An application of ERBB2 receptor inhibitors in a rare case of S310F somatic ERBB2 mutation of primary signet-ring cell adenocarcinoma of vagina: A case report and review literature of S310F somatic ERBB2 mutation in breast and gynecologic cancers

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1. Introduction
Primary vaginal cancers are uncommon cancers accounting for less than 1% in gynecologic cancers. The majority, up to 80%, of vaginal cancer is squamous cell carcinoma, and less than 15% is adenocarcinoma histology. Signet-ring cell carcinoma (SRCC) is the rarest subtype of adenocarcinoma. SRCC has histologically characterized by an accumulation of intracellular mucin that displaces the nucleus into the periphery. We reported an unusual case of this rare tumor and the utility of actionable targeted drugs based on comprehensive somatic genomic sequencing. Fig. 1.

2. Case presentation
This patient is a 76-year-old postmenopausal Caucasian woman, multiparous, with no known severe underlying illness. She had previously undergone laparoscopic cholecystectomy and parathyroid surgery from benign illnesses. Her father died from lung cancer, and she has a history of kidney, colon, esophagus, and cervical cancer among her second-degree relatives. In mid-2003, she presented with vulvar extramammary Paget's disease. A workup for the extra-periphery. We reported an unusual case of this rare tumor and the utility of actionable targeted drugs based on comprehensive somatic genomic sequencing. Fig. 1.

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without any pelvic or abdominal discomfort. Thus far, she is alive with the 14 months of progression-free since lapatinib was introduced. Lastly, she received concurrent radiation therapy and continue lapatinib for disease control.

3. Discussion

Malignant lesions of the vagina are usually directly spreading or metastasizing from other gynecologic or adjacent organ malignancies, like cervix, vulva, bladder, colon, and rectum. Squamous cell carcinoma is the most common histology subtype, followed by adenocarcinoma, accounting for 80% and 15%, respectively, of primary vaginal cancer. Adenocarcinoma could further be subtyped into clear cell, endometrioid, serous, and mucinous subtypes. Furthermore, mucinous histology is sub-classified as endocervical, intestinal, signet-ring cell, minimal deviation, and villoglandular features. SRCC is an extremely rare subtype of mucinous adenocarcinoma of the vagina. This subtype is frequently seen arising in the stomach and less frequently, in breast, colon, ovary, or cervix. Thus far, 15 cases of primary cervical SRCC and one case in primary vaginal SRCC have been reported in peer-reviewed English literature (Giordano et al., 2012; Cracchiolo et al., 2016; Dhorepatil et al., 2013). Due to the limited number of primary vaginal SRCC cases, the prognosis is unclear, unlike other cell types of epithelial vaginal carcinoma. Importantly, it must be considered to rule out the

Fig. 1. Hematoxylin and eosin (H&E) of intestinal type, vaginal mucinous adenocarcinoma (10X) b) H&E of signet-ring cell feature of vaginal mucinous adenocarcinoma (40X).
metastatic cancers to the vagina before determining the diagnosis of primary vaginal SRCC.

SRCC is a highly malignant dedifferentiated carcinoma and believed to harbor worse prognosis in some cancers. There are two main pathogenesis mechanisms of SRCC: 1) loss of cell–cell adhesion and 2) accumulation of mucin in large vacuoles (Pernot et al., 2015). On a molecular level, erb-b2 receptor tyrosine kinase 2 (ERBB2)/ErbB3 pathway activations are believed to play a significant role in the pathogenesis of SRCC by downstream activation of RAS/RAF/MEK/ERK and PI3K/AKT/mTOR cell signaling pathway. MEK1 and p38 MAP kinase are activated downstream, which in turn phosphorylates effectors that leads to loss of adherence and tight junctions and tumor cells scattering. The mucin production of SRCC is also under the activation of the ERBB2/ErbB3 complex and PI3K/AKT pathway. Once the cells lose their cell-cell interactions, mucin four protein (MUC4), which is usually separated from ERBB2, can activate ERBB2 and forming mucin accumulation, leading to the formation of signet-ring cell features. Aberrant E-cadherin function, which is encoded by the CDH1 gene, is hypothesized as another pathogenesis of SRCC. E-cadherin mutation results in loss of cell’s adherence and tight junctions, which leads to activation of ERBB2 via MUC4 interaction as aforementioned (Pernot et al., 2015; Fukui, 2014).

Treatment options for invasive vaginal carcinoma depend on the individual stage and histology. For the majority of early-stage disease, surgery remains a crucial role treatment, whereas radiation therapy, with or without chemotherapy, is preferable in advanced stage (II-IV) primary epithelial vaginal cancers. However, due to the rarity of reported cases, there is no consensus in treatment for primary vaginal SRCC. Precision medicine is an emerging platform that considers variability in molecular characteristics and genetic environment, as well as an individual’s histopathology. This approach has prompted significant changes in individualized clinical cancer treatment.

