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Multiple recurrences of postmenopausal endometriosis associated with estrogen pellet therapy: clinical implications for hormone therapy and surgical management

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Abstract

Objectives: To challenge the perception that endometriosis uniformly regresses after menopause by presenting the case of repeated, pathology-confirmed symptomatic recurrences spanning two decades after menopause, and to emphasize key considerations for hormone therapy use and surgical management in postmenopausal endometriosis.

Methods: We report the case of a 70-year-old postmenopausal patient with prior hysterectomy, bilateral salpingo-oophorectomy, appendectomy, and pathology-confirmed endometriosis who presented with pelvic pain while receiving subcutaneous estrogen pellet therapy. Preoperative imaging was suggestive of recurrent endometriosis. The patient underwent laparoscopic excision for diagnostic and therapeutic purposes, with final pathology confirming recurrent disease. Written informed consent was obtained for publication of this case report and use of de-identified clinical images. A focused narrative literature review was performed to contextualize this case within existing data on postmenopausal endometriosis.

Results: Laparoscopy revealed a cystic mass arising from the right round ligament with associated retroperitoneal fibrosis and multiple peritoneal implants consistent with endometriosis. Surgical management included resection of the round ligament mass, excision of peritoneal implants, lysis of adhesions, and right ureterolysis. Histopathologic examination confirmed a round ligament adenomyoma and peritoneal endometriosis. Postoperatively, the patient experienced symptomatic improvement and was transitioned to low-dose transdermal estradiol combined with progestogen therapy.

Conclusions: Endometriosis can develop, persist, or recur after menopause, particularly in the setting of unopposed and potentially supraphysiologic exogenous estrogen. This case highlights the importance of appropriate menopausal hormone therapy selection, including consideration of progestogen use regardless of uterine status, and reinforces the role of surgical excision in postmenopausal patients with suspected disease.

Key Words: Adenomyosis, Endometriosis, Estrogen pellets, Hormone therapy, Postmenopause, Progestogens.

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Endometriosis is a predominantly hormone-responsive condition of the reproductive years and is therefore generally expected to become inactive after menopause.[1] Consequently, endometriosis is often not included in the differential diagnosis of pelvic pain or masses in postmenopausal patients.[2] Nevertheless, postmenopausal endometriosis is well documented, challenging the assumption that disease activity uniformly resolves after menopause.[3]

The etiology and clinical significance of endometriosis in postmenopausal patients remain incompletely understood. Proposed explanations include ongoing estrogenic stimulation from endogenous or exogenous sources, and estrogen-independent pathways.[4] In parallel, the use of menopausal hormone therapy continues to increase, yet guidance regarding its use in patients with a history of endometriosis is limited, and clinical practice varies.[5]

Management of suspected postmenopausal endometriosis is similarly complex. Surgical intervention may be pursued to establish a definitive diagnosis, exclude malignancy, and provide symptomatic relief. However, the role of surgery must be considered alongside long-term hormone therapy decisions in this population.[6]

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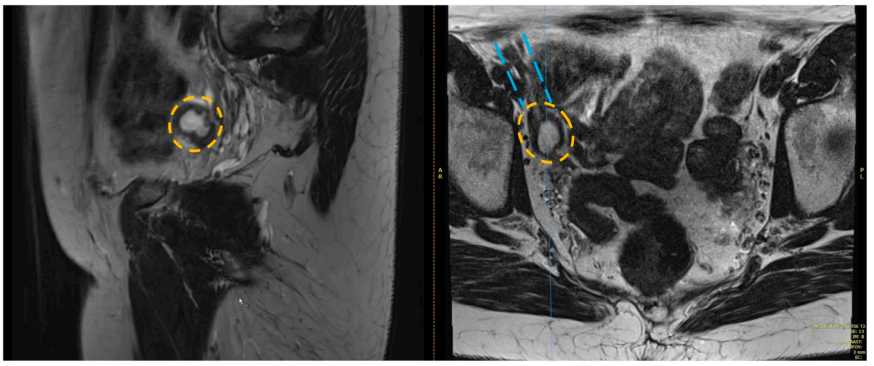

FIG. 1. Preoperative magnetic resonance imaging of the pelvis demonstrating a cystic lesion (yellow dashed outline) arising from the right round ligament (blue dashed outline).

We present the case of symptomatic, pathology-confirmed endometriosis with repeated recurrences spanning two decades after menopause in a patient with long-term, unopposed exogenous estrogen exposure from subcutaneous estrogen pellet therapy. This case underscores ongoing diagnostic and management challenges in postmenopausal endometriosis and provides context for discussing hormone therapy considerations and the role of surgical management in this setting.

