Case Reports in Oncology

Case Rep Oncol 2024;17:1229–1238
DOI: 10.1159/000541823
Received: August 13, 2024
Accepted: October 1, 2024
Published online: October 25, 2024

Case Report

Low-Grade Uterine Adenosarcoma with Overexpression of MDM2 and CDK4 by Immunohistochemistry: A Case Report and Literature Review

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Keywords
Adenosarcoma · Case report · CDK4 · MDM2

Abstract
Introduction: Uterine adenosarcoma (UA) is a rare malignant mesenchymal neoplasm characterized by benign epithelial and malignant stromal components. Comprehensive genomic profiling has identified a high frequency of murine double-minute type 2 (MDM2) and cyclin-dependent kinase 4 (CDK4) amplification in UA. However, the significance of these genetic alterations in tumor biology remains poorly understood. This report presents a case of UA with immunohistochemically positive MDM2 and CDK4 expression. ***Case Presentation:*** The patient was a 72-year-old woman with a history of genital bleeding. Magnetic resonance imaging revealed an 11 × 5 × 7 cm mass in the endometrial cavity, extending into the uterine cervix. Biopsy of the tumor showed no malignant findings. The patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. Microscopically, the tumor consisted of benign glandular epithelial components and low-grade sarcoma. The diagnosis was UA stage IA, pT1aNxM0. No sarcomatous overgrowth and no myometrial or lymphovascular invasions were observed. Immunohistochemistry confirmed MDM2 and CDK4 expression in the mesenchymal tissue. No recurrence was observed 12 months post-surgery. ***Conclusion:*** The pathological diagnosis of UA was based on histomorphological features. This study demonstrates that immunohistochemistry for MDM2 and CDK4 can help elucidate the molecular genetic features of UA. Further studies are needed to correlate the expression of these genes with the biological behavior of UA.

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Introduction

Uterine adenosarcoma (UA) is the rarest form of uterine sarcoma, accounting for less than 0.2% of all uterine malignancies [1]. Histologically, UA is characterized by benign epithelial and malignant stromal components [1]. The pathological diagnosis of UA is primarily based on histomorphological findings of characteristic structures with peri-glandular cuffing [1]. While immunohistochemistry can also be used for diagnosing UA, no specific immunohistochemical markers have been identified. Molecular genetic profiling has revealed that UA is a genetically heterogeneous mesenchymal neoplasm [2]. Recently, amplification of murine double-minute type 2 (MDM2) and cyclin-dependent kinase 4 (CDK4) has been reported in UA [3]. CDK4 and MDM2 are known oncogenes involved in well-differentiated and dedifferentiated liposarcomas, and their simultaneous amplification is believed to promote proliferation through combined effects on p53 and the cell cycle [4]. However, the relationship between these molecular genetic features and UA prognosis remains unclear. This case report discusses the potential utility of MDM2 and CDK4 immunohistochemistry in treatment of UA. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000541823).

