Case report

Uterine carcinosarcoma associated with a germline nibrin (NBN) mutation

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A R T I C L E   I N F O

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A B S T R A C T

We report a 62-year-old patient with uterine carcinosarcoma associated with a germline mutation in the NBN gene which is involved in the homologous recombination repair (HRR) pathway. This patient responded well to several different treatment strategies including platinum-based chemotherapy twice, PARP inhibitor therapy and immunotherapy, and is currently alive and with disease control, more than four years after diagnosis. This case is the first report of uterine carcinosarcoma associated with a germline mutation in NBN and highlights how specific genomic alterations may guide treatment decisions that may alter the natural history of an otherwise devastating disease.

1. Introduction

Uterine carcinosarcoma (UCS) is a rare but highly aggressive subtype of endometrial cancer. It is a biphasic, malignant tumor arising in the uterus, composed of both carcinomatous and sarcomatous elements. (Cantrell et al., 2015) Histologically, the epithelial component is most commonly endometrioid or serous carcinoma; however, undifferentiated and clear cell carcinoma may also be seen. (Cantrell et al., 2015) Large scale genomic studies have demonstrated that UCS originates from a carcinoma precursor undergoing late sarcomatous dedifferentiation, rather than from two independent progenitors, epithelial and mesenchymal, as previously thought. (Roque and Matei, 2022).

UCS accounts for 5% of endometrial cancers, with increasing incidence over the last decade. (Matsuzaki et al., 2021) It has a median age of onset of 70 years and affects Black women with twice the incidence of other races. (Cantrell et al., 2015) Prognosis is poor, with a median overall survival of 23 months; (Matsuzaki et al., 2021) despite advancements in treatment options, there has been no change in the 5-year overall survival rate from 1975 to 2012. (Matsuzaki et al., 2021) UCS also has a high propensity for recurrence with rates of 37–46% for stage I/II disease and rates of 63–80% for stage III/IV disease. (Cantrell et al., 2015).

Standard of care involves a multimodality approach consisting of surgery, radiotherapy, and chemotherapy. (Cantrell et al., 2015; Matsuzaki et al., 2021) First-line chemotherapy is typically platinum-based; however, when used as second-line, chemotherapy (including platinum-based) exhibits only modest activity, which has fueled investigations into better second and third line treatment options. (Matsuzaki et al., 2021).

Here, we report a patient with UCS that is associated with a germline NBN mutation who responded well to second-line platinum-based treatment, followed by poly-ADP ribose polymerase inhibitor (PARPi), and is currently responding to immunotherapy with avelumab and axitinib.

2. Case presentation

A 62-year-old woman with notable family history of cancer (skin, liver, lung, prostate, penile, and pancreatic, all present within second-degree relatives) presented initially for routine Pap testing which found atypical endometrial cells; follow-up endometrial biopsy confirmed the diagnosis of carcinosarcoma. She underwent laparoscopic total abdominal hysterectomy and bilateral salpingo-oophorectomy with sentinel node dissection and pelvic washings. The hysterectomy specimen showed carcinosarcoma confined to a polyp without myometrial or lymphovascular invasion; while the carcinomatous component composed 5% of tumor volume, was high-grade, and did not exhibit heterologous differentiation (Fig. 1.). The cervix, bilateral ovaries,
falloues tubes, pelvic lymph nodes and pelvic washings were all negative for tumor. She was diagnosed with FIGO stage IA uterine carcinosarcoma.

Immunohistochemistry for mismatch repair (MMR) proteins MLH1, PMS2, MSH2 and MSH6 was intact, and HER2 staining was negative (1+). Targeted next generation sequencing using our institutional Oncopanel assay was performed on the tumor specimen. The OncoPanel assay surveys exonic DNA sequences of 447 cancer genes and 191 regions across 60 genes for rearrangement detection. DNA is isolated from tissue containing at least 20% tumor nuclei and analyzed by massively parallel sequencing using a solution-phase Agilent SureSelect hybrid capture kit and an Illumina HiSeq 2500 sequencer. This tumor was notable for a tumor mutational burden (TMB) of 14 mutations/mega-base (MB), with mismatch repair proficient (MMRP) status. Additionally, Oncopanel testing identified three different mutations: TP53 mutation (c.722C > T (p.S241F), exon 7), ARHGAP35 mutation (c.3859G > A (p.G1287R), exon 3), and a nonsense NBN mutation (c.2117C > G (p.S706*), exon 14). Copy number variant analysis showed numerous copy number alterations (CNAs), including 19q12 amplification of CCNE1 (estimated 10 copies).

