

Case report

A case of vaginal adenositis with gastric differentiation

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1. Background

Vaginal adenositis, thought to be a non-obligate precursor for clear cell carcinoma (Wong, 2018), occurs when normal squamous cell mucosa is replaced with metaplastic glandular epithelium. One known risk factor for vaginal adenositis is in utero diethylstilbestrol (DES) exposure, which has a reported prevalence of anywhere from 35 to 90% in exposed women (Kranl, 1998).

DES is a synthetic estrogen that was developed in 1938 and prescribed to 5–10 million pregnant women to prevent miscarriages and preterm labor. In 1971, published research showed DES to be the cause of rare vaginal adenocarcinomas. It was removed from the market by the United States Food and Drug Administration that same year (“DES History” <https://www.cdc.gov/des/consumers/about/history.html> Accessed January 28, 2020). Since the removal of DES from the market, vaginal adenositis has become an increasingly rare disease that can be difficult to diagnose and even more difficult to treat and perform appropriate cancer screening for. Adenositis may present with a variety of symptoms including vulvar pain or soreness, vaginal bleeding, vaginal discharge, vulvar lesions, or can be found incidentally on exam (Martin, 2013). Furthermore, the causes of vaginal adenositis in the absence of DES exposure, as well as the ideal treatment, have yet to be determined.

We present below a case of vaginal adenositis found in a non-DES exposed woman who had initially been diagnosed with vaginal adenocarcinoma; her course, treatment, and a review of the literature will

hopefully aid other clinicians if presented with this rare diagnosis.

2. Case

A previously healthy 47-year-old female gravida 3 para 3 smoker presented to a urogynecologist with symptoms of stress urinary incontinence. See Fig. 1 for sequence of events. She was amenorrhoeic secondary to a levonorgestrel intrauterine device (IUD), in place for 6 years. She had no history of abnormal Papanicolaou (Pap) tests. Her eldest sister was the only one of five siblings exposed to DES in utero. Family history for gynecologic or colon cancers was negative. Her surgical history was notable for an open appendectomy at age fourteen and a laparoscopic cholecystectomy.

Office examination revealed a cystic appearing mucosa overlying the distal urethra and a friable, cystic, tender 4 × 3 cm exophytic mass in the mid-vagina. Cystourethroscopy demonstrated a normal urethra and bladder. Cervical biopsies and an endocervical curettage (ECC) were consistent with normal cervical tissue. Fig. 2 shows a pelvic magnetic resonance imaging (MRI) study with and without contrast which demonstrated innumerable sub-centimeter T2 hyperintense, well-circumscribed cystic-appearing lesions distributed circumferentially within the vaginal wall. Some lesions demonstrated thin enhancing internal septations without solid enhancing components or restricted diffusion. The lesions did not invade the vaginal wall and paravaginal fat planes were well preserved. The remainder of the pelvis was

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unremarkable.

She was referred to a gynecologic oncologist. A speculum examination was consistent with the aforementioned exam. There was no lymphadenopathy. She underwent examination under anesthesia with vaginal biopsies and removal and insertion of a levonorgestrel IUD. The

cystic lesions were mostly clustered in the posterior fornix while the largest and most prominent lesion was at the distal anterior vagina. Pathology reported infiltrating mucinous adenocarcinoma from five biopsy sites. Due to the rare nature of this diagnosis, the patient underwent further testing to rule out another primary cancer source.

