Histology-specific FGFR2 alterations and FGFR2-TACC2 fusion in mixed adenoid cystic and neuroendocrine small cell carcinoma of the uterine cervix

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ABSTRACT
Neuroendocrine small cell carcinoma of the uterine cervix portends a dismal prognosis with limited treatment options. Rarely, tumors of mixed-lineage appear in gynecologic malignancies. Here, we report a 77-year-old woman who presented with complete uterine prolapse and 4-month history of vaginal bleeding. Histopathologic evaluation revealed a mixed adenoid cystic carcinoma and neuroendocrine small cell carcinoma of the uterine cervix. The tumor was PD-L1 and HPV 35 positive. The patient was treated with up-front surgery and adjuvant radiation. Independent, histology-specific alterations in FGFR2 and a FGFR2-TACC2 fusion were identified. Progression of disease occurred within 6 months for which she received chemotherapy and immunotherapy. However, the patient expired within a year. We comprehensively review how screening for and targeting of FGFR alterations in recurrent and metastatic cervical cancer might serve as a touchstone for future treatment regimens.

1. Introduction
Neuroendocrine small cell carcinoma of the uterine cervix (NESC) is a rare malignancy (Rickman et al., 2017) with limited treatment options (Satoh, 2014). The mean annual incidence is 0.06 per 100,000 women (Chen et al., 2008). According to the SEER database, 5-year disease specific survival is 33.0% (Zhou, 2017). Smoking and advanced stage are associated with worse prognosis (Chan et al., 2003). Given its neuroendocrine lineage, NESC of the cervix may present with unique symptomology including, Cushing’s syndrome (Hashi, 1996), syndrome of inappropriate antidiuretic hormone secretion (Ishibashi-Ueda et al., 1996), and insulin-secretion induced hypoglycemia (Seckl, 1999).

Few cases have been described whereby NESC of the cervix is intermixed with a second cell lineage, including adenocarcinoma and squamous cell carcinoma (Alphandery et al., 2007; Toki et al., 1996; Horn, 2006; Li, 2018; Ishida, 2004). Three cases have been reported where adenoid cystic carcinoma (ACC) were involved with squamous cell carcinoma in the cervix (Shi, 2015). However, no case of a mixed cervical ACC and NESC has been previously reported.

2. Case
A 77-year-old G1P1 woman with history of hypertension and remarkable gynecologic, surgical, and family history presented with a four-month history of vaginal bleeding. Physical exam revealed a non-reducible complete procidentia and a 6–7 cm barrel-shaped ulcerated cervix, with gross tumor present approximately 3–4 cm outside of the vaginal introitus.

The patient underwent a Positron Emission Tomography - Computed Tomography (PET/CT) that showed a soft tissue exophytic mass in the perineum at the level of the vaginal introitus measuring approximately 6.6 × 5 cm with maximum SUV of 9. No distant disease or lymphadenopathy was noted. Magnetic resonance imaging (MRI) examination of...
the pelvis was obtained to better characterize the origin of the cervical mass. The MRI revealed complete external cervical prolapse (Fig. 1A and B). There was evidence of a large, heterogeneous bulky mass arising from the cervix with heterogeneous enhancement, measuring $5.1 \times 6.2 \times 6.1$ cm. Definite invasion of adjacent organs was not radiologically evident. Central areas of T2 signal hyperintensity that likely represented areas of necrosis within the mass were appreciated.

Based on the clinical, histologic, and radiologic features the case was managed as a stage IB2 high-grade carcinoma of suspected cervical origin, using the current FIGO cervical cancer staging from 2009. The patient would have been a candidate for concurrent chemoradiation; however, a hysterectomy was favored in the setting of complete procidentia, as the treating fields of radiation would have been extracorporeal. The patient underwent a laparoscopic assisted, radical vaginal hysterectomy with bilateral salpingo-oophorectomy (Fig. 2). Inoperative course was uncomplicated. The laparoscopic survey showed a small postmenopausal uterus with two fundal subserosal fibroids. Pelvic adhesions were seen between the uterus and posterior cul de sac and sidewalls bilaterally. There was neither evidence of extraterine or abdominal disease nor evidence of gross pelvic lymphadenopathy. The patient’s postoperative course was uncomplicated, and the patient was discharged home on postoperative day (POD) two.

