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Case Report

Clear Cell Carcinoma Arising in Low-Grade Mullerian Adenosarcoma: First Reported Case with Insight into Molecular Profile

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Uterus · Adenosarcoma · Clear cell carcinoma · Immunohistochemistry · Next-generation sequencing

Abstract
Uterine adenosarcoma (AS) is a rare biphasic neoplasm composed of a malignant, usually low-grade stromal component and benign epithelial component, usually endometrioid. Pathogenesis is unknown; some cases are undoubtably associated with tamoxifen use. Endometrial clear cell carcinoma (CCC) is an aggressive subtype of endometrial cancer, accounting for less than 10% of all uterine carcinomas. The etiology is unknown but can rarely be associated with Lynch syndrome and tamoxifen administration. The development of a composite neoplasm consisting of adenocarcinoma in AS is extremely rare. Endometrioid carcinoma typically represents the epithelial component of the composite tumor. Here we present the very first case of composite tumor, namely, AS with CCC in which next-generation sequencing was performed. Patient was an 85-year-old woman treated with tamoxifen for 5 years. To better understand the pathobiology of two tumors, a targeted genomic analysis of both components was performed. We found seven identical somatic variants in the samples of both tumors, indicating that the tumors have a high probability of having the same origin. Dual amplification of CDK4 and MDM2 was the most likely primary cause of tumor formation, but also one driver variant in the DHX15 gene that was present in both tumor components, suggesting that DHX15 may play an important role in the initiation and development of sarcoma and carcinoma. The patient is followed by regular clinical controls and is alive without signs of disease recurrence 18 months after surgery.

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Introduction

Uterine adenosarcoma (AS) is a rare biphasic neoplasm with «phyllodes-like» architecture. It is composed of a malignant stromal component, usually low-grade, and a benign to mildly atypical epithelial component [1]. The glandular component is typically endometrioid in type. Most often, AS develops in postmenopausal women in the uterine corpus, although it can develop in other parts of the female genital tract as well as outside of it [2]. The pathogenesis is unknown; however, some cases are undoubtably associated with the tamoxifen use [3]. On the molecular level, there are no specific alterations. Amplification of 8q13 and high-level copy number gains of MYBL1, KRAS, PTEN, and PIK3CA mutations are sometimes seen, as well as NCOA2/3 fusions; TP53 mutation is rare and associated with sarcomatous overgrowth [1]. Compared to the prognosis of other gynecological sarcomas, the prognosis is favorable because the majority of women with AS present with early-stage disease. Five-year survival for patients with stage I to stage II disease is 63–84%, for stage III 48%, and for stage IV 15% [4].

Endometrial clear cell carcinoma (CCC) is an aggressive subtype of endometrial cancer, accounting for less than 10% of all uterine carcinomas [1]. Endometrial CCC usually presents with abnormal uterine bleeding in older postmenopausal women [1]. Etiology is unknown but can rarely be associated with Lynch syndrome [1]. There is no known specific molecular profile; recurrent mutations of TP53, PPP2R1A, PIK3CA, PIK3R1, KRAS, and ARID1A are the most frequent [1].

The development of a composite/collisional neoplasm consisting of adenocarcinoma in AS is extremely rare. Until recently, only single case reports have been published, endometrioid carcinoma being an epithelial component of collisional tumor [5]. CCC as a collisional neoplasm in AS has never been described so far. To better understand the pathobiology of these two primary tumors and address their eventual clonal relationship, we performed targeted genomic analysis of both components.

Case Report

An 85-year-old woman, gravida 2, para 2, was referred to gynecological oncology department after uterine curettage in a secondary hospital due to postmenopausal uterine bleeding. Her familiar anamnesis was uneventful. She was diagnosed with breast cancer at the age of 69. Mastectomy with sentinel node biopsy was performed. Histological examination showed invasive ductal carcinoma grade II, measuring 1.4 cm, with negative sentinel node biopsy. Hormone receptor status was positive and Her-2 was negative. The multidisciplinary team for breast carcinoma decided for 5 years of tamoxifen therapy. She has never experienced recurrence or progression of the disease. Computed tomography of the abdomen showed a uterine tumor measuring 5.5 × 6.3 × 7.2 cm with a multiseptated cystic appearance and heterogeneous solid components. On computed tomography scans, there were no signs of progression of the disease outside the uterus. Hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and pelvic lymphadenectomy was performed. Macroscopically, the uterus was enlarged measuring 9 × 8 × 4 cm, weighing 160 g. Uterine cavity was completely filled with tumor tissue of harder consistency and leaf-like architecture. Microscopically (Fig. 1), the tumor showed a «phyllodes-like» architecture (Fig. 1a) with periglandular stromal condensation. Stromal cells (Fig. 1b) were spindled with low-grade atypia and increased mitotic activity (up to 10 mitosis/mm^2). The epithelial component on the surface of the leaves was cuboid to cylindrical with no architectural complexity or cytologic atypia. Only at the very top of the AS there was an approximately 1.5 cm large area of atypical

