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Mifepristone and Endometrial Polyps: A Paradigm Shift in Gynecological Outcomes – A Case Report

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ABSTRACT: Mifepristone, a selective progesterone receptor modulator (SPRM), is increasingly used for the medical management of uterine leiomyomas and abnormal uterine bleeding. Prolonged exposure, however, may induce a distinct spectrum of endometrial change termed progesterone receptor modulator-associated endometrial changes (PAEC), characterised by cystic glandular dilatation, endometrial thickening, polypoid change and an altered gland-to-stroma ratio, which can mimic premalignant pathology. We report the case of a 45-year-old multiparous woman with heavy and irregular menstrual bleeding, previously treated outside with mifepristone 25 mg once daily for six months for symptomatic fibroids. Ultrasonography showed intramural leiomyomas together with cystic endometrial change and a focal vascular endometrial lesion. Hysteroscopy revealed a polypoidal endometrium with a dominant 1 x 1.5 cm mucosal polyp and several smaller satellite polyps. She underwent hysteroscopy-guided polypectomy with endometrial biopsy and levonorgestrel intrauterine system insertion. Histopathology confirmed a benign endometrial polyp with proliferative glands and no atypia. This case illustrates that a detailed drug history is essential to recognise mifepristone-related PAEC, avoid diagnostic overcall and unnecessary intervention, and guide targeted hysteroscopic management.

BACKGROUND

Mifepristone is a selective progesterone receptor modulator (SPRM) widely used for the management of uterine leiomyomas and abnormal uterine bleeding (AUB), where it effectively reduces fibroid volume and menstrual blood loss [1][2]. Long-term exposure, however, may induce a recognised spectrum of endometrial change known as progesterone receptor modulator-associated endometrial changes (PAEC). PAEC encompasses cystic glandular dilatation, endometrial thickening, polypoid change and an altered gland-to-stroma ratio, and was first characterised histologically by Mutter et al in patients exposed to SPRMs [1]. Murphy et al demonstrated that long-term low-dose mifepristone administration induces benign cystic endometrial changes without atypia or malignant transformation [2], while Berger et al showed that PAEC has distinct molecular and histological features that differentiate it from endometrial hyperplasia [3]. Clinically, these changes can be difficult to distinguish from premalignant or malignant endometrial pathology on ultrasonography alone, as emphasised by Whitaker et al [5], creating a genuine diagnostic challenge in women on prolonged SPRM therapy. Dinh et al highlighted that awareness of PAEC as a distinct entity prevents overdiagnosis and unnecessary hysterectomy [4], underscoring the importance of a detailed medication history whenever a patient on mifepristone presents with new or worsening endometrial findings. Hysteroscopy with targeted biopsy and histopathological evaluation remains the gold standard for definitive diagnosis in this setting. Case-based documentation of PAEC therefore continues to add value in sharpening clinical suspicion and avoiding overtreatment.

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CASE PRESENTATION

A 45-year-old woman, para 1 living 1, with a previous lower-segment caesarean section and married for 23 years, presented with a one-year history of heavy menstrual bleeding. Her cycles had shortened to four days of flow followed by 7–8 days of spotting. Menstrual history was notable for irregular cycles, previously regular at 5/28 days with 3–4 pads/day, and no dysmenorrhoea or clots. She had been on tablet mifepristone 25 mg once daily (Fibrocase) for six months, prescribed and monitored outside the institution for symptomatic fibroids. She had recently been diagnosed with hypothyroidism and was on tablet thyronorm 25 micrograms. A previous endometrial biopsy performed elsewhere had shown histopathology consistent with early secretory phase endometrium. There was no history of diabetes mellitus, hypertension, bronchial asthma, or seizure disorder.

On general examination, the patient was afebrile with mild pallor and no pedal edema. Blood pressure was 120/80 mmHg, pulse rate 88/min, and SpO2 99% on room air. Cardiovascular and respiratory examination were unremarkable (S1, S2 heard; normal vesicular breath sounds), and central nervous system examination was normal. Abdominal examination revealed a soft, non-tender abdomen with the caesarean scar present. On speculum examination, the cervix appeared hypertrophied with erosions and mucoid discharge was noted. Bimanual pelvic examination revealed a cervix pointing downwards and an irregularly enlarged, mobile uterus corresponding to approximately 8–10 weeks' size, with bilateral fornices free and non-tender. Given her prolonged mifepristone exposure together with heavy menstrual bleeding and an enlarged uterus, further imaging and endometrial evaluation were undertaken to characterise the structural pathology.

