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Case report

Treatment of neuroendocrine carcinoma of the cervix with a PARP inhibitor based on next generation sequencing☆

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1. Introduction

Neuroendocrine carcinomas of the cervix are rare cancers occurring in 0.9% of cervical cancers (Atienza-Amores et al., 2014). Chan et al. reported on 280 neuroendocrine carcinomas of the cervix from the SEER database and demonstrated that these patients presented with more advanced FIGO stage, larger tumor size, and frequent nodal involvement than squamous or adenocarcinomas of the cervix (Chen et al., 2008). Their treatment less frequently involve hysterectomy, and patients more often receive adjuvant radiotherapy compared with both squamous cell carcinoma and adenocarcinoma of the cervix ($p < .05$) (Chen et al., 2008). Not surprisingly they have a significantly poorer survival than the more common squamous or adenocarcinomas of the cervix. Utilizing the SEER database, Dores et al. reported a 3 year survival of 9.4% for patients with small cell carcinoma of the cervix who presented with distant disease (Dores et al., 2015).

Because of the rarity there are no prospective trials addressing their clinical management. Treatment is often modeled after the more common neuroendocrine small cell carcinoma of the lung. In the setting of metastatic disease patients are primarily treated with carboplatin and etoposide (Horn et al., 2018). When this is ineffective, oral topotecan is a commonly used second line therapy (O'Brien et al., 2006). In small cell carcinoma of the cervix, a retrospective study demonstrated the combination of topotecan/bevaciziumab/paclitaxel improved the progression-free survival in previously chemotherapy exposed patients compared to patients who received other regimens (Frumovitz et al., 2017). In review of gynecologic small cell neuroendocrine tumors by Atienza-Amores et al. from Memorial Sloan-Kettering in 2015, the authors state “Molecularly targeted treatments are not yet available clinically for patients with small cell carcinoma cervix. Akin to small cell carcinoma in the lung, the genomic characterization of small cell carcinoma cervix may lead to the identification of molecular targets that could be exploited for the treatment of subgroups of the disease” (Atienza-Amores et al., 2014). However, Next Generation Sequencing has demonstrated recurrent somatic mutations involving MAPK, P13K/AKT/mTOR and TP53/BRCA pathways in small cell neuroendocrine carcinoma of the cervix (Xing et al., 2018). Furthermore, one case report utilizing Next Generation Sequencing to identify therapeutic targets has been published (Lyons et al., 2014). This patient's tumor demonstrated a *KRAS* mutation and the patient received the MEK inhibitor trametinib. She had a complete response and was disease-free for over 9 months before disease recurrence. We report a second case of molecular directed treatment based on Next Gene Sequencing.

2. Case report

A 58-year-old African-American female gravida 2 para 2 with a past history of asthma, hypothyroidism, renal failure and morbid obesity presented with postmenopausal bleeding. She had been evaluated by pelvic exam and saline infusion sonography 7 months previously and had no pathology identified. However at this time, pelvic exam demonstrated an exophytic tumor protruding from the cervix. A biopsy was performed.

Pathology demonstrated the tumor forms solid nests without

☆ Records for this case report were obtained under IRB approved process.

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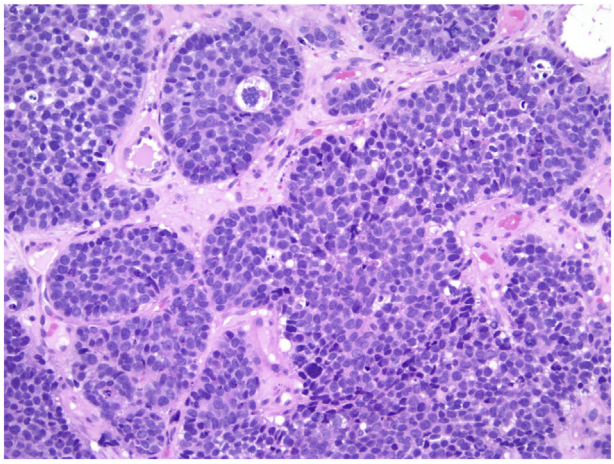

Fig. 1. Poorly differentiated carcinoma with neuroendocrine differentiation.

definite gland lumen formation. The cells contain scant-to-moderate cytoplasm with interspersed single large cells with abundant eosinophilic cytoplasm (Fig. 1). Immunohistochemistry was obtained to clarify tumor characteristics. The tumor cells are strongly positive for keratins AE1/3 and CK7 with a minority of cells showing weak-to-moderate reactivity for CK20. p53 is wild type. p16 shows patchy moderate-to-strong reactivity, synaptophysin diffuse moderate reactivity (Supplementary Fig. 1), chromogranin patchy reactivity in approximately 5% of cells and PAX8 positivity. p40, ER, PR, TTF-1 and GATA3 are negative.

