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CASE REPORT

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A case report and literature review: A 19-year-old with endometrial carcinoma treated with medroxyprogesterone acetate. Importance of the medical interview and endometrial examination

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Key Clinical Message

A 19-year-old woman had stage IA endometrial carcinoma treated with medroxyprogesterone acetate and experienced a recurrence. This patient's experience illustrates the importance of a thorough history and endometrial assessment in younger patients.

KEYWORDS

adolescent, conservative treatment, endometrial neoplasms, fertility preservation, medroxyprogesterone acetate

1 | INTRODUCTION

In Japan, endometrial carcinoma (EC) is most commonly diagnosed in patients in their fifties; onset at a young age is very rare.[1] Because young patients typically want to preserve their fertility, the usual treatment is medroxyprogesterone acetate (MPA) with a long follow-up period. However, EC is prone to recurrence after MPA therapy, and decisions regarding the most appropriate treatment after recurrence are often difficult. In this report, we describe a patient who developed EC at less than 20 years of age. We also review the literature to discuss the diagnosis and treatment of such patients.

2 | CASE HISTORY/EXAMINATION

A 19-year-old woman presented to a local gynecologist for assessment of irregular and excessively heavy menstrual periods for several months. She experienced menarche at age 11, and her menstrual periods were previously regular, on a 25-day cycle. She was sexually active but nulligravid. Transvaginal ultrasonography (TV-US) indicated that her endometrium was thickened to 17 mm, and endometrial cytology showed atypical glandular cells. The patient was referred to our hospital for further examination and treatment.

3 | METHODS (INVESTIGATIONS AND TREATMENT)

The patient was 151.9 cm tall and weighed 58.1 kg, with a body mass index (BMI) of 25.4 kg/m^2. She had hirsutism on her face and torso. Her family history was significant for lung cancer in her maternal grandfather.

Speculum examination revealed a cervix of normal size, with a 7-mm polyp protruding from the external os. TV-US revealed an area of mixed echogenicity in the uterine cavity (Figure 1). A Papanicolaou smear was negative for intraepithelial lesion or malignancy, but repeat endometrial cytology was suspicious for malignancy. The polyp and endometrial histology were suggestive of endometrioid carcinoma, grade 1. Contrast-enhanced pelvic magnetic resonance imaging (MRI) was performed to evaluate for myometrial invasion. The uterine cavity was dilated and occupied by a 37-mm thick area with a high signal on T2-weighted images; there was no evidence of myometrial invasion. The region was diffusion limited, and there was poor gadolinium contrast in the myometrium, suggesting endometrial hyperplasia or EC. Both ovaries were polycystic (Figure 2A,B). Contrast-enhanced computed tomography (CT) from chest to pelvis, performed to evaluate for metastasis, showed no lymphadenopathy or distant metastasis. Blood tests showed an elevated cancer antigen (CA) 19-9 level, at 190 U/mL (normal range, <37 U/mL), and normal CA125 and carcinoembryonic antigen (CEA) levels. Her luteinizing hormone (LH) level was 3.10 mIU/mL, and her follicle-stimulating hormone (FSH) level was 4.17 mIU/mL, both normal levels for a woman during ovulation. Based on her laboratory and imaging findings, we diagnosed the patient with polycystic ovarian syndrome (PCOS) and with EC versus endometrial hyperplasia.[2] We performed dilation and curettage (D&C) to obtain a definitive tissue sample; histologic examination revealed endometrioid carcinoma, grade 1 (Figure 3).

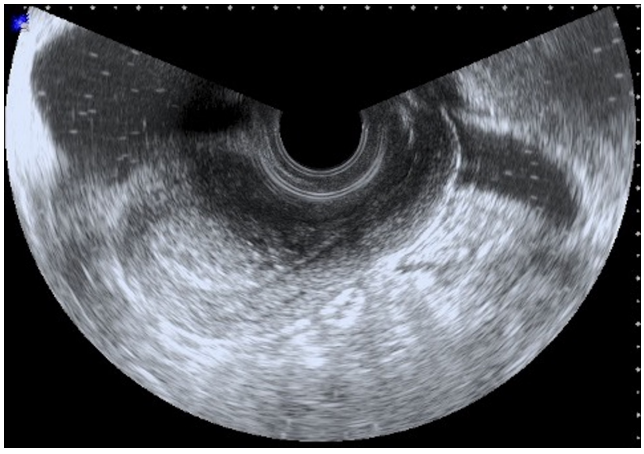

FIGURE 1 Transvaginal ultrasound shows a 4.2 × 1.8 cm area of mixed echogenicity in the uterine cavity.