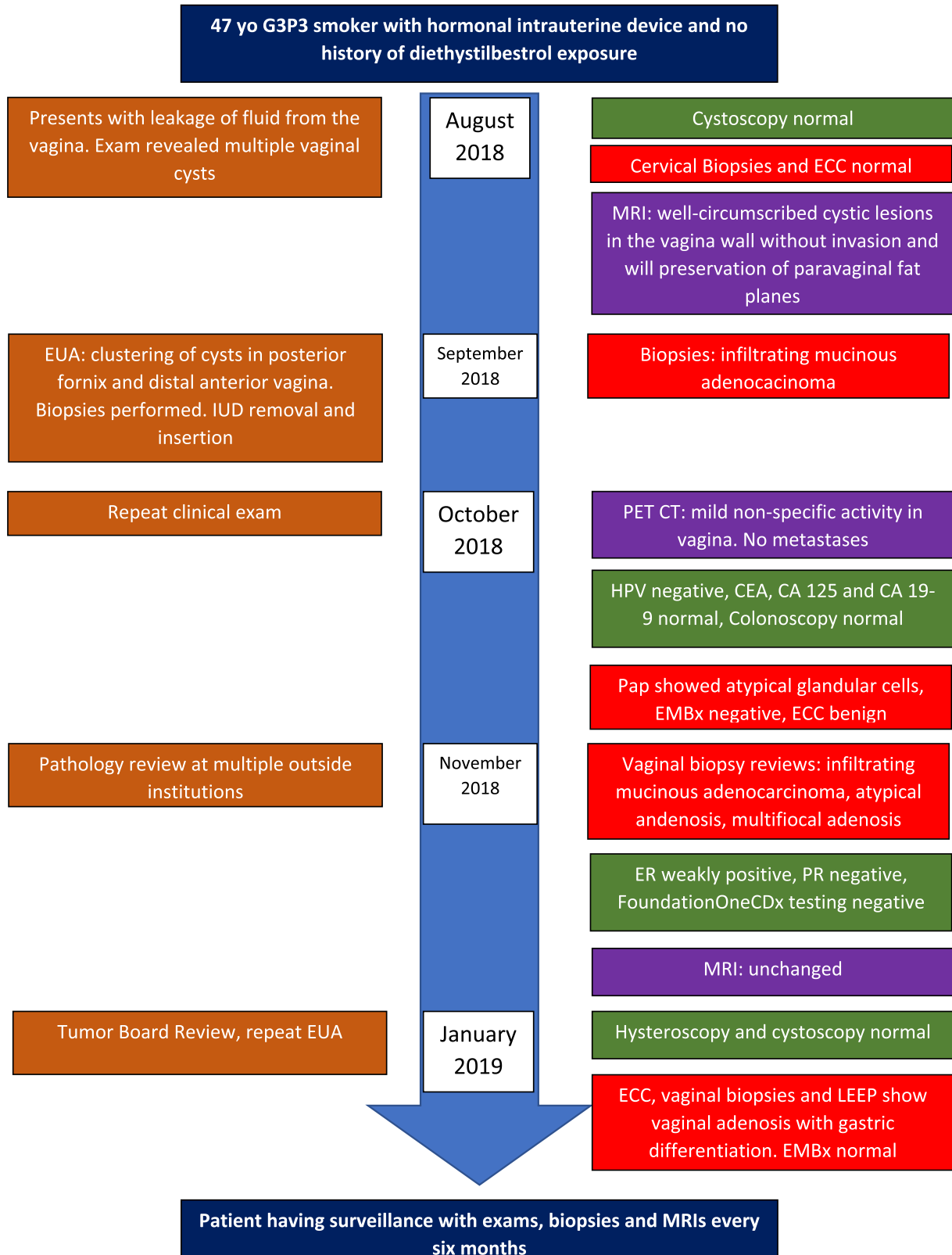


Fig. 1. Timeline of clinical events.



Fig. 2. Sagittal T2-weighted magnetic resonance image of the pelvis demonstrates innumerable small, well-circumscribed, T2 hyperintense lesions circumferentially lining the vaginal wall. Several have thin septations but there were no solid nodular components or evidence of invasion through the vaginal wall.

Positron emission tomography-computed tomography (PET CT) revealed non-specific mild activity in the vagina and no evidence of metastatic disease. Repeat clinical exam showed stable lesions while repeat biopsies of the cervix and vagina lesion were inconclusive, citing disrupted cervical tissue with endocervical type epithelium and stromal reaction. Invasive tumor could not be ruled out. The ECC showed focally immature squamous metaplasia with strips of endocervical type epithelium with mild focal atypia. The endometrial biopsy was benign. Repeat Pap testing showed atypical glandular cells suspicious for neoplasm. Her HPV testing was negative for high-risk types. Tumor markers carcinoembryonic antigen (CEA), cancer antigen (CA) 125 and CA 19-9 were all within normal limits (3.7 ng/mL, 17.9 U/mL, <2 U/mL, respectively). She underwent lower endoscopy, which revealed a 0.4 cm benign tubular adenoma and was otherwise unremarkable.