glandular proliferation consisting of back-to-back lying glands covered with cells with round vesicular nuclei with 1–2 small, membrane-bound nucleoli and copious clear to slightly eosinophilic cytoplasms (Fig. 1c). Immunohistochemically, they were positive for Napsin A (Fig. 1d) and P504s, weakly for ER, negative for PR. p53 was expressed according to wild type in both components. The expression of mismatch repair proteins was intact in both components. The POLE gene was wild-type. There was no lymphovascular invasion or cervical infiltration. Based on the morphology and immunoprofile, the carcinoma was classified as CCC. AS infiltrated approximately slightly more than half of the myometrium and was classified as T1c according to the classification of TNM and IC according to FIGO. CCC was in stage T1a according to TNM and IA according to FIGO. Altogether, 11 lymph nodes have been isolated being negative. The omentum was not infiltrated. The multidisciplinary team for gynecologic oncology decided that, regarding the age of the patient and the stage of the disease, adjuvant treatment is not necessary.

In the meantime, targeted genomic analysis was performed from both components to address their eventual clonal relationship. All precautionary measures have been taken to prevent contamination of either component. Genomic DNA and total RNA were isolated from a FFPE-tissue tumor using MagMax DNA/RNA kit (Thermo Fisher Scientific, MA, USA) according to established laboratory protocol. The extracted was quantified using the Qubit dsDNA HS Assay Kit (Thermo Fisher) and the Qubit 3.0 Fluorometer (Thermo Fisher). Targeted next-generation sequencing (NGS) of selected tumor DNA samples was performed using TruSight Oncology 500 (Illumina, San Diego, USA) according to the manufacturer's protocol. The samples were sequenced in the Illumina NextSeq 550 Sequencing System with the NextSeq Reagent Kit v3 (Illumina) following the manufacturer's protocol and recommendations for quality control. Read alignment to the hg19 reference genome and variant calling was performed using TruSight Oncology 500 v2.1 Local App software (Illumina). The variant annotation was performed using the Variant Studio 3.0 software and the Alamut Visual Plus v1.5.1 software. Samples were successfully sequenced if >95% of the targeted regions were covered >×250. The tumor samples tested were covered between 1,800 and 2,100 times. Single nucleotide variants, insertions/deletions (indels), copy number variations, and tumor mutational burden (TMB) were determined. Variants and indels with ≥250 reads and allele frequency ≥5% were called positive. Copy number variations were considered as gain (amplified) when more than 2.5-fold change was determined and passed quality filter having score 157. TMB was defined as the number of somatic non-synonymous or non-synonymous and synonymous base substitution and small indels (insertions and deletions less than 20 nucleotides) in the coding regions per megabase (mut/Mb). Furthermore, for both tumor components, gene fusions were detected using Archer FusionPlex Sarcoma (ArcherDX, Boulder, CO, USA), covering 26 genes involved in sarcoma-associated fusions. Data analysis (variant and/or fusion calling) was performed using Suite_Analysis v6.0 (ArcherDX). Variants detected in tumor samples were checked for their description in OncoKB and COSMIC database. We performed an in silico prediction analysis using AlignGVGD and SIFT. Furthermore, Cancer Genome Interpreter was used to determine the oncogenic prediction of variant as driver or passenger. The variants are described according to the HGVS v20.05 nomenclature. After data analysis (review), variants were confirmed as somatic or germline using the gnomAD database. Germline variants were excluded from further analysis.

