A Case of Uterine Cervical Adenocarcinoma in Which Initial Total Laparoscopic Hysterectomy Was Performed for Suspected Atypical Endometrial Hyperplasia

Toshinari MURAMATSU[*1], Taro SUGIYAMA[*1], Yuki KURIYAMA[*1], Takatoshi MANABE[*1], Ippei OIWA[*1], Rie NAKAJIMA[*1], Chisa NARAYAMA[*1], Tomoaki NARAYAMA[*1], Tetsuji IIDA[*1], Ken-ichi GOYA[*1], Hitomi TSUKADA[*1], Hironobu MAEDA[*1] and Mikio MIKAMI[*2]

[*1]*Department of Obstetrics and Gynecology, Tokai University Hachioji Hospital*
[*2]*Department of Obstetrics and Gynecology, Tokai University School of Medicine*

(Received July 19, 2019; Accepted November 28, 2019)

The patient was a 69-year-old multiparous female (gravida/para, 3/3) who had hypertension and arrhythmia. Her history included cerebral infarction treated with conservative therapy. She visited our hospital for atypical genital bleeding. She was diagnosed with atypical glandular cells (AGC) based on cervical cytology, atypical cells in endometrial cytology, and atypical endometrial hyperplasia on preoperative endometrial biopsy, and underwent total laparoscopic hysterectomy. However, in a postoperative pathologic examination, she was diagnosed with stage IB1 cervical adenocarcinoma without endometrial abnormality. AGC appeared in cervical cytology before surgery, but a surgical plan was not made with consideration of cervical adenocarcinoma.

Key words: laparoscopic surgery, atypical endometrial hyperplasia, cervical adenocarcinoma

INTRODUCTION

Laparoscopic surgery for gynecological malignancy has become common. In Japan, laparoscopic surgery has been covered by health insurance for early-stage endometrial cancer since April 2014 and for cervical cancer since April 2018. The treatment guidelines for endometrial cancer and gynecological endoscopic surgery recommend use of laparoscopic surgery for atypical endometrial hyperplasia (AEH) and early-stage endometrial cancer [1, 2]. Our hospital started to use laparoscopic surgery for early-stage endometrial cancer in January 2015. Here, we describe a case treated with laparoscopic surgery for a preoperative diagnosis of AEH that was then diagnosed pathologically as stage IB1 cervical adenocarcinoma postoperatively. Surgical procedures and safety management are discussed in this report.

CASE REPORT

The patient was a 69-year-old multiparous female (gravida/para, 3/3). Her chief complaints were atypical genital bleeding. Her medical history included cerebral infarction that had been treated with conservative therapy (Fig. 1A), and she currently had hypertension and arrhythmia. She had visited a previous gynecologist for atypical genital bleeding. Atypical glandular cells (AGC) were confirmed by cervical cytology, atypical cells were found in endometrial cytology, and AEH on endometrial biopsy (Fig. 2A–C). The patient was referred to our hospital for workup and treatment. Pelvic MRI showed 9mm endometrial thickening and a cystic change of several mm in the cervix (Fig. 1B). Laparoscopic surgery was planned for treatment of AEH and abnormal cervical cytology.

In surgery, trocars were inserted 12 mm from the hilum and 5 mm from the right and left and midline lower abdomen in a diamond style. Surrounding organs were observed using a camera that was inserted from the hilum; however, no marked abnormal findings, such as intestinal adhesion, were found and cytology of the ascites was negative. The intestinal tract was kept cephalad due to the head-down position during surgery and the bilateral oviducts were closed using vessel sealing system (Fig. 3A). A uterine manipulator was inserted to keep the uterus movable. The peritoneum of the pouch between the bladder and uterus was incised to open the retroperitoneum. After confirming running of the right ureter, the crossing uterine artery was removed and the outer and inner parts were ligated with a 3–0 absorbable thread (Fig. 3B) and using vessel sealing system, respectively. The uterine artery was kept upward and the bladder was kept downward. After coagulation of the anterior layer of the bladder and uterine ligaments (Fig. 3C), the vaginal wall was incised in a circle and the cervix was detected (Fig. 3D). The cervix in a retrieval pack was extirpated through the vagina and extended total hysterectomy and bilateral adnexal resection were performed (operation time: 197 min, hemorrhage: 25 mL) (Fig. 4A). No tumor lesion was found macroscopically in the removed uterine body (Fig. 4B) and no marked