INVESTIGATIONS If relevant

Baseline investigations were all within normal limits. Transvaginal ultrasonography showed a uterus measuring approximately 10.1 x 4.2 x 6.2 cm. A well-defined hypoechoic lesion measuring 3.7 x 3.1 cm was noted in the fundal anterior left lateral myometrium, and a second well-defined oval hypoechoic lesion measuring 1.5 x 1.1 cm was seen in the posterior subserosal myometrium, both consistent with leiomyomas. The endometrium showed few cystic changes within it, with endometrial thickness of 12 mm. A hypoechoic lesion measuring approximately 1.6 x 1.0 cm was noted within the endometrium, with minimal internal and peripheral vascularity. A subcentimetric nabothian cyst was noted in the cervix. In view of the cystic endometrial changes and focal endometrial lesion in a patient on prolonged mifepristone therapy, diagnostic hysteroscopy was planned to differentiate PAEC-related polypoid change from other structural or premalignant endometrial pathology. Hysteroscopy showed a polypoidal endometrium, with a dominant mucosal polyp measuring 1 x 1.5 cm arising from the posterior aspect of the uterine cavity, along with a few smaller satellite polyps of about 0.5 cm each. The surrounding endometrium appeared irregular but without grossly suspicious malignant features.

Hysteroscopy-guided polypectomy was performed, followed by endometrial curettage and tissue sampling; all excised tissue was sent for histopathological examination. Histopathology reported endometrial glands displaying proliferative features without atypia, confirming a benign endometrial polyp consistent with progesterone receptor modulator-associated endometrial changes. No premalignant or malignant features were identified.

DIFFERENTIAL DIAGNOSIS If relevant

In a woman with heavy and irregular uterine bleeding and a six-month history of mifepristone therapy, the differential diagnosis included both drug-related and independent structural causes of endometrial change. Considerations included progesterone receptor modulator-associated endometrial changes (PAEC), simple or multiple endometrial polyps unrelated to drug exposure, endometrial hyperplasia, submucous or intramural fibroid contributing to bleeding, and, given the cystic and thickened endometrial appearance, endometrial malignancy as a rule-out diagnosis. The cystic endometrial changes on ultrasonography in the setting of prolonged mifepristone exposure made PAEC-related polypoid change the leading provisional diagnosis, while the coexisting intramural and subserosal leiomyomas were considered a contributing but secondary factor.

Endometrial hyperplasia was considered given her age and bleeding pattern, but the polypoid rather than diffuse nature of the endometrial thickening, together with a prior biopsy showing only early secretory phase endometrium, made diffuse hyperplasia less likely. Malignancy was considered a rule-out diagnosis given her age and the ultrasound findings, warranting hysteroscopic-directed biopsy rather than reassurance based on imaging alone. Crucially, the temporal relationship with six months of

mifepristone use distinguished this presentation from de novo endometrial pathology and supported PAEC as the most probable underlying process, to be confirmed on histopathology.

TREATMENT If relevant

After anaesthesia fitness was obtained, the patient was taken up for hysteroscopy-guided polypectomy and endometrial biopsy, with planned levonorgestrel intrauterine system (Mirena) insertion. On hysteroscopy, the endometrium appeared diffusely polypoidal. A dominant mucosal polyp measuring 1 x 1.5 cm was identified arising from the posterior aspect of the uterine cavity, along with a few smaller satellite polyps of about 0.5 cm each. No suspicious malignant features were observed on direct visualisation. Polypectomy was performed with removal of the dominant polyp and the visible satellite polyps, followed by endometrial curettage to sample the surrounding endometrium and ensure adequate cavity clearance.