We found 7 identical somatic variants in the samples of both tumors, indicating that the tumors have a high probability of having the same origin (Table 1; Fig. 2). Dual amplification of CDK4 and MDM2 is the most likely primary cause of tumor formation. Additionally, we have

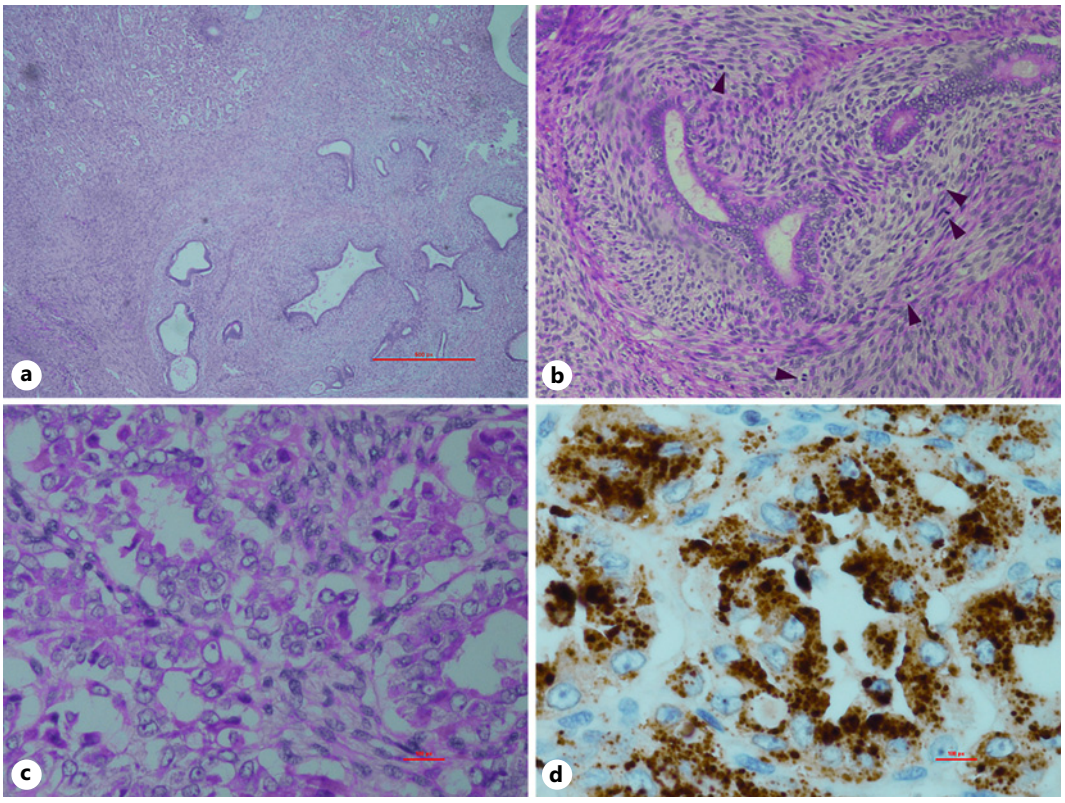

Fig. 1. a AS (lower part) with CCC (upper part); H&E. ×10. **b** AS – numerous mitotic figures in stromal component indicated by arrowheads; H&E. ×10. **c** CCC, H&E. ×20. **d** Napsin A immunohistochemistry in CCC, ×20.

identified 7 additional variants in the carcinoma component and 3 in the sarcoma component (Table 1; Fig. 2). The patient was followed by regular clinical controls, and 18 months after surgery, she is alive without any symptoms or signs of recurrence of the disease.

Discussion

Mullerian AS is a rare and unusual female genital tract tumor characterized by a malignant stromal component, usually of low-grade type, and an epithelial component, usually endometrioid [1]. The epithelial component is by far benign to at most mildly atypical. Extremely rarely can cytological atypia and/or architectural complexity satisfy the diagnosis of atypical hyperplasia.

The development of adenocarcinoma within AS is distinctly uncommon. Until recently, this unusual phenomenon has been described only in the form of single-case reports [6, 7]. In 2021, El Hallani et al. [5] published a series of 26 combined Mullerian AS and adenocarcinomas that included only cases of intimate admixture of both components. Twenty-two cases (84%) were located in the uterus, the rest in the ovary and pelvis. The most common type of adenocarcinoma that arises in AS was endometrioid being present in 25/26 (96%) of all cases, while one case was dedifferentiated carcinoma. In other words, other than endometrioid types of carcinomas are extremely rare. Bai et al. [7] reported a case of dedifferentiated carcinoma associated with AS, while CCC has never been described so far.