Case Report

A 72-year-old woman presented to our hospital with a complaint of postmenopausal bleeding. Transvaginal ultrasonography revealed a mass extending from the uterine body into the cervix. The patient had a history of appendectomy and cholecystectomy. Serum levels of cancer antigen 125 and cancer antigen 19–9 were 113 U/mL (normal range: 0–35 U/mL) and 63.7 U/mL (normal range: 0–37 U/mL), respectively. Serum lactate dehydrogenase level was 277 IU/L, with the following isoenzyme distribution: LD1: 32% (20–31%), LD2: 33.8% (28.8–37%), LD3: 20.6% (21.5–27.6%), LD4: 7.2% (6.3–12.4%), and LD5: 6.4% (5.4–13.2%). A biopsy specimen showed spindle-shaped cell proliferation covered by non-atypical epithelium. Immunohistochemistry indicated that the stromal cells were positive for smooth muscle markers, including h-caldesmon (Fig. 1a) and α-smooth muscle actin (SMA) (Fig. 1b). Nuclear signal transducer and activator of transcription 6 (STAT6) was also positive (Fig. 1c); however, CD34 (Fig. 1d), CD99 (Fig. 1e), and ALK (Fig. 1f) were negative. Magnetic resonance imaging (MRI) revealed a heterogeneous high-intensity mass measuring 11 × 5 × 7 cm, without myometrial invasion, extending into the uterine cavity and the cervical canal (Fig. 2a). The mass exhibited low intensity with some areas of slightly high signal intensity on T1-weighted imaging (Fig. 2b) and low intensity (0.97×10^{-3} mm^2/s) on apparent diffusion coefficient maps (Fig. 2c). The mass also showed inhomogeneous contrast enhancement (Fig. 2d) and high intensity on diffusion-weighted imaging (DWI) (Fig. 2e). Whole-body 18F-fluorodeoxyglucose (FDG) positron emission tomography -MRI demonstrated increased FDG uptake (maximum standardized uptake value: 6.2) in the uterine tumors (Fig. 2f). Differential diagnoses based on the imaging findings included uterine sarcoma, carcinosarcoma, and adenosarcoma. The patient underwent total abdominal hysterectomy and bilateral adnexectomy. Macroscopically, a polypoid tumor originating from the uterine corpus extended into the cervix (Fig. 3a). Microscopically, the tumor was composed of mesenchymal cells with round or short spindle-shaped nuclei covered by benign glandular epithelium, resembling the intimal surface epithelium, and exhibited a leaf-like architecture (Fig. 3b, c). The density of mesenchymal cells was increased around the glandular epithelium, forming peri-glandular cuffs (Fig. 3b). Mesenchymal cells did not show heterologous differentiation, with

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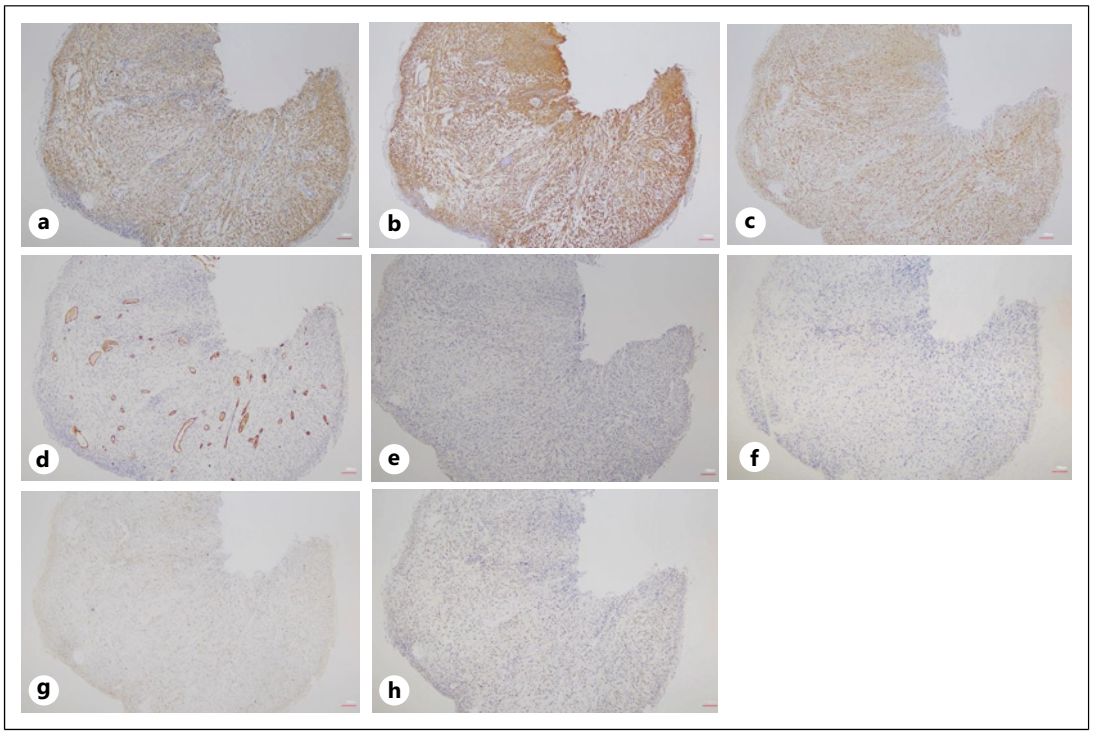

