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Case Report

Significant response to trametinib in a woman with recurrent KRAS-mutated low-grade serous carcinoma of the ovary-a case report

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Abstract: Background: Invasive low-grade ovarian carcinomas differ from more common high-grade serous carcinomas in their pathogenesis, molecular markers, clinical behavior and response to treatment. *KRAS* gene mutations are present in 20 to 40 percent of low-grade serous ovarian cancer, and a smaller percentage of tumors with a wild-type *KRAS* carry *BRAF* gene mutations. As part of the RAS-RAF-MEK pathway, the MEK1 and MEK2 kinases have crucial roles in tumorigenesis, cell proliferation and inhibition of apoptosis and, therefore, MEK1/2 inhibition is an attractive therapeutic strategy. Case presentation: We present a case of a 42 year old Caucasian woman with 14 year history of recurrent low-grade invasive serous carcinoma of the ovary characterized by somatic KRAS 12D mutation, who had significant sustained response to MEK inhibitor trametinib. Conclusion: Molecular profiling of low grade ovarian carcinoma identified a druggable mutation and the tumor responded to targeted treatment with MEK inhibitor trametinib. Clinical trials with MEK inhibitors are ongoing in low grade ovarian cancer.

Keywords: Ovarian cancer, low grade serous, MEK inhibitor, trametinib, *KRAS*

Background

In recent years, a new model of ovarian carcinogenesis has been proposed, suggesting that a subset of serous ovarian cystadenomas evolve through serous borderline ovarian tumors to low-grade invasive epithelial ovarian cancer [1]. In this low-grade pathway, serous borderline ovarian tumor is the precursor lesion and carcinoma evolves through a continuum of histological precursor lesions similar to colorectal adenocarcinoma [2]. Progression is rare, however, as only 2% of borderline serous ovarian tumors go on to invasive carcinoma via the low-grade pathway [3]. Invasive low-grade ovarian carcinomas differ from more common high grade serous carcinomas not only in their pathogenesis, but also in their molecular markers, clinical behavior and response to treatment [4]. Despite these profound differences, low-grade and high-grade ovarian carcinomas are currently treated with the same platinum-based chemotherapy regimens. This treatment approach is usually ineffective in low-grade serous carcinomas, which are considered largely a chemoresistant disease. Therefore, new therapeutic strategies are needed to improve the outcome of these patients. Recent reports have demonstrated that activating mutations in *KRAS* and *BRAF* are common in low-grade ovarian serous carcinomas, [5, 6] suggesting that molecules targeting the MAP kinase pathway may be promising therapeutics [6].

Case report

A 42-year old woman was diagnosed with Stage IIIB serous ovarian tumor of low malignant potential in 1992. She underwent bilateral salpingoopherectomy, lymph node dissection, appendectomy, and omentectomy.

Eight years later, in 2000, invasive low-grade papillary serous ovarian cancer was found in a left supraclavicular lymph node, upper tracheal and mediastinal lymph nodes as well as in the right bronchus. After incomplete surgical cytoreduction the patient was treated with single

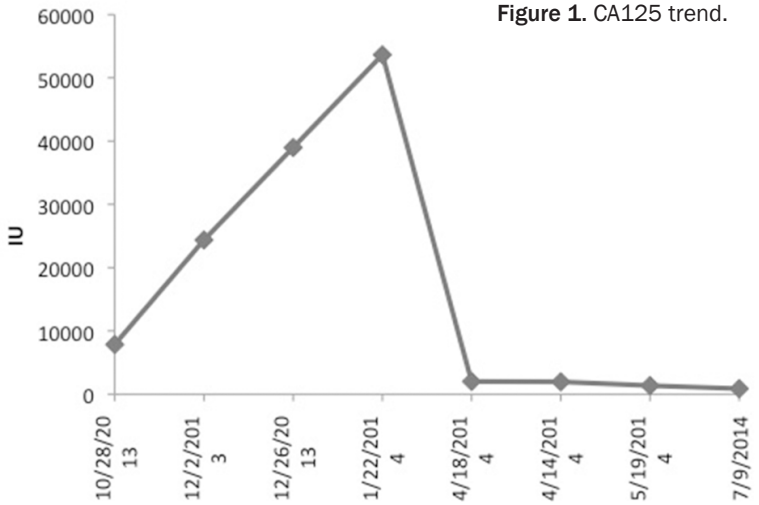

Figure 1. CA125 trend.

agent carboplatin monthly for 15 months followed by maintenance treatment with the aromatase inhibitor anastrozole. Further recurrence led to right axillary and bilateral neck dissections. Metastatic disease of the spine and chest wall was found in 2004 and treated with radiation. A year later a right intrabronchial metastatic lesion was resected and the patient received docetaxel. Over the next 9 years she continued to experience periods of stable disease on treatment followed by recurrent progression of metastatic disease and received in succession topotecan for 6 cycles (10/04-2/05), gemcitabine for 2 cycles (3/05-4/05), and ifosfamide-mesna for 3 cycles (5/05-7/05). A right breast lumpectomy for metastatic tumor was performed in August 2005 and treatment was continued with paclitaxel and gemcitabine, followed by bevacizumab and cyclophosphamide for 7 cycles (9/06-1/07), bevacizumab and protein bound paclitaxel for 10 cycles, liposomal doxorubicin, and finally carboplatin in the later half of 2013. At that time patient had a near complete occlusion of the right main stem bronchus by metastatic disease. The archival tumor material was still available however the patient had received multiple chemotherapy regimens and we sought to obtain a new biopsy to molecularly profile the recurrent disease. With patient's permission and consent an excisional biopsy was obtained through a right bronchoscopy and tumor DNA was screened for mutations across 37 cancer genes using next-generation sequencing (GeneTrails® Solid Tumor Panel). A *KRAS* G12D mutation was identified. A single patient IND was obtained from the FDA on 1/1/2014 for use of the MEK inhibitor trametinib (Mekinist®) at a dose of 2 mg orally per day. Four months after the initiation of treatment the CA125 had decreased from 53,642 to 1,953 (**Figure 1**). At that time a CT scan showed stable disease in the brain, and significant improvement of neck lymphadenopathy (**Figure 2**). Respiratory symptoms that had resulted from collapse of the right lung resolved completely. No significant side effects associated with the use of trametinib were observed. As of the writing of this report, the patient's disease continues to partially respond to trametinib therapy (10 months). Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Discussion

