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Case Series

FGFR3–TACC3: A novel gene fusion in cervical cancer

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ABSTRACT

Cervical cancer epitomizes the success of cancer prevention through the human papillomavirus (HPV) vaccine, but significant challenges remain in the treatment of advanced disease. We report the first three cases of cervical carcinoma harboring an *FGFR3–TACC3* fusion, which serves as a novel therapeutic target. The fusion, identified by comprehensive genomic profiling, activates the FGFR pathway that has been implicated in HPV-driven carcinogenesis. One of the patients whose tumor contained the *FGFR3–TACC3* fusion was treated with an investigational FGFR tyrosine kinase inhibitor. Concomitant molecular alterations involving the PI3K/AKT/mTOR and RAF/MEK pathways were also identified and suggest other treatment strategies that deserve investigation. This case series highlights the role of comprehensive genomic profiling in the identification of new therapeutic targets and in targeted therapy selection for patients with cervical cancer.

1. Introduction

Cervical cancer is a major health challenge with approximately 530,000 news cases and 270,000 deaths annually worldwide despite remarkable advances in screening and prevention through the development of human papillomavirus (HPV) vaccine. While the majority of cervical cancer cases can be potentially cured with surgery, chemoradiation or a combination of these strategies, treatment options for recurrent or metastatic disease are limited to pelvic exenteration or palliative chemotherapy. A recent phase III trial evaluating the combination of cisplatin, paclitaxel and bevacizumab (monoclonal antibody against vascular endothelial growth factor receptor) in the first-line treatment of metastatic disease elicited a 50% response rate and median overall survival (OS) of approximately 17 months (Tewari et al., 2014). Despite these relatively positive data that led to the approval of the first targeted therapy for this disease (bevacizumab), the median progression-free survival of 8 months demonstrates the aggressive behavior of this disease. Hence, there is an urgent need to advance the understanding of the molecular abnormalities driving cervical cancer pathogenesis that could lead to novel targeted therapies. Comprehensive genomic profiling of metastatic tumors is an increasingly relevant tool to identify somatic alterations leading to additional therapeutic options and a better understanding of tumor molecular pathogenesis. Herein, we describe the first three cases of cervical carcinoma harboring *FGFR3–TACC3* fusions revealed by a next-generation sequencing assay able to detect all classes of genomic alterations including gene fusions. The fusion of the fibroblast growth factor receptor gene 3 (*FGFR3*) with the transforming acidic coiled-coil containing gene (*TACC3*) has been described in glioblastoma multiforme, bladder urothelial carcinoma, and non-small cell lung cancer (Wu et al., 2013). While FGFR mutations have been described in cervical carcinomas, the *FGFR3–TACC3* fusion has not been reported previously (Cappellen et al., 1999). This fusion resulting in FGFR pathway activation provided the rationale for treating one of the patients with a FGFR tyrosine kinase inhibitor (TKI) in a clinical study setting and other molecular alterations involving the PI3K/AKT/mTOR pathway hold the potential to inform treatment decisions.

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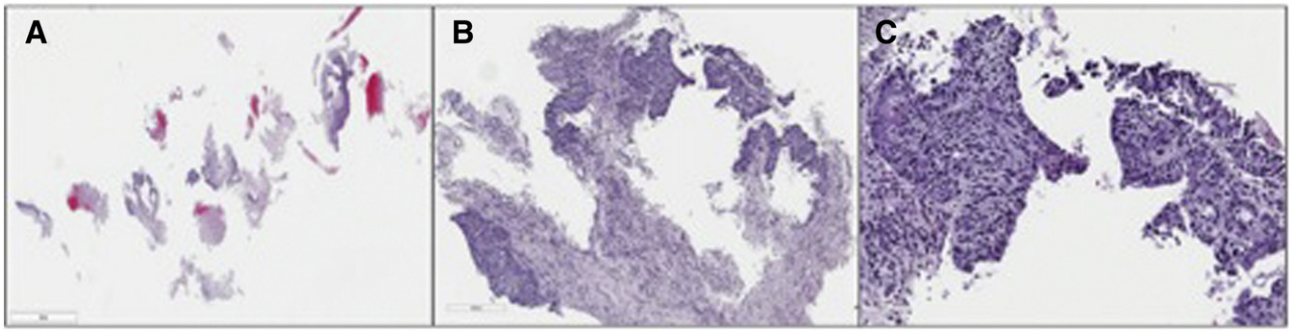

Fig. 1. Left upper lobe lung transbronchial biopsy of cervical carcinoma metastasis utilized for comprehensive genomic profiling (A, H&E, 4× mag). B) Representative tissue fragment is a mixture of metastatic carcinoma, reactive stroma, and inflammatory cells. Tumor nuclei account for approximately 30% of total nuclei (H&E, 20× mag). C) Carcinoma demonstrates both squamous and glandular differentiation (H&E, 200× mag).

