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An uncommon case of POLE mutated uterine carcinosarcoma – complemented by a review of literature

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ABSTRACT

Carcinosarcomas are high-grade endometrial cancers which enclose mesenchymal and epithelial differentiated components. The vast majority of these cancers belong to the p53 abnormal molecular subgroup and usually come with an unfavorable prognosis. POLE mutant carcinosarcomas are a rarity and only make up about 5% of this histologic subtype. Recent literature even suggests that this number is still an overestimation and the result of misclassification of undifferentiated or dedifferentiated endometrial cancers.

Here we present a case of a 56-years old patient diagnosed with carcinosarcoma of the uterus. Hysterectomy, bilateral salpingo-oophorectomy with pelvic lymph node staging was performed and complete molecular workup of the tumor revealed an abnormal p53 expression as well as a pathologic POLE mutation. NGS was performed separately on the epithelial and mesenchymal component of this high-grade cancer and both components shared two identical *POLE* mutations, a known pathologic mutation, and a variant of unknown significance (VUS). This finding hints to a clonal origin of both histologic components of this tumor and supports conversion theory as mechanism of carcinosarcoma emergence. The cancer was correctly staged as FIGO 2023 Stage $IAm_{POLEmut}$ and according to ESGO-ESTRO-ESP guidelines adjuvant chemotherapy no longer considered and our patient entered follow-up after a detailed discussion.

1. Introduction

Implementation of molecular subgroups in endometrial cancer in 2013 marked the beginning of a new era for this very common gynecologic malignancy. Since then, the disease has gained high granularity and molecular classification was implemented into clinical routine (Getz, 2013). The new FIGO classification system for endometrial cancer, published in 2023, incorporates molecular markers into tumor staging. For the first time in a gynecologic cancer, risk factors such as lymph-vascular space invasion (LVSI), histologic subtype, p53 abnormality or polymerase-epsilon exonuclease domain mutation (*POLE*-EDM) alter staging directly (Berek, 2023).

Carcinosarcoma is a unique type of cancer of the endometrium as it consists of epithelial and mesenchymal malignant components. It is considered a high-risk histology and although it accounts for only about 5 % of uterine cancers, it is responsible for 10–15 % of the deaths related to uterine malignancies. Various theories have been postulated as to the origin of this tumor. The theory supported by the most current evidence is the conversion theory, which states that the mesenchymal part of carcinosarcoma is a metaplastic constituent derived from epithelial malignant tissue that undergoes epithelial-to-mesenchymal transition. The carcinomatous component is typically a high-grade cancer and may be of endometrioid, serous, clear cell, mixed or undifferentiated histology. If the sarcomatous component mimics tissue that is inert to the uterus, such as leiomyosarcoma, fibrosarcoma or endometrial stromal sarcoma, it is called homologous. Tumors that mimic mesenchymal tissue that is not found in a normal uterus, like chondrosarcoma, rhabdomyosarcoma, or osteosarcoma, are referred to as heterologous (Pezzicoli, 2021; Bogani, 2023).

The case reported herein describes a patient with a carcinosarcoma expressing an unusual molecular profile. Treatment decisions made in this case follow current recommendations and differ greatly from what was considered standard of care a few years ago.

2. Case report

A 56-year-old patient was sent to a district hospital for dilation and curettage after her gynecologist in office detected an abnormal

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endometrium during routine sonography. The pathology report of the curettage material described a poorly differentiated carcinoma with malignant mesenchymal components and thus diagnosed as a carcinosarcoma of the endometrium. Immunohistochemistry (IHC) following the ProMisE criteria showed regular expression of mismatch repair proteins MLH1, PMS2, MSH2 and MSH6 but aberrant p53 expression. However, determination of *POLE* mutational status was uncommon in the district hospital. Due to the high-risk histology and the aberrant p53 status the patient was told that she will need adjuvant chemotherapy. To get a second opinion, the patient was referred to the Department of Gynecology and Obstetrics at the University Hospital Innsbruck, by her gynecologist in office. PET-CT showed hypermetabolic activity in the uterine corpus but no evidence of disease beyond the uterus or distant metastasis. After discussion of all results, the interdisciplinary tumor board recommended total laparoscopic hysterectomy with bilateral salpingo-oophorectomy and sentinel lymph node (SLN) biopsies. Because indocyanin green (ICG) sentinel identification failed on both side a bilateral systematic pelvic lymph node dissection was performed.