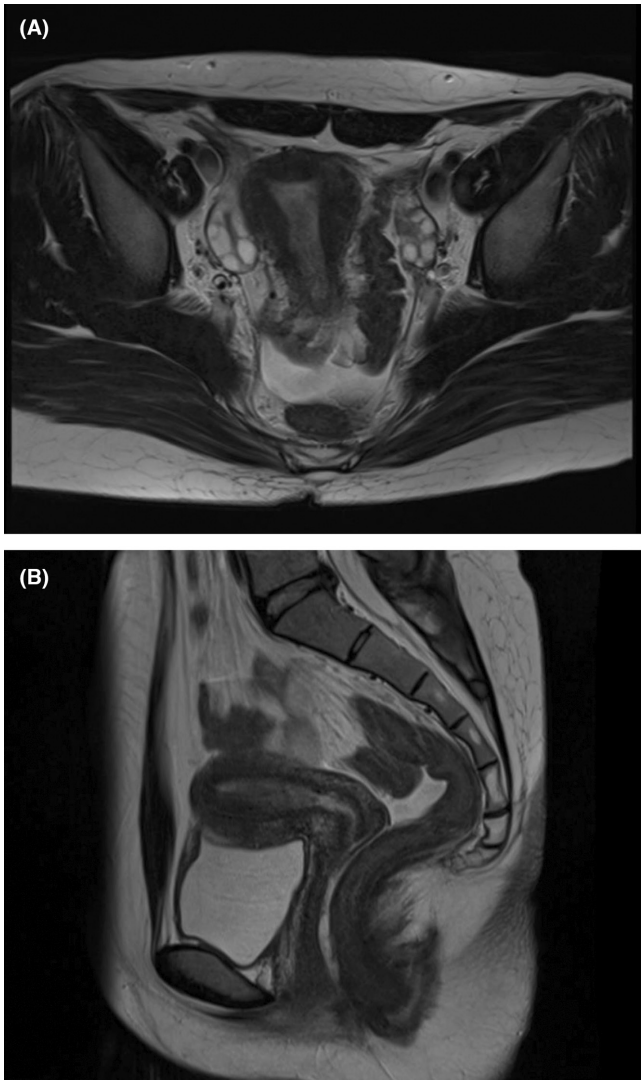

FIGURE 2 Pelvic magnetic resonance imaging (MRI) cross-section (A) and sagittal section (B) before medroxyprogesterone acetate (MPA) therapy.

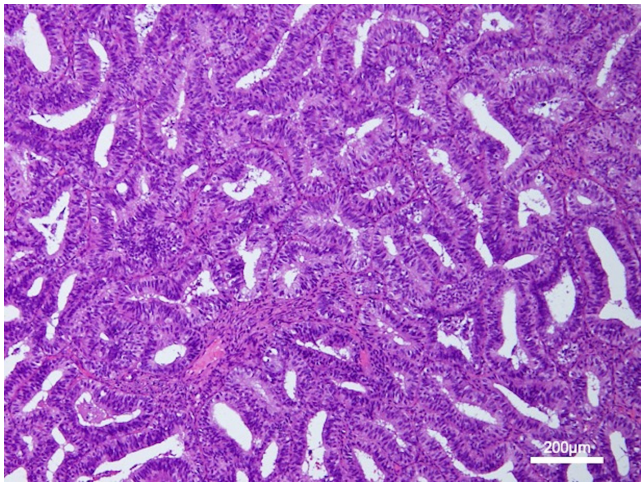

FIGURE 3 Endometrial histology before treatment. Hematoxylin and eosin (H&E) staining (magnification: ×100).