Fig. 1. Immunohistochemical staining of the biopsy tissue showed positivity for h-caldesmon (**a**), α-SMA (**b**), STAT6 (**c**), and MDM2 (**g**). **h** CDK4 was weakly positive. CD34 (**d**), CD99 (**e**), and ALK (**f**) were negative (original magnification ×40).

approximately 10% of the tumor consisting exclusively of mesenchymal cell proliferation (Fig. 3b, d). No tumor necrosis, myometrial invasion, or lymphovascular invasion was observed. Immunohistochemical staining revealed that the mesenchymal regions were positive for h-caldesmon, α-SMA, desmin, CD10, Wilms' tumor 1 (WT1), estrogen receptor (ER), progesterone receptor (PR), wild-type p53, MDM2 (Fig. 3e), CDK4 (Fig. 3f), high mobility group AT-hook 2 (HMGA2) (Fig. 3g), and STAT6 (Fig. 3h). In the area of mesenchymal overgrowth, immunohistochemical staining was positive for h-caldesmon, α-SMA, and desmin, whereas the expression of CD10, WT1, ER, and PR decreased. The mesenchymal cells remained positive for wild-type p53, MDM2 (Fig. 3i), CDK4 (Fig. 3j), HMGA2 (Fig. 3k), and STAT6 (Fig. 3l). The tumor was diagnosed as UA stage IA, pT1aNxM0, without sarcomatous overgrowth. There was no evidence of recurrence 12 months post-surgery (Fig. 4).

Discussion

UA comprises a benign glandular epithelial component and a malignant mesenchymal component [1]. In most cases of UA, the mesenchymal component is of low grade, making the diagnosis of malignancy via biopsy often difficult. Heterologous mesenchymal elements, such as rhabdomyosarcoma, cartilage, fat, and others, are found in 10–15% of cases [5]. Sarcomatous overgrowth, where the sarcomatous component constitutes more than 25% of the tumor, is associated with a poor prognosis. Pathological diagnosis of UA relies on histomorphological examination of tissue specimens [6]. Immunohistochemistry commonly reveals the most common positive markers for UA including CD10 (71–100%), WT1 (79%), and vimentin (86%) [6]. ER and PR are also well expressed [3]. Overexpression of p53 has been

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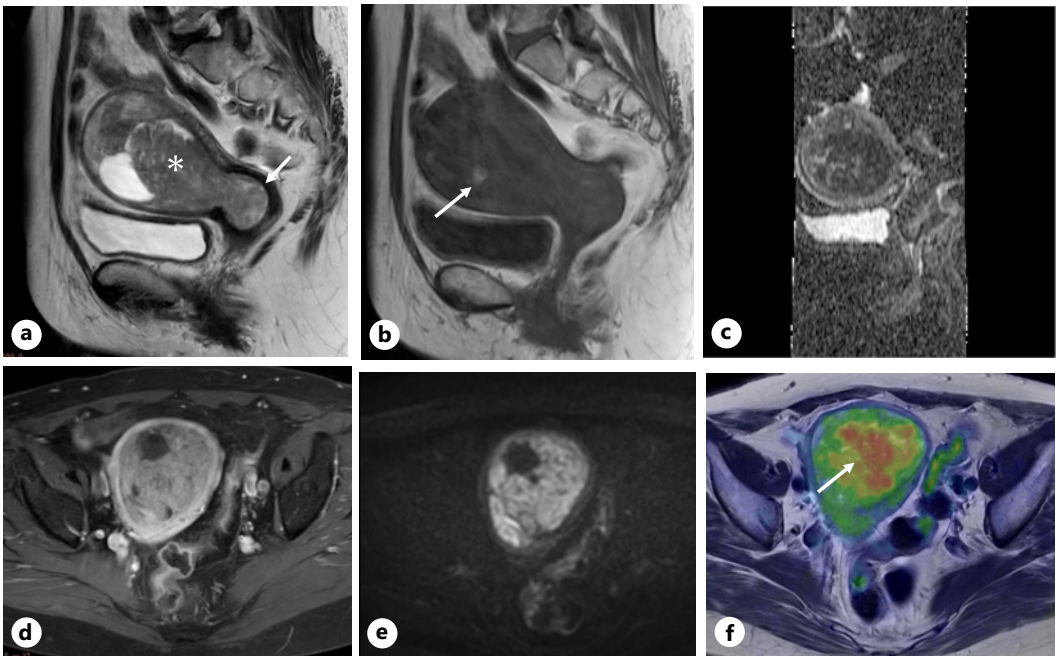