CASE REPORT

A 70-year-old postmenopausal gravida 1, para 1, presented with recurrent pelvic pain. The patient experienced her final menstrual period at approximately age 50 and initiated subcutaneous estrogen plus progestogen pellet therapy around the time of menopause. Eleven years before presentation, at the age of 59, she underwent total vaginal hysterectomy for postmenopausal bleeding with benign pathology. She discontinued progestogen therapy and continued estrogen pellet therapy, with reported insertions approximately every 3-4 months. Specific details regarding the patient's estrogen pellet formulation and dosing were not available in the medical record and could not be recalled by the patient. However, documented serum estradiol measurements during this period demonstrated levels ranging from 151 to 336 pg/mL. Five years after hysterectomy, the patient developed pelvic pain and was found to have a complex left adnexal mass and an elevated serum CA-125. Laparoscopic bilateral salpingo-oophorectomy was performed, with final pathology demonstrating a 6-cm left ovarian endometrioma. Of note, the patient denied a prior diagnosis of endometriosis or history of significant dysmenorrhea before menopause. In the following year, the patient developed intermittent right lower quadrant abdominal pain, with imaging findings suggestive of chronic appendicitis versus appendiceal neoplasm. She underwent a laparoscopic appendectomy, with final pathology again showing endometriosis.

At presentation, the patient reported a 1.5-year history of recurrent pelvic pain. Magnetic resonance imaging of the pelvis revealed a 1.7-cm right adnexal cyst consistent with an endometrioma (Fig. 1), along with findings suggestive of endometriosis involving both round ligaments, more prominent on the right, and a punctate lesion suspicious for an endometriotic implant along the serosal surface of the sigmoid colon. The patient was advised to discontinue estrogen pellet therapy. Surgical evaluation was discussed for both diagnostic and therapeutic purposes; however, the patient declined operative intervention at that time. She gradually discontinued estrogen pellet therapy over the following year and initiated pelvic floor physical therapy. Her pain partially improved but remained bothersome. Interval computed tomography of the abdomen and pelvis and pelvic ultrasonography demonstrated enlargement of the right adnexal lesion to 3.1 cm with associated nodular thickening. Given her persistent symptoms and progressive imaging findings, the patient elected to proceed with surgical management.

The patient underwent diagnostic laparoscopy, resection of the adnexal mass, excision of suspected endometriosis, lysis of adhesions, and right ureterolysis. Intraoperative findings included a 3-cm cystic structure arising from the right round ligament with associated retroperitoneal fibrosis (Fig. 2). Peritoneal endometriotic lesions were identified and excised from the right vaginal cuff, right ovarian fossa, and posterior peritoneum overlying the sacral promontory. Histopathologic examination demonstrated a round ligament adenomyoma and peritoneal endometriosis. A summary of the patient's clinical course is provided in Table 1.

The patient had an uncomplicated postoperative course with improvement in her pain. However, she reported vasomotor symptoms, mood disturbance, and fatigue after discontinuation of estrogen pellet therapy. She subsequently reinitiated hormone therapy with a transdermal estradiol 0.025 mg/day patch combined with oral micronized progesterone 100 mg nightly, after which her vasomotor symptoms diminished and both mood and energy improved.

