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Precision Medicine Clinic: Molecular Tumor Board

Tumor Mutational Burden Guides Therapy in a Treatment Refractory *POLE*-Mutant Uterine Carcinosarcoma

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Abstract

Gynecologic carcinosarcomas, previously known as malignant mixed Müllerian tumors, are uncommon malignancies that demonstrate an aggressive biology and lack a standard therapeutic approach. Molecular analyses have revealed recurrent alterations in chromatin remodeling genes, but clinical support for therapeutic significance is lacking. We prospectively identified a patient with refractory uterine carcinosarcoma whose tumor was subject to molecular profiling at diagnosis and again at radiographic progression. Initial molecular testing did not assess tumor mutational burden, DNA polymerase ε (*POLE*), or microsatellite status. After the failure of several lines of chemotherapy, comprehensive genomic profiling of a repeat biopsy identified two missense mutations of the exonuclease domain of *POLE* (P286R and T323A). Tumor mutational burden was elevated (169 mutations per DNA megabase), consistent with an ultramutator phenotype. As seen in previously reported *POLE*-endometrioid cases, our patient harbored alterations in *PIK3CA*, *ARID1A*, and *PTEN* and was microsatellite stable, with appreciable tumor-infiltrating lymphocytes. She achieved an ongoing durable response with pembrolizumab. This is the first report of programmed cell death protein 1 response in uterine carcinosarcoma. ***The Oncologist*** 2018;23:518–523

Key Points

- Uterine carcinosarcoma is an uncommon and aggressive histologic variant of endometrial carcinoma with a poor prognosis.
- Inactivating DNA polymerase ε (*POLE*) mutations have been associated with high tumor mutational burden (TMB) and response to immune checkpoint inhibition.
- To the authors' knowledge, this is the first report of response to immune checkpoint inhibitor therapy in a patient with uterine carcinosarcoma.
- This case further supports expanding genomic profiling to include assessment of tumor mutational burden across tumor types, given the potential for immune checkpoint inhibitor therapy in TMB-high tumors.

Patient Story

Inactivating DNA polymerase ε (*POLE*) mutations have been associated with high tumor mutational burden (TMB) uterine endometrioid adenocarcinomas. When restricted to uterine carcinosarcoma, an elevated TMB has been observed at variable rates [1, 2]. Our case provides orthogonal support for the responsiveness of tumors with elevated TMB to immune checkpoint inhibitors, regardless of histology. The importance and evolution of comprehensive genomic profiling is highlighted by the clinical impact of microsatellite instability (MSI), *POLE*, and TMB in subsequent testing for our patient.

A 55-year-old woman was diagnosed with a uterine carcinosarcoma after presenting with postmenopausal bleeding in July 2014 (Fig. 1A–C). She underwent curative attempt total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy. Surgical pathology revealed an International Federation of Gynecology and Obstetrics stage IIIA (pT3aN0M0) uterine carcinosarcoma with lymphovascular invasion (Fig. 1D, E). Surgical margins were negative. However, an 8-week postoperative positron emission tomography and computed tomography in September 2014 revealed persistent and recurrent nodal metastases. Re-resection was attempted but

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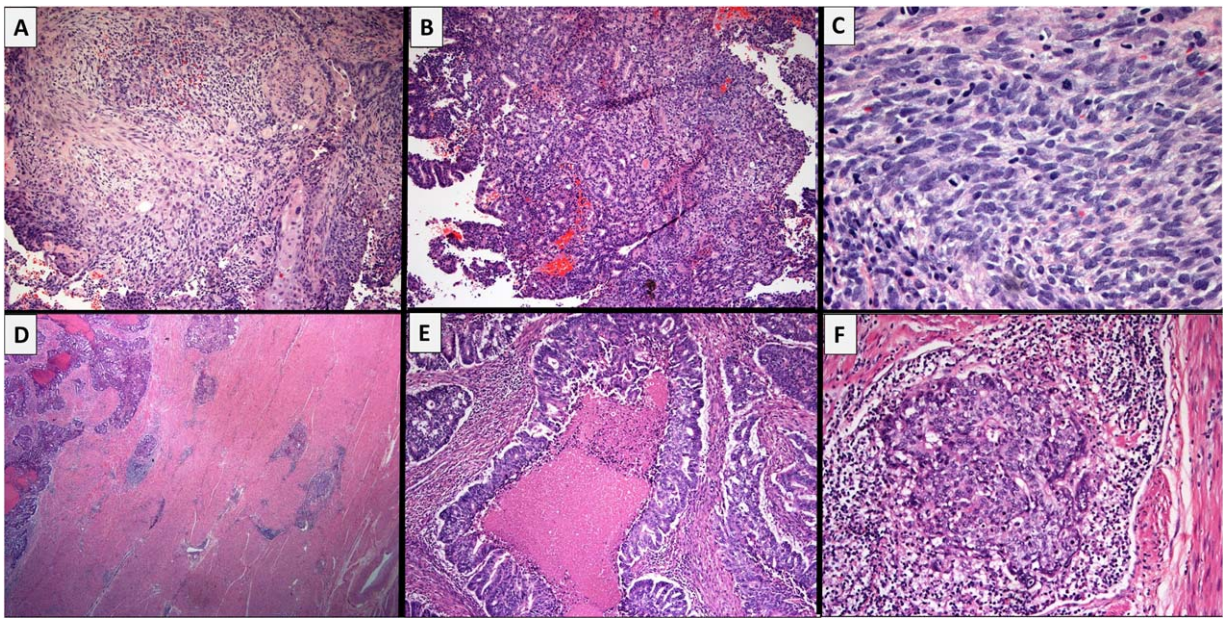