Toshinari MURAMATSU, Department of Obstetrics and Gynecology, Tokai University Hachioji Hospital, 1838 Ishikawa-machi, Hachioji, Tokyo 192-0032, Japan Tel: +81-42-639-1111 Fax: +81-42-639-1144 E-mail: mura-to@is.icc.u-tokai.ac.jp

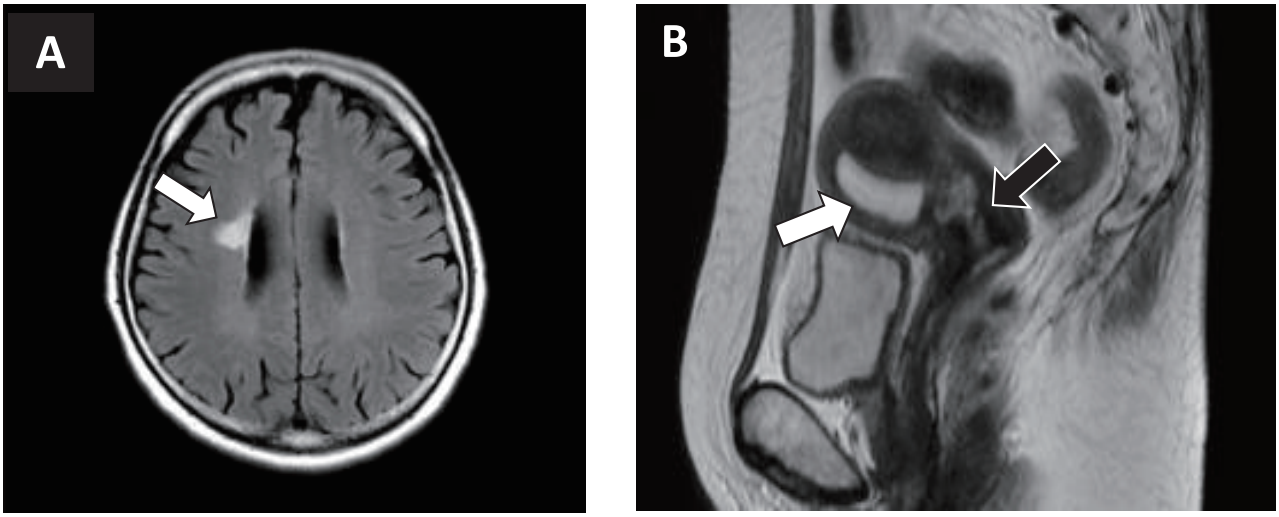

Fig. 1 Brain and pelvic MRI.
A: Brain MRI FLAIR showed high intensity in the right basal nucleus (⇨), indicating old cerebral infarction.
B: Pelvic sagittal MRI (T2-weighted image) showed endometrial hypertrophy (9 mm; ⇨) and cystic findings in the cervix (➡), but no tumorigenic changes in the cervix.