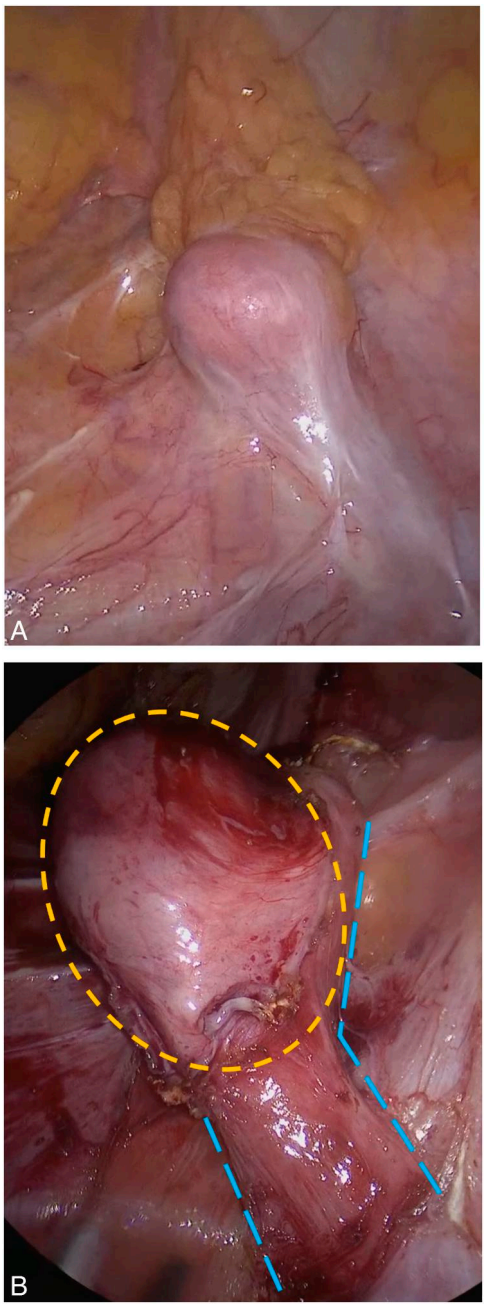

FIG. 2. (A) Upper panel: intraoperative findings demonstrating the lesion before dissection **(B)** Lower panel: dissection isolating the right round ligament (blue dashed outline), which was continuous with the lesion (yellow dashed outline). Histopathologic examination subsequently revealed a round ligament adenomyoma.

DISCUSSION

Endometriosis is classically regarded as a disease of reproductive-aged individuals, with symptoms typically regressing after menopause due to declining endogenous estrogen levels.[1] As a result, endometriosis in postmenopausal patients is often perceived as rare.[7] However, available data suggest that it may be under-recognized rather than exceptional, with studies indicating a prevalence of ~2%-5% among postmenopausal women.[8] This case highlights a striking example of symptomatic, pathology-confirmed endometriosis with multiple recurrences spanning two decades after menopause, underscoring the capacity of long-term estrogen exposure to induce, perpetuate, or reactivate hormone-responsive disease.

Several mechanisms have been proposed to explain the persistence or development of endometriosis after menopause, including extraovarian estrogen production (such as from adipose tissue, adrenal glands, and skin), local estrogen production through aromatase activity within endometriosis lesions, and estrogen-independent inflammatory pathways.[4] However, in the present case, the clinical course strongly suggests a dominant contribution of exogenous estrogen, as this patient received long-term estrogen pellet therapy before the development and progression of symptomatic disease. Estrogen pellets are associated with unpredictable pharmacokinetics, prolonged duration of action, and limited ability to titrate or discontinue therapy in the setting of adverse effects.[9] They are not approved by the US Food and Drug Administration (FDA) for the treatment of menopausal symptoms.[10] Unlike FDA-approved menopausal hormone therapy regimens, pellet therapy may result in sustained supraphysiologic estrogen exposure, which is of particular concern in patients with a history of estrogen-responsive disease.

In this patient, long-term exposure to exogenous estrogen is believed to have contributed to the development and progression of endometriosis well beyond the menopause transition. Although detailed information regarding the formulation and dosing of the patient's pellet therapy was not available, documented serum hormone measurements demonstrated estradiol levels above the expected postmenopausal range (typically < 10 pg/mL).[11] Although systemic menopausal hormone therapy is expected to increase circulating estradiol levels above typical postmenopausal ranges, this patient's values seem to exceed those generally observed with standard FDA-approved regimens. For example, even the highest transdermal estradiol patch dose available in the United States (0.1 mg/day) is associated with a mean serum estradiol level of 89 pg/mL,[12] which remains lower than the levels observed in this case. These findings suggest supraphysiologic systemic estrogen exposure and support a biologically plausible mechanism for the development or reactivation of endometriosis in the postmenopausal setting.

An additional consideration is whether this case represents de novo postmenopausal endometriosis or reactivation of previously unrecognized disease. The patient denied a prior diagnosis of endometriosis and did not report a history of significant dysmenorrhea before menopause, which may suggest new disease development in the postmenopausal setting. However,

