BMC Women's Health

CASE REPORT Open Access

Sequential therapy of dienogest following relugolix for adenomyosis and impact on symptoms and serum CA125 levels: a case series

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Abstract

Background Adenomyosis, characterized by endometrial tissue within the uterine muscle, often presents with severe pelvic pain and menorrhagia. This case series demonstrates the efficacy of sequential therapy involving relugolix followed by dienogest in managing adenomyosis.

Case presentation In five patients with adenomyosis, the gonadotropin-releasing hormone antagonist relugolix initially mitigated symptoms and reduced the levels of serum CA125, a marker associated with disease activity. After six months of relugolix, patients were transitioned to dienogest. This sequential approach maintained symptom relief and further stabilized CA125 levels.

Conclusions Our findings demonstrate that sequential therapy provides effective symptom management and long-term disease control. Further, CA125 remains a valuable biomarker for monitoring therapeutic success.

Keywords Adenomyosis, Relugolix, Dienogest, CA125, GnRH antagonist, Hormonal therapy, Sequential therapy

Background

Adenomyosis is a common, yet challenging, gynecological disorder characterized by the presence of endometrial tissue within the myometrium. The overall adenomyosis incidence rate was 1.03% in the United States [1], but the actual prevalence remains unclear in many countries, including Japan. This is due to variations in diagnostic criteria, underreporting, and a lack of large-scale epidemiological studies, making it difficult to accurately estimate the true incidence of adenomyosis across different populations. It leads to significant symptoms, including severe pelvic pain, menorrhagia, and impaired quality of life [2, 3]. Adenomyosis diagnosis traditionally relies on histopathological examination; however, imaging studies such as magnetic resonance imaging (MRI) and transvaginal ultrasound play crucial roles in clinical diagnosis and management. MRI diagnostic criteria typically include diffuse or focal thickening of the junctional zone (> 12 mm), myometrial cysts, heterogeneous myometrial texture, and asymmetry in uterine wall thickness [4]. Ultrasound findings indicative of adenomyosis include heterogeneous myometrial echotexture, presence of myometrial cysts, indistinct endometrial-myometrial junction, and increased vascularity, as supported by recent guidelines [5]. Risk factors for adenomyosis include age, with a higher incidence observed in women aged 30 to 50 years, particularly those in the perimenopausal stage [6]. Multiparity, especially with cesarean sections, have

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also been linked to a greater risk [6]. Hormonal factors, particularly elevated estrogen levels, and a history of endometriosis or uterine fibroids, further increase the likelihood of developing adenomyosis [7]. These factors contribute to the development of the condition and are important in its early identification and management. Traditional treatments for adenomyosis include hormonal therapies such as progestins, gonadotropin-releasing hormone (GnRH) analogs, and combined oral contraceptives [8].

Relugolix, an oral GnRH antagonist, effectively reduces estrogen levels, providing rapid symptom relief [9]. Approved for endometriosis-related pain in December 2021 in Japan with a recommended dose of 40 mg once daily, the efficacy of relugolix for adenomyosis has also been investigated [9]. Dienogest, an oral progestin, is commonly prescribed for the management of adenomyosis symptoms. The recommended dose for the treatment of adenomyosis is typically 2 mg per day, taken continuously without a break, for long-term symptom management. This dosage may be adjusted based on the patient's response and tolerance, and it is important to follow a healthcare provider's guidance regarding duration and any necessary adjustments. Rare adverse events, such as mood changes, headaches, and changes in menstrual bleeding patterns, have been reported, but overall, dienogest is considered effective for symptom relief. [10]. Sequential therapy, involving an initial course of relugolix followed by dienogest, represents a novel approach aimed at maximizing symptom control and maintaining disease management.

CA125 is a glycoprotein that is frequently elevated in ovarian cancer; it is commonly used as a biomarker for monitoring treatment response and disease progression in patients with ovarian cancer [11]. Elevated serum CA125 levels are often associated with advanced stages of ovarian cancer; however, elevated levels are not exclusive to malignant conditions [12]. Additionally, elevated serum CA125 levels are frequently observed in adenomyosis and can reflect disease activity and response to treatment [13]. However, the possibility of coincidental ovarian cancer should not be overlooked, particularly in women presenting with elevated CA125 levels and significant symptom burden [12]. As CA125 elevation is not specific to ovarian cancer, its levels should be interpreted cautiously, and any persistent elevation despite treatment warrants further investigation [14]. CA125 monitoring is useful for assessing disease activity in benign gynecological conditions such as adenomyosis, as it can reflect the extent of inflammation and treatment response. Moreover, persistent or rising CA125 levels, even in the absence of symptomatic improvement, should prompt further evaluation to rule out potential malignancies, including ovarian cancer. CA125 is widely used as a biomarker in clinical practice, helping differentiate between benign and malignant conditions, especially in cases where the clinical presentation overlaps with malignancy [15].

Serum CA125, a biomarker frequently associated with endometriosis and adenomyosis, reflects disease activity and response to treatment [16]. The CA-125 elimination rate constant (KELIM) score is a prognostic biomarker that can help predict the outcome of ovarian cancer patients treated with neoadjuvant chemotherapy (NACT) (on https://www.biomarker-kinetics.org/CA-125-neo for patients treated with NACT, and on https://www.biomarker-kinetics.org/CA-125 for patients treated with adjuvant chemotherapy) [17].