The pathology slides were reviewed by three additional institutions,

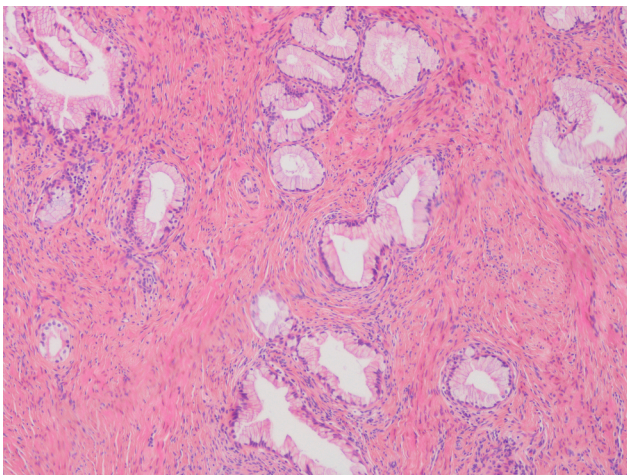


Fig. 3. Hematoxylin and eosin section at (40×) shows the overall architectural pattern of simple glands. There is a retained lobular architecture and lack of desmoplastic response within stroma.

but there were differing opinions amongst the gynecologic pathologists (See Figs. 3 and 4). Interpretations included: infiltrating mucinous adenocarcinoma, atypical adenosis with gastric mucinous phenotype, and multifocal adenosis.

Due to the complex nature of the pathological findings and unclear diagnosis, a repeat MRI of the pelvis was performed with no significant changes. Estrogen receptor/progesterone receptor (ER/PR) staining was weakly ER positive (50%) and PR negative. The tumor was also sent to Foundation Medicine for FoundationOneCDx testing and was negative for actionable mutations.

The patient was evaluated by radiation oncology and discussed at tumor board with consideration for chemoradiotherapy for presumed vaginal adenocarcinoma. However, given the uncertainty, the team and the patient elected for surveillance that consisted of repeat imaging and biopsies.

Approximately 6 months after her initial presentation, multiple vaginal biopsies, ECCs and a cervical loop electrosurgical excision procedure (LEEP) revealed adenosis with gastric mucinous phenotype and atypia. Pathology noted that the biopsies were deeper, providing underlying stroma that better demonstrated the lack of an infiltrative growth pattern. Repeat endometrial biopsy was unremarkable. Hysteroscopy and cystoscopy revealed a grossly normal endometrial cavity and bladder, respectively. Currently she is doing well and continuing surveillance with every 6-month exams, biopsies and MRIs.

3. Discussion

Adenosis is a histopathological phenomenon that occurs when squamous epithelial cells lining the vagina and the ectocervix distal to the squamocolumnar junction are replaced by glandular columnar epithelium (Laronda, 2012). During normal embryological development, the proximal two-thirds of the vagina forms from fused Müllerian (paramesonephric) ducts and the distal one-third of the vagina comes from cranial evaginations of the urogenital sinus (Hoffman, et al., 2016). It is currently believed that the vaginal epithelium originates from the Müllerian ducts and that these cells are stimulated by nearby paracrine hormones to become squamous or columnar epithelium. DES has been shown in mouse models to inhibit the generation of Müllerian epithelium, replacing it with that of epithelium originating from the urogenital sinus (Hoffman et al., 2016). This level of differentiation occurs in utero. By the time that a woman reaches adulthood, the cells lining her vagina have typically lost the potential to differentiate in this way (Laronda, 2012).