The initial pathology report of the hysterectomy specimen described a carcinosarcoma of the endometrium, infiltrating the inner half of the myometrium. Immunohistochemistry showed differences in protein expression in the epithelial and the mesenchymal tumor component. The mesenchymal component showed aberrant p53 expression (p53abn) and a negative estrogen- and progesterone-receptor status while the carcinoma component expressed a p53 wildtype pattern and showed positivity for mentioned hormone receptors (Fig. 1). However, L1CAM, a biomarker for high-risk clinical behavior of endometrial cancers was negative in both tumor components (Zeimet, 2013). Both components showed regular expression of the mismatch repair proteins. No lymph-vascular space invasion was detected and no lymph node metastases were found. Before the next generation sequencing (NGS) results were available, the tumor was classified as stage IIC according to FIGO Classification of Endometrial Cancer 2023 due to its high-risk histology.

Once this first histologic report was available, the diagnosis was discussed with the patient. It was explained that besides the small anatomical spread of the tumor, the histological subtype and the p53 mutation were risk factors for disease recurrence and adjuvant chemotherapy would most likely be required.

In the meantime, a more detailed molecular pathological report became available. NGS utilizing AmpliSeq for Illumina Custom Cancer Hotspot Panel v2, was performed and showed a pathological *POLE*-EDM (p.V411L) with an allele frequency of 39 % in a specimen with 80 % tumor content. Furthermore, pathologic mutations were found in *PTEN*,