In adenomyosis management specifically, CA125 may serve as a useful adjunct biomarker for assessing therapeutic efficacy and disease activity [18]. Monitoring serum CA125 concentrations can complement clinical evaluation by potentially predicting symptom recurrence or exacerbation. In our case series of sequential relugolix followed by dienogest therapy, significant reductions and subsequent stabilization of CA125 levels were observed alongside clinical symptom improvement, indicating its potential utility for monitoring therapeutic effectiveness. However, there is a notable gap in the literature regarding biomarkers for evaluating the treatment of adenomyosis. Unlike other gynecological conditions such as ovarian cancer, where CA-125 can be used as a prognostic marker, no standardized biomarkers are currently available for monitoring the therapeutic response or disease progression in adenomyosis. This gap underscores the need for further research to identify reliable biomarkers that could facilitate better management and individualized treatment strategies for patients with adenomyosis.

Case presentation

Case 1

A 48-year-old woman (gravida, 3; para, 2) presented to our hospital with severe dysmenorrhea. Initial evaluation included a magnetic resonance imaging (MRI) scan, which revealed adenomyosis, a right endometrial ovarian cyst, right hydronephrosis, and right hydroureter (Fig. 2A). Two months after her initial visit, she commenced treatment with dienogest (2 mg/day), with the delay due to the time taken for her referral to our hospital. Figure 1 illustrates the transition in CA125 levels throughout the therapy. Although her CA125 level subsequently increased to 151.7 U/mL (the normal reference range for CA125 is below 35.0 U/mL), it was followed by a gradual decline. By six months of treatment, her CA125 level had decreased to 12.3 U/mL, and she experienced significantly less abdominal pain. Consequently, dienogest was reduced to 1 mg/day. After two years of

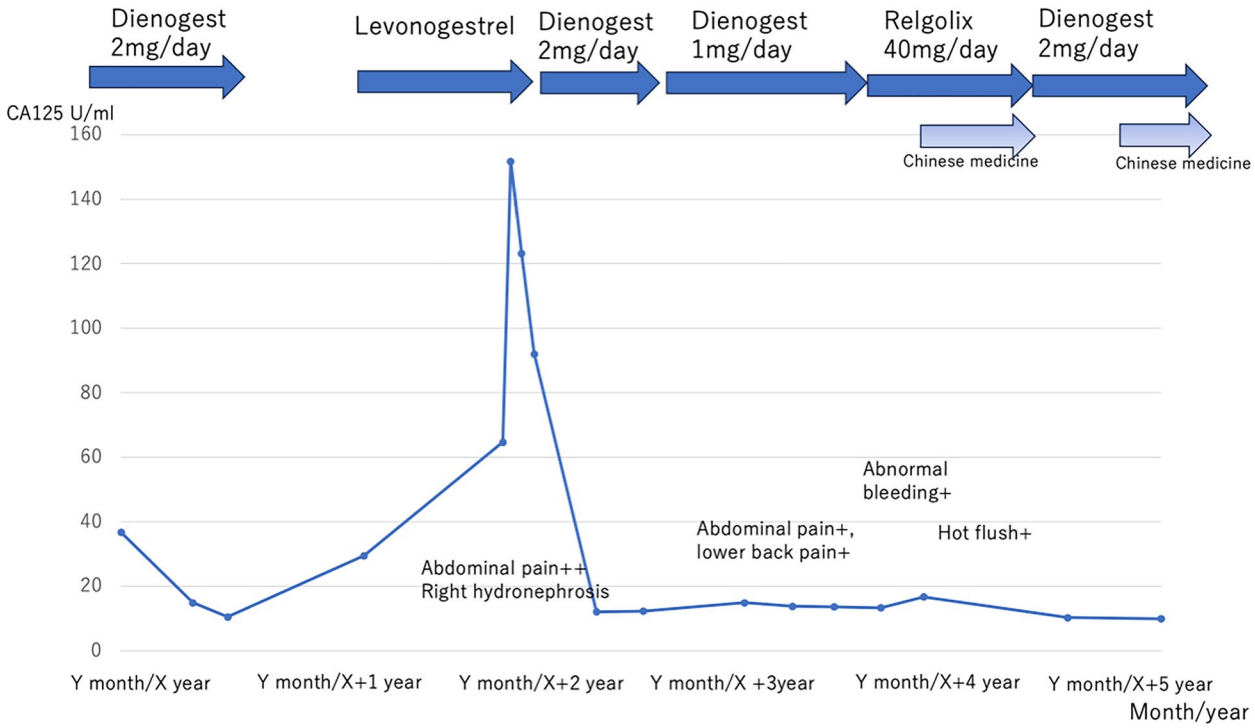

Fig. 1 Case 1: Changes in serum CA125 levels during therapy. After 10 months of resuming dienogest, bone mineral density measurements revealed normal bone density in the right hip joint (123%) and left hip joint (95%), but mild bone loss in the lumbar vertebrae (Lumbar 1–4: 79%), indicating the need for monitoring

dienogest treatment, she experienced an increase in the frequency of irregular bleeding. Therefore, she was transitioned to relugolix (40 mg/day). At this time, a pelvic examination revealed tenderness in the posterior wall of the uterus and a 2-cm right ovarian cyst. After one month of relugolix treatment, Kami-Shoyo-san, a traditional Kampo medicine, was introduced to manage her menopausal symptoms, which included irritability and hot flashes [13]. At two months after relugolix initiation, an MRI scan indicated resolution of the right ovarian cyst (Fig. 2B), and she reported significant relief from abdominal pain. However, despite these improvements, she continued to experience menopausal symptoms, leading to further adjustments in her treatment. After six months on relugolix, she was transitioned back to dienogest (2 mg/day). This resulted in the stabilization of her abdominal pain and mitigation of menopausal symptoms. At this stage, since the menopausal symptoms had resolved, Kami-Shoyo-san, a traditional Kampo medicine, was discontinued.