Fig. 2. a Sagittal T2-weighted imaging (repetition time [TR]/echo time [TE], 5,857/100 ms) showed a large, heterogeneous, high-intensity mass without myometrial invasion expanding the uterine cavity (*) and extending into the cervical canal (arrow). **b** The mass showed low signal intensity with areas of slightly high intensity (arrow) on T1-weighted imaging (TR/TE, 625.1/10 ms). **c** The mass showed low intensity (0.97×10^{-3} mm^2/s) on apparent diffusion coefficient maps. **d** Axial diffusion-weighted imaging. The mass showed inhomogeneous contrast on post-contrast fat-suppressed T1-weighted imaging (TR/TE, 587/10 ms). **e** The mass showed high intensity on diffusion-weighted imaging (b = 1,500 s/mm^2, TR/TE, 7,500/93.4 ms). **f** Pelvic 18F-FDG positron emission tomography-MRI (PET-MRI) showed increased FDG uptake (maximum standardized uptake value: 6.2) in the uterine tumor (arrow).

reported in UA cases with sarcomatous overgrowth [3]. Molecular genetic profiling has revealed that UA is genetically heterogeneous. In addition to mutations in genes within the TP53, PI3K/AKT/PTEN pathways, and α-thalassemia/mental retardation syndrome X-linked (ATRX), which are found in uterine sarcomas [7, 8], UA has been reported to have DICER1 and FGFR2 mutations, as well as MDM2/CDK4 gene amplification [9]. However, understanding the relationship between these molecular genetic features and tumor biology remains unclear due to the rarity of UA.

In this case, minimal mesenchymal cell atypia was observed in the tissue biopsy, which did not contribute to the diagnosis of UA based on hematoxylin and eosin staining. Immunohistochemical analysis showed positive staining of smooth muscle markers, h-caldesmon (Fig. 1a), and α-SMA (Fig. 1b), suggesting differential diagnoses including leiomyoma, leiomyosarcoma (LMS), solitary fibrous tumor (SFT), and inflammatory myofibroblastic tumor. Although STAT6 positivity (Fig. 1c) is specific for SFT [10], CD34 (Fig. 1d) and CD99 (Fig. 1e), which are representative markers of SFT [10, 11], were both negative, ruling out SFT. ALK, which is positive in 50% of inflammatory myofibroblastic tumor cases [12], was also negative (Fig. 1f). Combined with the results of MDM2 positivity (Fig. 1g) and weak CDK4 positivity (Fig. 1h), the findings were consistent with UA.

One of the diseases that needs to be differentiated from UA is uterine polyps. Genomic profiling has shown that benign endometrial polyps do not exhibit gene amplification of CDK4 or MDM2 [13]. However, in atypical uterine polyps, that is, polyps with atypical stromal