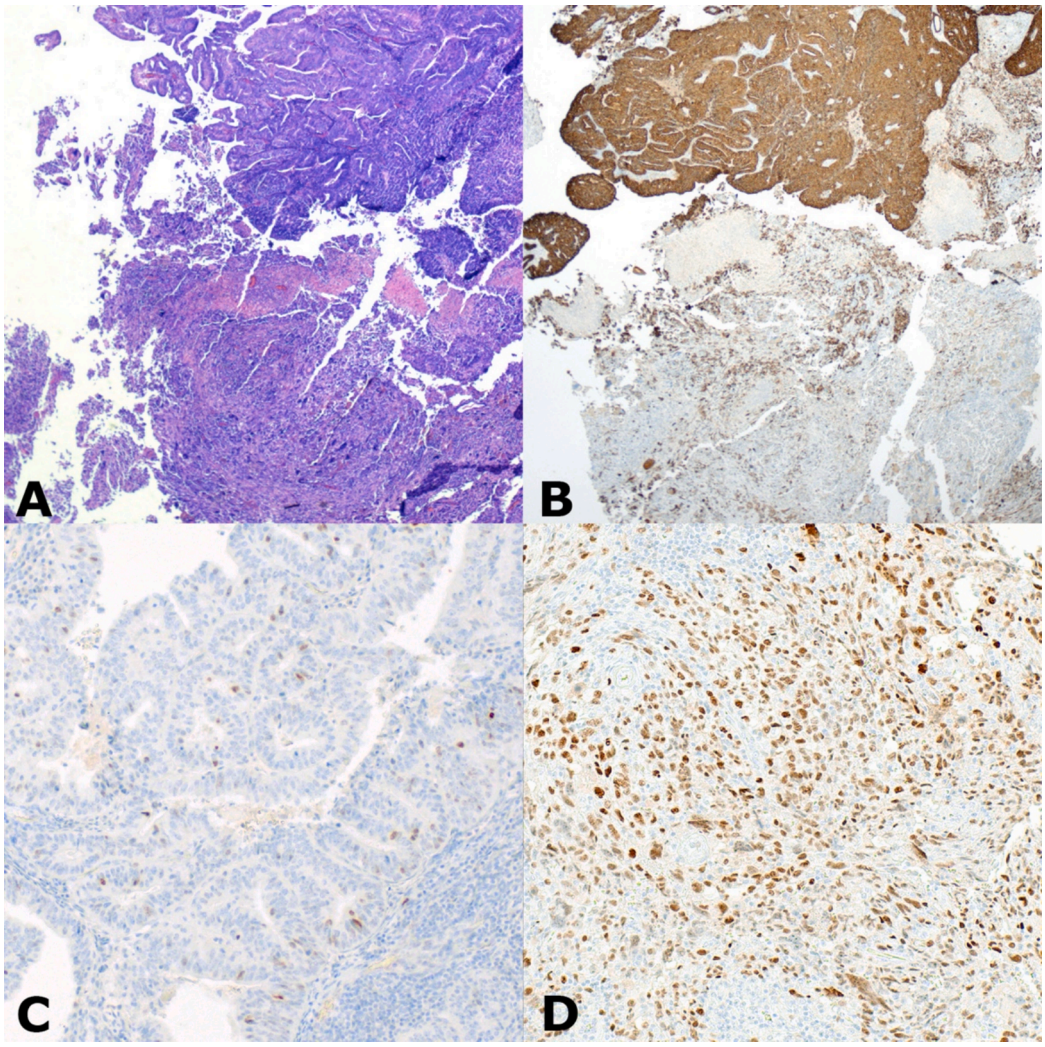

Fig. 1. A: hematoxylin and eosin stain depicting the epithelial and the mesenchymal component of the carcinosarcoma, The epithelial component is composed of tubular structures lined by cells with an altered nucleus:cytoplasm ratio and enlarged nuclei with prominent nucleoli. The adjacent are areas of a pleomorphic sarcoma exhibit cells with enlarged, hyperchromatic, and pleomorphic nuclei embedded in abundant cytoplasm. B: Immunohistochemistry stain for Cytokeratin differentiating the epithelial and the mesenchymal component, C: Immunohistochemistry for p53 depicting a wild-type expression pattern in the epithelial component, D: Immunohistochemistry for p53 depicting an abnormal overexpression pattern in the mesenchymal component.

PIK3CA, *CTNNB1* and *TP53* as well as aberrations of unknown significance in a large number of genes. Due to bi-histological composition of the tumor, NGS was performed separately on either of the different components to verify whether both the epithelial and mesenchymal constituents were affected by a pathologic *POLE* mutation.

In fact, both histological components shared the same pathologic *POLE*-EDM (p.V411L) mutation and a *POLE*-EDM (p.1601S) mutation representing a VUS. The sarcomatoid part showed an additional VUS in the *POLE* gene and two pathologic *TP53* mutations. To substantiate the diagnosis of a carcinosarcoma with dual pathologic POLE mutation in both tumor fractions it was decided to further investigate the two distinct histologic components using the TruSight Oncology 500 Panel to obtain a precise TMB for each tumor compound. The TMB in the mesenchymal part was 788 muts/Mb and 483 muts/Mb in the adenocarcinomatous fraction. In the latter a pathologic copy number gain in *ERBB2* was additionally revealed, but no other pathologic mutations of clinical significance were detected (Table 1).

The pathologic *POLE*-EDM mutation in both histologic constituents of the tumor led to a down-staging from FIGO stage IIc to stage $IAm_{POLEmut}$ according to the new classification system of 2023. The case was discussed again in the interdisciplinary tumor board and no adjuvant chemotherapy was considered necessary.