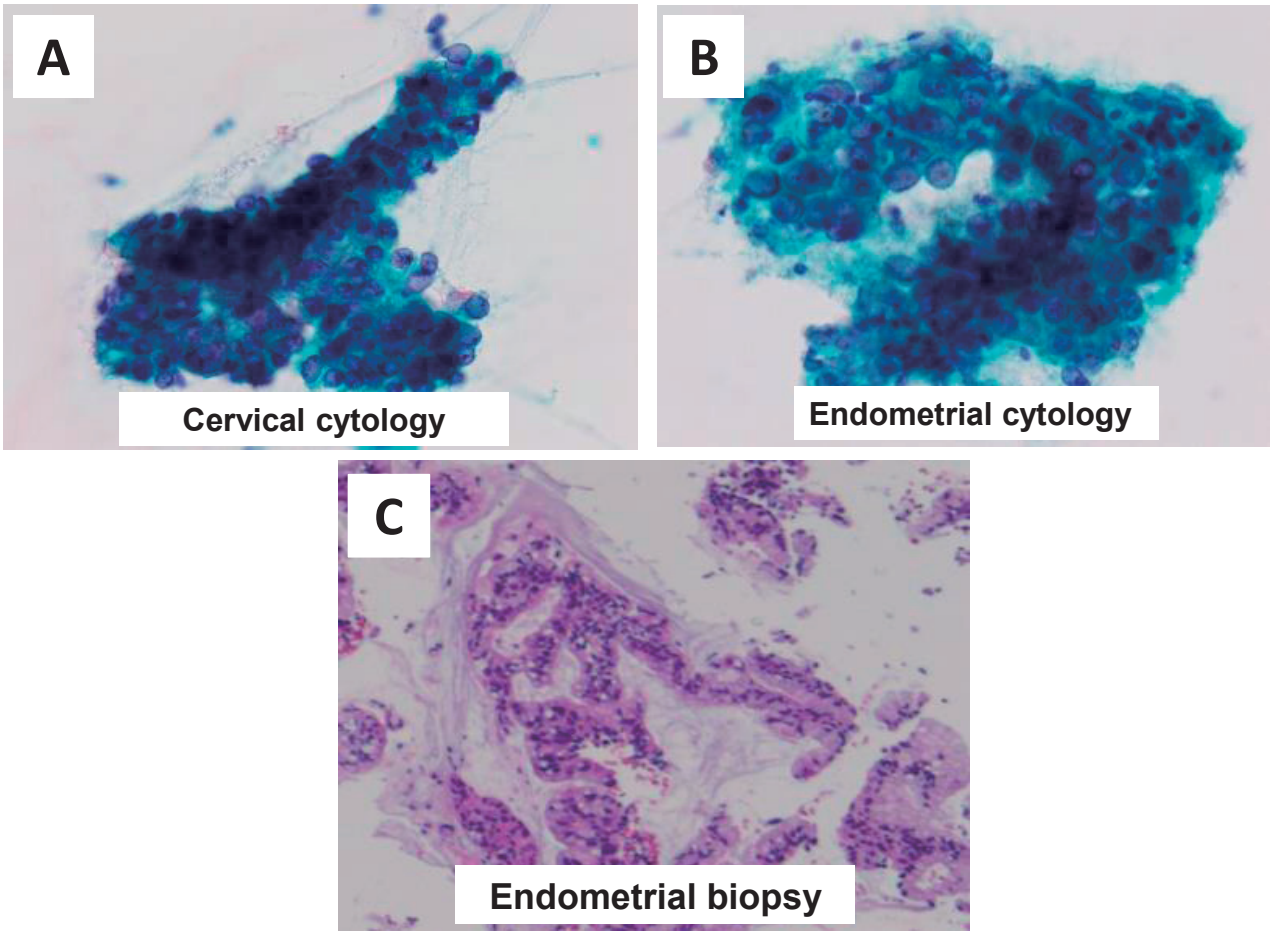

Fig. 2 Preoperative diagnosis of cytology and biopsy.
A: Cervical cytology showed dominant parabasal cells, anisonucleosis, increased nuclear density, and nuclear bodies with distinct heteroplasmic glandular cells and atypical glandular cells (AGC).
B: Endometrial cytology gave a cellular image with yellowish mucus in clumps with distinct nucleoli, which was identified as atypical endometrial hyperplasia (AEH).
C: Endometrial biopsy led to diagnosis of atypical endometrial hyperplasia based on cell size and cell disorder, a disordered glandular structure, nuclear enlargement and chromatin increase.