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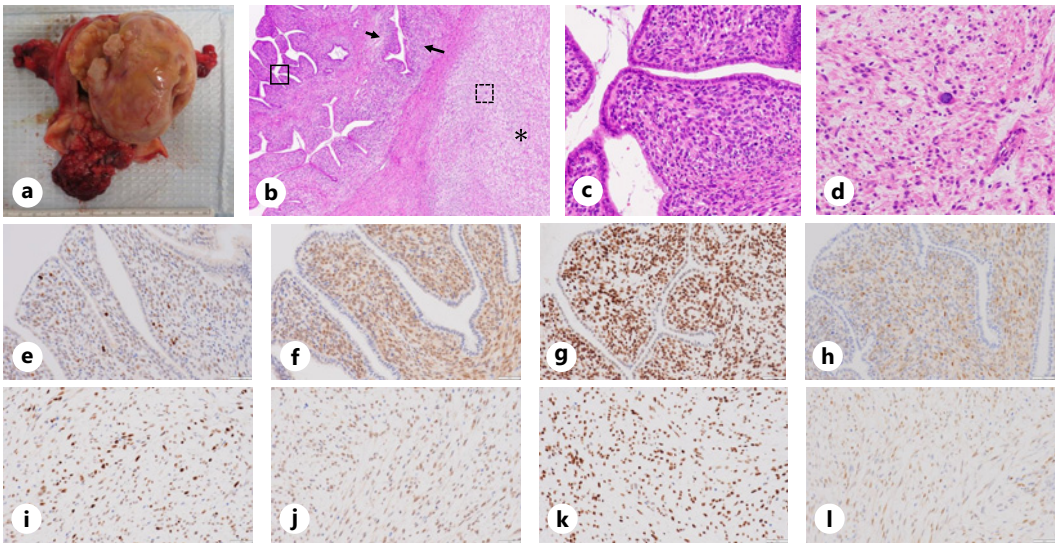

Fig. 3. a Macroscopic findings. A polypoid tumor arises from the uterine corpus and protrudes into the cervix. **b** Hematoxylin and eosin staining. Glandular epithelium is distributed with tubular structures, complex branching structures, and some slit-like structures. Mesenchymal cells proliferate around the glandular epithelium, forming peri-glandular cuffing (arrows). Areas only mesenchymal cells (*) accounted for about 10% of the total and did not correspond to sarcomatous overgrowth (original magnification ×40). **c** The high magnification view of the black square area in (**b**). Leaf-like structures are present. There is no atypia in the epithelium (original magnification ×200). **d** High magnification view of the black dotted square area in (**b**). Nuclear atypia is prominent in areas of mesenchymal cell overgrowth (original magnification ×200). **e–h** The high magnification view of the black square area in (**b**). Immunohistochemical staining shows mesenchymal cells positive for MDM2 (**e**), CDK4 (**f**), HMGA2 (**g**), and STAT6 (**h**). **i–l** The high magnification view of the black dotted square area in (**b**). Mesenchymal cells were diffusely positive for MDM2 (**i**), CDK4 (**j**), HMGA2 (**k**), and STAT6 (**l**).

features that partially overlap morphologically with adenosarcoma, focal gene amplification of CDK4 and MDM2 has been confirmed, suggesting a biological overlap with adenosarcoma [14]. Therefore, while immunostaining for CDK4 and MDM2 may be useful in differentiating benign endometrial polyps, distinguishing atypical uterine polyps remains challenging; therefore, a comprehensive diagnosis considering clinical course and imaging findings is necessary.

MRI, the preferred imaging modality for UA [1], revealed a solitary, externally proliferating polypoid mass within the endometrial cavity. The tumor exhibited a heterogeneous contrast effect and a low apparent diffusion coefficient value (0.97×10^{-3} mm^2/s), raising suspicion of a uterine malignant tumor, including UA [15]. FDG-positron emission tomography-MRI showed strong FDG uptake (standardized uptake value: 6.28) in the tumor (Fig. 2f), further supporting the diagnosis of UA. Microscopically, the tumor was covered by a single layer of glandular epithelial cells, forming a lobulated mass. The stromal cells exhibited peri-glandular cuffing, and the tumor was diagnosed with UA. Approximately 10% of the tumor showed mesenchymal overgrowth, though this did not correspond to sarcomatous overgrowth. Immunohistochemistry revealed that the mesenchymal cells were positive for CD10, WT1, ER, and PR. Their expression decreased in areas of mesenchymal cell overgrowth, suggesting tumor dedifferentiation [1, 6]. Additionally, mesenchymal cells were diffusely positive for MDM2, CDK4, HMGA2, and STAT6, with these staining patterns remaining consistent between areas with and without mesenchymal cell overgrowth (Fig. 3). Studies on the molecular genetic profiling of UA have reported frequent