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Table 1. Genotyping results of endometrial tumor with two components: AS and CCC

Tumor component	Gene	Variant	VAF	In silico prediction		Cancer Genome Interpreter	OncoKB description	COSMIC database
		c. and p. notation	fold amplification	AlignGVGD	SIFT	oncogenic prediction		
Both tumor components	MDM2 (NM_002392.5)	Amplification	AS: 16.7-fold CCC: 12.3-fold	N/A	N/A	Predicted to be oncogenic	Oncogenic	Gain of function (endometrium: 0.68% of tested samples)
	CDK4 (NM_000075.3)	Amplification	AS: 3.1-fold CCC: 2.7-fold	N/A	N/A	Predicted to be oncogenic	Oncogenic	Gain of function (endometrium:/)
	ERBB3 (NM_001982.3)	Amplification	AS: 3.0-fold CCC: 2.7-fold	N/A	N/A	Predicted passenger	Oncogenic	Gain of function (endometrium: 1.16% of tested samples)
	DHX15 (NM_001358.2)	c.16C>T p.(Arg6Trp) (R6W)	AS: 46.9% CCC: 36.5%	Class C0 (GV: 241.31, GD: 94.79)	Deleterious (score: 0.00, median: 4.32)	Predicted driver	Not described	Not described
	IGF1R (NM_000875.3)	c.14C>G p.(Ser5Cys) (S5c)	AS: 48.1% CCC: 38.3%	Class C0 (GV: 167.89, GD: 91.34)	Tolerated (score: 0.07, median: 4.32)	Predicted passenger	Not described	Not described
	NRG1 (NM_004495.3)	c.142G>T p.(Ala48Ser) (A48S)	AS: 11.1% CCC: 23.2%	Class C0 (GV: 171.12, GD: 0.00)	Tolerated (score: 0.73, median: 2.95)	Predicted passenger	Not described	Not described
	NUTM1 (NM_175741.1)	c.3215C>G p.(Ser1072Cys) (S1072c)	AS: 6.6% CCC: 15.6%	Class C0 (GV: 221.66, GD: 0.00)	Tolerated (score: 0.14, median: 3.75)	Predicted passenger	Not described	Not described
AS	HGF (NM_000601.4)	c.1278C>T p.(Ile426 =)	10.3%	/	/	N/A	Not described	Prediction: N/A Endometrium (n = 1)
	IRF2 (NM_002199.3)	c.88–3C>T p.?	21.6%	/	/	N/A	Not described	Not described
	NOTCH4 (NM_004557.3)	c.318C>G p.(Leu106 =)	6.0%	/	/	Non-affecting	Not described	Not described
	NTRK2 (NM_006180.3)	c.2472G>C p.(Gln824His) (Q824H)	8.6%	Class C0 (GV: 112.44, GD: 0.00)	Deleterious (score: 0.04, median: 4.32)	Predicted passenger	Not described	Not described
	TMB(NS) = 4 TMB(NS + S) = 6							

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Table 1 (continued)

Tumor component	Gene	Variant	VAF	In silico prediction		Cancer Genome Interpreter	OncoKB description	COSMIC database
		c. and p. notation	fold amplification	AlignGVGD	SIFT	oncogenic prediction		
CCC	DHX15 (NM_001358.2)	c.761A>T p.(Tyr254Phe) (Y254F)	VAF = 6.8%	Class C15 (GV: 0.00, GD: 21.61)	Deleterious (score: 0.00, median: 4.32)	Predicted driver	Not described	Not described
	JAK1 (NM_002227.2)	c.2956C>T p.(Gln986*) (Q986*)	VAF = 9.6%	/	/	Predicted passenger	Likely oncogenic	Pathogenic (score 0.98) Breast (n = 2)
	NOTCH2 (NM_024408.3)	c.7277C>G p.(Ser2426*) (S2426*)	VAF = 12.6%	/	/	N/A	Likely oncogenic	Not described
	PHF6 (NM_001015877.1)	c.571G>A p.(Glu191Lys) (E191K)	VAF = 10.5%	Class C55 (GV: 0.00, GD: 56.87)	Deleterious (score: 0, median: 4.32)	Predicted passenger	Not described	Not described
	PPP2R1A (NM_014225.5)	c.767C>T p.(Ser256Phe) (S256f)	VAF = 11.3%	Class C15 (GV: 99.13, GD: 111.66)	Deleterious (score: 0.01, median: 3.67)	Predicted driver	Likely oncogenic	Pathogenic (score 0.91) Endometrium (n = 34); breast (n = 3)
	PPP2R1A (NM_014225.5)	c.1686C>T p.(Pro562 =)	VAF = 12.2%	/	/	N/A	Not described	Not described
	SPOP (NM_001007228.1)	c.136G>A p.(Glu46Lys) (E46K)	VAF = 19.7%	Class C0 (GV: 112.66, GD: 46.08)	Tolerated (score: 0.14, median: 2.93)	Predicted passenger	Not described	Pathogenic (score 0.91) Endometrium (n = 3) Ovary (n = 1)
	TMB(NS) = 11 TMB(NS + S) = 14							