The patient received six cycles of adjuvant carboplatin/paclitaxel combined with brachytherapy; cycles 1–2 with carboplatin alone due to paclitaxel reaction and cycles 3–6 carboplatin with paclitaxel. The patient remained without evidence of disease recurrence until 12 months after finishing chemotherapy when her CA-125 rose to 169 (Fig. 2). Imaging at that time demonstrated disease recurrence with extensive peritoneal carcinomatosis and malignant ascites. Her CA-125 peaked at 454, and she received six cycles of second-line, platinum-based chemotherapy with carboplatin/paclitaxel. She responded very well with normalization of her CA-125 to 9 and her imaging demonstrated significantly decreased omental nodularity.

Given the NBN mutation found on Oncopanel testing, she underwent germline testing which confirmed that the same NBN mutation was present at germline; no other germline alterations were identified. After completion of 6 cycles of second-line platinum chemotherapy, she initiated PARP inhibitor (PARPi) maintenance therapy with niraparib.

The patient was maintained on niraparib with stable CA-125 and scans until 13 months later when her CA-125 increased to 127. Imaging showed nodules along the pancreatic tail, right anterior abdominal wall, and bilateral external iliac lymph nodes, as well increased size of previously identified paraaortic nodes. Given the high TMB identified on Oncopanel, she was transitioned to a clinical trial of immunotherapy with the PD-L1 inhibitor avelumab in combination with the oral tyrosine kinase inhibitor axitinib which targets vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2, and VEGFR-3. Imaging has shown a decrease in size and number of metastatic nodes since beginning avelumab/axitinib and she remains on protocol therapy for over 15 months.

3. Discussion

We present a patient with UCS associated with a germline nibrin (NBN) mutation who responded to several different treatment strategies and is currently alive more than four years after diagnosis. Other mutations in UCS have been well studied; for example, UCS is notable for high incidence of TP53 mutations, with rates of 62–91% reported, KRAS mutations (10–24%), and PI3K pathway mutations (15–41%). (Cantrell et al., 2015; Matsuzaki et al., 2021) Recent studies have also identified germline BRCA1 mutations; (Matsuzaki et al., 2021) however, NBN mutations have not been previously reported.

NBN occupies a central role in maintaining telomere length, sensing DNA damage and maintaining DNA integrity and genomic stability. (Uzunoglu et al., 2016) Specifically, NBN is part of and the main regulator of the MRN complex (Mre11, Rad50, and NBN) which aids in initially recognizing double strand breaks and recruiting proteins to assist with both nonhomologous end-joining (NHEJ) and homologous recombination repair (HRR). (Uzunoglu et al., 2016) The MRN complex is responsible for DNA end resection, which guides double strand break repair to HRR in the presence of sister chromatids. As such, a significant association has been demonstrated between mutation of NBN and malignancies, specifically: conferring worse prognosis in prostate cancer, (Berardinelli et al., 2013; Cybulski et al., 2013) and conferring up to a 5.5-fold risk for development of breast cancer. (Uzunoglu et al., 2016; Berardinelli et al., 2013) Other associations, including with ovarian cancer, (Berardinelli et al., 2013) have been reported; however, more information about the oncologic implications of an inherited alteration in the NBN gene is needed. In endometrial cancer, an association between germline mutations in HRR pathway genes has been reported for uterine serous carcinomas (specifically with germline BRCA1/2 mutations); (Cybulski et al., 2013; Wallbillich et al., 2020) however, to our knowledge, there have been no reported cases of germline NBN mutations identified in UCS or other uterine cancers.

Germline NBN mutations are also known to cause Nijmegen breakage syndrome (NBS), a chromosomal instability syndrome which arises when a child inherits two altered copies of the NBN gene and has been associated with microcephaly, immunodeficiency, growth retardation, a high frequency of lymphoid malignancies and an aging phenotype. (Berardinelli et al., 2013; Varon et al., 1999) Children with NBS have a high incidence of malignancies, particularly non-Hodgkin lymphoma, with some reports as high as 40% of children developing malignancies before age 20. (Varon et al., 1999) This can have implications for family planning; therefore, if any relatives are found to carry

Fig. 1. Hematoxylin and eosin stained sections from the hysterectomy specimen. A. The majority of the carcinosarcoma was composed of high-grade Mullerian carcinoma. B. There was a small component of subjacent high-grade sarcoma composed of pleomorphic spindle cells.
an NBN alteration, then partner testing is recommended. (Berardinelli et al., 2013; Varon et al., 1999).