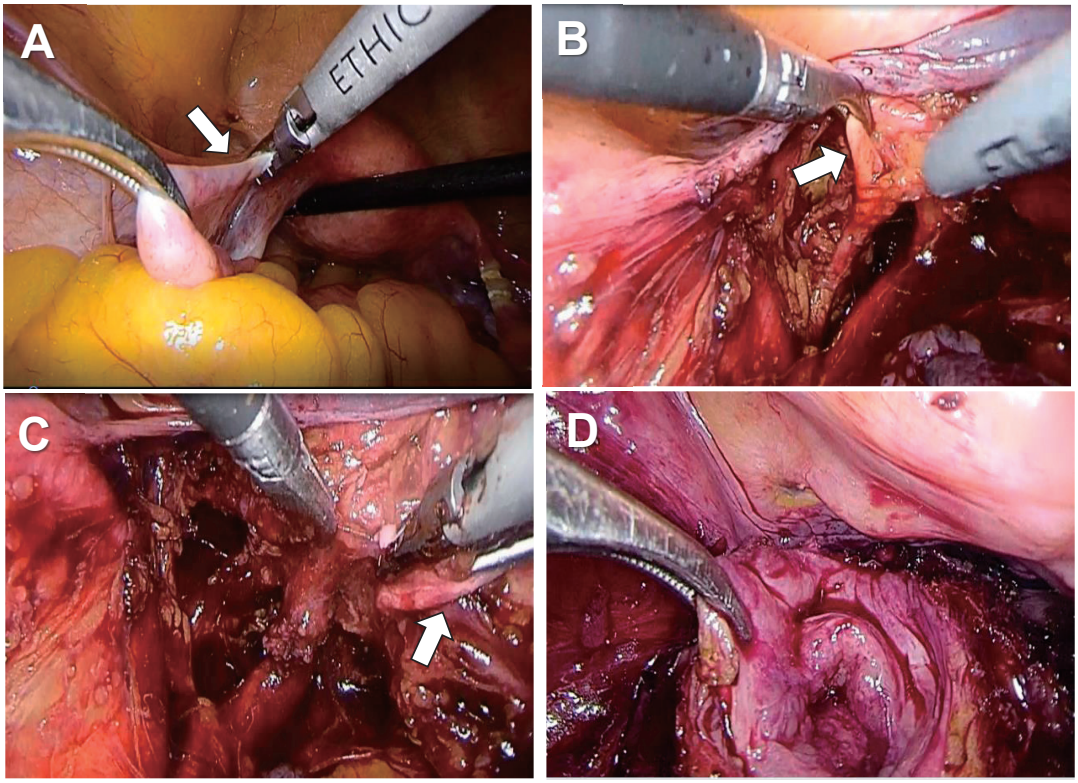

Fig. 3 Intraoperative photography.
A: The fallopian tube (⇨) was sealed in two places and a uterine manipulator was inserted.
B: The uterine artery was isolated and ligated (⇨).
C: The uterine artery (⇨) was lifted and the ureter was pushed downwards to ligate the anterior of the vesico-uterine ligament.
D: After an incision in the vaginal wall, the uterine opening was confirmed, and the uterus was placed in a collection bag and collected from the body through the vagina.