An MRI was obtained that demonstrated enhancing cervical mass with cervical stromal invasion, parametrial invasion, extension into the vagina and abutment without definitive invasion of the rectal wall. Additionally, there was bilateral inguinal, bilateral iliac, left obturator and left internal iliac adenopathy (Fig. 2).

A PET scan was obtained (Fig. 3) that demonstrated small bilateral cervical lymph nodes with mild FDG uptake SUV of 2.7, concerning for metastases. FDG avid bilateral axillary lymphadenopathy measuring 2.4 × 1.4 cm in the left axilla with an SUV of 11.8, and measuring 2.7 × 1.5 cm in the right axilla with an SUV of 5.7, left anterior shoulder subcutaneous soft tissue nodule measuring 2.7 × 1.7 cm with

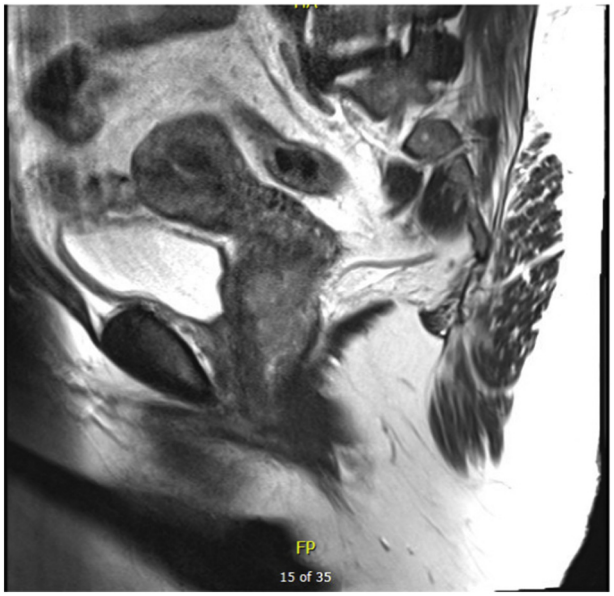

Fig. 2. MRI of the pelvis Sagittal section of the uterus and cervix demonstrating cervical tumor.

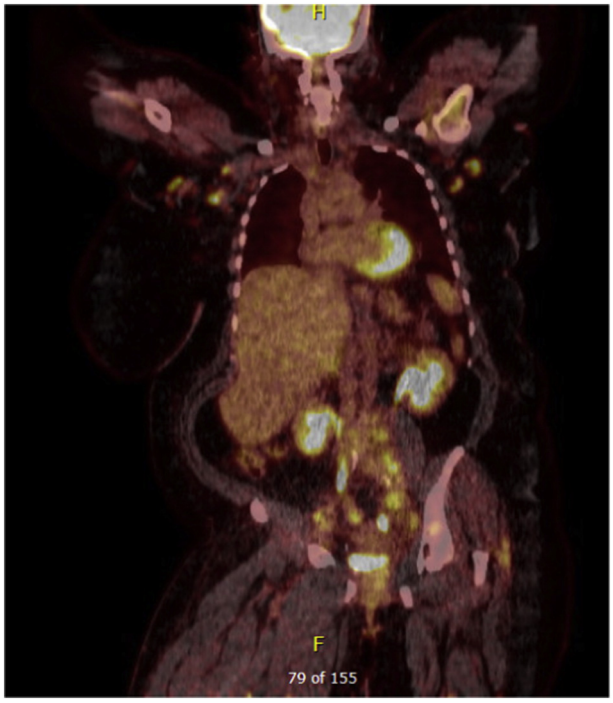

Fig. 3. PET/CT demonstrating FDG avid cervical tumor and metastatic sites.

