International Journal of Women's Health

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CASE REPORT

Uterine Serous Carcinoma Following the Insertion of Levonorgestrel Intrauterine System: A Case Report and Literature Review

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Background: The levonorgestrel-releasing intrauterine system (LNG-IUS) is now widely used for the treatment of heavy menstrual bleeding and endometrial hyperplasia, and its clinical application has been extended to adenomyosis. By releasing levonorgestrel directly into the uterine cavity, the LNG-IUS induces endometrial atrophy and thinning, effectively reversing hyperplastic changes, thereby conferring a distinct protective effect on the endometrium. Nevertheless, even under this potent progestogenic protection, malignant transformation remains an exceedingly rare event. To date, only 11 cases of endometrial carcinoma arising after LNG-IUS placement have been reported worldwide. The majority of these patients were perimenopausal women who presented with variable degrees of vaginal bleeding after LNG-IUS insertion; all lesions were subsequently confirmed as endometrioid adenocarcinoma, and no cases of uterine serous carcinoma (USC) were documented. Herein, we report the first documented case of a 44-year-old patient with adenomyosis and menorrhagia who, despite long-term LNG-IUS therapy, progressed to USC.

Case Presentation: A 44-year-old woman was admitted to the hospital due to "irregular vaginal bleeding for over 1 month". Five years earlier, the patient had an LNG-IUS inserted at our institution for menorrhagia secondary to adenomyosis. Pre-insertion transvaginal ultrasound showed no endometrial abnormality, and endometrial biopsy was not performed. On the current admission, diagnostic curettage revealed a markedly enlarged uterine cavity. Histopathologic examination was consistent with serous endometrial intraepithelial carcinoma (SEIC). The patient underwent complete oncological staging surgery according to International Federation of Gynecology and Obstetrics (FIGO) guidelines, followed by adjuvant platinum-based chemoradiation. Surveillance at 6 months post-treatment confirmed continued complete remission.

Conclusion: Through a systematic review and analysis of this case, special caution is warranted in patients presenting with abnormal uterine bleeding—especially when the uterine cavity is enlarged; ideally, endometrial biopsy should be performed before LNG-IUS placement to rule out endometrial pathology. Any alteration in vaginal bleeding patterns in LNG-IUS users should prompt vigilance for possible endometrial pathology, and repeat endometrial biopsy should be performed. This case provides valuable evidence to help reduce the risk of missed diagnosis of endometrial cancer in such patients.

Keywords: endometrial cancer, levonorgestrel-releasing intrauterine system, uterine serous carcinoma, case report

Introduction

The LNG-IUS is now widely used not only for the treatment of heavy menstrual bleeding and contraception but also for the management of endometrial hyperplasia and fertility-sparing treatment of early-stage endometrial cancer. The development of endometrial cancer following long-term use of LNG-IUS is infrequent, and there have been no reported cases of progression to USC. Here, we present a case of a patient who developed USC despite long-term LNG-IUS therapy. This case provides valuable insights and experience for clinicians to reduce the risk of missed diagnosis of endometrial cancer.

Received: 16 May 2025
Accepted: 29 October 2025
Published: 4 November 2025

Case Presentation

A 44-year-old married, parous woman was admitted to the hospital due to "irregular vaginal bleeding for over 1 month". She denied any history of obesity, diabetes, or hypertension and had no family history of endometrial cancer. Five years ago, she presented to our hospital with a one-year history of menorrhagia and progressive dysmenorrhea. Transvaginal ultrasound at that time revealed a normal-sized uterus with thickened, heterogeneous myometrial echoes (Figure 1), leading to a clinical diagnosis of adenomyosis. As the patient had no future fertility wishes and declined surgery, an LNG-IUS was inserted after thorough counselling to reduce menstrual blood loss and relieve dysmenorrhoea. Because the patient had regular menses, no identifiable risk factors for endometrial carcinoma, and imaging showed no endometrial abnormality, endometrial biopsy was therefore omitted before LNG-IUS insertion. She reported significant relief of pain and a marked reduction in menstrual bleeding during the first 4 years after insertion. However, over the past year she began experiencing recurrent abnormal vaginal bleeding, characterized by scanty, intermittent spotting. Additionally, she noticed an increase in the size of her adenomyoma. The patient did not seek any specific treatment for these symptoms. One month before admission, the patient had the LNG-IUS removed at another hospital because it needed to be replaced. However, because of intra-operative bleeding, re-insertion was deferred. Persistent vaginal bleeding thereafter prompted her to seek further care at our institution. On gynecological examination, the vulva is normally developed and consistent with the findings expected in a parous, married woman. The vagina was patent with a small amount of blood visible inside. The cervix was smooth and of normal size. The uterus was anteverted, enlarged to the size of a 3-month pregnancy, firm in consistency, and without tenderness. No significant abnormalities were palpated in the bilateral adnexa.