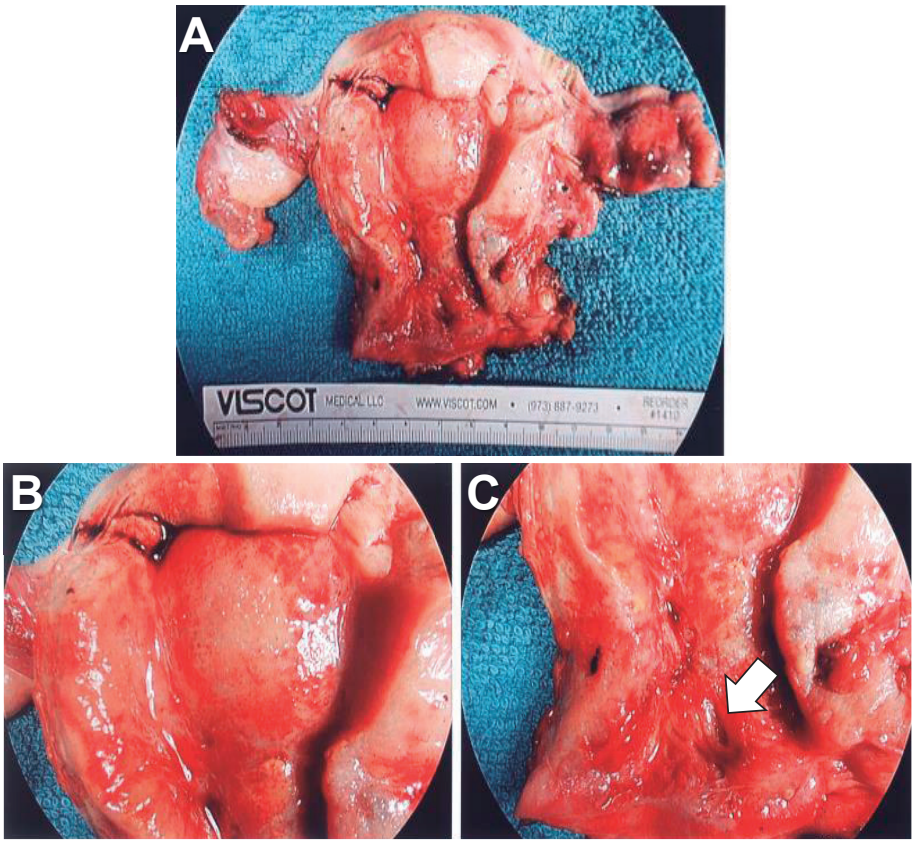

Fig. 4 Extracted uterus.
A: The extracted uterus (plus appendages on both sides) was cut into a Y shape.
B: The endometrium was smooth, with no evidence of rough-surface due to a tumor.
C: The cervix had a small cystic region (⇨), but there was no tumorous bulge.

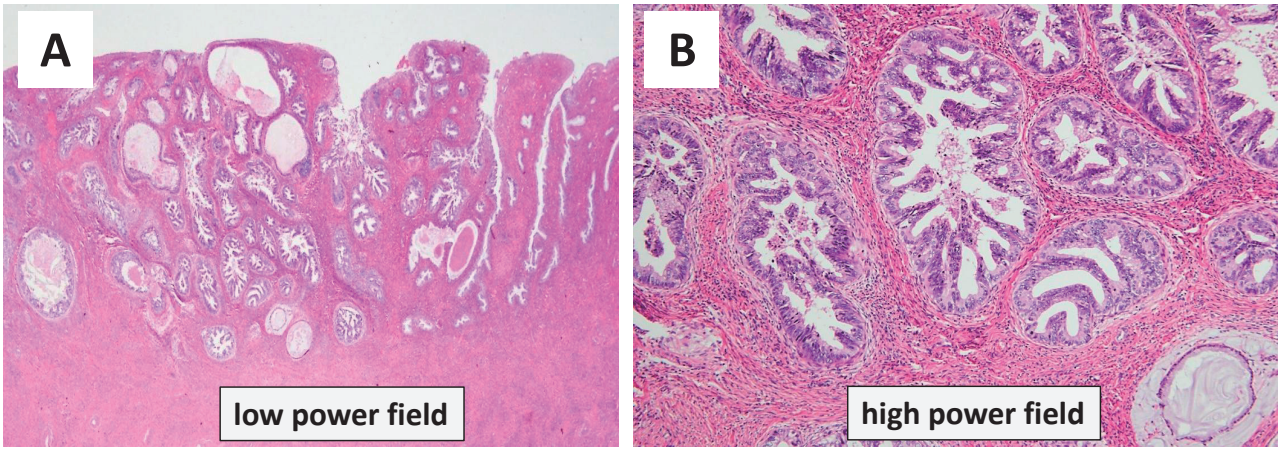

Fig. 5 Postoperative pathological diagnosis.
A: Cervical duct with strong nuclear atypia showing an irregular fence alignment.
B: Mucus inside the duct structure and an image of endocervical adenocarcinoma, usual type.

macroscopic changes were found in the cervix (Fig. 4C).