Figure 1. Results of biopsies. Panels **(A–C)** show the endometrial biopsy performed for postmenopausal bleeding in July 2014. The tumor shows a biphasic pattern of epithelial (carcinomatous) and spindled (sarcomatous) differentiation. **(D, E):** The hysterectomy specimen from September 2014 shows a large, friable, fungating tumor with >50% myometrial invasion. The tumor consists predominantly of crowded, fused, and cribriform glands, as well as solid nests making up >50% of the tumor and large areas of comedonecrosis, consistent with an endometrioid-type, International Federation of Gynecology and Obstetrics grade 3, endometrial adenocarcinoma. This matches the carcinomatous component seen on the previous biopsy. **(F):** The recurrence biopsy from April 2016 shows predominantly carcinomatous differentiation with some areas of spindled pattern consistent with the original diagnosis of uterine carcinosarcoma. Tumor nests are accompanied by a moderate peritumoral lymphocytic response; however, tumor infiltrating lymphocytes are, by and large, non-brisk.

not possible. Broad molecular hot-spot testing from the patient's original specimen was not considered to reveal actionable therapeutic alterations (Table 1).

Beginning in late 2014, the patient was treated with several lines of systemic therapy, initially carboplatin and paclitaxel, followed by gemcitabine and oxaliplatin and later single-agent topotecan. Ultimately, in 2016, she developed increasing abdominal pain and significant left lower extremity lymphedema with radiographic disease progression (Fig. 2). Given the widespread and symptomatic progression despite several lines of conventional cytotoxic chemotherapy, a new biopsy was submitted for comprehensive genomic profiling (CGP; Fig. 1E; FoundationONE, Foundation Medicine, Cambridge, MA, http://www.foundationone.com), revealing an elevated tumor mutational burden as well as inactivating missense mutations in the exonuclease domain of *POLE*.

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Uterine carcinosarcomas, formerly known as malignant mixed Müllerian tumors, compose a minority of endometrial cancers and morphologically appear biphasic, containing foci of carcinoma and sarcoma, which gives rise to the carcinosarcoma label [1, 3, 4]. The clinical course for most uterine carcinosarcomas is worse compared with the more common endometrioid adenocarcinomas or even with those with pure serous histology [5–7]. Surgery remains the mainstay of therapy for localized disease, and advanced disease is managed with systemic chemotherapy, largely carboplatin and paclitaxel [8–10].

Large collaborative molecular classification efforts such as the Cancer Genome Atlas (TCGA) have improved biologic understanding and identified molecular subtypes across multiple tumor types, including endometrial cancers [11]. Although the endometrial TCGA identified two groups (*POLE* mutant and hypermutated microsatellite instable [MSI-H]) with increased numbers of nonsynonymous mutations, the analysis was largely restricted to early-stage, surgically resected cases with endometrioid or serous histology (360 of 373 cases) [11]. Smaller series have investigated the molecular landscape of uterine carcinosarcomas, and cases with increased TMB have been reported, although clinical response data are lacking [1, 12].

Current National Comprehensive Cancer Network guidelines (version 1.2017) endorse MSI testing for all endometrial cancers, but determination of tumor mutational burden or *POLE* status is not standard. However, across other tumor types, elevated MSI-H and elevated TMB have been associated with responsiveness to immune checkpoint inhibitor therapy based on the presumed increase in tumor-specific neoantigens in these patients [13–15]. Within this context, tumor tissue from the index patient was submitted for CGP to identify additional therapeutic options.