The patient's final diagnosis was EC stage IA (cT1aN0M0 endometrioid carcinoma, grade 1) and PCOS. Because she strongly wanted to preserve her fertility, we started MPA therapy at 600 mg/day for 26 weeks. According to our protocol, we planned to re-assess with D&C at 8 and 16 weeks after starting MPA therapy, and with pelvic MRI 16 weeks after starting MPA therapy. After 26 weeks of MPA therapy, if endometrial histology showed a complete response (CR) to therapy, we planned to prescribe estrogen-progestin tablets for 6 months.[3] The patient took MPA every day and had no adverse effects. The sample obtained at her 8-week D&C demonstrated a CR to therapy, as did the sample obtained at her 16-week D&C. Pelvic MRI at 16 weeks showed no thickening of the endometrium or mass in the uterine cavity (Figure 4A,B). After 26 weeks of MPA therapy, endometrial histology showed a CR to therapy and her CA19-9 level at 73 U/mL. At that point, we switched to medical suppression of the endometrium using oral norgestrel–ethinyl estradiol tablets to prevent EC recurrence. Our plan was to continue oral contraception until the patient expressed a desire for

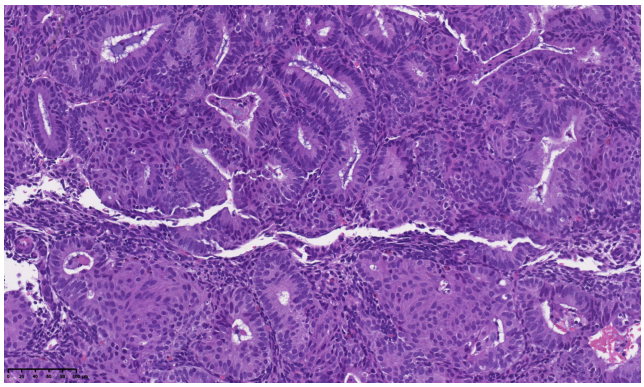

FIGURE 5 Endometrial histology at time of recurrence. H&E staining (magnification: 200).

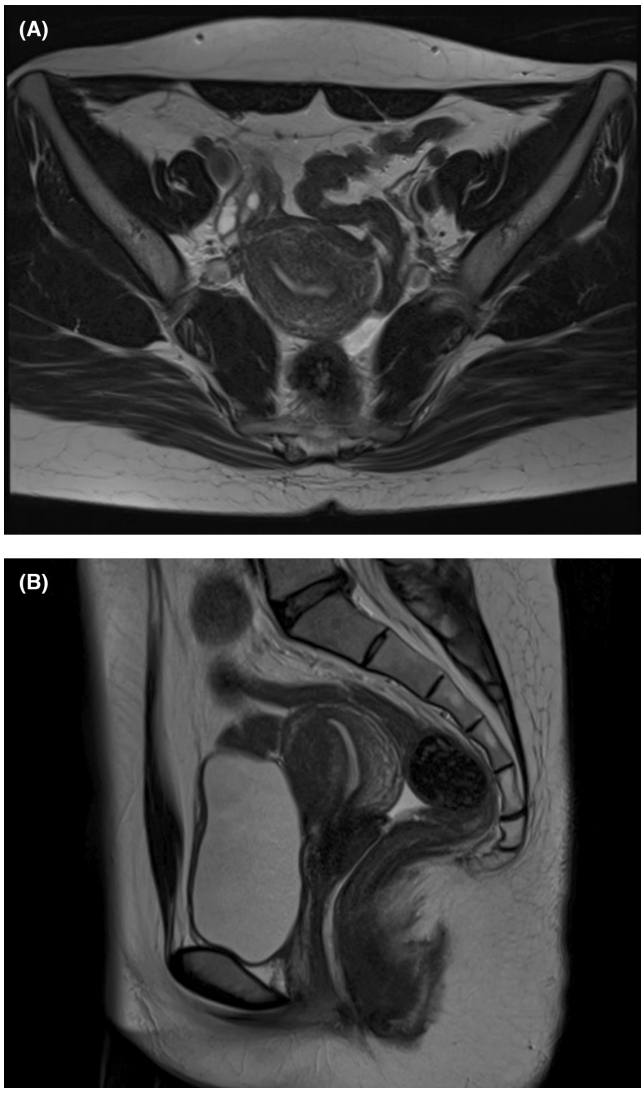

FIGURE 4 Pelvic MRI cross-section (A) and sagittal section (B) after MPA therapy.

