Bilateral Low-Grade Serous Ovarian Carcinoma with Multiple Metastases in Neurofibromatosis Type 1 Due to Germline *NF1*: c.4236_4237insAlu

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Case Presentation

A 34-year-old woman presented with gradually worsening abdominal distention, pelvic pressure, and early satiety. She carried a clinical diagnosis of neurofibromatosis type 1 (NF1), with characteristic findings including multiple café-au-lait macules, axillary freckling, and numerous cutaneous neurofibromas, along with a family history of similarly affected relatives. Imaging studies revealed bilateral complex adnexal masses, diffuse peritoneal carcinomatosis, ascites, and small pulmonary nodules. Diagnostic laparoscopy confirmed extensive peritoneal disease, and biopsy specimens demonstrated classic low-grade serous ovarian carcinoma (LGSOC), featuring micropapillary architecture, uniform low-grade nuclei, psammoma bodies, and wild-type p53 staining. She subsequently underwent optimal cytoreductive surgery, with final staging of FIGO stage IIIC bilateral LGSOC and widespread metastatic involvement. Tumor-only next-generation sequencing (NGS) did not identify pathogenic variants in *KRAS, BRAF, NRAS, TP53*, or *NF1*. Given her clinical features consistent with NF1 despite negative somatic testing, her young age, bilateral tumors, and unusually extensive metastatic burden, comprehensive germline evaluation was pursued. DNA-based multigene testing was nondiagnostic. However, RNA sequencing identified a pathogenic germline *NF1* c.4236_4237insAlu insertion, confirming Alu-mediated disruption of neurofibromin as the underlying molecular mechanism of her NF1. Clinically, she initially demonstrated platinum sensitivity and later achieved a durable partial response with combined RAF/MEK inhibition and focal adhesion kinase inhibition.

Discussion

This case represents the first reported instance of bilateral metastatic LGSOC in a patient with NF1 due to a germline Alu insertion. Ovarian carcinoma is exceedingly rare in NF1, and previously described cases have almost exclusively involved high-grade serous histology. The development of LGSOC in this context suggests that *NF1* alteration may serve as an alternative mechanism of MAPK pathway activation, substituting for the *KRAS* or *BRAF* mutations typically seen in LGSOC. Her extensive metastatic disease at presentation and partial platinum responsiveness are atypical for LGSOC, which generally follows an indolent course and exhibits relative chemoresistance. Although speculative, *NF1* alteration may have contributed to this unusually aggressive clinical behavior through enhanced RAS-MAPK signaling. Her response to RAF/MEK and FAK inhibition further supports MAPK pathway dependence in *NF1*-driven LGSOC. This case also highlights the limitations of tumor-only sequencing. Retrotransposon insertions such as Alu elements frequently escape detection by standard short-read NGS pipelines, leading to incomplete molecular characterization. RNA-based germline testing was essential for identifying the pathogenic Alu insertion, underscoring the importance of comprehensive germline evaluation in patients with clinical suspicion. Overall, this case expands the recognized spectrum of NF1-associated malignancies and illustrates a novel mechanism of MAPK activation in LGSOC.