Following removal of the hysteroscope and completion of curettage, a levonorgestrel-releasing intrauterine system (Mirena) was inserted in the same sitting to provide ongoing endometrial suppression and prevent recurrence of polypoid change. There was no undue bleeding per vaginum after insertion. The intraoperative period was uneventful, haemostasis was adequate, and the patient tolerated the procedure well. All resected tissue was sent for histopathological examination.

OUTCOME AND FOLLOW-UP

Both the intraoperative and postoperative periods were uneventful. The patient recovered well from anaesthesia and remained haemodynamically stable, with no excessive postoperative bleeding or procedure-related complication. She was discharged after routine observation with standard postoperative advice. At early follow-up she reported that she was symptomatically better, with a marked reduction in bleeding compared with her pre-procedural pattern. There were no reported adverse effects related to the Mirena insertion, and she did not report new pelvic pain, abnormal discharge, or febrile symptoms.

Histopathology confirmed endometrial glands displaying proliferative features without atypia, consistent with a benign endometrial polyp and progesterone receptor modulator-associated endometrial changes; no premalignant or malignant features were identified. These findings, and their relationship to her prior mifepristone therapy, were discussed with the patient, and continued clinical follow-up was advised. Longer-term surveillance was planned to assess menstrual pattern control and Mirena tolerance, with instructions to report any recurrence of heavy bleeding or new symptoms.

DISCUSSION

Include a very brief review of similar published cases

The development of multiple endometrial polyps after six months of mifepristone therapy in this patient suggests a probable association with progesterone receptor modulator-associated endometrial changes (PAEC) [1]. Murphy et al demonstrated that long-term low-dose mifepristone administration induces benign cystic endometrial changes without atypia or malignant transformation [2], a pattern mirrored by the cystic endometrial changes seen on our patient's ultrasonography. Berger et al further showed that PAEC has distinct molecular and histological features that differentiate it from endometrial hyperplasia [3], which is clinically important because the two entities can appear similar on imaging but require very different management. Whitaker et al emphasised that PAEC may mimic premalignant lesions on ultrasonography, necessitating histopathological confirmation before any escalation of treatment [5], and this was borne out in our case, where the absence of atypia on histopathology was reassuring despite the concerning cystic and polypoidal appearance on scanning.

Dinh et al highlighted that clinician awareness of PAEC as a distinct, benign entity prevents overdiagnosis and unnecessary hysterectomy in women on prolonged SPRM therapy [4], a point of direct relevance here since the cystic and polypoidal endometrial appearance could otherwise have prompted more radical surgery. Mutter et al, who first characterised the spectrum of endometrial pathology induced by progesterone receptor modulators, concluded that hysteroscopy with targeted biopsy and histopathological evaluation remains the gold standard for definitive diagnosis [1], and this stepwise approach was followed in our patient, allowing conservative, fertility- and uterus-preserving management. Insertion of a levonorgestrel intrauterine system at the time of hysteroscopic polypectomy is a pragmatic adjunct in such patients, addressing both the focal polypoid lesions and the underlying endometrial proliferative drive, and our patient's early symptomatic improvement and haemodynamic stability are consistent with this combined strategy.

This case also illustrates the coexistence of leiomyomas, the original indication for mifepristone, with drug-induced polypoid endometrial change, a combination that is likely to become more frequent as SPRM use for fibroids increases. While the fibroids may have contributed to her bleeding severity, the multiple polyps arising against a background of cystic endometrial change were the more probable principal driver of her symptoms once mifepristone therapy was factored in. From a practice perspective, the key learning point is not the rarity of PAEC itself but the importance of a detailed medication history: persistent or new abnormal uterine bleeding in a woman on prolonged mifepristone therapy should prompt directed hysteroscopic assessment with biopsy, both to confirm the benign nature of PAEC and to avoid unnecessary invasive intervention or misdiagnosis as premalignant disease.

LEARNING POINTS/TAKE HOME MESSAGES 3-5 bullet points

Prolonged mifepristone therapy for leiomyomas can induce progesterone receptor modulator-associated endometrial changes (PAEC), including cystic glandular dilatation, endometrial thickening, and polypoid change.

PAEC can mimic premalignant or malignant endometrial pathology on ultrasonography, creating genuine diagnostic uncertainty in the absence of histopathological confirmation.