Postoperative pathology revealed the presence of a tumor in the inner cervix that had an irregular palisade structure containing mucus inside the gland structure. The focal size was 22 mm and the tumor was diagnosed as endocervical adenocarcinoma, usual type [3], stage IB1 (pTb1, ly-, v-) with 8mm invasion (Fig. 5A, B). After surgery, the patient and her family were informed of the findings; the necessity for re-operation with pelvic lymphadenectomy; and possible complications including lymphedema. After seeking a second opinion, the patient decided not to undergo reoperation. Instead, she was treated with 6 courses of paclitaxel and carboplatin. She is currently under follow-up with no signs of recurrence.

DISCUSSION

Preoperative examinations for endometrial cancer include cervical cytology, endometrial cytology and endometrial biopsy, together with imaging using transvaginal ultrasonography, pelvic MRI, and CT [4, 5]. In our patient, no tumor lesion was found in the cervix, but AGC was detected by cervical cytology. The patient was diagnosed with class III by endometrial cytology and AEH by endometrial biopsy. Early cervical adenocarcinoma is sometimes detected as AGC in cervical cytology [6]. However, the patient had almost no cervical findings in preoperative imaging and only slight endometrial thickening (Fig. 1B). Cervical curettage was performed, but without detection of an adenocarcinomatous component. An endometrial examination found atypical cells and tissues. Consequently, the patient was not diagnosed with cervical adenocarcinoma preoperatively.

Cases with AGC in preoperative cervical cytology may have cervical adenocarcinoma, based on prevalences of cervical cancer of 0.2% in low-grade squamous intraepithelial lesion (LSIL), 2.5% in high-grade squamous intraepithelial lesion (HSIL), and 1.4% in AGC found in cytology in a cohort study in more than 3 million women aged 23 to 59 years in Sweden. In particular, cervical adenocarcinoma accounted for 73% of the subjects with AGC who had a tumor. Recurrence of adenocarcinoma in women with AGC in cervical screening was 61 times higher than that in women with normal cytology [7]. Thus, a case with AGC in cervical cytology should be suspected to have cervical adenocarcinoma. In our patient, cervical cytology showed AGC, but there was no cervical enlargement or abnormal finding in clinical practice and no cancerous changes in the cervix in imaging; therefore, a preoperative diagnosis of cervical adenocarcinoma was not made. Preoperative MRI and CT were reassessed, but no definite invasive shadow was found. However, endometrial thickening of approximately 9 mm was found. This finding, the invasion in muscular layers surrounding the endometrium, and the patient's age prompted planning of surgery for AEH and very early endometrial cancer [8, 9].

In our procedure for laparoscopic surgery for AEH and initial endometrial cancer, forceps are installed in a diamond pattern and ascites is collected after observation in the abdominal cavity using a 12mm endoscopic camera inserted into the hilum. Next, two points in the uterine side of bilateral oviducts are sealed with a power source, and a uterine manipulator is inserted to keep the uterus movable. A problem with manipulator insertion is dispersion of atypical and malignant cells during endometrial surgery for an atypical or malignant tumor. Many clinical studies have examined this problem. In a case control study of biopsy of pelvic ascites in 333 patients with endometrial cancer stage I to IV, the incidences of atypical cells were 2.9% in 103 subjects and 4.8% in 230 subjects in samples collected after and before manipulator insertion, respectively. The respective rates of malignant cells were 5.8% and 9.6% ($p = 0.36$), showing no significant difference in the positive rate of pelvic cytology between the two groups [10]. In a clinical study in 951 patients with endometrial cancer at 7 Italian facilities, the recurrence rates were 13.5% and 11.6% ($p = 0.37$) in cases with and without manipulator insertion, respectively, in a median follow-up period of 46 months (12–163 months). Use of a manipulator had no effect on recurrence risk in univariate analysis (odds ratio, 1.18; 95% CI: 0.80–1.77) and multivariate analysis (odds ratio, 1.00; 95% CI: 0.60–1.70), but “lymph node metastasis-positive” and “50% or more myometrial invasion” were found to be independent factors for recurrence risk [11]. Other studies have also shown negative results for the effect of manipulator insertion