Case 2

A 38-year-old woman (gravida, 1; para, 1) presented with worsening menorrhagia and dysmenorrhea. Six years prior, she had undergone laparotomy with bilateral ovarian cystectomy, left salpingectomy, and myomectomy because of bilateral endometriotic cysts, a left hydrosalpinx, and uterine fibroids. Postoperatively, she was prescribed a low-dose oral contraceptive pill. Two years after the initial surgery, her symptoms of menorrhagia and dysmenorrhea intensified. A transvaginal ultrasound suggested the presence of an endometrial polyp, but no significant issues were detected in the ovaries. Hysteroscopic resection was not pursued due to hospitalization constraints, and she resumed the low-dose oral contraceptive pill therapy. One year later, despite continued use of the low-dose pill, the left ovarian endometriotic cyst had increased in size to 46×38 mm. Consequently, her treatment was switched to dienogest. Within two weeks of dienogest initiation, she was admitted to the hospital because of severe lower abdominal pain. Diagnostic imaging revealed a micro-rupture of the endometriotic cyst and intraovarian hemorrhage, resulting in hospitalization for several days. Her pain was managed with analgesics, and she continued treatment with dienogest following discharge. Three years later, her abdominal pain worsened, and the left ovarian cyst had expanded to 57 mm. Therefore, she was transitioned from dienogest to relugolix. Before this transition, her CA125 levels were elevated, at 199.2 U/mL. Following relugolix

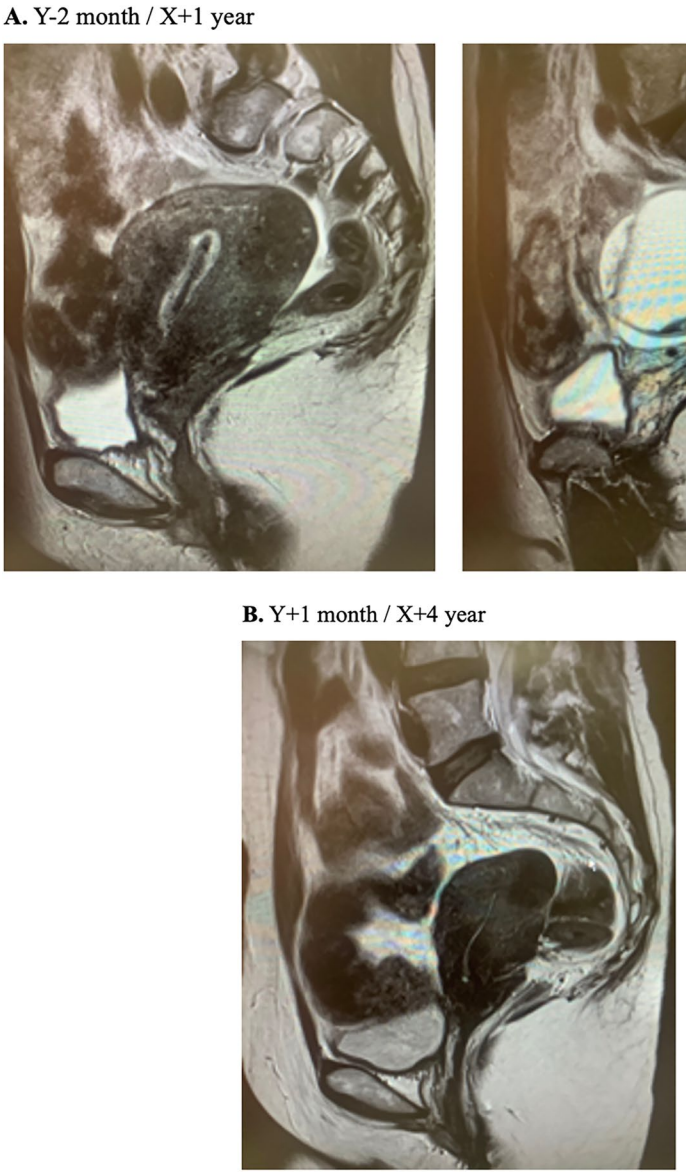

Fig. 2 Case 1: Images demonstrating the effects of treatments. **A** MRI image showing the adenomyosis in the uterus. **B** Following the sequential therapy involving dienogest and relugolix, the left ovarian endometriotic cyst has disappeared, with a significant reduction in uterine size

initiation, her CA125 levels normalized, abdominal pain subsided, and the left ovarian cyst reduced in size to 35 mm. However, four months after relugolix initiation, she began experiencing menopausal symptoms, including insomnia, irritability, and headache. To address these symptoms, Kami-Shoyo-san, a Kampo medicine, was introduced [19]. Six months after relugolix initiation, she was transitioned back to dienogest. With dienogest reinitiation, her abdominal pain was managed effectively, and no further significant increase in cyst size was noted. Her CA125 levels remained stable, and no additional major symptoms were reported. Sequential therapy involving dienogest and relugolix resulted in rapid symptom relief and normalization of CA125 levels. Transitioning to dienogest maintained these improvements with minimal adverse effects. Her treatment course and changes in CA125 levels are shown in Fig. 3 and relevant images are shown in Fig. 4.

