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Case report

A 24 year-old patient with no prior history of endometriosis diagnosed with bilateral ovarian endometrioid adenocarcinoma arising in endometriosis

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1. Introduction

Endometriosis, defined as the growth of endometrial glands and stroma outside of the uterine cavity, is a common disease affecting up to 15% of reproductive age women (Bulun et al., 2019). The prevalence is dramatically increased in the following subgroups: women with infertility, women requiring long-term hormonal contraceptives and women with chronic pelvic pain. The disease can manifest with various acute and chronic symptoms that affect quality of life including pelvic pain, dysmenorrhea, infertility, and dyspareunia, however it can also exist in women who are completely asymptomatic (Bulun et al., 2019).

Beyond the burden of symptoms and fertility-related sequelae of the disease, endometriosis also comes with an increased risk of developing endometriosis-associated ovarian cancer (EAOC). The relationship between endometriosis and ovarian cancer was first postulated by Sampson in 1927 and has remained an intense area of focused research since then. The malignant transformation of endometriosis is complex but most simply put represents a transformation of benign endometriosis to atypical endometriosis and eventually to EAOC. This pathway between endometriosis, atypical endometriosis, and EAOC is triggered by oxidative stress, inflammation, hyperestrogenism, and genomic alterations, specifically mutations in ARID1A, PTEN, HNF1B, PIK3CA and/or

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KRAS (Bolivar et al., 2019).

The lifetime risk of developing ovarian cancer in the general population is estimated to be 1 in 76 or 1.31% (Kvaskoff et al., 2017). Using relative risks calculated from multiple meta-analyses, the lifetime risk of women with endometriosis developing ovarian cancer is 1.8% which, although overall reassuring, must be interpreted with appropriate scrutiny as the prevalence of endometriosis in the general population is largely understood to be underestimated and underdiagnosed (Kvaskoff et al., 2017). Atypical endometriosis, especially when involving the ovary, is considered a precursor lesion for both endometrioid and clear-cell ovarian cancers and carries up to a 4-fold increased risk of malignant transformation compared to benign or typical appearing endometriosis (Tanase et al., 2013). The reported incidence of atypical endometriosis in the current literature ranges from 1.7% to 4.4% of endometriotic lesions (Guo et al., 2008; Fukunaga et al., 1997). In a national database study including 49,933 patients with surgically confirmed endometriosis, Saavalainen et al showed that ovarian endometriosis was associated with a 5-fold increase in incidence of endometrioid ovarian cancer and a 10-fold increase in incidence of clear cell ovarian cancer (Saavalainen et al., 2018). Given that endometriosis is reported to be found in association with up to 51% of all endometrioid or clear cell ovarian carcinomas, a large volume of research has been performed attempting to stratify patients by clinical, molecular, and/or pathological risk factors to determine which subset(s) of patients with endometriosis are at highest risk for malignant transformation and who may subsequently benefit from more aggressive management or possibly even risk-reducing strategies (Dawson et al., 2018).

In this case study, we present a case of bilateral ovarian endometrioid adenocarcinoma arising in the background of endometriosis in a 24-year-old woman with no prior history or symptoms suggestive of endometriosis. The patient provided informed consent prior to initiation of this case report.

2. Case report

A 24-year-old woman, gravida 0, presented to her gynecologist with a complaint of abdominal bloating for several months. She was sent for an abdominal and pelvic ultrasound which revealed a large, complex, predominantly cystic mass extending to the level of the abdominal aorta and epigastrium to the pelvis measuring 23 × 17 × 24 cm. This mass was noted to have multiple septations with thick walls and some solid components and was compressing the ureters causing bilateral hydro-ureteronephrosis. Subsequently, she was referred to a gynecologic oncologist for consultation.

An abdominal and pelvic MRI was obtained which again demonstrated a 26 × 18.9 × 20.1 cm cystic and solid mass displacing the uterus anteriorly (Fig. 1). No normal ovary was identified on either side. Tumor markers resulted as follows: CA-125 was 235 U/mL, CA19-9 49.1 U/mL and CEA 1.0 U/mL. The patient had no significant past medical, surgical or gynecological history, no toxic habits and no reported family history of malignancy.

She was taken to the operating room and an exploratory laparotomy was performed. Upon entry into the abdomen, the patient was noted to have bilateral massively enlarged ovaries which were each replaced entirely by tumor (Fig. 1). The right side was enlarged to approximately 20 cm in greatest diameter and the left side was enlarged to approximately 15 cm. Of note, the left ovary was noted to have a 1.0 cm tumor implant on the capsule wall. The remainder of the pelvic and abdominal survey was unremarkable. Due to the nature of the cysts entirely replacing each ovary, it was not technically feasible to perform a cystectomy on either side or to preserve any normal ovarian parenchyma, thus both ovaries and fallopian tubes were removed entirely intact with no spillage of cystic contents. The uterus was left in situ.