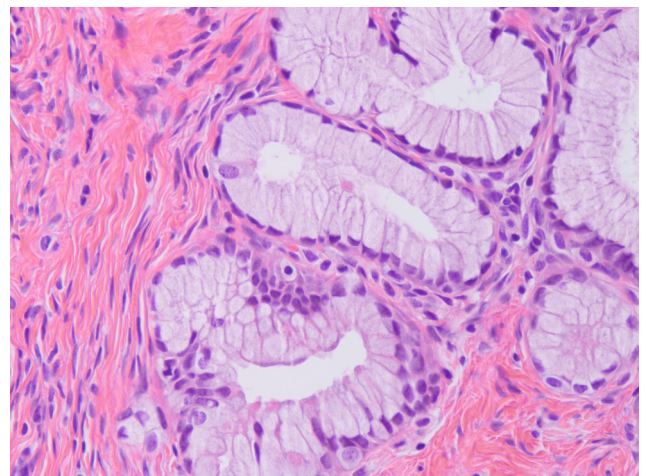


Fig. 4. Hematoxylin and eosin section at (200×) with simple glands within background stroma with small nuclei, no distinct nucleoli, and abundant amphophilic luminal cytoplasm. The distinct cell borders and gastric foveolar-type resemblance supports a gastric-type adenosis.

One theory on the origin of vaginal adenosis suggests it is linked to stimulation by sex hormones in the prepubertal stages of development. This theory is supported by autopsy-derived studies examining DES-naïve female fetuses and women up to age 25. The studies showed increased rates of vaginal adenosis among fetuses in utero until 1 month of age as well as in patients ages 15–25 years, periods of time in development during which exposure to sex hormones is physiologically elevated (Kranl, 1998).

Because of the association between vaginal adenosis and clear cell adenocarcinoma learned from the experience with DES, this lesion is widely regarded as a non-obligate precursor of clear cell adenocarcinoma. The documented incidence of vaginal adenosis among women with DES-exposure ranges from 35 to 90% (Kranl, 1998) and importantly, almost all DES-exposed women diagnosed with vaginal clear cell adenocarcinoma were found to have vaginal adenosis (Laronda, 2012). Although the histopathologic progression from vaginal adenosis to vaginal clear cell carcinoma is still unknown, vaginal adenosis in DES exposed women is deemed a lesion with malignant potential that must be followed closely with exams and dedicated vaginal cytology.

The incidence and clinical significance of vaginal adenosis in the absence of DES exposure is not completely understood. The largest study to date by Han, et al examined 20 years of medical records at a large academic medical hospital in China. Of the 997 patients identified with primary vaginal disease, 20 patients were identified with histologically confirmed vaginal adenosis. All 20 patients underwent local excision of their lesions. Four patients went on to develop malignancy (one squamous cell, one mucinous, and two clear cell carcinomas) (Han, 2018). These findings would seem to confirm that while the incidence is very rare its malignant potential is still quite high. However, this study is small and occurred in a single region. There may be yet unknown regional or genetic risk factors that would change the incidence and outcomes in other populations.

This case of vaginal adenosis in a non-DES exposed woman highlights the potential challenges of histological diagnosis of this rare condition. It additionally demonstrates that while the association between vaginal adenosis and vaginal clear cell carcinoma is well established, the management of a diagnosis of vaginal adenosis is not. Current screening recommendations for women who were exposed to DES in utero may provide insight into screening and surveillance strategies for a woman with vaginal adenosis. The American College of Obstetricians and Gynecologists (ACOG) and the National Cancer Institute (NCI) both recommend annual clinical examinations as well as cervical and vaginal cytology with or without colposcopy among DES-exposed women (Diethylstilbestrol (DES) and Cancer. <https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones/des-fact-sheet#q9> Accessed January 28, 2020) (College, 2016). Vaginal sampling should include all four quadrants of the vaginal walls in the upper third of the vagina. Studies have shown that adenosis will likely regress over time (Noller,

1983). Treatment, therefore, is recommended only for symptomatic adenosis. Until the natural history of this condition is better understood, mirroring the screening practices for DES-exposed women appears to be an appropriate practice for the management of vaginal adenosis.

Author Contribution

Temitope P. Awosogba: conceived of the idea for the report, performed the literature review, collected figures, wrote the paper and prepared the manuscript and accessory documents.

Janelle Whitney: performed the literature review and wrote the paper.

Jennifer C. Broder: provided significant edits to the paper and contributed figures.

Andrea McKee: provided significant edits to the paper.

Cherie Paquette: provided figures associated captions and provided significant edits to the paper.

Caroline C. Nitschmann: conceived of the idea for the report and provided significant edits to the paper.

Declaration of Competing Interest

The authors whose names are listed immediately below certify that they have no affiliations with or involvement in any organization entity with a financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. Each author has indicated that she has met the journal's requirements for authorship.

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