Genotyping Results and the Interpretation of the Molecular Results

Formalin-fixed, paraffin-embedded material from the April 2016 biopsy was sent for CGP using another commercial platform, as previously described [16, 17]. The CGP results revealed a microsatellite-stable, ultramutated tumor with a TMB of 169 mutations per DNA megabase (Table 1). Two missense mutations of the exonuclease domain of *POLE* (P286R and T323A) were also identified. Notably, despite the biphasic histologic

Table 1. Comparison of molecular testing results conducted on original surgical specimen and repeat testing from progression biopsy in a case of endometrial carcinosarcoma

Gene or additional test characteristic	Caris MI profile from primary surgical specimen, July 2014	FoundationOne testing from April 2016 progression biopsy
BRCA1	Y1703*, C903G	C903G, E597K, F1316L
BRCA2	K3263N, L2573V, S28R	K3263N, L2573V, S28R
APC	S1415C	S1415C, S2497L, L2168I, R2237*
c-KIT	K710N	Not found
FGFR2	S252W	S252W
PIK3CA	*1069W, T1025A	*1069W, T1025A, C407F
PTEN	E7*, E291*	E7*, E291*
RET	D771Y	Not found
POLE	Not tested	P286R, T323A
PD-1 IHC	Positive in TILs (MRQ-22 Ab clone)	Not tested
PDL-1 IHC	Not tested	1+, low positive in tumor cells (SP142 Ab clone)
Tissue source	Uterus	Lymph node
Number of genes	44	315
NGS panel	TruSeq Amplicon Cancer Hotspot	Custom, full exon coverage
MSI testing	Not performed	MSS (NGS)
TMB	Not performed	High, 169 mutations/Mb
Date of testing	September 2014	May 2016

Additional variants of unknown significance were identified but not reported because of space constraints.
Abbreviations: Ab, antibody; IHC, immunohistochemistry; Mb, DNA megabase; MI, Molecular Intelligence; MSI, microsatellite instability; MSS, microsatellite stable; NGS, next-generation sequencing; PD-1, programmed cell death protein 1; PDL-1, programmed cell death ligand 1; TMB, tumor mutational burden; TIL, tumor infiltrating lymphocytes.

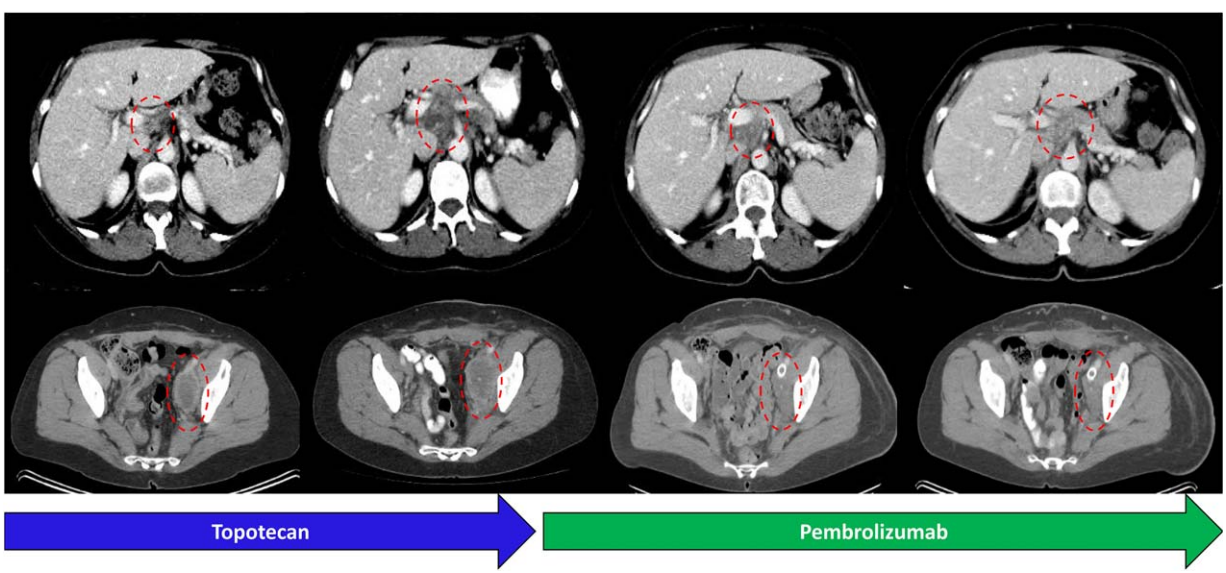

Figure 2. Response to immune checkpoint inhibition in a case of endometrial carcinosarcoma with an elevated tumor mutational burden and *POLE* mutation. Axial computed tomography images demonstrate progression in a periportal nodal conglomerate and necrotic pelvic sidewall followed by response after initiation of pembrolizumab, now lasting over 12 months.