Case 3

A 39-year-old woman (gravida, 1; para, 1) was referred to our department for the management of menstrual pain and adenomyosis. Eight years prior, she had undergone laparoscopic bilateral ovarian endometrial cystectomy.

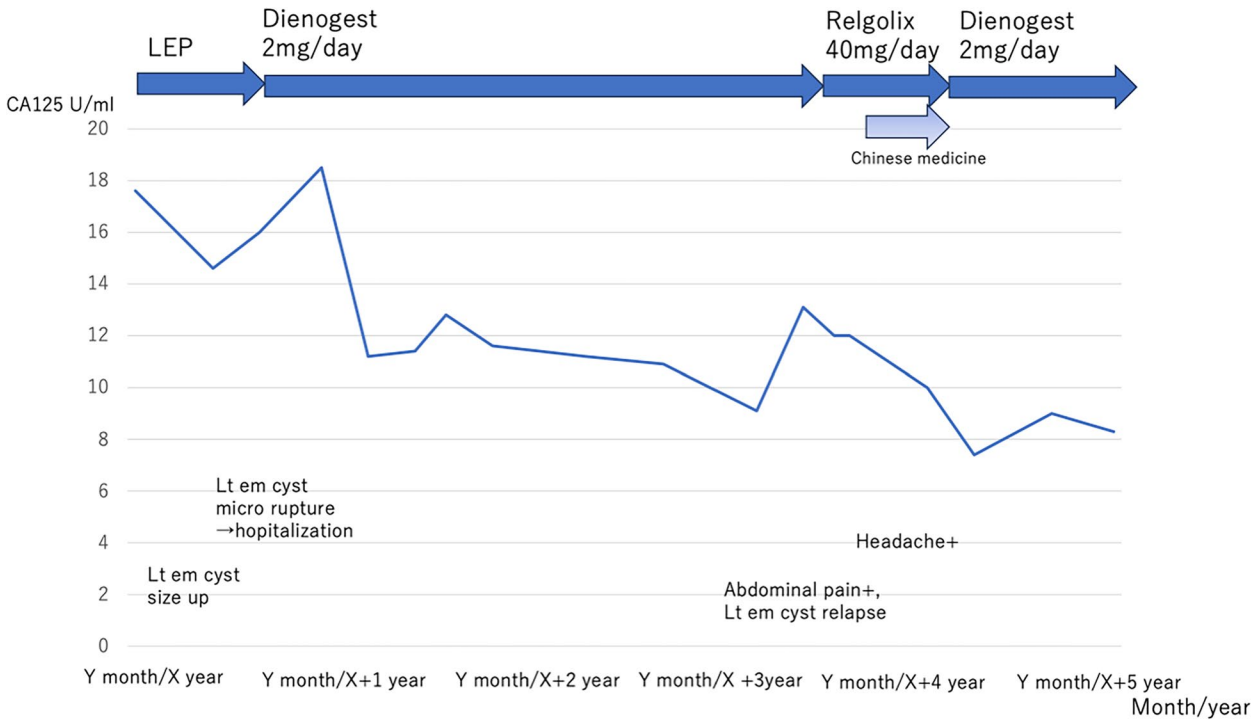

Fig. 3 Case 2: CA125 levels during the treatment course. **A** MRI image after the treatment course. **B** Dienogest and relugolix resulted in rapid symptom relief and normalization of CA125 levels

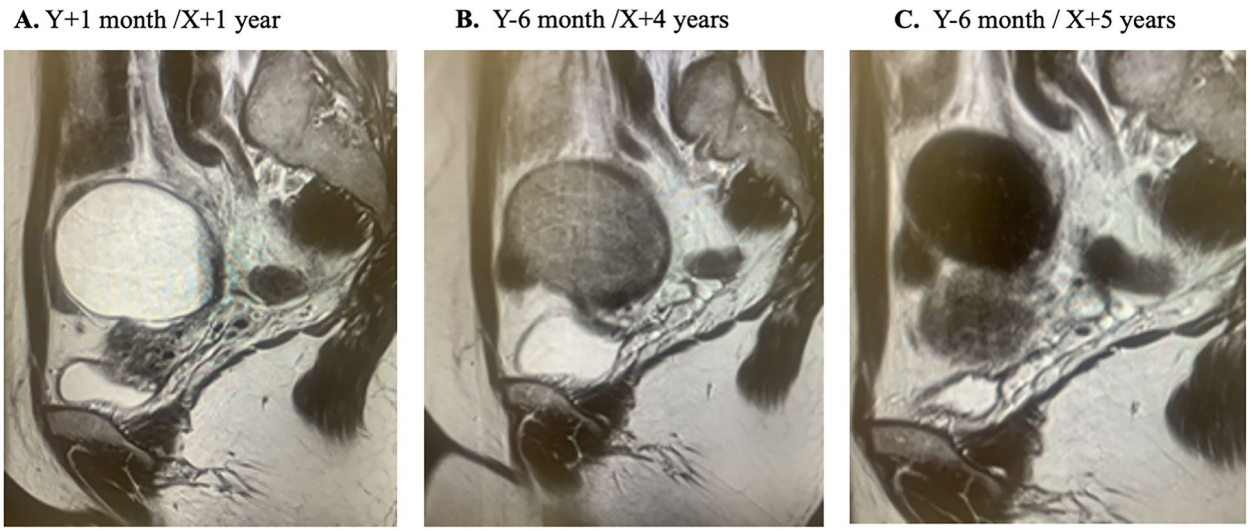

Fig. 4 Case 2: Images demonstrating the treatment effects. **A** Y + 1 month /X + 1 year, (**B**) Y-6 month /X + 4 years, (**C**) Y-6 month / X + 5 years. Her left ovarian cyst has reduced in size to 35 mm