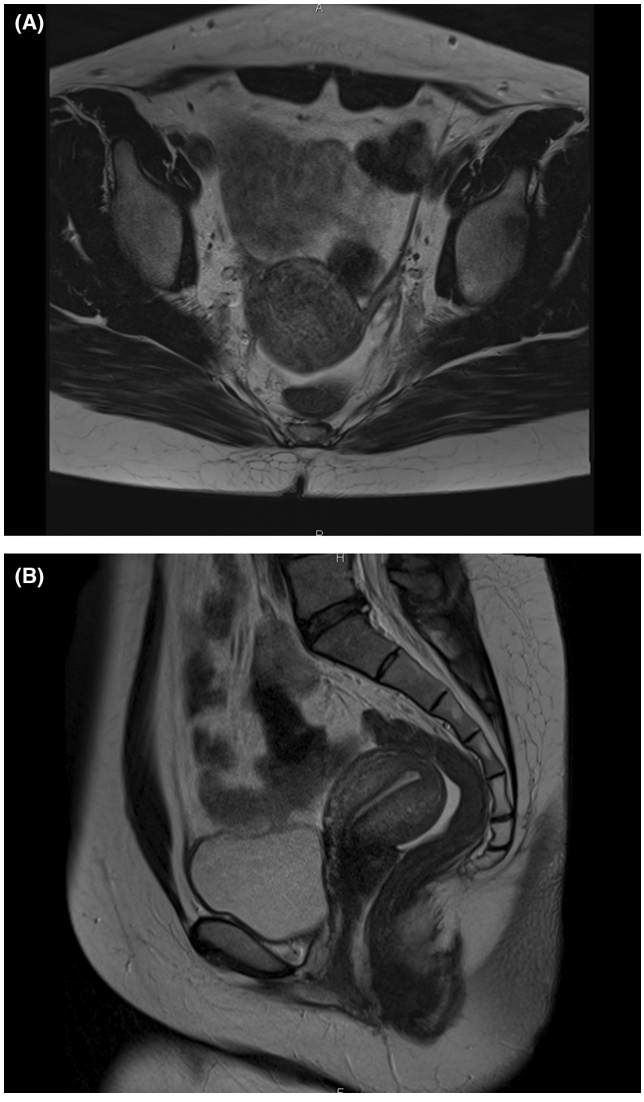

FIGURE 6 Pelvic MRI cross-section (A) and sagittal section (B) after MPA therapy for recurrence.

pregnancy.[3] We also advised her to reduce her weight in order to prevent recurrence and to cure her PCOS.

Our policy is to assess patients for local recurrence every 3 months after completing treatment, and to assess for distant metastasis every 6 months. Therefore, the patient visited our hospital every 3 months for TV-US, endometrial histology, and blood testing, including CA19-9 levels. She also underwent CT every 6 months.

4 | RESULTS (OUTCOME AND FOLLOW UP)

One year and 7 months after beginning treatment, the patient weighed 66.9 kg, with a BMI of 29.3 kg/m^2. At this time, endometrial histology showed atypical glandular cells and her CA19-9 level at 64 U/mL. She underwent D&C again; histologic examination revealed atypical endometrial hyperplasia (Figure 5). We diagnosed an EC recurrence in the form of atypical endometrial hyperplasia and decided to reintroduce MPA therapy because of her strong desire to preserve fertility. She was treated with the same protocol as before and underwent D&C at 8 and 16 weeks after starting the second round of MPA therapy; both samples demonstrated a CR to therapy. Pelvic MRI 16 weeks after starting the second round of MPA therapy showed no thickening of the endometrium or mass in the uterine cavity (Figure 6A,B). As before, the patient switched to oral norgestrel–ethinyl estradiol tablets after 16 weeks of MPA therapy and continued follow-up care.

Although blood testing showed an elevated CA19-9 at the time of her initial visit to our hospital, this level did not change significantly during treatment, including at the time of recurrence. Gastrointestinal endoscopy was performed to search for gastrointestinal lesions, but no neoplastic lesions were found. Chest-to-pelvic CT during follow up showed no lesions other than in the uterus.

Since this patient's young-onset EC had recurred, we suspected a hereditary tumor such as those associated with Lynch syndrome (LS). Although the patient did not meet the Amsterdam criteria, we decided to screen for LS.[4] However, immunostaining of the endometrial histology specimen at the time of initial diagnosis was normal, without decreased expression of mismatch repair (MMR) protein (Figure 7).

5 | DISCUSSION

The total number of patients with EC in Japan between 2017 and 2021 was 62,006; of these, nine were under 20 years of age and all nine had stage IA disease.[1,5–8] In the past 20 years at our hospital (2002–2021), there were 1070 cases of new-onset EC; only the patient featured in this report was younger than 20 years of age. Risk factors for EC in young patients include excess estrogen due to PCOS, obesity, diabetes, or a genetic predisposition.[9,10] National Comprehensive Cancer Network (NCCN) guidelines recommend LS evaluation for an individual who is diagnosed with a LS-related cancer—including endometrial neoplasms—below 50 years of age.[11] Immunohistochemistry (IHC) and microsatellite instability (MSI) analyses are used as screening tests (either individually or in conjunction) and are typically performed on colorectal and endometrial cancer tissue.