Ancillary Examinations: Pelvic MRI: A mass-like signal abnormality was observed in the left uterine fundus and corpus. The adjacent endometrial–myometrial junction appeared irregular and discontinuous. The lesion extended outward to the serosal layer, with a smooth adjacent uterine serosal surface. The findings suggested a malignant uterine lesion, with a high possibility of endometrial cancer involving deep myometrial invasion. The possibility of malignant transformation of a uterine fibroid could not be ruled out (Figure 2). Tumor Markers: Carbohydrate antigen 125 was 641 IU/mL, and Carbohydrate antigen 199 was 111 IU/mL.

After admission, diagnostic curettage was performed. Histopathology suggested endometrial carcinoma; to determine the subtype, immunohistochemistry was carried out and showed: estrogen receptor (ER) (focal +, weak–moderate); oncogene (P53) (-, suggestive of nonsense mutation); nucleus related antigen (Ki-67) (+, ~70%), cyclin-dependent kinase inhibitor 2A (P16) (+); progesterone receptor (PR) (focal +, weak). Immunoprofile analysis supported a diagnosis of SEIC. Because an early serous lesion was identified and imaging suggested deep myometrial invasion, comprehensive surgical staging for endometrial cancer was performed (total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, and omentectomy).

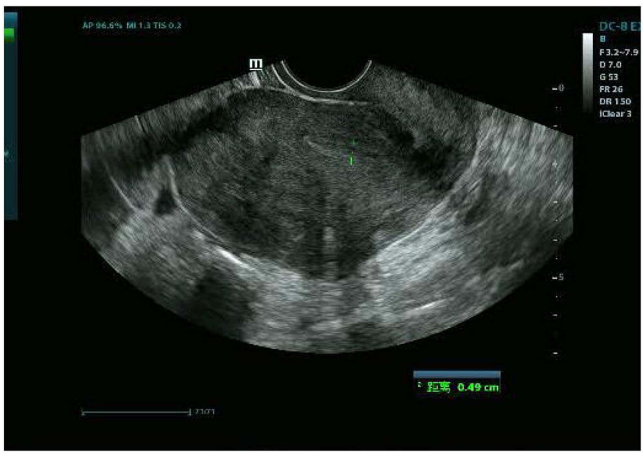

Figure 1 Transvaginal ultrasonographic images of the uterus.