an SUV of 11.8, mediastinal and hilar small lymph nodes measuring 1.6 × 1.1 cm with an SUV of 3.9 consistent with metastases. FDG avid soft tissue mass in the cervix with an SUV of 15.6 is consistent with known neoplasm. Periportal 2.5 × 1.3 cm with an SUV of 5.3, retroperitoneal 2.2 × 1.1 cm with an SUV of 6.8 and bilateral pelvic and inguinal (right 1.3 short axis lymph node with an SUV of 7.6, left 1.3 short axis with a SUV of 4.2) metastatic lymphadenopathy. Nonspecific diffuse bone marrow uptake. The patient was initiated on chemotherapy with carboplatin at an AUC of 5 Day 1 and etoposide 100 mg/m squared days 1–3 every 21 days for 11 cycles from 7/25/17 to 2/23/2018.

A CT scan after cycle 3 demonstrated that her disease was overall stable to minimally decreased in size.

In late October 2017, the patient was symptomatic with severe back pain. Imaging demonstrated a large pulmonary embolism and multiple sites of metastatic disease were largely stable. An MRI of the spine was unremarkable.

After 9 cycles of therapy her disease and was stable and the patient was agreeable to undergoing Foundation One testing to assess for other potential therapeutic targets.

Foundation One testing demonstrated the following genomic alterations; BRCA2 loss exons 17–27, KMT2C (MLL3) splice site 1012 + 1G > A – subclonal, NOTCH2 Q1634, and *PARK2* loss exons 1–10. Microsatellite status stable tumor mutation burden low 4 Muts/Mb. Potential therapies included the PARP; inhibitors niraparib, rucaparib and olaparib. No clinical trials or approved therapies were available for the other mutations. The In Vitae Common Hereditary Cancer (48 gene) Panel demonstrated no germ-line mutations. Because the patient had a somatic mutation, and only 1 of the 3 FDA approved PARP inhibitors had an indication for somatic mutation, therapy with rucaparib 600 mg orally BID was prescribed. The patient has received 15 months of therapy and imaging every 3 months continues to demonstrate stable disease.

3. Discussion

Systematic studies evaluating clinical benefit of tumor genomic profiling are lacking. Sohal et al. conducted a prospective study in 250

patients with non-gynecologic solid tumors at the Cleveland Clinic (Sohal et al., 2015). Of 223 evaluable samples, 49% of patients were recommended a specific therapy, but only 11% received such therapy. Lack of molecularly targeted agents, via either clinical trial access or insurance coverage, were the most common reasons for nonreceipt of genomics-driven therapy. The NCI MATCH (molecular analysis for therapeutic choice) trial was prospectively designed to evaluate the efficacy of molecular profiling in which all patients were provided the molecularly targeted agent free of charge. The NCI-MATCH trial is for adults whose tumors have progressed on standard treatment or rare cancers for which there is no standard treatment. Results from this trial are slowly being reported (https://www.cancer.gov/news-events/press-releases/2018/nci-match-first-results, 2019). Arm I studied the drug taselisib in 65 patients with mutations in the *PIK3CA* gene. There were no objective responses to the drug, however 24% of the patients had progression-free survival of greater than six months. Arm Q, the drug ado-trastuzumab emtansine (T-DM1) was studied in patients with HER2-overexpressing non-breast, gastric tumors. An 8% partial response and 46% stable disease rate was reported. Arm W tested the drug AZD4547 in 50 patients with mutations in the FGFR pathway. Ten percent of patients had a partial response.

Small cell carcinoma of the cervix is a very deadly disease with mortality rates of 91% at 3 years. Therefore, we undertook Next Generation Sequencing of this patient's tumor with a goal of finding an actionable mutation. The patient demonstrated mutation in BRCA 2 for which there were clinically available therapeutic options namely the PARP inhibitors niraparib, rucaparib and olaparib. Previous studies utilizing target directed therapy against the BRCA mutation have not been previously reported in small cell carcinoma of the cervix. However, review of the literature demonstrated previous reports of this mutation in small cell carcinoma of the cervix with Next Generation Sequencing (Xing et al., 2018). While the patient reported in this case report has stable disease, and is progression-free at 15 month. Stable disease is quite remarkable in a disease which has such a very high mortality.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2019.100499.

Author contribution

Peter Rose: Conception, Design, Execution, Interpretation.
Anne Sierk: Design, Execution.

Declaration of Competing Interest

None.

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