Upon presentation, her CA125 level was elevated, at 155.7 U/mL. Transvaginal ultrasonography revealed thickening of the posterior uterine wall consistent with adenomyosis, while the bilateral ovaries appeared normal. Dienogest was initiated. Over time, her CA125 level gradually decreased. However, 1 year and 4 months after dienogest initiation, she experienced worsening abdominal pain and irregular bleeding. A transvaginal ultrasound indicated no significant improvement in adenomyosis. Therefore, she was transitioned from

dienogest to relugolix. Relugolix administration led to a marked improvement; her irregular bleeding ceased and her CA125 level significantly dropped to 21.4 U/mL. Despite these positive outcomes, relugolix treatment was discontinued after 2 months because of worsening pre-existing depression, which had been managed by another healthcare provider. Thus, she was transitioned back to oral dienogest. Eleven months after dienogest reinitiation, she reported worsening left back pain and tenderness upon pelvic examination. Given these new symptoms, she was transitioned back to relugolix, and her symptoms and CA125 level were closely monitored. Following a two-month course of relugolix, she resumed dienogest, which has effectively managed her symptoms and maintained her CA125 level. The management adjustments in this case aimed to address the resurgence of her symptoms while maintaining effective control of adenomyosis. Her treatment course and changes in CA125 levels are shown in Fig. 5.

Case 4

A 42-year-old woman (gravida, 1; para, 1) presented with symptoms of adenomyosis. She had initially been treated with a low-dose estrogen-progestin regimen for 2 years following delivery. During this period, her abdominal pain improved, and there was a reduction in the size of her adenomyosis. At 41 years of age, her treatment was transitioned to dienogest (0.5 mg/day). However, this transition was associated with worsening abnormal bleeding and progression of both adenomyosis and myoma. Consequently, dienogest was increased to 1 mg/day. Despite this, her abdominal pain worsened over the course of one year. Thus, she was transitioned to relugolix. However, she experienced adverse effects, including left arm pain, hot flushes, and dizziness. Because of these intolerable side effects, relugolix was discontinued at four months after initiation. Two months after the cessation of relugolix, her abdominal pain recurred, leading to the reintroduction of relugolix. Despite relugolix reinitiation, the adverse effects persisted. To address ongoing symptoms, a levonorgestrel-releasing intrauterine system (IUS) was inserted. One year after levonorgestrel IUS insertion, she reported significant mitigation of irregular bleeding and abdominal pain. However, the IUS was found to have fallen out, leading to the decision to observe her condition without immediate further intervention. Kami-Shoyo-san, a Kampo medicine, was added to manage her menopausal symptoms [19]. Her treatment course and changes in CA125 levels are shown in Fig. 6.

Case 5

A 46-year-old woman (nulliparous) presented to our hospital with symptoms related to multiple myomas and a left ovarian endometriotic cyst. Her medical history included menorrhagia and abnormal bleeding. At 22 years of age, she had been diagnosed with a 7-cm right ovarian cyst, which was treated with a low-dose