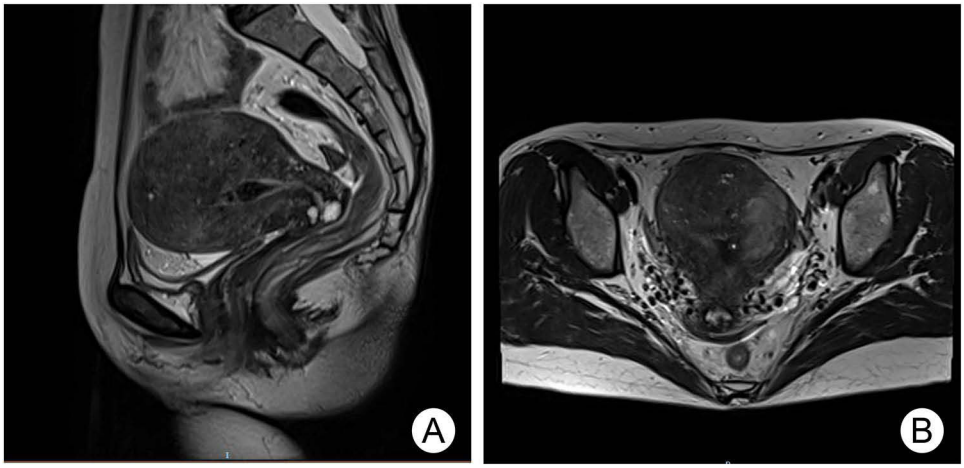

Figure 2 Preoperative MRI. (**A**) Sagittal plane. (**B**) Coronal plane.

Intraoperatively, the uterus was found to be anteverted and enlarged to the size of a 3-month pregnancy, with a smooth surface and firm consistency. No significant enlargement of pelvic or abdominal lymph nodes was observed. Examination of the intestines, mesentery, peritoneum, omentum, appendix, liver, spleen, gallbladder, and stomach revealed no metastatic nodules. On gross examination of the surgical specimen, the myometrium exhibited a wood-grain-like appearance. A 3×3×2 cm infiltrative lesion was identified in the left cornual region of the uterus, with an invasion depth greater than 1/2 of the myometrial thickness (Figure 3A).

Postoperative Pathological Findings: A tumor measuring 32×25×15 mm was identified in the uterine cornu. The tumor involved adenomyosis and exhibited multifocal infiltration with an invasion depth greater than 1/2 of the myometrial thickness. The pathological diagnosis was serous carcinoma (Figure 3). SEIC was also observed in the lower segment of the uterine corpus. The cervix, cervical canal, bilateral adnexa, and omentum were not involved. There was no evidence of neural invasion. The surgical margins were free of tumor. No metastasis was found in the pelvic or para-aortic lymph nodes, and no tumor cells were detected in the peritoneal fluid. Immunohistochemistry was routinely performed on the radical specimen, which had already been confirmed as invasive carcinoma on histopathology (Table 1 and Figure 4). The low PR expression, complete p53 loss, and diffuse p16 positivity collectively corroborate the diagnosis of SEIC. Intact expression of the mismatch repair proteins (MMR) excludes Lynch-associated mismatch-repair deficiency and suggests a low likelihood of hyper-mutated endometrial cancer. Post-operative staging in accordance with the 2023 FIGO criteria established a diagnosis of stage II USC.[1] The patient had a good recovery after the surgery and was discharged on the 5th postoperative day.

The patient began adjuvant chemotherapy in the third postoperative week, receiving the TC regimen (paclitaxel plus carboplatin) every 3 weeks for a total of six cycles. Concomitant pelvic radiotherapy was delivered to a total dose of 45

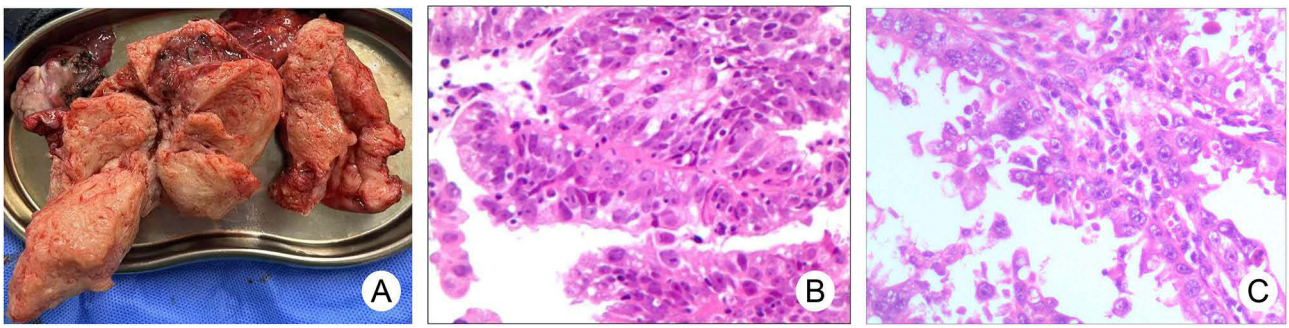

Figure 3 Postoperative pathology. (**A**) Gross specimen of total hysterectomy with bilateral adnexa. (**B**) HE staining of the lesion×40. (**C**) HE staining of the lesion×200.