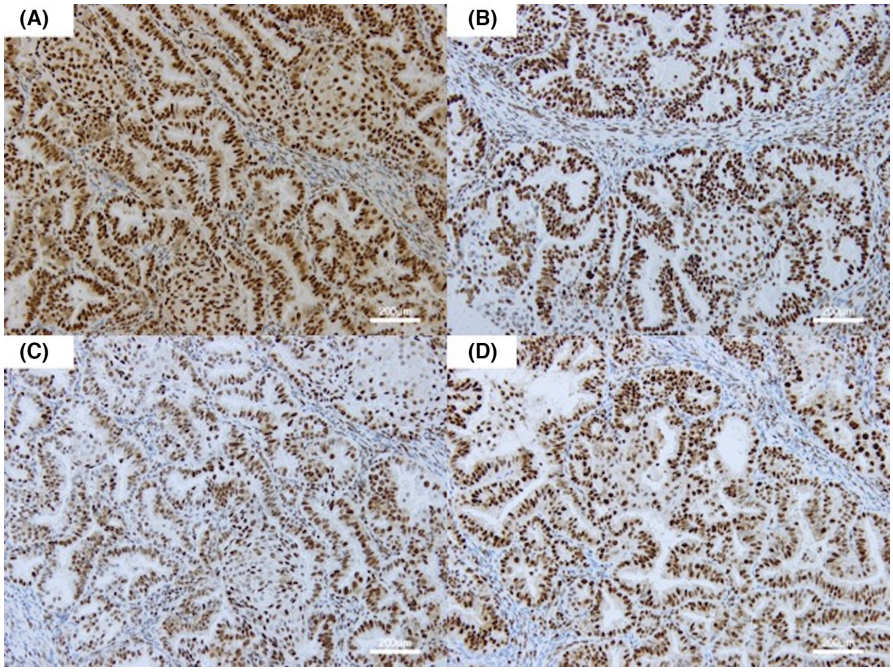

FIGURE 7 Mismatch repair protein immunostaining. (A) MSH2 staining; (B) MSH6 staining; (C) MLH1 staining; (D) PMS2 staining.

The process of IHC stains tumor tissue for protein expression of the 4 MMR genes known to be mutated in LS: *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Concordance between MSI and IHC is reportedly very high (99.1%).[12] We performed IHC for the patient in this report, but her tissue sample stained positive for all MMR proteins. Since MMR protein expression was not decreased, LS was ruled out; excess estrogen was deemed the likely cause of this patient's EC. The excess estrogen, in turn, was attributed to the PCOS that was diagnosed based on clinical and imaging findings.[2]

In the last 10 years, there have been five reported instances of EC at a very young age (<20 years) in the literature.[13–17] The clinical characteristics of these patients, and of our patient, are presented in Table 1. The pathology of EC can be classified as either endocrine or hereditary: the table shows that EC at a young age does not necessarily involve a genetic abnormality but may instead involve risk factors such as PCOS, obesity, and type 2 diabetes. In terms of treatment, hysterectomy was performed in three patients and a levonorgestrel-releasing intrauterine system was used for fertility preservation in two patients. One patient underwent bariatric surgery; her weight loss was presumed to be effective in controlling recurrence. In a related report, Atiomo et al., found that weight-loss interventions (i.e., dietary changes) in patients with PCOS can improve endometrial thickness and increase the number of menstrual cycles.[18] This suggests that weight loss in patients with PCOS may lead to a reduction in uterine cancer risk. We believe that our patient's weight gain after MPA therapy resulted in her EC recurrence. This suggests the importance of weight control in young patients with EC.