Hysteroscopy with targeted biopsy and histopathological evaluation remains the gold standard for definitive diagnosis and safe, uterus-preserving management of PAEC.

Early recognition of PAEC can prevent unnecessary invasive procedures, overtreatment, and patient anxiety in women receiving mifepristone for leiomyomas or AUB.

Appropriate surveillance and timely intervention, integrating drug history, imaging, hysteroscopy and histology, can optimise patient outcomes and long-term gynaecological care.

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FIGURE/VIDEO CAPTIONS

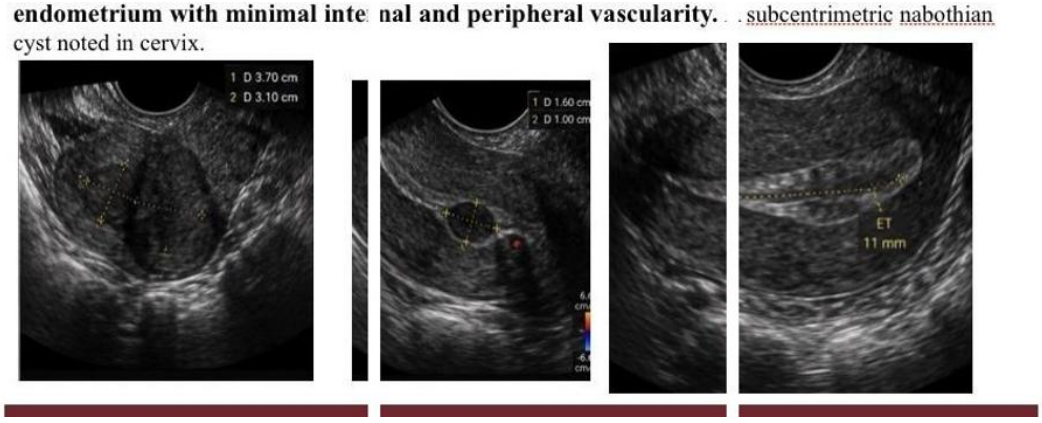

Figure 1. Transvaginal ultrasonography showing intramural leiomyomas (3.7 x 3.1 cm and 1.5 x 1.1 cm), cystic endometrial change, and a focal hypoechoic endometrial lesion (1.6 x 1.0 cm) with minimal vascularity.

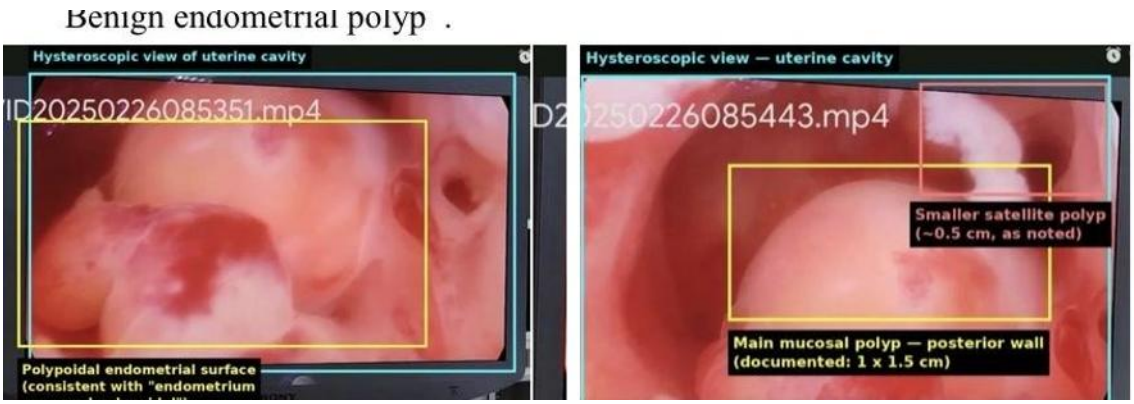

Figure 2. Hysteroscopic view showing a polypoidal endometrium with the dominant mucosal polyp (1 x 1.5 cm, posterior wall) and a smaller satellite polyp (~0.5 cm).