2. Case 1

The patient was diagnosed in 1997 at age 36 with stage IB1 adenocarcinoma of the cervix and underwent a modified radical hysterectomy, left salpingo-oophorectomy and bilateral pelvic lymphadenectomy. Adjuvant therapy was not indicated. Twelve years later she developed sudden, significant hemoptysis, and work-up revealed bilateral upper and lower lobe lung masses with left hilar adenopathy. She developed respiratory failure requiring intubation, two arterial embolizations and eventually palliative right middle lobectomy to ameliorate the persistent bleeding. Histopathologic examination of the resected lung mass revealed a carcinoma with mixed glandular and squamous features (adenosquamous carcinoma). The tumor cells were diffusely immunoreactive for p16 and were positive for HPV by PCR, consistent with recurrent cervical cancer. The original hysterectomy specimen was unavailable for comparison.

The patient received multiple palliative chemotherapy regimens (i.e., paclitaxel/carboplatin, cisplatin/topotecan, pemetrexed) as well as stereotactic body radiation therapy. Following two years of active surveillance, her PET/CT scans showed an enlarging left upper lobe mass (5.4 cm with SUV 12.6) causing destruction of the left third rib, and a pleural-based lesion in the right lung (SUV 2.9). Transbronchial lung biopsy of the left upper lobe mass revealed a tumor with both squamous and focal glandular differentiation (Fig. 1). The tumor cells were diffusely positive for p16, Pax8, and p63 by immunohistochemistry and HPV 16 by PCR. The morphology, immunohistochemical staining pattern, and HPV results were consistent with those of the right lung metastatic lesion resected 5 years previously. Comprehensive genomic profiling of the left upper lobe lung tumor was performed to identify additional therapeutic options. Hybridization capture of 236 cancer-related genes and 19 genes commonly rearranged in cancer (FoundationOne®) was applied to ≥50 ng of DNA extracted from archival formalin-fixed, paraffin embedded left upper lung tumor tissue and sequenced to high, uniform coverage. All classes of genomic alterations (base substitutions, small indels, rearrangements, copy number alterations) were determined and revealed the following: *FGFR3–TACC3* fusion (breakpoints at *FGFR3* intron 17 and *TACC3* intron 10), *AKT1* missense mutation (E17K), *mTOR* point mutation (P1312L), and *ATRX* truncating nonsense mutation (W1883*).

Based on the genomic profiling results, the patient was enrolled in a clinical study evaluating a multi-kinase TKI targeting FGFR (NCT1831726). The patient was treated with the study drug for four cycles with best response of stable disease suggesting expected target (FGFR) inhibition (Fig. 2). The treatment was complicated by skin rash and significant fatigue requiring suspension of therapy.

3. Case 2

A 47 year-old female underwent investigation of abnormal uterine bleeding and a cervical biopsy showed an invasive well-differentiated keratinizing squamous cell carcinoma of the cervix. At the time of diagnosis pelvic soft tissue and pelvic lymph node involvement were demonstrated radiographically (FIGO stage IIIB), and she was treated with primary chemoradiation achieving remission. No additional tissue sampling or surgical procedures were performed at this time. The patient developed recurrent disease in the pelvis and adnexa 20 months later and was treated with carboplatin and paclitaxel with partial response after three cycles, receiving a total of five cycles. In July 2014, CT scans showed disease progression, and the patient was started on topotecan and bevacizumab, which was administered for 4 cycles

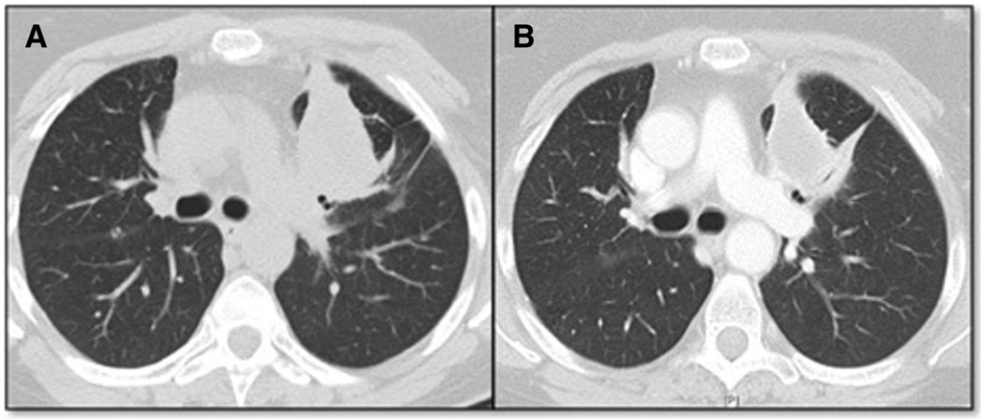

Fig. 2. Chest computed tomography showing the tumor response to treatment with FGFR inhibitor. Panel A: baseline tumor measuring 61 mm. Panel B: tumor after 4 cycles measuring 54 mm.