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Case report

Clonal lineage of high grade serous ovarian cancer in a patient with neurofibromatosis type 1

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ABSTRACT

Neurofibromatosis type 1 (NF1) is caused by mutations in the *NF1* gene encoding neurofibromin, which negatively regulates Ras signaling. NF1 patients have an increased risk of developing early onset breast cancer, however, the association between NF1 and high grade serous ovarian cancer (HGSOC) is unclear. Since most NF1-related tumors exhibit early biallelic inactivation of *NF1*, we evaluated the evolution of genetic alterations in HGSOC in an NF1 patient. Somatic variation analysis of whole exome sequencing of tumor samples from both ovaries and a peritoneal metastasis showed a clonal lineage originating from an ancestral clone within the left adnexa, which exhibited copy number (CN) loss of heterozygosity (LOH) in the region of chromosome 17 containing *TP53, NF1*, and *BRCA*1 and mutation of the other *TP53* allele. This event led to biallelic inactivation of *NF1* and *TP53* and LOH for the *BRCA1* germline mutation. Subsequent CN alterations were found in the dominant tumor clone in the left ovary and nearly 100% of tumor at other sites. Neurofibromin modeling studies suggested that the germline *NF1* mutation could potentially alter protein function. These results demonstrate early, biallelic inactivation of neurofibromin in HGSOC and highlight the potential of targeting RAS signaling in NF1 patients.

1. Introduction

Neurofibromatosis type 1 (NF1) is one of the most common autosomal dominant disorders affecting approximately 1 in 3500 individuals. The disease is caused by mutations in the *NF1* gene and shows complete penetrance (Yap et al., 2014). *NF1*, which encodes a GTPase-activating protein (neurofibromin) that negatively regulates RAS-signaling pathways, is considered a classical tumor suppressor gene. NF1 patients have an estimated lifetime risk of 59.6% of developing cancer resulting in a decreased life expectancy of 10–15 years (Walker et al., 2006). While *NF1* haploinsufficiency may have functional consequences, biallelic inactivation of *NF1* frequently precedes or occurs simultaneously with malignant transformation in NF1-related cancers (Yap et al., 2014; Maertens et al., 2006).

Recent evidence suggests that NF1 is associated with an increased incidence of early onset breast cancer and biallelic inactivation of *NF1* is an early event in tumorigenesis (McPherson et al., 2015). An association between NF1 and ovarian cancer is emerging and somatic mutations and copy number alterations (CNA) of *NF1* are frequently observed in high grade serous ovarian cancer (HGSOC) (Cancer Genome Atlas Research N, 2011; Patil and Chamberlain, 2012; Kanchi et al., 2014; Salud et al., 1991; Ceccaroni et al., 2002; Jeon et al., 2015). We present the case of a woman who developed two separate NF1-related malignancies (malignant peripheral nerve sheath tumor (MPNST) and HGSOC) before the age of 44. Whole exome sequencing (WES) of tumor DNA from bilateral ovaries and peritoneal metastasis was performed to investigate tumor evolution and determine whether biallelic inactivation of *NF1* is an early event of ovarian carcinogenesis.