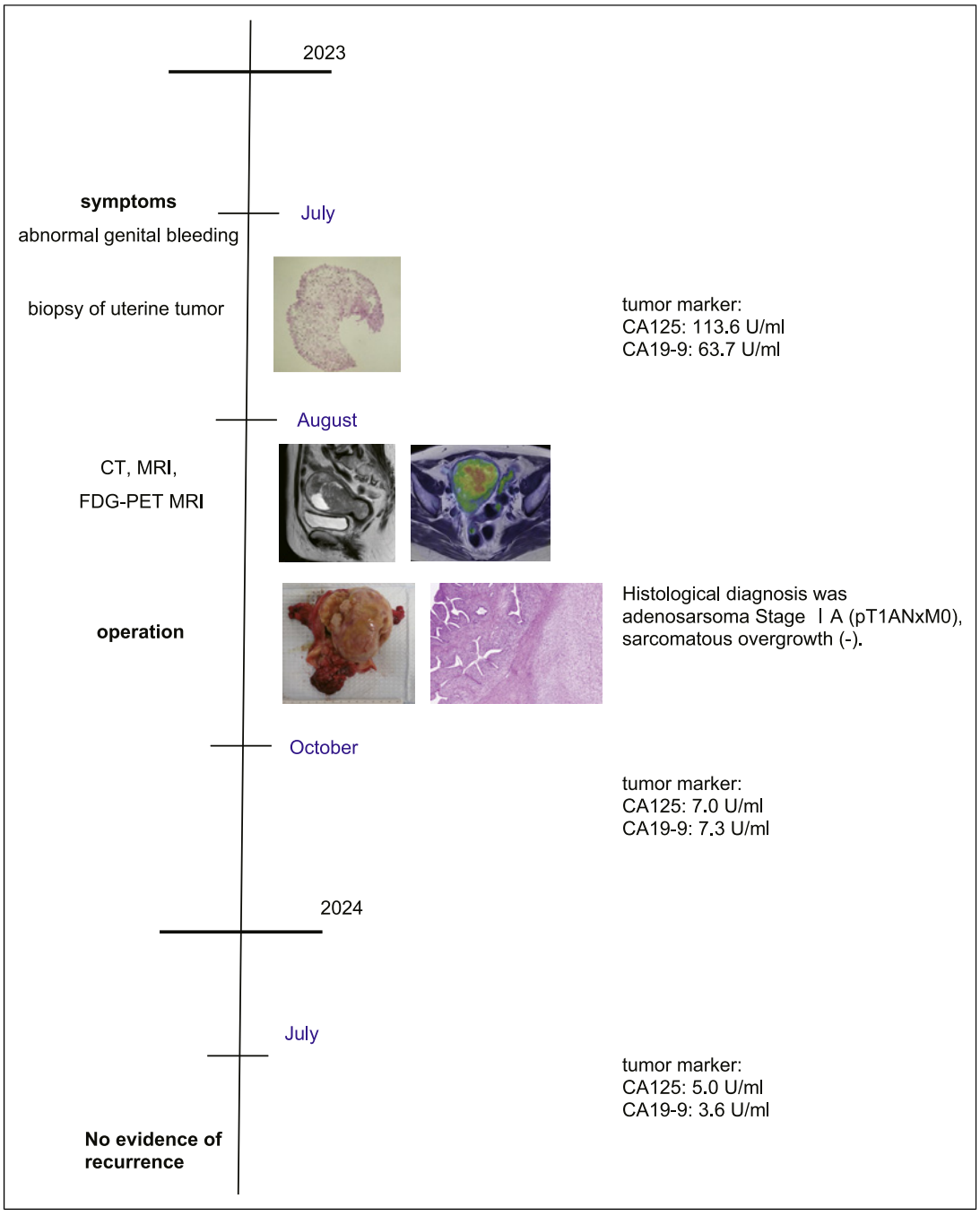

Fig. 4. Clinical timeline of the case report events.