The specimens were brought to the pathology lab and each ovary was bisected and examined (Fig. 1). They were both noted to have cystic and solid components as implied by pre-operative imaging. The solid components had innumerable papillary excrescences and the cystic components with chocolate colored cystic fluid consistent with endometriomas. Histopathological evaluation of her specimens revealed a bilateral, well-differentiated (grade 1), at least stage IC2 endometrioid ovarian adenocarcinoma arising in the background of atypical endometriosis. She was treated with three cycles of adjuvant chemotherapy, carboplatin AUC6 and paclitaxel 175 mg/m² every 21 days, after which she has remained no evidence of disease. She has remained asymptomatic and disease-free since her diagnosis, approximately 16 months.

3. Materials and methods

Archival formalin-fixed, paraffin-embedded samples (FFPE) were obtained from the patient's surgical specimens (Fig. 2). A board certified pathologist reviewed Hematoxylin and Eosin (H&E) slides. Unstained slides were obtained from the best representative samples of typical endometriosis, atypical endometriosis and adenocarcinoma. DNA was extracted from FFPE fixed benign endometriosis, atypical endometriosis and endometrioid adenocarcinoma specimens using All Prep DNA/RNA mini kit. Next generation sequencing was performed on extracted DNA using OncoPrint comprehensive assay v3 on Ion S5XL sequencer according to manufacturer's instruction. Sequencing data were analyzed

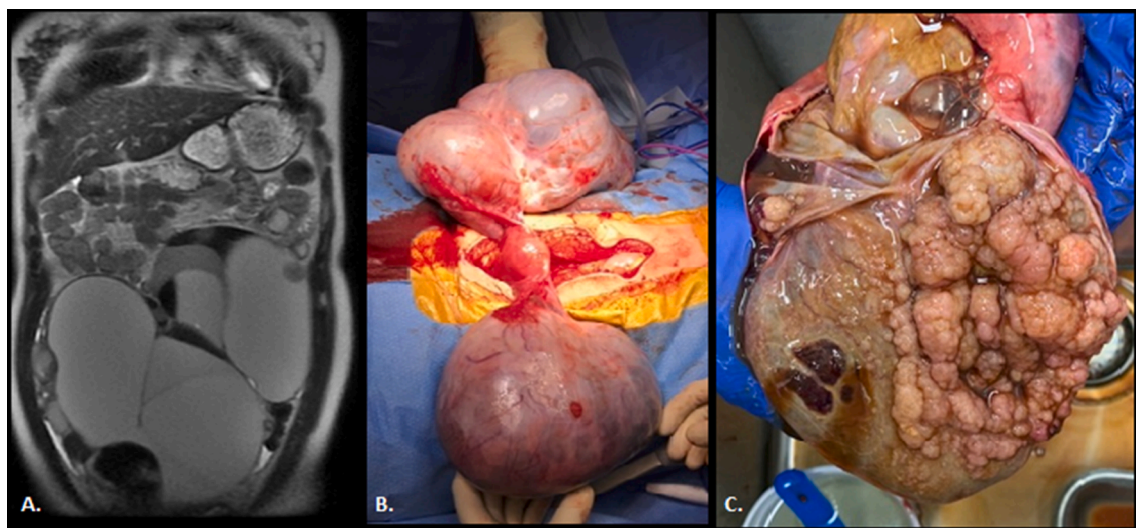


Fig. 1. (A) MRI abdomen/pelvis coronal view (B) Intraoperative findings (C) Bisected ovary.