TMB (NS) – tumor mutational burden was defined as the number of somatic non-synonymous base substitution and small indels (insertions and deletions less than 20 nucleotides) in coding regions per megabase (mut/Mb); TMB (NS + S) – tumor mutational burden was defined as the number of somatic non-synonymous and synonymous base substitution and small indels (insertions and deletions less than 20 nucleotides) in coding regions per megabase (mut/Mb). VAF, variant allele frequency; N/A, not applicable; TMB, tumor mutational burden.

Searching the recent literature on CCC that arises in mixed epithelial and mesenchymal tumors of the female genital tract resulted in one single case describing CCC that arises in endometrial adenofibroma [8]. According to the classification of tumors in the female genital tract [9], adenofibroma was defined as a subtype of mixed epithelial and mesenchymal tumors composed of benign stromal and Mullerian epithelial components. The diagnosis of adenofibroma has been removed from the newest edition of the WHO classification [1]. Basically, it is believed that most tumors diagnosed as adenofibromas, in fact, represent either low-grade AS or benign endometrial polyps. According to the original description of the mesenchymal component of the collisional tumor described by Mikami et al. [8], it is more probable that the tumor described represented an endometrial polyp in which CCC arose.

In terms of etiology, the coexistence of AS and endometrioid carcinoma is no surprise, as both are linked to hyperestrogenism, including tamoxifen treatment. CCC, on the other hand, is estrogen-independent. However, the use of tamoxifen has been implicated in the etiology of a subset of these tumors [3]. CCC in extrauterine sites is often associated with endometriosis, although endometriosis does not appear to be a risk factor for the development of CCC of the uterus [1]. Therefore, the development of both components of the collisional tumor in our patient could be related to the use of tamoxifen.

Of all the cases described so far, only three have been tested using NGS [5, 7]. In two cases described by El Hallani et al. [5], the targeted NGS showed identical mutations in both components, AS and endometrioid carcinoma (KRAS (p.G12V) in one and KRAS (p.G13D), PIK3CA (p.E542K), and FBXW7 (p.R479G) in the second case). Bai et al. [7] identified the same mutations in three-component tumor, namely, AS, endometrioid carcinoma, and dedifferentiated carcinoma (KRAS [p.G12D], PIK3CA [p.R88Q], and PTEN [p.130G]). These results suggested the clonal origin of three morphologically different neoplastic components. Our molecular data indicate that tumors have a high probability of having the same origin. Three of the seven variants are oncogenic or driver variants according to the Cancer Genome Interpreter (Table 1). The amplification of the MDM2 and CDK4 genes has been detected in both tumor components. These two genes play key roles in cancer development – CDK4, a key regulator of cell cycle progression, and MDM2, a proto-oncogene involved in the regulation of p53 signaling [10, 11]. Dual amplification of CDK4 and MDM2 is the most likely primary cause of tumor formation. Furthermore, we have identified 7 additional variants in the carcinoma component, 2 of which are according to the Cancer Genome Interpreter driver variants. Interestingly, we detected a driver variant in the DHX15 gene in both tumor components and an additional driver variant in the DHX15 gene only in the carcinoma component. This result suggests that DHX15 may play an important role in the initiation and development of sarcoma and carcinoma. Otherwise, DHX15 is a member of the DEAH-box RNA helicase family, is located in the nucleus, and is involved in the modulation of pre-mRNA splicing by its helicase activities. Several studies suggest that mutations or abnormal expression of DHX15 may contribute to carcinogenesis [12, 13]. Furthermore, a driver variant in the PPP2R1A gene was detected in the carcinoma component, which is consistent with previous reports describing the PPP2R1A gene as one of the most frequently affected by mutations in endometrial CCC [14]. The TMB in the carcinoma component was 11 and 14 which is more than two times higher than in the sarcoma component (Table 1). In the sarcoma component, we detected 3 additional variants that have not been previously described in the COSMIC database and for which we cannot clearly define their role in the tumor (Table 1). However, these are likely to be passenger variants with no major impact on cell differentiation and their malignant potential. As expected, given the less aggressive histological type of tumor, we also obtained lower TMB values (4 and 6) (Table 1).