amplification of MDM2 and CDK [1–3, 6, 16]. MDM2 and CDK4 are known oncogenes involved in cell cycle regulation and progression and have been implicated in various human cancers [16]. However, there are few reports on the relationship between MDM2 and CDK4 amplification and UA prognosis. Previous reports on UA with MDM2 and CDK4 amplification indicate that the presence or absence of sarcomatous overgrowth correlates with prognosis, regardless of MDM2 and CDK4 amplification (Table 1). Lee et al. [16] suggested that MDM2 and CDK4 amplification do not correlate with chromosomal instability, which is a poor prognostic factor.

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Table 1. Clinicopathologic features of UAs

Case	Age	Stage[a]	SO	Treatment	Follow-up (months)
Howitt et al. [3] (2015)	56	N/A	–	TAH+BSO, CT	ANED (39.9)
Howitt et al. [3] (2015)	68	N/A	–	TAH+BSO+LN	ANED (207)
Howitt et al. [3] (2015)	77	N/A	–	TAH+BSO+LN+OM+RT	ANED (14.7)
Howitt et al. [3] (2015)	72	N/A	+	TAH+BSO+LN+OM	ANED (181.5)
Bean et al. [17] (2019)	79	IA	–	TAH+BSO	LFU
Bean et al. [17] (2019)	73	IA	–	TAH+BSO+LN+OM+CT	LFU (6 years)
Bean et al. [17] (2019)	48	IVA	N/A	Recurrence excision+CT+RT	DOD (8 years)
Piscuoglio et al. [2] (2016)	N/A	N/A	–	N/A	N/A
Piscuoglio et al. [2] (2016)	N/A	N/A	–	N/A	N/A
Piscuoglio et al. [2] (2016)	N/A	N/A	–	N/A	N/A
Piscuoglio et al. [2] (2016)	N/A	N/A	–	N/A	N/A
Piscuoglio et al. [2] (2016)	N/A	N/A	–	N/A	N/A
Lee et al. [16] (2016)	49	IA	–	TAH+BSO+LN	ANED (107)
Lee et al. [16] (2016)	31	IIIA	–	TAH+BSO+LN+CR, RT	ANED (95)
Lee et al. [16] (2016)	56	IVB	+	Curettage, CT, HT	DOD at 1 week
Lee et al. [16] (2016)	64	IB	+	TAH+BSO+LN, CT, HT	DOD (72)
Lee et al. [16] (2016)	38	IB	+	TAH+BSO+LN+CR, CT, HT, RT	DOD (18)
Present case	72	IA	–	TAH+BSO	ANED (12)

(For treatment) BSO, bilateral salpingo-oophorectomy; CR, cytoreductive surgery; CT, chemotherapy; HT, hormone therapy; LN, lymphadenectomy; OM, omentectomy; RT, radiation therapy; TAH, total abdominal hysterectomy; (for status) ANED, alive with no evidence of disease; DOD, died of disease; LFU, lost to follow up; (others) N/A, not applicable; SO, sarcomatous overgrowth.

[a]FIGO stage.

Piscuoglio et al. [2] investigated gene mutations in 20 patients with UA and reported MDM2, CDK4, and HMGA2 amplification in 5 of these patients. MDM2, CDK4, and HMGA2 are the products of genes located on 12q15, 12q14.1, and 12q14.3, respectively. The 12q13-15 region, which includes several tumor-related genes, is associated with well-differentiated and dedifferentiated liposarcomas, with high CDK4 amplification being a poor prognostic factor in liposarcoma [18]. In our case, the patient exhibited amplification of MDM2, CDK4, and HMGA2, as well as positivity for STAT6, a gene product located on 12q13.3. STAT6 is a typical marker of SFTs, and repetitive intrachromosomal rearrangements on 12q can lead to the formation of the NAB2–STAT6 fusion oncogene [19]. However, PCR did not confirm the amplification of the NAB2–STAT6 fusion oncogene in this case. Since STAT6 is located near MDM2 and CDK4, its expression may be due to passenger mutations [20]. Moreover, STAT6 expression in UA may pose a risk of misdiagnosis of other STAT6-positive spindle cell neoplasms, such as SFT, particularly in biopsy samples. Therefore, diagnosis of UA should be based on the clinical course, imaging findings, and other pathological features.