In a report describing young patients with EC who have genetic abnormalities, 1.5% of Japanese patients with EC aged 40 years or younger were diagnosed with LS, and 12.3% had somatic mutations in the *MMR* gene.[19] An independent prognostic factor after treatment was a CA125 level of less than 35 U/mL.[20] In addition, Shih reports that patients with EC who are younger than 40 years of age and who have *MMR* variants have significantly more advanced disease stages (>II), differentiation (grade >2), myometrial invasion (>50%), and vascular invasion, as well as poorer overall survival and progression-free survival.[21]

There is no solid evidence that MPA therapy should be administered again for recurrence of EC after initial MPA therapy. However, there are several articles showing the efficacy of MPA therapy after recurrence. The European Society of Gynecological Oncology (ESGO) provides a clinical recommendation that repeat MPA therapy is acceptable for recurrence.[22] A phase 2 study on repeated high-dose progestin therapy for intrauterine

TABLE 1 Summary of the literature.

First author (year)	Patient age	Presentation	BMI (kg/m^2)	CA125 (U/mL)	Risk factor	Treatment	FIGO stage	Histology	Adjuvant therapy	RFS	Genetic disorder
Baker et al.[13] (2013)	14	Menorrhagia	24	-	None	Laparoscopic hysterectomy	IA	EC, G1	None	>6 years	Cowden syndrome
Liu et al.[14] (2014)	15	Anemia	50.2	-	PCOS	TAH, RSO, Ly	IA	EC, G2	None	>5 years	None
Elnaggar et al.[15] (2013)	15	Menorrhagia	-	-	None	TAH, Ly	IA	EC, G1	None	>3 years	Cowden syndrome
Benito et al.[16] (2015)	17	Menorrhagia	36.2	Normal	PCOS	LNG-IUD LSG	IA	EC, G1	LNG-IUD	>9 months	None
Brown et al.[17] (2012)	18	Protruding polyp	47.7	-	PCOS, type 2 DM	Conization, D&C	IA	EC, G2	LNG-IUD	>1 year	None
Current patient	19	Menorrhagia	26.9	Normal	PCOS	MPA	IA	EC, G1	OC	19 months	None

Abbreviations: -, not reported; BMI, body mass index; CA125, cancer antigen 125; D&C, dilation and curettage; DM, diabetes mellitus; EC, endometrioid carcinoma; FIGO, 2008 International Federation of Gynecology and Obstetrics; G, grade; LNG-IUD, levonorgestrel intrauterine device; LSG, laparoscopic sleeve gastrectomy; Ly, pelvic and para-aortic lymphadenectomy; MPA, medroxyprogesterone acetate; OC, oral contraceptive pill; PCOS, polycystic ovarian syndrome; RFS, recurrence-free survival; RSO, right salpingo-oophorectomy; TAH, total abdominal hysterectomy.

recurrence after fertility-preservation treatment for uterine cancer or endometrial atypia (Japanese Gynecologic Oncology Group 2051 study) is currently being conducted in Japan.

Patients diagnosed with EC at less than 20 years of age require long-term follow up when they are cured using fertility-preserving MPA therapy. Establishment of regular menstrual cycles through hormone therapy or weight loss is considered necessary to prevent recurrence; frequent endometrial curettage may actually worsen the endometrial microenvironment. Appropriate assisted reproductive technology is also recommended. Young patients need long follow up and adjustment of treatment strategies according to their life stage. In some patients, due to the long duration of the condition, attention to their mental health is also necessary.

In the future, EC will be managed based on not only traditional histopathological classification, but also the results of molecular profiling.[23] The introduction of molecular features will help clinicians decide on optimum treatment strategies, and the combination of radiomic findings and molecular signatures could help with prognostication.[24]

6 | CONCLUSION

Even in patients younger than 20 years of age, endometrial thickening may indicate a rare young-onset uterine cancer. In addition to the history of current disease, a detailed history of menstruation, medical history, and family history is useful, including the possibility of hereditary tumors such as LS. Blood tests (including hormone assessment), cytology, histology, and imaging should be performed, and clinicians should not hesitate to perform D&C to confirm the diagnosis, even in young patients. Obesity not only contributes to PCOS and potentially interferes with treatment of uterine cancer, but it may also exacerbate glucose intolerance and dyslipidemia. Ideally, clinicians will practice holistic medicine based on each woman's healthcare status and stage of life.

AUTHOR CONTRIBUTIONS

Shinichiro Katsuma: Conceptualization; data curation; formal analysis; investigation; visualization; writing – original draft. **Kazuya Ariyoshi:** Data curation; visualization; writing – review and editing. **Ai Nio:** Writing – review and editing. **Kenichi Taguchi:** Data curation; visualization; writing – review and editing. **Kenzo Sonoda:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; supervision; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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