on prognostic factors [12–14]. In our patient, cytology of ascites before manipulator insertion gave negative results. Another concern in manipulator insertion is blunt uterine injury. It is important not to insert the tip of the manipulator into the uterine cavity and to prevent manipulator over-ballooning. In older women, the uterus is particularly contracted and the uterine cavity is narrow, and care is required in insertion of a manipulator [15–17]. If cervical cancer is diagnosed before surgery, we suggest that a uterine manipulator should not be used based on a concern of scattering of cancer cells.

The detailed procedures for hysterectomy in patients with AEH in our hospital are as follows. The peritoneum of the vesico-uterine pouch is incised and opened wide. After ureteral running in the retroperitoneum and the crossing point with the uterine artery are confirmed, the uterine artery is removed outside the ureter, both ends of the artery are coagulated, and then the artery is incised to complete anterior processing of the artery (Fig. 3B). The anterior layer of the peritoneum of the vesico-uterine pouch to keep the ureter outside as much as possible. To prevent coagulation damage to the ureter, it is important to keep the ureter away from the coagulated area when using an energy device. The ureter is rolled outside and the bladder is kept sufficiently apart from the vaginal wall (Fig. 3C). The paracolpium is processed at the ligated points of the uterine artery to keep the uterine wall free, the inserted manipulator is removed and replaced with a vaginal pipe, and the uterus and some of the vaginal wall are resected simultaneously with a sufficient incision margin (Fig. 3D). In the current case, the patient was diagnosed with cervical adenocarcinoma, but the vaginal wall was removed over a wide area with a margin of 10–15 mm.

The patient was under treatment for hypertension and arrhythmia and had a history of conservative therapy for cerebral infarction. The head-down position required for laparoscopic surgery is a concern in a patient with a potentially fatal complication. We completed surgery with a short operative time and low bleeding volume while maintaining the head-down position that kept the intestine and mesentery above the uterus and appendages, while changes in blood pressure were monitored by an anesthesiologist. There were almost no changes in blood pressure and vital signs after surgery; therefore, the laparoscopic surgery was performed in a minimally invasive and safe manner.

In conclusion, the patient was diagnosed with AEH preoperatively and underwent laparoscopic hysterectomy, but was then diagnosed with stage IB1 cervical adenocarcinoma (mucinous carcinoma) postoperatively by pathologic examination. We explained to the patient and her family that a cytoreductive surgery was required and that tests for metastasis using pelvic lymphadenectomy should be performed. However, the patient did not want to undergo a reoperation, and chemotherapy was added. If abnormalities of cervical cytology appear before surgery, it is necessary to evaluate cervical disease abnormalities.