The final molecular and histological results were comprehensively explained to the patient followed by a detailed risk–benefit weighting with respect to possible adjuvant treatment options in order to achieve an informed consent. The patient agreed and entered follow-up after this discussion. At time of publication the patient was followed for 10 months without any evidence of disease.

3. Discussion

The presented case is a rare case of a uterine carcinosarcoma with a pathological *POLE*-EDM as driver mutation. Only about 5 % of uterine carcinosarcomas are classified as *POLE* mutated, while with close to 74 %, the majority of cases belong to the copy number high or, as a surrogate, the p53 aberrant molecular subgroup of endometrial cancers (Travaglino, 2020). Recently it was suggested that 5 % is even an overestimation resulting from histologic misclassification (Huvila, 2024). The presented tumor showed abnormal p53 expression and two different *TP53* mutations but in the mesenchymal fraction only. *TP53* mutations is often an early event in uterine carcinosarcoma tumorigenesis. In most cases p53 expression is equally in both histologic components but overexpression is more common in the non-epithelial area (De Jong, 2011; Taylor, 2006).

In terms of molecular classification, this tumor is a multiple classifier. If both a pathologic *POLE* mutation and a *TP53* mutation are found in the same cancer, it is recommended to classify it as *POLE* mutated (Bogani, 2024). Therefore it can be concluded that in this constellation, the *TP53* mutation is most likely a passenger rather than the oncogenic driver. The correct categorization in the *POLE* mutated subgroup was the reason to recommend de-escalation in this case, regardless of the p53 status and the high-risk histologic features (Berek, 2023; Travaglino, 2022).

The molecular profile of this tumor also demonstrates beautifully that the carcinomatous and the sarcomatous components of the herein reported uterine carcinosarcoma share a common clonal origin, as both components carry the same pathologic *POLE* mutation and the same *POLE* VUS. This finding is in line with the "conversion theory" that postulates metaplastic epithelial to mesenchymal transformation of a formerly epithelial cancer as the origin of carcinosarcoma pathogenesis. This also confirms that uterine carcinosarcoma is a variant of high-grade endometrial cancer that should be staged and treated according to endometrial cancer guidelines (Concin, et al., 2021).

The TMB of endometrial cancers with a hotspot *POLE* mutation commonly exceeds 100 muts/Mb with a median of 286 muts/Mb. A high proportion of C > A and T > G substitutions are found in *POLE* hotspot-mutant endometrial cancers while C > G substitutions and indels are found less commonly. With 788 muts/Mb the TMB in the mesenchymal part of the presented cancer was approximately 60 % higher than that in the epithelial part and much higher than the described median TMB found in literature (León-Castillo, 2020). Our case demonstrates that the two constituents of this carcinosarcoma accumulate mutations with two different velocities steering the sarcomatous component to more and more into dedifferentiation.

It is hypothesized that the final evolution of hyper- or ultramutated endometrial cancer is undifferentiated or dedeferentiated carcinoma (UDC/DDC) and that carcinosarcoma only arises from copy number high or p53 abrnomal endometrial cancers of any histotype (Travaglino, 2020). Recent data shows that many non p53 abnormal carcinosarcomas must be reclassified as other types of high-grade endometrial cancer like endometrioid carcinoma with spindle cell growth or with reactive stromal proliferation (Huvila, 2024). In our case the initial diagnosis of carcinosarcoma was made by an external institute of pathology on the curettage material and was later confirmed by the department of pathology at University Hospital Innsbruck. In the present case it can be hypothesized that the initial *POLE* mutation is the oncogenic driver of this high-grade cancer and the acquired *TP53* mutation in the mesenchymal part is responsible for the sarcomatous differentiation. Independent of the exact etiology in the process of histological differentiation, according to society guidelines clinical risk stratification is performed on the basis of molecular classification and even in carcinosarcomas the pathological *POLE* mutation paves the way for de-escalation of adjuvant treatment as a valid management option that indispensably needs to be discussed with our patients (Concin, et al., 2021).