Ovarian cancer has been intensively and comprehensively studied by The Cancer Genome Atlas Project and in many other studies [7]. As the result of these large-scale integrated genomic analyses our understanding of the molecular abnormalities and pathways associated with ovarian cancer has significantly increased. Today ovarian cancer can be more precisely divided into molecular categories rather than into the traditional histologic subtypes and patients are being enrolled in clinical trials that take into consideration molecular markers of disease subtype.

KRAS gene mutations are present in 20 to 40 percent of low-grade serous ovarian cancer, and a smaller percentage of those with a wild-type (wt) *KRAS* carry *BRAF* gene mutations [6]. As part of the RAS-RAF-MEK pathway, the MEK1 and MEK2 kinases have crucial roles in tumorigenesis, cell proliferation and inhibition of apoptosis and, therefore, MEK1/2 inhibition is an attractive therapeutic strategy.

Selective and potent non-ATP-competitive allosteric MEK1/2 inhibitors have been developed

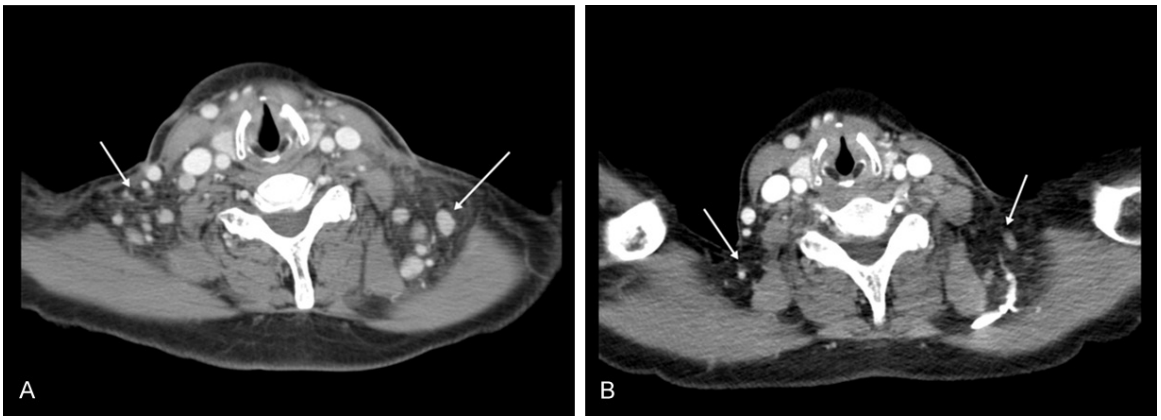

Figure 2. Significant response to treatment. Pretreatment (A) and post treatment (B) contrast-enhanced CT images of the neck performed approximately 6 weeks apart reveal significant improvement in cervical adenopathy. Representative comparison lymph nodes are as marked: bilateral level V nodes (white arrows).

and assessed in numerous clinical studies across several tumor types over the past few years, but with mixed results. For example, the oral MEK1/2 inhibitor trametinib was FDA approved in 2013 for patients with advanced metastatic melanoma whose tumors harbor BRAF V600 mutations [8]. While the drug has significant activity in this setting, it is less effective in tumors harboring *KRAS* mutations (e.g. colorectal and non-small cell lung carcinoma), possibly due to upregulation of ERBB3 signaling [9]. In a GOG (Gynecologic Oncology Group) phase II clinical trial (GOG 0239), 8 of 52 women with recurrent low-grade serous ovarian cancers showed substantial tumor response after treatment with the oral MEK inhibitor selumetinib, and one patient had a complete clinical response [10]. These results are encouraging, however, the surprise in this trial was that responses did not correlate with *BRAF* or *KRAS* mutation status, leaving open the question as to whether these mutations are the right biomarkers in this disease. Our patient, with a particularly indolent *KRAS*-mutant subtype of low-grade serous carcinoma, clearly benefited from trametinib therapy, providing another example of low grade serous carcinoma responding well to a MEK inhibitor. Pending the outcome of ongoing trials such as GOG 0281: A Randomized Phase II/III Study to Assess the Efficacy of Trametinib (GSK 1120212) in Patients with Recurrent or Progressive Low-Grade Serous Ovarian Cancer or Peritoneal Cancer, it may be appropriate to consider treatment of cases of low grade serous carcinoma characterized by *KRAS* and *BRAF* mutation with a MEK inhibitor.

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Disclosure ofconflict of interest

None.

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