pattern of the carcinosarcoma, our patient shared clinicopathologic features with *POLE*-mutant endometrioid endometrial adenocarcinomas, including mutations in *PIK3CA*, *ARID1A*, and *PTEN*; MSI status; increased TILs; and relative insensitivity to platinum agents, suggesting shared biologic mechanisms despite divergent appearance (Fig. 1, Table 2) [18, 19].

Potential Strategies to Target the Pathway and Implications for Clinical Practice

POLE-mutant microsatellite stable (MSS) and MSI-H endometrial adenocarcinomas have been linked with increased immunogenic mutations [20, 21]. Both *POLE*-mutant and MSI-H endometrial cancers demonstrate enhanced antitumor

Table 2. Literature review of reported *POLE*-mutant, high-tumor mutational burden, solid tumors with response to immune checkpoint inhibitor therapy

Case (age in years, sex)	Tumor histology	Key genomic alteration	Tumor mutational burden (mutations/exome)	Treatment	Response	Ref
55, female[a]	Uterine carcinosarcoma	*POLE* missense (P286R); missense (T323A)	169 mutations/DNA megabase[b]	Pembrolizumab 200 mg IV q3wk	PR, >12 months (ongoing)	N/A
49, male	Colorectal adenocarcinoma, signet ring cell	*POLE* missense (V411L)	116 mutations/DNA megabase[b]	Pembrolizumab	Progressive disease, 12 weeks	22
80, male	Colorectal adenocarcinoma	*POLE* missense (V411L)	122 mutations/DNA megabase[b]	Pembrolizumab 200 mg IV q3wk	PR, >6 months (ongoing)	23
53, female	Endometrial adenocarcinoma, high-grade endometrioid type	*POLE* missense (V411L); *POLE* nonsense (R114*)	4,500 (primary tumor); 6,500 metastatic tumor)	Pembrolizumab 10 mg/kg q2wk	PR, >14 months (ongoing)	24
57, female	Endometrial adenocarcinoma, mixed clear cell/endometrioid	*POLE* missense (P286R)	4,660	Nivolumab 3 mg/kg q2wk	PR, >7 months (ongoing)	25
60, female	Uterine serous carcinoma	*MSH6* nonsense (F1088*)	1,037	Nivolumab 3 mg/kg q2wk	PR, >9 months (ongoing)	25
6, female	Glioblastoma multiforme	*POLE* missense (P436H)	24,680	Nivolumab 3 mg/kg q2wk	PR, >9 months (ongoing)	26
3.5, male	Glioblastoma multiforme	*POLE* missense (S461P)	21,919	Nivolumab 3 mg/kg q2wk	PR, >5 months (ongoing)	26

[a]Denotes incident case reported herein.
[b]Tumor mutational burden (TMB) from next-generation sequencing, whereas other reported cases determined TMB from whole exome sequencing.
Abbreviations: IV, intravenously; N/A, not applicable; PR, partial response; q2wk, once every 2 weeks; q3wk, once every 3 weeks; Ref, reference.

immune activity with infiltration of T lymphocytes [20–24]. The histologic appearance of the endometrial tumor is not a reliable predictor of the underlying molecular defect, especially for the *POLE*-mutant subgroup, which has been previously reported to show low-grade or high-grade endometrioid, serous, or mixed histology. Taken together, these preclinical data provide a scientific rationale for the use of programmed cell death protein 1 (PD-1) inhibitors among endometrial tumors with a relevant molecular profile, even if they demonstrate uncommon histologic phenotypes. This hypothesis is further supported by several case reports demonstrating significant clinical responses to PD-1 inhibitors in patients with advanced, recurrent tumors with an ultramutated molecular phenotype (Table 2) [25–27]. Previously, Castelucci et al. reported two cases of *POLE*-mutant colorectal carcinoma with an ultramutated phenotype; one patient experienced partial and durable response to single-agent pembrolizumab [22]. Our case differs in that the histopathologic classification is uterine carcinosarcoma and expands the description of *POLE* across tumor types.