The involvement of NBN in the HRR pathway contributed to our decision to rechallenge this patient with platinum-based chemotherapy followed by PARPi maintenance. While platinum treatment is standard for first-line therapy in UCS, response to second-line platinum therapy is typically modest. (Matsuzaki et al., 2021) In a retrospective analysis of patients with ovarian or uterine carcinosarcoma who received second-line chemotherapy for advanced or recurrent disease, median progression-free survival and overall survival were only 6.3 months and 12.9 months respectively. (Ebata et al., 2020) In this case, our patient had an excellent serologic and radiographic response to second-line platinum chemotherapy with rapid normalization of her CA-125 and significantly decreased omental nodularity on imaging. Due to the high likelihood of disease recurrence after completion of second-line platinum chemotherapy, we decided to treat this patient with PARPi maintenance therapy following response to first and second-line platinum chemotherapy. (Mirza et al., 2016; Golan et al., 2019; Tutt et al., 2021) Notably, the disease remained stable on PARPi treatment for 13 months after completion of second-line platinum therapy – a longer period than the disease stability after completion of first-line platinum/taxane therapy which was administered as adjuvant treatment for stage IA disease. Given that recurrence after second-line therapy typically occurs sooner than recurrence after first-line therapy, it is reasonable to assume that our patient derived benefit from maintenance PARPi therapy.

The presence of the germline NBN mutation in this patient may have also contributed to the high TMB (≥10 mutations/MB) identified in her tumor. Several studies have shown that HRR deficient tumors are associated with higher tumor mutational loads, albeit not as high as other DNA repair deficient tumors such as mismatch repair deficient and POLE-mutated tumors. (Matsuzaki et al., 2021; Marabelle et al., 2020; Chan et al., 2019) Given the central role of NBN in DNA damage response, it is possible that, in the setting of NBN loss, alternative, error-prone, highly mutagenic DNA repair mechanisms such as translesion synthesis may have contributed to the high mutational load observed in this tumor. Studies evaluating TMB specifically in NBN mutated tumors are lacking; nonetheless, the association between NBN mutations and high TMB warrants further investigation.

Although pembrolizumab monotherapy has received disease-agnostic FDA approval for tumors with a TMB ≥ 10, we chose to enroll this patient in a clinical trial of combined immune checkpoint blockade with antiangiogenic therapy (avelumab/axitinib) given her otherwise aggressive uterine carcinosarcoma diagnosis. It is important to highlight that uterine carcinosarcomas were excluded from the pembrolizumab/lenvatinib KEYNOTE-775 endometrial cancer study. (Marabelle et al., 2020; Makker et al., 2022) Our patient had a gratifying response to immunotherapy and remains on avelumab/axitinib for more than 15 months. If her disease progresses on immunotherapy, participation in clinical trials of cell cycle checkpoint inhibitors such as WEE1, PKMYT1 or ATR inhibitors would be a reasonable consideration given the presence of CCNE1 amplification in her tumor (as detected by Oncopanel) and given the critical role of NBN in cell cycle checkpoint control. WEE1 inhibition has also shown prominent single agent activity in patients with uterine serous histology. (Liu et al., 2021) Given the highly aggressive nature of UCS and the potential therapeutic targets identified through targeted sequencing in this patient, routine molecular testing of these tumors may be warranted.

In conclusion, this case highlights how specific genomic alterations (in this case an HRR alteration) may guide treatment decisions that may alter the natural history of an otherwise devastating disease like uterine carcinosarcoma.

4. Consent

Informed consent was obtained from the patient for discussion of her case in this report.

Declaration of Competing Interest

Tahireh Markert and David Kolin have nothing to disclose. Panagiotis Konstantinopoulos reports consulting fees from AstraZeneca, Bayer, GSK, Alkermes, Kadmon, BMS, IMV, Repare, Artios, and Mersana,
all outside of the submitted work. Panagiotis Konstantinopoulos also reports institutional funding as clinical trial investigator from AstraZeneca, Pfizer, Eli Lilly, Bayer, Merck, GSK, Tesaro, Merck KGaA all outside the submitted work.

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All outside of the submitted work.