2. Case history

A 44-year-old gravida 5, para 3 African American female presented

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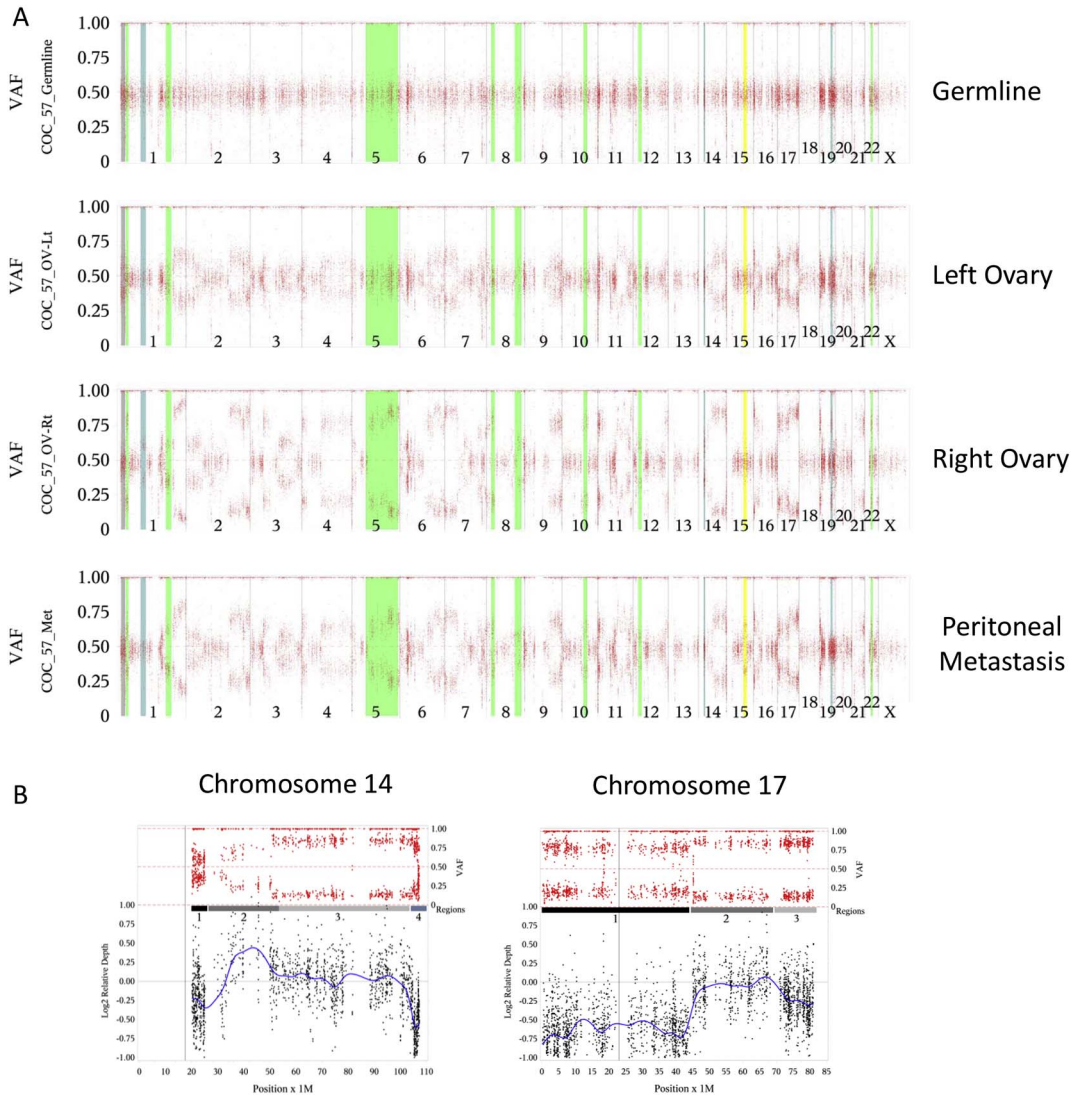

Fig. 1. Copy Number Alterations. (A) Genomic profile of CNA in tumor samples isolated from the left ovary, right ovary, and peritoneal metastasis. Germline DNA was used as a reference. Regions of interest are shaded as unique to left ovary (grey), unique to right ovary (blue), unique to peritoneal metastasis (yellow), and common between right ovary and peritoneal metastasis (green). (B) A detailed Variant Allele Frequency and Relative Depth Log Ratio plot from the right ovary tumor sample indicating the regions where copy number alterations occurred on chromosomes 14 and 17. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to the emergency department complaining of back and abdominal pain associated with weight loss, constipation, and anemia. A computed tomography scan revealed a 12 × 12 × 10 cm mass with displacement of the uterus, peritoneal carcinomatosis, ascites, and pelvic adenopathy. The CA125 level was 1971 U/mL. Her past medical history was significant for NF1 and two NF1-related tumors: a benign schwannoma excised from the breast 25 years previously and a T2bN0M0 PMNST of the right knee, treated with excision and radiation 7 years previously. A fine needle aspirate biopsy of the pelvic mass showed PAX8 (marker of Müllerian origin) positive HGSOC revealing a new primary gynecological malignancy, not a MPNST recurrence. The patient underwent radical tumor resection with total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy and tumor resection, for optimal cytoreduction. Pathological review was performed per sectioning and extensively examining of the fimbriated end (SEE-FIM) protocols. HGSOC was noted in both ovaries and peritoneal metastasis with < 1% of the right fallopian tube (serosal side) involved. No serous tubal intraepithelial carcinomas were observed. Final pathological diagnosis was HGSOC arising from the ovary, stage IIB. After an uneventful post-surgery recovery, the patient refused adjuvant chemotherapy. Six months after surgery the patient experienced tumor progression and began a course of dose dense carboplatin/paclitaxel. After 9 cycles of chemotherapy, CA125 levels normalized (< 5 U/mL), but a CT scan showed a residual 11 × 12 mm nodule in the pelvic mesentery. At the time of this manuscript, the patient is alive and receiving salvage chemotherapy for platinum-resistant progressive disease.

3. Results and discussion

Since malignant transformation of NF1-related cancers frequently involves early somatic mutation of the wild-type *NF1* allele followed by an additional genomic event (e.g. *TP53*, *CD2KNA* loss), we hypothesized that biallelic *NF1* inactivation was an early event in the development of HGSOC in this patient (Upadhyaya et al., 2004). To study tumor evolution, we performed WES on tumor samples obtained from each ovary and one peritoneal metastasis. Sequencing of germline DNA (average depth 130 ×) revealed a missense mutation (c.7161C > G) in *NF1* and a deletion in *BRCA1* (c.1846_1848del), located in trans. The mutation in *NF1*, which leads to substitution of asparagine 2387 to lysine has not been previously reported and is characterized as a variant of unknown significance (VUS). However, based on the patient's clinical diagnosis and a previous report of a pathogenic *NF1* mutation involving