Histopathologic analysis of the tumor specimen revealed an endocervical mixed carcinoma (Fig. 3A), consisting of areas of adenoid cystic carcinoma (10–40%) (Fig. 3B) and neuroendocrine small cell carcinoma (60–90%) (Fig. 3C). The entire tumor size was 5.5 cm in diameter, penetrating into 82% of the cervical wall (23 mm/28 mm) with extensive lymphovascular space invasion. All margins and bilateral parametria were free of tumor. The tumor grade for the ACC component was G3: poorly differentiated. Immunohistochemistry confirmed synaptophysin positivity exclusive to areas of neuroendocrine differentiation (Fig. 3D). Additional analysis revealed PD-L1 positivity in 5% of cells using IHC. Finally, the tumor was positive for the high-risk human papillomavirus (HPV) 35 and negative for HPV 16 and HPV 18.

The patient returned to gynecologic oncology clinic on POD 20 without complaints and with adequate healing of the surgical site. The case was discussed at the gynecologic oncology tumor board as a stage IB2 endocervical mixed carcinoma consisting of adenoid cystic carcinoma and neuroendocrine small cell carcinoma. The consensus was for systemic adjuvant chemotherapy with cisplatin and etoposide considering that 60–90% of the mixed tumor was expressing the neuroendocrine phenotype on IHC. The patient declined chemotherapy due to a concern for toxicity.

Alternatively, she was offered and agreed to receive adjuvant radiotherapy. External pelvic irradiation was administered with 15 MV photon beam by the multiportal technique. The total dose of radiation was 4500 cGy in 25 factions of 180 cGy given daily over 5 weeks. The patient completed radiotherapy without any issues. Upon completion of radiotherapy, the patient underwent observation with physical exams every 3 months.

Interval re-staging PET/CT at 6 months from completion of radiotherapy showed multiple FDG avid retroperitoneal lymph nodes that were highly suspicious for recurrent disease. A chemotherapeutic regimen of carboplatin AUC 5/etoposide 100 mg/m² was initiated targeting the aggressive oncologic profile of the neuroendocrine component of the tumor.

After completion of 6 cycles of chemotherapy, and while patient was admitted with uremia, a follow-up CT showed partial response and new moderate left hydronephrosis due to left mid-ureteral obstruction by retroperitoneal lymphadenopathy, which prompted the placement of a left nephrostomy tube for decompression. Once the patient recovered from the acute process of uremia, a PET/CT was performed which revealed multiple FDG avid retroperitoneal lymph nodes that were increased in size when compared to the previous study and interval development of a left supraclavicular lymph node consistent with advancement of metastatic disease.

Given the positive PD-L1 status from the initial tumor and the radiologic evidence of progression of disease, the patient received pembrolizumab 200 mg every 3 weeks. Interval PET/CT in 3 months showed significant disease progression with worsening supraclavicular, paraaortic, and pelvic lymphadenopathy as well as interval development of two tracer avid right hepatic metastatic masses.

Given the rarity of the mixed histology of the tumor and paucity of literature examining the different options of therapy in the recurrent setting, targeted next generation sequencing (NGS) of a 50-gene panel was requested in an attempt to expand the medical options and personalize the treatment plan. NGS analysis revealed a fibroblast growth factor receptor 2 (FGFR2) amplification in the small cell carcinoma component. A FGFR2 c.755C $\rightarrow$ G, p.S252W (15.2%, 679 $\times$) gene variant was detected in and specific to the ACC component. FoundationOne CDx analysis of bulk tumor sample (85–90% SCC and 10–15% ACC) identified FGFR2 amplification and insulin-like growth factor 1 receptor (IGF1R) amplification, presence of a FGFR2- transforming acidic coiled-coil-containing protein 2 (TACC2) fusion, and a subclonal CTNNB1 S45F variant, a gene which encodes for the catenin beta-1 protein, known for being involved in regulation and coordination of

**Fig. 1.** T2 MRI in the A) sagittal and B) axial planes demonstrating a large, heterogeneous bulky mass arising from the cervix with heterogeneous enhancement and complete prolapse through the vaginal opening.
cell–cell adhesion and gene transcription.

In light of the above genomic analysis, targeted therapy with possible enrollment to a clinical trial protocol involving an anti-FGFR agent was discussed with the patient; however, her worsening kidney and hepatic function made her a poor candidate and the patient and her family opted for home hospice care. The patient expired at home a year after the first recurrence of her disease and 18 months from the initial diagnosis of cervical cancer.