The novel system of the 2023 FIGO classification of endometrial cancer is perfectly applicable on this case. Based on the inclusion of high-risk histology in staging, this cancer would be staged as stage IIC, whereas based on anatomical borders alone, it is stage IA according to 2009 FIGO classification. In this case, a complete molecular workup was available as required and included in the staging classification. As the tumor is classified as *POLE* mutated, it is now staged as $IAm_{POLEmut}$ regardless of histology or LVSI status. Although the new FIGO

Table 1
Molecular characteristics of the different histologic components. ER = Estrogen receptor, PR = progesterone receptor, muts/mb = mutations per megabase, MSS = microsatellite stable, VUS = Variant of Uncertain Significance.

	epithelial component	**mesenchymal component**
Immunohistochemistry		
p53 expression	wild type pattern	aberrant expression
Hormone receptors	ER 80 %, PR 70 % positivity	negative
Mismatch-Repair-Proteins	regular expression	regular expression
L1CAM	negative	negative
Next Generation Sequencing		
selection of detected mutations (shared mutations in **Bold**)	***POLE* (p.V411L)** ***POLE (p.P1601S, VUS)*** ***PTEN (p.R130Q)*** ***PIK3CA* (p.R88Q)** *CTNNB1* (p.S45Y)	***POLE* (p.V411L)** ***POLE* (p.P1601S, VUS)** *POLE* (p.N813S, VUS) *POLE* (p.S803L, VUS) *POLE* (p.L942I, VUS) ***PTEN* (p.R130Q)** ***PIK3CA* (p.R88Q)** *PIK3CA* (p.Y1021C) *CTNNB1* (p.V22A) *TP53* (p.R175H) *TP53* (p.R213*)
Tumor mutational burden	high, 483 muts/Mb	high, 788 muts/Mb
Microsatellite Stability	MSS	MSS

classification is more complex, it shows a better correlation between the various tumor stages and survival. Unfortunately it has to be acknowledged that expensive molecular testing is not universally accessible, which was one of the main criticisms of this new classification (Schwameis, 2023).

Nonetheless, the tumor board decision to de-escalate adjuvant therapy in the present case has been done with some hesitation as in early stage uterine carcinosarcomas adjuvant chemoradiotherapy or chemotherapy is the mainstay of treatment beside surgery in most gyneco-oncologic centers due to the poor outcome with a 5-year overall survival of less than 30 %. Furthermore, we have to acknowledge that changes in treatment recommendations in *POLE* mutated endometrial cancer are based on much less data than is generally usual for such profound dogmatic shifts in clinical care. This proves true to a much greater extend for *POLE* mutated carcinosarcomas, for which available data and empirical evidence are extremely limited.

4. Conclusion

In endometrial cancer fast and reliable availability of molecular markers, including *POLE* mutation status, can be key to sparing patients from overtreatment especially in cancers with high-risk histology. When molecular classification is considered in the treatment decision, the classification should not be made based on incomplete molecular work-up due to the possibility of multiple classifiers.

Reliable long-term data on the prognosis of *POLE* mutated uterine carcinosarcomas is currently unavailable and is not to be expected soon due to the rarity of these tumors in question. Nontheless, today de-escalation could be a feasible option for concerned patients but with keeping in mind that the outcome remains uncertain. Therefore, as performed in the presented case, a shared decision with the patient after comprehensive discussion, mentioning the lack of reliable evidence and a careful weighting of the risks and benefits is an absolute prerequisite.

Informed consent

Our patient gave written informed consent for publication of anonymized medical data for scientific use.

CRediT authorship contribution statement

C. Ebner: Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization. **A. Frosch:** Visualization, Resources, Investigation. **K. Leitner:** Writing – review & editing. **R. Soucek:** Resources, Investigation. **C. Marth:** Writing – review & editing, Supervision. **AG. Zeimet:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

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