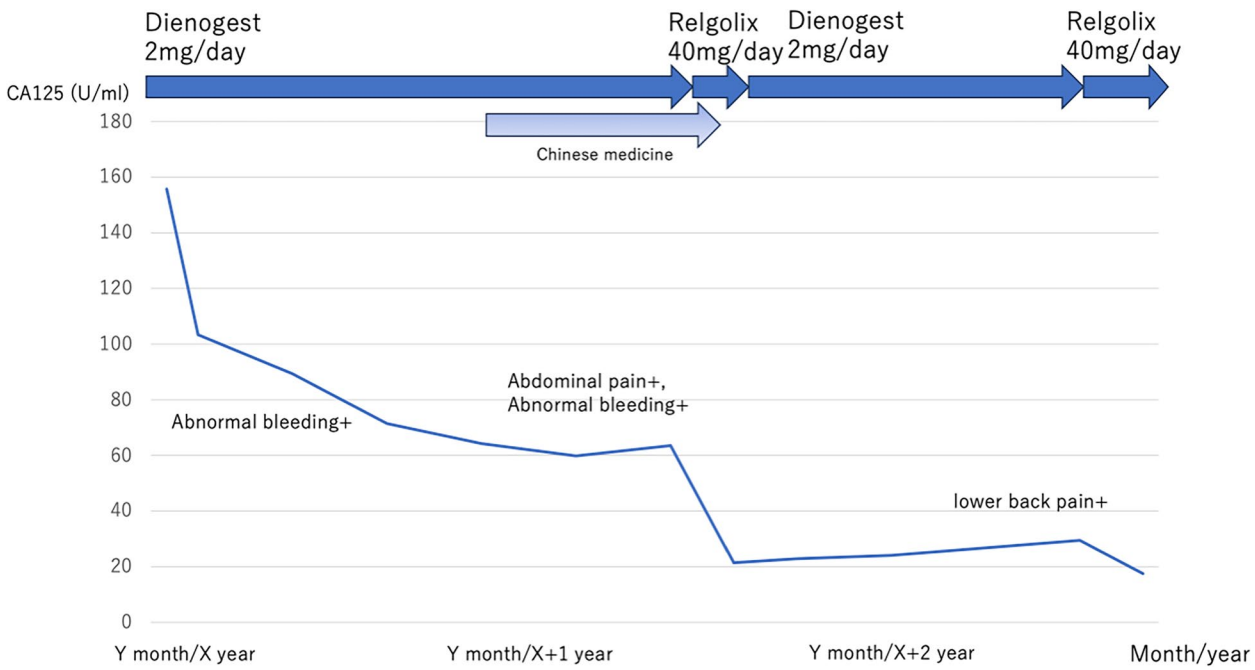

Fig. 5 Case 3: CA125 levels during the treatment course. Relugolix administration has led to a marked improvement in the CA125 level

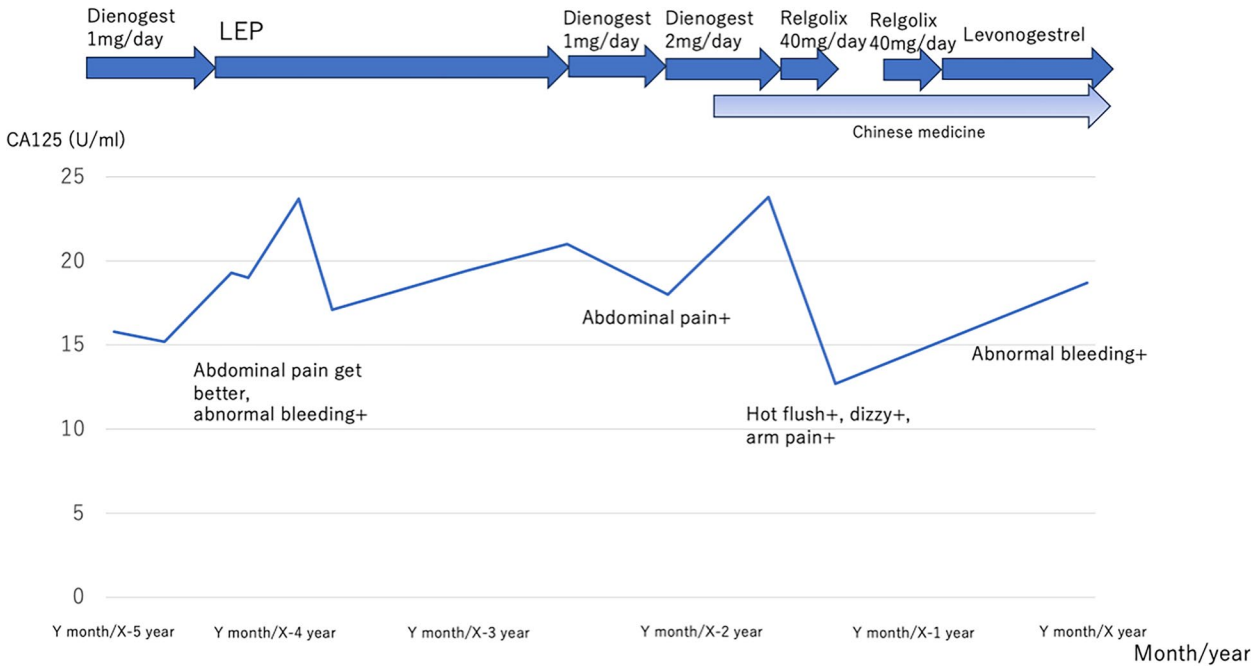

Fig. 6 Case 4: CA125 levels during the treatment course. Short-term relugolix therapy has resulted in a significant decrease in CA125 levels

estrogen-progestin regimen along with GnRH analog injections. At her first visit to our hospital, a transvaginal examination revealed that the uterus had increased in size to that of a goose egg and was immobile. Additionally, the Douglas fossa was indurated. Adenomyosis was detected, along with a left endometriotic cyst measuring 50 mm (Fig. 7A). Treatment with relugolix (40 mg/day) was initiated. One month after relugolix initiation, she experienced mild hot flushes. However, she reported that the menopausal symptoms were mild compared to those experienced during previous GnRH analog therapy, and the symptoms were considered manageable without the need for additional traditional Kampo medicine. Two months after relugolix initiation, the mild hot flushes persisted; thus, Keishi-bukuryo-gan, a traditional Kampo medicine, was introduced [20]. Despite the resolution of menstruation, she continued to experience slight abdominal pain; however, the Keishi-bukuryo-gan led to an improvement in menopausal symptoms. Six months after relugolix initiation, her MRI images showed a marked improvement (Fig. 7B), and she was transitioned to dienogest (2 mg/day). Her treatment course and changes in CA125 levels are shown in Fig. 7C. Although she experienced a worsening of abdominal pain and a slight increase in abnormal bleeding, these symptoms were tolerable. Sequential therapy with dienogest preserved the benefits of relugolix treatment, demonstrating the efficacy of this approach in managing adenomyosis.