3. Discussion

3.1. Historical overview

Treatment regimens for NESCC of the cervix have largely been developed from trial designs from small cell carcinoma of pulmonary origin (Zivanovic, 2009), as recruitment to randomized clinical trials of NESCC of the cervix by cooperative groups have thus far been limited given low disease incidence. Given the aggressive clinical course, NESCC of the cervix has historically been treated with multimodal therapies including radical hysterectomy and radiation (Sevin et al., 1996), as well as platinum-based chemotherapeutics (Hoskins, 1995, 2003; Morris, 1992; Tokunaga, 2013). In patients with FIGO stage I-II NESCC of the cervix, primary radiation with chemotherapy compared to those treated with surgery is associated with improved survival (Chen, 2015). On the other hand, the largest randomized clinical trial of radical surgery versus radiotherapy for stage Ib-Iia cervical cancer included 3% of patients with small cell carcinoma histology, showing that there was no difference in terms of overall or disease free survival (Landoni et al., 2012). Furthermore, retrospective data from two studies on stage I-II NESCC of the cervix showed that adjuvant treatment after radical surgery with combination platinum-based chemotherapy is associated with improved 3-year survival outcomes (Huang, 2014; Pei, 2017). Additionally, neo-adjuvant chemotherapy combined with surgical resection favors improved outcomes (Li, 2015; Yin, 2015). In our case, surgical management was favored versus upfront concurrent chemoradiation due to the completely distorted pelvic anatomy from the procidentia.

Several studies have attempted to identify IHC biomarkers that are uniquely associated with NESCC of the cervix and that may impact prognosis. Carlson et al used IHC to discern histologic differences between small cell carcinoma from ovarian, cervical, and pulmonary origins (Carlson et al., 2007). Using a monoclonal antibody to Wilms’ tumor protein (WT-1), thyroid transcription factor 1 (TTF-1), and p16, these markers were positive in 13%, 38%, and 88% of cases, respectively. IHC of p16 in other studies were positive in 91% (Wang and Lu, 2004) and 100% of cases (Horn, 2006; Masumoto, 2003). Additionally, overexpression of the proto-oncogene c-KIT was variably identified.
between 25% and 43% of cases (Carlson et al., 2007; Ohwada, 2006). In a cohort of 24 patients with NESCC of the cervix, expression of the vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER-2/neu), and cyclooxygenase-2 (COX-2) were evaluated and identified in 95.8%, 33.3%, 41.7%, and 29.2% of cases, respectively. Notably, HER-2/neu expression was associated with prognosis: those with negative HER-2/neu expression had a median survival of 14.2 months compared to 33.1 months in those with HER-2/neu expression (Tangjitgamol, 2005).

Moreover, one study evaluated the expression of the neural cell adhesion molecule (NCAM), also called CD56, a homophilic binding glycoprotein expressed on the surface of neurons, glia and skeletal muscle, in NESCC of the cervix, and determined that this marker was 88% sensitive in identifying NESCC of the cervix (Albores-Saavedra et al., 2005). Others have found that positive IHC staining for chromogranin A may serve as a marker for poor survival (Liao, 2012). However, a separate study of 23 cases of NESCC of the cervix and 56 cases of pulmonary small cell carcinoma found similar IHC staining for CD56 and chromogranin A (Liu et al., 2018).

3.2. Emerging genomic characterization

Beyond IHC evaluation, few studies have examined the underlying genomic characteristics of NESCC of the cervix. Preliminary work from 44 patients with NESCC of the cervix using microRNA (miRNA) analysis revealed downregulation of 6 miRNA that were associated with advanced tumor stage, lymph node metastasis, and poor prognosis (Huang, 2012). Whole exome sequencing of five tumor-normal pairs identified frequent mutations in ATRX and ERBB4, as well as genes in the Akt/mTOR pathway, including NF1, PTEN, RICTOR, and TSC2. Additionally, in this study, ERBB4 IHC staining was appreciated in all primary specimens, but not in surrounding normal tissue (Cho, 2017).

To identify mutations that have been previously associated with cancer, NGS of a 50 gene cancer panel was performed in 44 patients with NESCC of the cervix (Frumovitz, 2016). Of the 44 patients, 48% of patients had a clinically actionable mutation. The most common mutations included PIK3CA (18%), KRAS (14%), and TP53 (11%). Notably, 18% of patients did not have an identifiable driver mutation as part of the 50-gene panel. Thus, future work focusing on comprehensive genomic evaluation, including whole genome and transcriptome sequencing, is warranted.

3.3. FGFR2 alterations

Genomic analysis in our case revealed a FGFR2 amplification in the SCC component and a FGFR2 c.755C > G, p.S252W variant which was detected in and specific to the ACC component. Analysis of bulk tumor sample (85–90% SCC and 10–15% ACC) identified FGFR2 amplification and IGF1R amplification, presence of a FGFR2-TACC2 fusion, and a subclonal CTNNB1 S45F variant. The occurrence of two independent, histology-specific alterations within FGFR2 (gene amplification in the SCC component and gain-of-function mutation in the ACC component) leading to a mixed carcinoma in the cervix is unique. Such an occurrence in the chemotherapy-naïve setting may represent evidence of unique evolutionary pressures (Hasting et al., 2004).