https://doi.org/10.2147/IJWH.S540517

Table 1 Macroscopic Specimen Immunohistochemistry Results

Macroscopic Specimen Immunohistochemistry Results	
Item	**Result**
ER	+(70%)
PR	+ (≈5%)
P53	Completely absent
Ki-67	+ (≈40%)
P16	Strong positive
HER2	2+
MMR (MLH-1 / MSH-2 / MSH-6)	All positive

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; P53, oncogene; Ki-67, nucleus related antigen; P16, cyclin-dependent kinase inhibitor 2A; HER2, Human Epidermal Growth Factor Receptor 2; MMR, mismatch repair proteins; MLH-1, mutL homolog 1; MSH-2, mutS homolog 2; MSH-6, mutS homolog 6.

Gy in 25 fractions. At the 6-month post-treatment follow-up, no evidence of recurrence was found; thereafter, she was scheduled for outpatient follow-up every 3 months.

Discussion

The LNG-IUS is an intrauterine sustained-release system of highly effective progestin, containing 52 mg of levonorgestrel (LNG), which is released at a rate of 20 μg/day within the uterine cavity. Clinically, it is commonly used for contraception, heavy menstrual bleeding, dysmenorrhea, and the treatment of endometrial hyperplasia. Current guidelines recommend the LNG-IUS as the first-line treatment for atypical endometrial hyperplasia[2] and also as a fertility-sparing first-line treatment for young patients with early-stage endometrial cancer.[3] From a pathophysiological perspective, endometrial carcinoma is broadly divided into two subtypes: type I, which is estrogen-driven, and type II, which arises independently of estrogen stimulation. Type I endometrial carcinogenesis hinges on the disruption of the estrogen–progesterone balance: a relative estrogen excess coupled with insufficient progesterone drives continuous endometrial proliferation and impairs normal cyclic shedding and repair. Type I endometrial carcinogenesis hinges on the disruption of the estrogen–progesterone balance: a relative estrogen excess coupled with insufficient progesterone drives continuous endometrial proliferation and impairs normal cyclic shedding and repair. Chronic, unopposed estrogen exposure markedly increases the probability that endometrial cells will acquire gene mutations during successive rounds of replication.[4,5] In contrast, the pathogenesis of type II endometrial carcinoma remains incompletely understood. The LNG-IUS creates a high-concentration progestin environment within the uterine cavity, inhibiting the endometrium and causing endometrial atrophy, thinning, and stromal swelling with decidualization.[5,6] Therefore, the occurrence of endometrial cancer in patients using LNG-IUS long-term is infrequent.

To date, only 11 related cases have been reported worldwide (Table 2).[6–15] Seven of the 11 patients were perimenopausal, and the LNG-IUS had been inserted principally to control heavy menstrual bleeding. In addition, four patients in this series had co-existing uterine fibroids or adenomyosis. Both disorders have been firmly linked to estrogen-driven pathophysiology, and their presence usually signals a chronic, high-estrogen microenvironment.[16,17] High estrogenic stimulation may partially override the local progestogenic effect of the LNG-IUS, creating an "estrogen-escape" phenomenon that ultimately permits progression of endometrial pathology.[18] Of particular concern, seven of the eleven patients had not undergone adequate endometrial sampling before LNG-IUS insertion, raising the possibility that pre-existing occult lesions were missed and allowed to evolve unchecked. Clinically, these cases were strikingly uniform: ten patients developed abnormal uterine bleeding while carrying the LNG-IUS, with most presenting as breakthrough