Discussion and conclusions

Sequential therapy with relugolix followed by dienogest has proven effective for managing adenomyosis. The key findings of this case series include rapid symptom alleviation with initial relugolix treatment, followed by sustained symptom stabilization with dienogest. Imaging evidence (MRI and transvaginal ultrasound) from our cases revealed significant reductions in adenomyosis size and severity, as indicated by decreased uterine volume, reduced thickness of the junctional zone, and disappearance of previously observed cystic lesions, supporting clinical symptom improvements. Notably, the therapy leads to a significant reduction in symptoms and stabilization of serum CA125 levels, underscoring the role of CA125 as a reliable biomarker for disease activity.

The dynamics of serum CA125 levels observed in our study, which showed a significant initial decline with relugolix and stabilization during dienogest therapy, are consistent with previous literature that associates CA125 reductions with improvements in clinical symptoms, such as dysmenorrhea and abnormal uterine bleeding [18, 21]. These results demonstrate that sequential therapy effectively balances immediate symptom relief with sustained disease control, offering a promising treatment strategy for patients with adenomyosis. Relugolix provides rapid symptom relief and reduces CA125 levels, while dienogest maintains these benefits over the long term. The correspondence between symptom relief and changes in CA125 levels underscores its role as a reliable

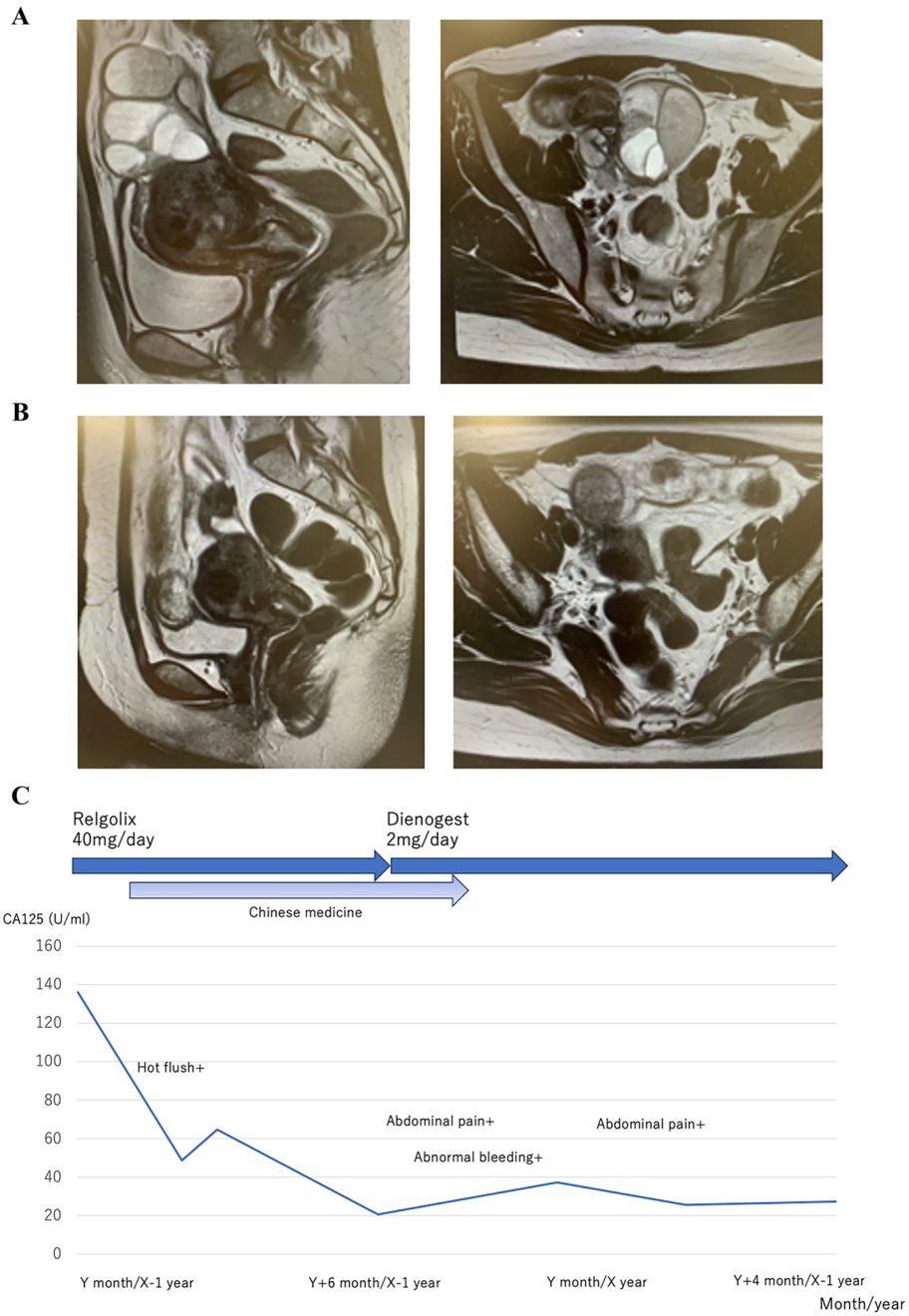

Fig. 7 Case 5: (**A**) Changes in CA125 levels throughout therapy, and (**B**) after the therapy. (**C**) The effects of relugolix treatments on CA125 levels during the treatment course. Relugolix administration has led to a marked improvement in CA125 levels and in her symptoms

biomarker for disease activity. Sequential therapy with relugolix followed by dienogest has demonstrated efficacy in managing adenomyosis by significantly reducing symptoms and stabilizing serum CA125 levels. This approach effectively balances immediate symptom relief with long-term disease control. However, interpretation of serum CA125 levels must be contextualized carefully, considering its nonspecific nature. Elevated CA125 can also be associated with ovarian cancer and other inflammatory conditions. Therefore, clinicians should interpret CA125 changes alongside clinical symptoms and imaging findings, remaining vigilant for persistent elevations or unexpected increases, which should prompt additional evaluations to rule out malignancies.