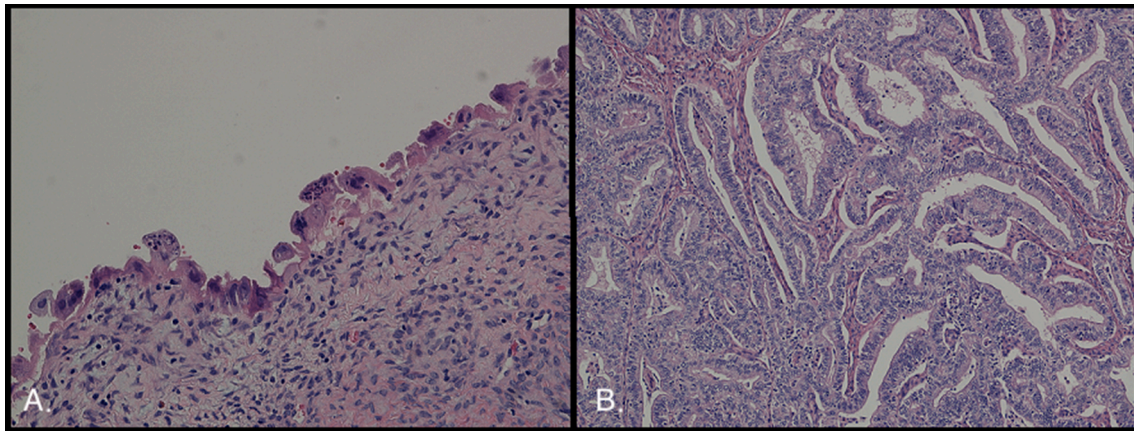


Fig. 2. (A) 20x view of atypical endometriosis, showing epithelial cells with nuclear and cytoplasmic enlargement, mild nuclear pleomorphism and prominent nucleoli. Subepithelial loose stroma characteristic of endometriosis. (B) 20x view of the tumor showing back to back arrangement of malignant glands.

using the Torrent Suite software (version 5.12), Agilent Alissa Interpret v5.2 and Ion Reporter (OCAv3) software.

4. Results

Next generation sequencing results of sequenced DNA showed genetic alterations in CTNNB1 (CTNNB1p.S37C, VAF = 23.7%), PIK3CA (PIK3CA p.H1047L; VAF = 25.2%), and PTEN (PTEN p.P269L VAF = 24%; PTEN p.F309S VAF = 25.7%) genes in the endometrioid adenocarcinoma specimen. An observed mutation in the atypical endometriosis tissue in PTEN (PTEN p.F309S VAF = 2.9%) was similar to that observed in endometrioid tumor but at higher allelic fraction. No genetic alterations were detected in the benign endometriosis specimen.

5. Discussion

We identified the youngest patient reported to date with bilateral ovarian endometrioid adenocarcinoma arising from endometriosis. From her available surgical specimens, we performed NGS on three distinct tissue types. The benign-appearing endometriosis tissue harbored no abnormal mutations. The atypical-appearing endometriosis tissue showed a PTEN mutation. Lastly, her endometrioid adenocarcinoma specimen revealed the same PTEN mutation found in the atypical endometriosis specimen with higher allelic fraction as well as additional mutations in CTNNB1 and PIK3CA genes. Thus, our data clearly demonstrates that there is a direct correlation between mutational burden and histologic findings in this patient.

The exact pathogenesis of endometriosis associated ovarian cancer (EAOC) remains a topic of ongoing research but genetic, immunological and hormonal factors have all been identified. From a genetic standpoint, multiple candidate genes have been implicated in the malignant transformation of benign endometriosis to carcinoma, with PTEN, ARID1A and PIK3CA being the most heavily studied (Bolivar et al., 2019; Wei et al., 2011). Mutations in the PTEN gene, specifically, have been frequently identified early in the development of neoplasia and thus PTEN mutations often serve as a predictive molecular biomarker for tumorigenesis (Lupini et al., 2019).

Similar to our study, Er et al. performed NGS on tissue from 6 patients (age 37–72) with EAOC (Er et al., 2016). For each patient, analysis was performed on normal endometrium, ectopic endometriotic lesion, atypical endometriosis and carcinoma. In 5 out of 6 patients, the investigators were able to demonstrate that identical somatic mutations were detected in atypical endometriosis and the tumor lesions. Their findings, like ours, suggest that there may be a role for genetic analysis of preneoplastic endometriotic lesions in helping to identify patients at risk for malignant transformation into EAOC. In contrast to their study,

our case involves a significantly younger patient with no prior history of endometriosis or symptoms suggestive of endometriosis.

The clinical risk factors for malignant transformation of endometriosis remain largely unknown although some retrospective studies have suggested the following features may confer higher risk: (1) history of long-standing endometriosis (2) endometriosis associated with infertility (3) endometriosis diagnosed at an early age (Sharma et al., 2012). Our presented case clearly demonstrates that very young women without any history of symptoms suggestive of endometriosis also remain at risk.

In summary, we emphasize the importance of initiating care with a gynecologist as early as clinically indicated (sexual debut vs age 21) in order to increase the detection of asymptomatic adnexal masses in very young women that may warrant work-up and either surveillance or surgical intervention. We further conclude that young women with evidence of endometriosis/endometrioma(s) by history, clinical exam or imaging should consider confirmatory diagnostic laparoscopy with biopsies and molecular testing of endometriotic lesions to help stratify patients which may require closer follow-up and perhaps more aggressive management in the future to prevent the development of EAOC.

CRediT authorship contribution statement

Shannon Tomita: Conceptualization, Methodology, Investigation, Writing - original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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