As our understanding of the therapeutic relevance of specific genomic features expands, so does the need for more extended molecular assessments. The differing information included in the initial molecular testing (September 2014) and repeat testing (April 2016) likely reflects methodologic differences in testing at the given time points (20-month interval; Table 1). Although the extent of molecular testing undertaken for this patient in 2014 would be considered beyond standard, it was nonetheless inadequate to identify the elevated tumor mutational burden subsequently identified in 2016. In a 2014 series of 22 gynecologic carcinosarcomas (17 of 22 uterine), two cases harbored oncogenic loss-of-function *POLE* alterations (*POLE* P286R and V411L); albeit at the time of publication this was *not* considered clinically actionable, reflecting how our understanding and annotation of genomic information evolves over time [1].

In this case history, the histologic analyses and overlap in genomic alterations identified strongly suggest that both samples shared a clonal origin and that an elevated TMB would have been found in the surgical specimen if this had been assessed on the original test (Fig. 1, Table 1). In fact, genomic profiling may aid in confirming clonality in similar clinical scenarios [28]. Although standard MSI testing captures the nearly 28% of endometrial cancers that are MSI-H, patients with high TMB and MSS tumors because of *POLE*-mediated mechanisms (7%) and others go undetected [11, 21, 25], and thus potentially relevant treatment options remain unexplored. A recent analysis suggests that genomic profiling aids in clinical decision-making in gynecologic cancers [29].

The observation that histologic evaluation is often subject to interobserver variability and may not be a reliable predictor of biologic behavior is a driving consideration in adding molecular characteristics to the classification system for endometrial tumors. Clinical examples of broad genomic tumor analyses, which identify unexpected oncogenic alterations within an anatomic or histologic subtype that subsequently respond to molecularly paired therapy, are accumulating despite variations of methodology and concerns about temporal and geographic sample heterogeneity [30–33].

This raises an important question: should all tumors with highly elevated TMB, regardless of histology, be considered for immune-mediated therapies? We recognize that prospective

clinical studies are needed to answer this question, but mounting evidence warrants pan-cancer study. In fact, the nationwide American Society of Clinical Oncology TAPUR trial (NCT02693535) was recently amended to match pembrolizumab to any tumor with a pathogenic *POLE* mutation, and an elevated TMB immunotherapy arm is planned as well.

Patient Update

Based on this high TMB, the index patient was treated with pembrolizumab after informed consent discussion. She achieved rapid symptomatic improvement with decreasing lymphedema and an excellent radiographic partial response, with 65% decrease by immune-related response criteria and 40% by RECIST version 1.1 criteria (Fig. 2) [34, 35]. She had continued pembrolizumab for over 12 months at the time of manuscript submission.

Glossary of Genomic Terms and Nomenclature

Comprehensive genomic profiling: Assay that examines multiple classes of genomic alterations across a broad panel of cancer-related genes

Missense mutations: A point mutation in which a single nucleotide alteration results in a codon for a different amino acid

Microsatellite instability: Pattern of genetic hypermutability that results from dysfunctional DNA mismatch repair

Nonsynonymous mutation: A nucleotide mutation that results in altered amino acid sequence

Tumor mutational burden: Total number of genetic mutations per coding area of a tumor genome

Ultramutator phenotype: Genetic profile associated with high tumor mutational burden

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Disclosures

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For Further Reading:

Andrew Sharabi, Sangwoo Shawn Kim, Shumei Kato et al. Exceptional Response to Nivolumab and Stereotactic Body Radiation Therapy (SBRT) in Neuroendocrine Cervical Carcinoma with High Tumor Mutational Burden: Management Considerations from the Center For Personalized Cancer Therapy at UC San Diego Moores Cancer Center. ***The Oncologist*** 2017;22:631–637.

Key Points.

- High–grade, large–cell neuroendocrine carcinoma of the cervix is an ultra–rare malignancy that carries a grim prognosis.
- Next–generation sequencing may reveal key mutations in MSH2 genes amongst others. MSH2 mutations target the DNA mismatch repair process and can predispose patients to malignancies with high mutational burdens.
- Immunotherapy combined with radiation therapy can elicit a significant response, both within and outside the field of radiation. The latter is termed the "abscopal" effect, perhaps mediated by radiation-induced cross presentation of tumor antigens resulting in immune activation.
- Sequencing of blood-derived ctDNA showed a high number of alterations, and tissue sequencing confirmed a high tumor mutational burden as a consequence of a mismatch repair gene defect. This observation led to a therapeutic "match" with an anti-programmed cell death protein 1 antibody combined with SBRT, resulting in a durable (10+ months), near-complete remission in a patient with advanced chemotherapy-refractory disease.