2 patients with data missing). No differences were observed in demographics and tumor characteristics (e.g., age, symptoms, grade, histology, and stage) and survival outcome of the patients between the two groups. Seventy-six percent of EC-AIA cases demonstrated endometroid histology, most of which comprised grade 1 or 2 tumor.

In addition, they assessed the histopathological findings and prognosis of EC-AIA compared with the control group of EC-A and reported that EC-AIA correlated with poor prognosis and tended to have aggressive tumor features, including deep myometrial invasion, advanced

stage, and nodal metastasis. Furthermore, most cases of EC-AIA were negative for estrogen receptors contrary to EC-A[3]. Notably, our case demonstrated almost all the aforementioned features corresponding EC-AIA. Difficulty in early-stage detection may be one of the possible factors for the aggressive tumor feature of EC-AIA. In the present case, MRI image of the uterine body revealed a higher signal intensity, which is not typical for adenomyosis, compared with that captured 4 years prior. Therefore, meticulous observation for change in signal intensity of MRI images may facilitate an early diagnosis of EC-AIA.

Till date, the oncogenic mechanism underlying the malignant transformation of adenomyosis remains unclear. The incidence of genetic mutations, including those in the *AT-rich interactive domain 1A gene* (*ARDIA*), which is often observed in endometriosis-associated ovarian cancer, has not been reported in the literature on EC-AIA[4]. Thus, further molecular genetics-based studies of EC-AIA are warranted to elucidate the pathogenesis and, hopefully, develop more individualized treatment strategy for this endometrial cancer subtype in the future.

Conclusion

In conclusion, we reported a case of advanced EC-AIA based on the clinical and histopathological characteristics. The criteria for diagnosing EC-AIA requires revision to precisely define advanced EC-AIA. Overall, this case highlights the necessity of considering aggressive diseases, such as EC-AIA, when following up on patients with adenomyosis.

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Conflicts of Interest: The authors declare that they have no conflict of interest.

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