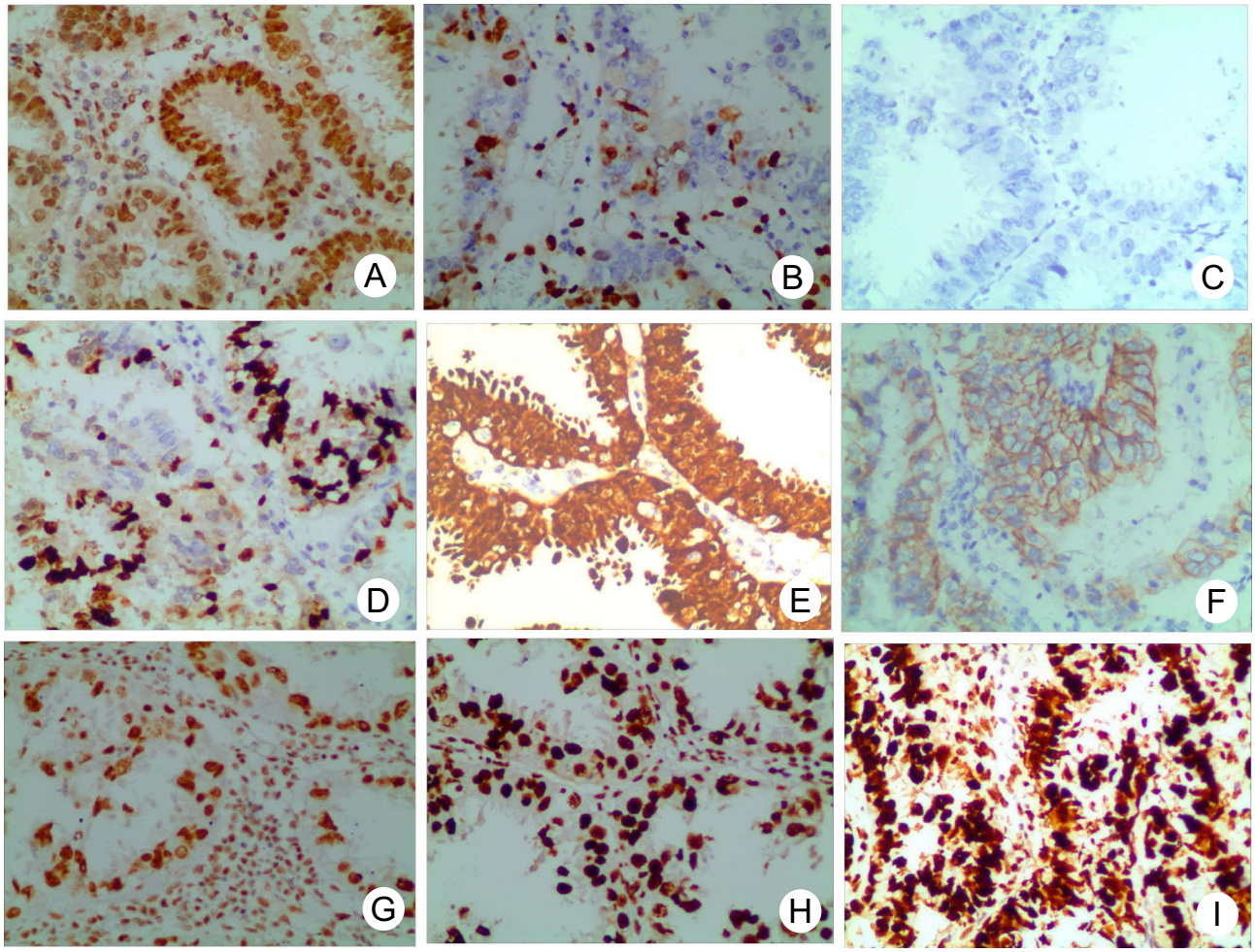

Figure 4 Gross specimen immunohistochemistry images: (**A**) ER IHC of the lesion×200. (**B**) PR of the lesion×200. (**C**) P53 IHC of the lesion×200. (**D**) Ki-67 IHC of the lesion×200. (**E**) P16 of the lesion×200. (**F**) Her2 IHC of the lesion×200. (**G**) MLH-1 IHC of the lesion×200. (**H**) MSH-2 IHC of the lesion×200. (**I**) MSH-6 IHC of the lesion×200.

bleeding after secondary amenorrhea or as irregular cycles that had re-established after device insertion. This consistent clinical signature carries a critical warning: any alteration in bleeding pattern among long-term LNG-IUS users should raise strong suspicion of underlying endometrial pathology, and an endometrial biopsy may be necessary to rule out the disease.