Mutations in FGFR2 are seen in approximately 1.5% of cancers (Helsten, 2016). Specifically, the S252W variant is well-described and

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**Fig. 3.** Representative hematoxylin and eosin stain (A–C) of tumor specimen revealing A) mixed carcinoma, 4×, with both B) adenoid cystic carcinoma, 10×, and C) small cell neuroendocrine, 60×, components. D) Representative section, 4×, with synaptophysin immunohistochemistry positivity exclusive to areas of neuroendocrine differentiation.
increases the affinity for fibroblast growth factors (Byron, 2012; Dutt, 2008; Polluck, 2007). In patients with endometrial cancer, the presence of a FGFR2 mutation is associated with significantly shorter progression-free survival and endometrial cancer specific survival (Jeske, 2017). A second study found that among 466 endometrial tumors, presence of a FGFR2 mutation was significantly associated with shorter disease free survival and overall survival (Byron, 2012). Moreover, whole exome sequencing of 24 cases of ACC from the head and neck region identified variants in FGFR2 in 12.5% of cases (Stephens, 2013).

Fusion events between FGFR and TACC genes are prevalent in glioblastoma and urothelial bladder carcinoma (and others), resulting in constitutive kinase activity, induction of mitotic and chromosomal segregation defects, and triggering of aneuploidy (Lasorella et al., 2016; Singh, 2012; The Cancer Genome Atlas Research Network, 2014). Within gynecologic malignancies, a case of metastatic endometrial carcinoma (Dharni, 2018) and three cases of cervical cancer (a) stage IB1 adenocarcinoma, b) invasive well-differentiated keratinizing squamous cell carcinoma, c) stage II poorly differentiated non-keratinizing (Carrero, 2015) harbored a FGFR3-TACC3 fusion, see also (Tamura, 2019). But, there have been no previous reports of a FGFR2-TACC2 fusion within gynecologic malignancies. The only other report of a FGFR2-TACC2 fusion amongst The Cancer Genome Atlas (TCGA) PanCancer studies is from a mucinous stomach adenocarcinoma sample (TCGA-BR-8080-01).

3.4. Clinical trials

There are currently four open, actively recruiting clinical trials targeting FGFR for which patients with gynecologic malignancies are eligible. First, Debio 1347, an oral selective pan-FGFR-inhibitor, is being evaluated in a Phase 2 trial (NCT03834420) in participants with solid tumors harboring FGFR1-3 gene fusion/rearrangements. Second, ponatinib, a multi-targeted tyrosine-kinase inhibitor, is under study in a Phase 2 trial (NCT02272998) in patients with activating mutations in FGFR1-4 and other genomic targets. Third, erdafitinib, which is an FGFR inhibitor, is under study in a Phase 2 trial (NCT02052778) in patients with relapsed or refractory tumors with FGF/FGFR mutations. Finally, Futibatinib, (aka TAS-120), is another anti-FGFR agent which is being evaluated in a Phase 1 dose-escalation, dose-expansion, and Phase 2 study in patients with advanced solid tumors with FGF/FGFR aberrations (NCT02052778).

4. Conclusions

We report a novel case of mixed adenoid cystic carcinoma and NESCC of the cervix with complete uterine prolapse. Genomic interrogation revealed independent, histology-specific alterations within FGFR2, and a first-in-disease report of a FGFR2-TACC2 fusion. Progression of disease occurred within 6 months after initial resection and radiotherapy, resulting in the initiation of systemic chemotherapeutics. Screening for FGFR2 alterations may be high yield to identify cervical cancer patients who are eligible for targeted therapeutic clinical trials that are currently underway.

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CRediT authorship contribution statement

Corey M. Gill: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. Theofano Orfanelli: Data curation, Writing - original draft, Writing - review & editing. Lorene Yoxthemer: Data curation, Writing - review & editing. Christine Roy-McMahon: Data curation, Writing - review & editing. Jessa Suhner: Data curation, Writing - review & editing. Shannon Tomita: Data curation, Writing - review & editing. Tamara Kalir: Data curation, Writing - review & editing. Yuxin Liu: Data curation, Writing - review & editing. Jane Houldsworth: Data curation, Formal analysis, Writing - review & editing. Valentin Kolev: Conceptualization, Data curation, Supervision, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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