Sarcomatous overgrowth and lymphovascular invasion are poor prognostic factors for UA [21]. The standard treatment for UA is surgical resection, typically involving total hysterectomy and bilateral salpingo-oophorectomy [1]. Due to the low incidence of lymph node metastasis, lymphadenectomy is generally not recommended unless there is strong clinical suspicion prior to resection. Moreover, there is no evidence supporting the use of adjuvant

radiotherapy, chemotherapy, or hormonal therapy for UA [22], and no prospective or randomized controlled trials evaluating the role of adjuvant chemotherapy in UA [22]. Instead, a sarcoma-based regimen is usually recommended [21]. The therapeutic efficacy of doxorubicin-based chemotherapy regimens and gemcitabine/docetaxel [1] and ifosfamide has been reported in cases of recurrence or metastasis [21].

The prognosis for uterine sarcomas is generally poor; due to the rarity and heterogeneity of these tumors, no definitive biomarkers for diagnosis or prognosis have been established. However, several candidate biomarkers have been identified, particularly for uterine LMS. Mutations and deletions in RB1, TP53, and PTEN, along with alterations in ATRX and frequent changes in the mediator complex subunit 12 (MED12), have been noted [7]. Specifically, MED12 serves as a valuable biomarker for diagnosing tumors originating from uterine LMS and is associated with a relatively favorable prognosis [8]. In contrast, TP53 and ATRX mutations are likely pivotal in LMS pathogenesis and correlate with poorer prognoses [8]. Furthermore, a notable subset of patients carrying putative BRCA-associated mutations could benefit from PARP inhibitor therapy [7]. As our understanding of gene mutations in uterine LMS evolves, the biological characteristics of UA may become clearer, which may further refine treatment strategies for these tumors. In clinical trials of other tumor types, selective therapeutic agents targeting MDM2 or CDK4 have shown some efficacy [16]. Testing for MDM2 and CDK4 amplification may expand treatment options for UA.

This study has some limitations. First, the expression of MDM2, CDK4, HMGA2, and STAT6 observed in this case was based on uterine immunostaining and hence did not confirm gene amplification. Second, some cases (shown in Table 1) exhibited genetic mutations in TP53 and ATRX, which are associated with tumor biology [17]. Therefore, these genetic abnormalities may have affected the patient's prognosis.

In conclusion, UA is suggested to be a genetically heterogeneous mesenchymal neoplasm. However, due to its rarity, little is known about the relationship between its molecular genetic features and tumor biology. The pathological diagnosis of UA primarily relies on histomorphological examinations, with immunohistochemistry serving as an adjunct. Immunohistochemical findings of MDM2 and CDK4 may provide insights into the molecular genetic features of UA. Accumulating more cases could help elucidate the relationship between the expression of these genes and tumor biology, potentially leading to the development of further effective treatment options for UA.

Acknowledgments

We extend our gratitude to the patient and their family for their cooperation and consent to share this case, which has made this report possible.

Statement of Ethics

Written informed consent was obtained from the patient for the publication of this case. This research protocol was reviewed by Institutional Ethics Committee of the University of Fukui and was exempted from the need for approval.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

Y.M. reviewed the data and literature and wrote the manuscript. A.Y. advised on the pathological findings in this case. H.N. was involved in the case treatment and the surgeon. A.S. was involved in case management and provided practical clinical findings. M.F. advised on pathological findings and provided resources and expertise for genetic analysis. M.O. and Y.Y. contributed to the manuscript revision. All the authors have read and approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author upon reasonable request.

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