All 11 cases reported to date have been endometrioid adenocarcinomas—type I, hormone receptor-positive, low-grade, diploid tumours, typically associated with a favorable prognosis. In contrast, the patient in this case was diagnosed with Type II endometrial cancer, specifically USC, after using the LNG-IUS. To date, no relevant literature has been identified reporting such a case. USC accounts for approximately 10% of all diagnosed endometrial cancers but is responsible for 40% of endometrial cancer-related deaths. Compared to endometrioid adenocarcinoma, USC has a higher risk of recurrence and a poorer prognosis.[19] In Type II endometrial cancer, the primary genetic alteration is a p53 mutation, which is present in 95% of cases and plays a significant role across almost all stages of the disease. In contrast, p53 alterations occur in less than 10% of Type I endometrial cancers.[20] Additionally, approximately one-third of USC cases exhibit HER2 overexpression, which is closely associated with a poor prognosis.[21] In this patient, the complete absence of p53 expression and the overexpression of HER2 were identified, both of which are consistent with the diagnosis of uterine serous carcinoma and suggest an unfavorable prognosis for the patient.

The pathogenesis of endometrial cancer occurring despite the use of LNG-IUS remains unclear. This patient did not have typical high-risk factors for endometrial cancer, such as obesity, diabetes, exposure to endogenous or exogenous estrogens,

https://doi.org/10.2147/IJWH.S540517

Table 2 Reported in Literature Cases of Endometrial Cancer in Patients with LNG-IUS

Author	Age (y)	Reasons for Use	LNG-IUS Time	Endometrial Biopsy	Develop symptoms	High-Risk Factors	BMI	Complications	Ending	Ref
David	52	N/A	Four years	None	Amenorrhea	None	26.73	Uterine fibroids	EEC IA	[7]
Franz	55	Menorrhagia	Four years	None	Secondary amenorrhea followed by intermittent vaginal bleeding	None	N/A	None	EEC(G2) IC	[8]
J. ABU	36	Contraception	One year	None	After 3 months of amenorrhea, regular menses resumed, followed by 2 months of irregular vaginal bleeding	None	N/A	None	EEC(G2) IA	[9]
Rhonda	39	Menorrhagia	Four years	Non-secretory endometrium	She has an 8-month history of prolonged bleeding, followed by amenorrhea.	Obesity	39.5	Uterine fibroids and adenomyosis;Enlarged uterus	EEC(G2) Ib	[10]
Jingjingjiang	34	Atypical endometrial hyperplasia	Two years	Atypical hyperplasia—secretory endometrium	Irregular vaginal bleeding for 5 months, with the discovery of a pelvic mass	Obesity	28.4	None	EEC(G2) IIIb	[11]
Kevin Jones	48	Menorrhagia	Three years	None	Six months of irregular vaginal bleeding	None	N/A	None	EEC(G2) IIIc	[12]
Kevin Jones	54	Irregular vaginal bleeding	One year	Proliferative endometrium	After amenorrhea, irregular heavy vaginal bleeding reoccurred	None	N/A	Uterine fibroids	EEC(G1) IIB	[12]
HongfaPeng	30	Menorrhagia	Seventeen months	Atypical endometrial polyps	Vaginal bleeding occurred 17 months later	None	22.3	None	EEC(G1)	[13]
Melisa	50	Persistent heavy vaginal bleeding	N/A	None	Persistent vaginal bleeding	None	N/A	None	EEC(G1) IA	[14]
A. C. L. van der Meer	56	Irregular and severe vaginal bleeding	Five years	Negative	Examination revealed endometrial thickening	Obesity	50.5	Enlarged uterus	EEC(G1)	[15]
Alexander Steshenko	52	Menorrhagia	Fourteen years	None	Subsequently, intermittent vaginal bleeding occurred.	None	N/A	None	EEC(G1) IA	[6]
In this case	44	Adenomyosis	Five years	None	In the fourth year, persistent vaginal bleeding occurred	None	20.5	Adenomyosis	USC IIC	