Literature review of molecular characteristics of SRCC, the most frequent mutations in vaginal carcinoma as cataloged in the COSMIC database are missense TP53 mutations (6 out of 28, 21%) (COSMIC, 2018; Forbes et al., 2017). Looking at SRCC, more specifically, the TCGA database reported three-fourth of the 14 gastric SRCC cases harboring a TP53 mutation. Even though ERBB2 plays a significant key in the pathophysiology of signet-ring cell formation, ERBB2 amplification was infrequently found, constituting approximately 21.4% in gastric SRCC from the TCGA database (Cancer Genome Atlas Research N, 2014). Non-amplified somatic ERBB2 mutation can be found in various cancer types, ranging from 0.14 to 10.1% (COSMIC, 2018; Forbes et al., 2017). Accurately, S310F somatic ERBB2 mutation was reported as one of the most common pathological hotspots of ERBB2 mutation-driven cancers; for example, in the urinary tract, skin, stomach, cervix, and colon (COSMIC, 2018; Cancer Genome Atlas Research N, 2014). Several published reports have revealed the significant association between somatic S310F ERBB2 mutation and response to ERBB2 inhibitors either in vitro or in vivo (Jasra et al., 2017; Chumsri et al., 2015; Greulich et al., 2012; Vornicova et al., 2014; Ali et al., 2014). Greulich et al. found the transformed lung cancer’s cells with the somatic S310F ERBB2 extracellular domain mutation is sensitive to ERBB2 receptor inhibitors like neratinib; afatinib; lapatinib, and trastuzumab, resulting dissolution of cells (Greulich et al., 2012). A review of the literature revealed three case reports of patients with somatic S310F ERRR2 mutation with breast cancer and one case with extramammary Paget’s disease (Jasra et al., 2017; Chumsri et al., 2015; Vornicova et al., 2014; Ali et al., 2014), as summarized in Table 1. Interestingly, HER2 status, as tested by IHC followed by FISH was negative in each of the case reports. Nevertheless, based on the somatic S310F mutation by next-generation sequencing (NGS), each patient was treated with an ERBB2 inhibitor. Progression-free survival ranged from 6 months to over 12 months, including the regression of metastatic liver lesions and improvement of lumbar bony metastasis after three months of trastuzumab and letrozole as reported by Jasra et al. (Jasra et al.,...
Based on our patient’s comprehensive genomic profiling, she was started on lapatinib treatment. Lapatinib is an oral, small-molecules, dual tyrosine kinase inhibitors of the EGFR-ERBB2 complex and prevents signaling downstream. It has been approved for use in combination with Capecitabine for the treatment of patients with advanced or metastatic breast cancer who overexpress ERBB2 since 2007. In January 2010, the FDA granted approval for use in combination with letrozole for the treatment of metastatic breast cancer patients who had ERBB2 overexpression. Currently, there is no available data in ERBB2 expression in vaginal cancers, but 22% of cervical cancers display ERBB2 expression (Ndubisi et al., 1997). In gynecological cancers, lapatinib has been explored in a phase II study as monotherapy or combined with Pazopanib in patients with advanced and recurrent cervical cancer. Median progression-free and overall survival were 17.1 and 39.1 weeks, respectively, and response rates were 5% (Monk et al., 2010). However, in this trial, the eligible patients were not pre-selected based on ERBB2 overexpression or amplification, which may contribute to the treatment’s minimally enhanced benefits. In this report, the patient experienced the progression of tumors after 14 months of clinical benefit from Lapatinib treatment. To our knowledge, this is the first case report of non-amplified S310F ERBB2 mutation in SRCC of the vagina, suggesting that the advantages of targeting aberrant ERBB2 receptors can be efficacious in lower genital tract cancers beyond breast cancer.

4. Conclusion

SRCC of the vagina is an extremely rare subtype in primary invasive vaginal cancers. Only one case has been reported in the published literature, and our case is the first that incorporated an actionable targeted therapy according to the patient’s comprehensive genomic profile. Lapatinib, ERBB2-inhibitor, demonstrates promising result for our patient, yielding over 12 months of progression-free period.

Author contribution section

June Y. Hou, MD., devised the project, the main conceptual ideas, proof outline, and provided revisions to scientific content of manuscript. Jason D. Wright, MD., devised the project, the main conceptual ideas and proof outline. Vuthinun Achariyapota, MD., wrote the manuscript in consultation with Dr. Hou and Dr. Wright. All authors provided critical feedback and helped shape the manuscript.

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