TABLE 1. Clinical timeline of the patient's disease course and hormone exposure

Age (y)	Clinical event	Hormone therapy	Imaging & labs	Intervention	Pathology
~50	Menopause	Estrogen & progestogen pellets initiated	—	—	—
59	Postmenopausal bleeding	Progestogen pellets discontinued after hysterectomy, estrogen pellets continued	—	Vaginal hysterectomy	Benign
65	Pelvic pain	Estrogen pellets continued	Left adnexal mass, ↑ CA-125	Bilateral salpingo-oophorectomy	Endometrioma
66-67	Right lower quadrant abdominal pain	Estrogen pellets continued	Chronic appendicitis vs. appendiceal neoplasm	Appendectomy	Endometriosis
69-72 (presentation)	Pelvic pain	Estrogen pellets continued → discontinued after initial consult	Right adnexal cyst, pelvic endometriosis implants	Operative laparoscopy	Endometriosis & adenomyoma

endometriosis is frequently underdiagnosed, and asymptomatic or minimally symptomatic disease may go unrecognized during the reproductive years.[13] In the context of prolonged exogenous estrogen exposure, particularly at supraphysiologic levels, it is therefore plausible that previously undetected endometriotic foci were stimulated, leading to clinically apparent disease after menopause. This distinction remains difficult to establish definitively but highlights the complex and heterogeneous pathophysiology of endometriosis across both premenopausal and postmenopausal populations.

Another critical point illustrated by this case is the potential role of progestogens in patients with a history of endometriosis, even in the absence of a uterus. Although progestogens are routinely prescribed with estrogen therapy to prevent endometrial hyperplasia in patients with an intact uterus,[14] their potential benefit in suppressing endometriotic activity is less widely appreciated. Progestogens exert antiproliferative effects on both eutopic and ectopic endometrial tissue[15] and are often recommended for patients with known or suspected endometriosis receiving menopausal hormone therapy. Available data suggest that postmenopausal endometriosis may occur more frequently among women receiving estrogen-only therapy compared with combined estrogen-progestogen therapy.[5,6] However, high-quality data in postmenopausal populations remain limited. In this case, the patient was not restarted on a progestogen after her initial diagnosis of endometriosis, reflecting a common misconception that hysterectomy alone eliminates the need for progestogen therapy. Her clinical course supports consideration of progestogen use in patients with a history of endometriosis receiving menopausal hormone therapy, regardless of uterine status.

Even when progestogen therapy was ultimately recommended, the patient expressed reluctance to initiate treatment due to concerns about breast cancer risk, reflecting persistent fears rooted in early interpretations of the Women's Health Initiative (WHI). Subsequent analyses have demonstrated that breast cancer risk associated with menopausal hormone therapy varies by formulation, duration of use, and patient characteristics, and that WHI findings should not be extrapolated indiscriminately to all hormone regimens or clinical situations.[16,17] Ongoing challenges in hormone therapy risk perception continue to influence patient decision-making and may inadvertently limit the use of appropriate therapies in selected patients.

It remains unknown whether earlier use of FDA-approved estrogen therapy in combination with a progestogen might have altered this patient's disease trajectory or reduced the need for repeated surgical intervention. This uncertainty highlights the importance of individualized, evidence-based hormone therapy counseling, particularly in patients with a history of estrogen-responsive disease.

Surgical management is frequently recommended in cases of postmenopausal endometriosis, both for symptomatic relief and to establish a definitive diagnosis, especially given its potential association with malignant

transformation.[6] Although malignant transformation of endometriosis is rare, with reported rates ranging from ~0.7%-2.5%,[18] the overlap in clinical and imaging features between benign endometriosis and malignancy in postmenopausal patients supports a surgical approach.[2] Surgical excision allows for histopathologic confirmation, exclusion of malignancy, and avoidance of prolonged empiric medical therapy in the setting of diagnostic uncertainty. In addition, available data suggest that malignant transformation may occur more frequently among postmenopausal women receiving estrogen-only hormone therapy compared with combined estrogen-progestogen therapy.[19] Accordingly, inclusion of a progestogen may be considered to mitigate both disease reactivation and the potential for malignant transformation.[5,6] In this patient, surgical excision resulted in pathologic confirmation of endometriosis and adenomyosis, informed subsequent hormone therapy decisions, and contributed to symptomatic improvement.

CONCLUSIONS

This case emphasizes several important clinical implications, including caution regarding the use of non-FDA-approved hormone therapy such as estrogen pellets, consideration of progestogen therapy in patients with a history of endometriosis regardless of uterine status, and the importance of individualized, evidence-based counseling regarding hormone therapy risks and benefits. It also highlights the diagnostic and therapeutic role of surgical excision in postmenopausal patients with suspected endometriosis, particularly when symptoms persist or malignancy is a concern. As the population of patients receiving menopausal hormone therapy continues to grow, heightened awareness of estrogen-dependent disease development, persistence, and recurrence remains essential to optimizing long-term patient outcomes.

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