REFERENCES

1) Guidelines for Obstetrics and gynecology endoscopic surgery: Japan Society of Gynecologic and Obstetric Endoscopy and Minimally Invasive Surgery (JSGOE) 2013 edition, Kanehara & Co., Ltd.
2) Guidelines for treatment of uterine body neoplasm: Japan Society of Gynecologic Oncology (JSOG) 2018 edition, Kanehara & Co., Ltd.
3) The General Rules of Clinical and Pathological Management of Uterine Cervical Cancer. Pathological edition. The 4th ed. July 2017. Kanehara & Co., Ltd.
4) Haldorsen IS, Salvesen HB. What Is the Best Preoperative Imaging for Endometrial Cancer? Curr Oncol Rep. 2016; 18(4): 25. doi: 10.1007/s11912-016-0506-0. Review.
5) Antonsen SL, Jensen LN, Loft A, Berthelsen AK, Costa J, Tabor A, *et al.* MRI, PET/CT and ultrasound in the preoperative staging of endometrial cancer -a multicenter prospective comparative study-Gynecol Oncol. 2013; 128(2):300–308.
6) Norman I, Hjerpe A, Dillner J. Risk of high-grade lesions after atypical glandular cells in cervical screening: a population-based cohort study. BMJ Open. 2017; 7(12): e017070. doi: 10.1136/bmjopen-2017-017070.
7) Wang J, Andrae B, Sundström K, Ström P, Ploner A, Elfström KM, *et al.* Risk of invasive cervical cancer after atypical glandular cells in cervical screening: nationwide cohort study. BMJ. 2016; 352: i276. doi: 10.1136/bmj.i276.
8) Haldorsen IS, Salvesen HB. Staging of endometrial carcinomas with MRI using traditional and novel MRI techniques. Clin Radiol. 2012; 67(1): 2–12.
9) Husby JA, Salvesen OO, Magnussen IJ, Trovik J, Bjorge L, Salvesen HB, *et al.* Tumour apparent diffusion coefficient is associated with depth of myometrial invasion and is negatively correlated to tumour volume in endometrial carcinomas. Clin Radiol. 2015; 70(5): 487–94.
10) Machida H, Casey JP, Garcia-Sayre J, Jung CE, Casabar JK, Moeini A, *et al.* Timing of Intrauterine Manipulator Insertion During Minimally Invasive Surgical Staging and Results of Pelvic Cytology in Endometrial Cancer.J Minim Invasive Gynecol. 2016; 23(2): 234–241.
11) Uccella S, Bonzini M, Malzoni M, Fanfani F, Palomba S, Aletti G, *et al.* The effect of a uterine manipulator on the recurrence and mortality of endometrial cancer: a multi-centric study by the Italian Society of Gynecological Endoscopy. Am J Obstet Gynecol. 2017; 216(6): 592.e1–592.e11.
12) Eltabbakh GH, Mount SL. Laparoscopic surgery does not increase the positive peritoneal cytology among women with endometrial carcinoma. Gynecol Oncol. 2006; 100(2): 361–364.
13) Lee M, Kim YT, Kim SW, Kim S, Kim JH, Nam EJ. Effects of uterine manipulation on surgical outcomes in laparoscopic management of endometrial cancer: a prospective randomized clinical trial. Int J Gynecol Cancer. 2013; 23(2): 372–379.
14) Sonoda Y, Zerbe M, Smith A, Lin O, Barakat RR, Hoskins WJ. High incidence of positive peritoneal cytology in low-risk endometrial cancer treated by laparoscopically assisted vaginal hysterectomy. Gynecol Oncol. 2001; 80(3): 378–382.
15) Lim S, Kim HS, Lee KB, Yoo CW, Park SY, Seo SS. Does the use of a uterine manipulator with an intrauterine balloon in total laparoscopic hysterectomy facilitate tumor cell spillage into the peritoneal cavity in patients with endometrial cancer? Int J Gynecol Cancer. 2008; 18(5): 1145–1149.
16) Marcos-Sanmartín J, López Fernández JA, Sánchez-Payá J, Piñero-Sánchez ÓC, Román-Sánchez MJ, Quijada-Cazorla MA, *et al.* does the type of surgical approach and the use of uterine manipulators influence the disease-free survival and recurrence rates in early-stage endometrial cancer? Int J Gynecol Cancer. 2016; 26(9): 1722–1726.
17) Singh S, Swarer K, Resnick K. Longer operative time is associated with increased post-operative complications in patients undergoing minimally-invasive surgery for endometrial cancer. Gynecol Oncol. 2017; 147(3): 554–557.