With the combination of whole-exome, targeted capture, massively parallel sequencing, and RNA sequencing, Piscuoglio et al. [15] showed that uterine AS are mesenchymal

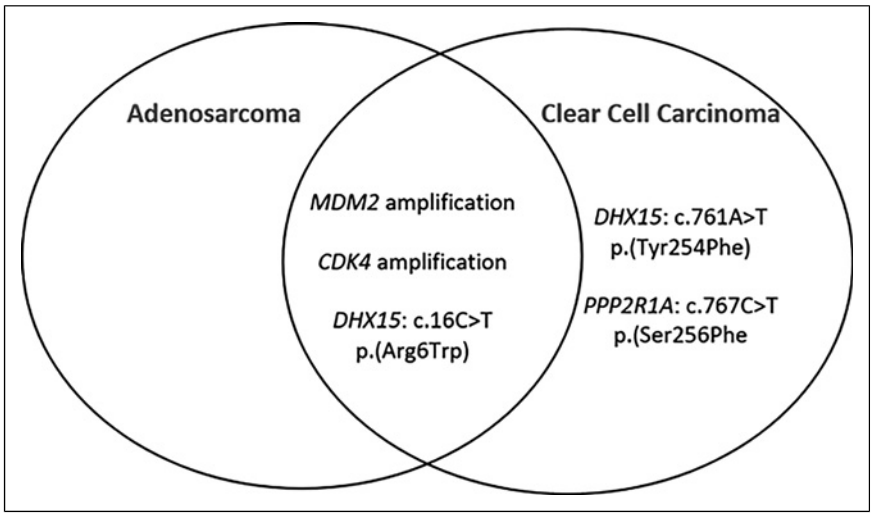

Fig. 2. Tumor variants with predicted oncogenic/driver potential according to Cancer Genome Interpreter.

neoplasms and that benign epithelial components do not harbor clonal somatic genetic alterations. However, in our case, analysis of the benign epithelial component was not performed. As well, one could hypothesize that our case represents a case of carcinosarcoma since clonal origin of both components is probable. However, these tumors have clear morphology of AS and CCC and TMBs in carcinoma and sarcoma components are distinctly different. Furthermore, *TP53*, *PIK3CA*, and *PIK3R1* mutations which are the most frequent mutations in carcinosarcomas were not present in our case.

The most important differential diagnosis for composite AS and carcinoma is carcinosarcoma. The sarcomatous component of carcinosarcoma is high-grade, usually pleomorphic, while AS usually consists of a low-grade stromal component. The stromal component of AS is only rarely high-grade and can include heterologous elements, most often rhabdomyoblastic. The epithelial component of carcinosarcoma is high-grade serous, while in AS, it is low-grade endometrioid. In addition, in carcinosarcoma, there is no benign glandular component present that is an unavoidable feature of AS. Although both are biphasic tumors, it is very important to distinguish one from the other since the prognosis is different. The prognosis of AS is generally favorable compared to other gynecological sarcomas, and in the case of associated carcinoma, the latter is usually of low stage [5]. Misdiagnosis of composite AS-carcinoma as carcinosarcoma, which has also occurred in the curettage specimen of our patient, could result in inappropriately aggressive treatment.

In conclusion, here we present the very first case of uterine AS in which CCC arose. CCC as a collisional neoplasm in AS has never been described so far. Targeted genomic analysis of both components was also performed, indicating that the tumors have a high probability of having the same origin. 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/10.1159/000531988).

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The study was reviewed and approved by the Ethical Committee of the Institute of Oncology Ljubljana (approval number ERIDEK 0006/23).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors have made substantial contributions to the conception of the work, acquisition, analysis, and interpretation of data for the work. All authors approved the final version of the manuscript. G.G.: biopsy interpretation, data collection, and writing of the initial draft of the manuscript; P.S. and S.N.: molecular testing, interpretation of the data, and writing of the manuscript; and G.V.: collection of data, writing, and revision of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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