In the present report, CA125 levels greatly decreased during treatment with relugolix and were stabilized with a transition to dienogest. This decline in CA125 level suggests that the therapy effectively managed adenomyosis-related inflammation and disease activity [22]. However, vigilance is necessary, given the overlapping symptomatology and the role of CA125 in both benign and malignant gynecological conditions [23]. Persistent or increasing CA125 levels during therapy should prompt additional diagnostic evaluations, including imaging studies or further gynecological assessments, to rule out the possibility of concurrent ovarian cancer [23]. The sequential approach of using relugolix followed by dienogest offers an effective treatment strategy for adenomyosis, but it is essential to monitor CA125 levels carefully throughout therapy. Regular monitoring helps to ensure that the observed changes in CA125 level are attributed to the management of adenomyosis and not to a malignancy [13]. In clinical practice, integrating CA125 monitoring with other diagnostic modalities, such as transvaginal ultrasound or MRI, can improve the accuracy of disease assessment and management [24]. The combination of sequential hormonal therapy with diligent monitoring provides a comprehensive approach to managing adenomyosis while mitigating the risk of missing an underlying malignancy.

Our findings also highlight advantages of GnRH antagonist therapy, such as relugolix, including rapid onset of symptom relief, fewer menopausal symptoms, and possibly improved adherence compared to traditional GnRH agonists [9]. However, prolonged use of GnRH analogs, including antagonists, poses potential risks to bone mineral density (BMD) [25]. Recent evidence from the LIBERTY randomized withdrawal study demonstrated that relugolix combination therapy for heavy menstrual bleeding associated with uterine fibroids was associated with decreased BMD after six months of continuous use, emphasizing the importance of careful monitoring and potential strategies such as add-back therapy to mitigate bone loss when GnRH antagonist therapy extends beyond six months [26]. Imaging outcomes from our cases indicated noticeable reductions in adenomyosis size and severity following sequential therapy. Specifically, MRI and ultrasound assessments demonstrated significant reductions in uterine volume, thickness of the junctional zone, and severity grading according to recognized imaging criteria. Recent literature has corroborated the efficacy of hormonal treatments in reducing adenomyosis severity, highlighting improvements in both focal and diffuse adenomyosis, and underscoring the clinical relevance of imaging-based evaluations in treatment monitoring [27, 28]. Further exploration with larger prospective studies could more precisely quantify these imaging-based improvements, potentially leading to refined clinical protocols and treatment strategies. Future research should continue investigating the optimal duration of GnRH antagonist therapy and strategies to balance effective symptom control with bone health preservation.

The primary limitation of this case series is its small sample size, which restricts the generalizability of the findings to a broader population. Additionally, the retrospective nature of the study may introduce selection bias and limit the ability to draw definitive conclusions about the long-term efficacy and safety of the treatment approach. Therefore, larger prospective studies are warranted to validate these findings and further elucidate the long-term benefits and potential risks of this sequential therapy.

In conclusion, sequential therapy with relugolix and dienogest effectively manages adenomyosis and stabilizes the CA125 level, reflecting improved disease control. The sequential approach provides an effective strategy for managing adenomyosis, balancing immediate symptom relief with long-term disease control. However, given the potential overlap of CA125 elevation with ovarian cancer, careful monitoring and diagnostic evaluation are essential to differentiate between benign and malignant causes of CA125 elevation. Regular monitoring throughout the treatment process is necessary to ensure continued safety and efficacy. This approach ensures optimal treatment efficacy while safeguarding against the potential risk of coincidental ovarian cancer. Future research should focus on optimizing treatment protocols and exploring long-term outcomes.

Abbreviations

GnRH	Gonadotropin-releasing hormone
IUS	Intrauterine system
MRI	Magnetic resonance imaging
NACT	Neoadjuvant chemotherapy

Acknowledgements

We thank our colleagues at the Department of Obstetrics and Gynecology, Teikyo University School of Medicine for their contributions to data analysis and manuscript review.

Authors' contributions

HN: Study design, data collection, Statistical analysis, manuscript drafting. KT: Data analysis, manuscript review. TO: Clinical management, manuscript review. SW: Clinical management, manuscript review. KT: Data interpretation, manuscript drafting. YT: Literature review, manuscript review. TI: Statistical analysis, manuscript review. MH: Patient management, manuscript review. HH: Clinical oversight, manuscript review. KN: Study conception, Clinical management, manuscript drafting, critical discussion.

Funding

This study was supported by departmental funds from the Department of Obstetrics and Gynecology, Teikyo University School of Medicine. No external funding was sought.

Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All reported cases were conducted following ethical guidelines and with informed consent obtained from all patients. The study was approved by the Institutional Review Board of Teikyo University School of Medicine, (13–003-5). Written informed consents were obtained from all patients for the publication of this case series report and any accompanying images. A copy of the written consents is available for review by the editor of this journal.

Competing interests
The authors declare no competing interests.

Received: 4 February 2025 Accepted: 20 March 2025
Published online: 29 March 2025

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