Abbreviations: N/A, information not available; EEC, endometrioid adenocarcinoma; USC, uterine serous carcinoma.

infertility, or use of tamoxifen, yet she still developed USC. The possible contributing factors may include the following: (1) The patient had LNG-IUS inserted due to heavy menstrual bleeding, but no endometrial biopsy was performed before insertion. It remains plausible that an occult endometrial focus with pre-existing malignant clonal features was already present before device insertion.[22] (2) In this patient, adenomyosis progressively enlarged the uterine cavity to 11 cm, so the 20 μg/day levonorgestrel release was "diluted" over a much larger endometrial surface. Consequently, local concentrations never reached the threshold required for full decidualization, creating a functionally hypo-progestogenic, high-estrogen milieu that permitted tumor progression. This is consistent with the findings by Pal et al,[23] who suggested that an enlarged uterus is associated with non-responsiveness to LNG-IUS. Additionally, adenomyosis-induced thickening and fibrosis of the myometrium impeded uniform drug distribution, further facilitating carcinogenic progression.[17] (3) Studies show that the LNG-IUS release rate declines with time, falling to ≈14 μg/day by year 5;[24] this progressive waning further eroded suppression of residual disease and coincides with the patient's new-onset spotting during years 4–5. (4) This patient exhibited a complete nonsense-mutation-mediated loss of p53 and HER2 protein over-expression (2+). Loss of p53 inactivates cell-cycle checkpoints and enables escape from progesterone-induced apoptosis, serving as an independent predictor of progestin resistance;[25] whereas HER2 activates the PI3K/AKT proliferative axis and counteracts progesterone's anti-growth signaling—both features portending a poor prognosis.[26] (5) With ER positivity at 70% and PR positivity barely 5%, the endometrium is locked in a state of severe signal imbalance: ER-driven proliferative signaling overwhelmingly outweighs the residual PR-mediated tumor-suppressive input, thereby fostering a high-estrogen, pro-carcinogenic microenvironment.[27]

Conclusion

In conclusion, the occurrence of endometrial cancer, especially uterine serous carcinoma, in patients with long-term use of LNG-IUS is extremely rare. Reviewing and summarizing relevant cases highlights the importance of performing an endometrial biopsy before LNG-IUS insertion to rule out any pre-existing endometrial pathology. Patients who experience any change in vaginal bleeding pattern after LNG-IUS insertion should be closely evaluated; this symptom warrants serious attention. A repeat endometrial biopsy may be necessary to exclude endometrial pathology and reduce the risk of missed diagnosis of endometrial cancer or other related diseases. Furthermore, the indications and contraindications for LNG-IUS placement should be strictly assessed. For patients with a uterine cavity depth greater than 10 cm, pre-treatment should be considered before LNG-IUS insertion to ensure adequate distribution of the progestin within the endometrium and to avoid potential therapeutic failure due to an enlarged uterine cavity.

Abbreviations

LNG-IUS, levonorgestrel-releasing intrauterine system; USC, uterine serous carcinoma; SEIC, serous endometrial intraepithelial carcinoma; FIGO, International Federation of Gynecology and Obstetrics; LNG, levonorgestrel; ER, estrogen receptor; P53, oncogene; Ki-67, nucleus related antigen; P16, cyclin-dependent kinase inhibitor 2A; PR, progesterone receptor; HER2, Human Epidermal Growth Factor Receptor 2; MLH-1, mutL homolog 1; MSH-2, mutS homolog 2; MSH-6, mutS homolog 6; MRI, magnetic resonance imaging.

Ethics Approval and Consent to Participate

Institutional approval for the publication of the case details was not required.

Consent for Publication

Written informed consent was obtained from the patient for publication of her case as well as the accompanying images.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was funded by Technology Support Project of Neijiang City, Sichuan Province (Z202328).

Disclosure

The authors report no conflicts of interest in this work.

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