Case report

A sporadic gastric-type endocervical adenocarcinoma with endometrial involvement and bilateral ovarian metastasis, a case report

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1. Introduction

The majority of endocervical adenocarcinomas are classified as usual-type and associated with high-risk Human Papilloma Virus (HPV) infection. Recently, it has been suggested linking morphologic features to the etiology might generate a new classification system (Stolnicu et al., 2018) in which the gastric-type adenocarcinoma represented the most common non-HPV associated endocervical adenocarcinoma subtype. The glandular lesions lined by gastric-type epithelium in the uterine cervix has a spectrum of changes including metaplasia, pseudoneoplastic glandular lesions, gastric-type adenocarcinoma in situ (gAIS), and gastric-type adenocarcinoma (GAS) with its well-differentiated form, minimal deviation adenocarcinoma (MDA) (Talia and McCluggage, 2018). GAS is an aggressive neoplasm, usually diagnosed at advanced stages compare to usual-type adenocarcinoma and it is resistant to conventional chemotherapy (Mikami, 2020). The relative low-incidence of the disease and lack of definitive biomarker expression create diagnostic challenges in routine practice, especially in small tissue biopsies. It might be particularly difficult to separate well-differentiated neoplasms from benign/pseudoneoplastic forms and metastatic lesions from second primary disease in other anatomical sites. Here, we present a patient with unappreciated GAS at time of hysterectomy, who developed bilateral ovarian metastasis within 2 years.

2. Case presentation

The patient is a 47-year-old woman who had a hysterectomy, bilateral salpingectomy, and transobturator tape procedure in 2017 for persistent abnormal uterine bleeding with a history of endometrial ablation and stress urinary incontinence. Initial pathologic evaluation was reported as microscopic foci of endocervical adenocarcinoma in situ without invasion and with negative resection margins, complex endometrial hyperplasia without atypia, and benign fallopian tubes. Two years later, she developed bloating and ultrasound showed an 11x 26x 16 cm complex mass with thick septations and tumor markers for CA-125 and CEA were 61 and 1.2, respectively. Computerized Tomography showed bilateral cystic mass lesions in the ovaries (20 cm and 10 cm), a splenic cyst, fatty liver, but otherwise normal organs and no adenopathy. She underwent an exploratory laparotomy and bilateral oophorectomy. The pathology was consistent with mucinous neoplasm with focal defect/rupture. The pelvic washings had atypical mucin. The patient was then referred to our gynecologic oncology department and a consultation for pathologic review was requested. Her medical history revealed a previous endoscopic hyperplastic colonic polyp removal and she was referred for gastrointestinal evaluation. Pathologic review found the cervical lesion had a spectrum of changes with similar lining epithelium demonstrating basally located nuclei, abundant pink cytoplasm and well-defined cell borders. The goblet-type intestinal epithelium was also scattered throughout the lesion. The cytological atypia was minimal and localized in a few glands. In rare foci, irregular glands invaded cervical stroma with subtle stromal reaction (Fig. 1A and B). Lobular endocervical glandular hyperplasia (LEGH) was identified next to invasive carcinoma component (Fig. 1A inset). gAIS was also mixed with well-differentiated GAS/MDA. gAIS epithelium exhibited intraluminal infoldings, minimal nuclear stratification and rare mitotic figures (Fig. 1B inset). Immunoperoxidase studies were performed in our institution. Immunostain for p16 was focally non-block-type positive. P53 expression was consistent with wild-type staining pattern. The gastric-type neoplastic epithelium was extending into the endometrial cavity with minimal stromal desmoplastic reaction and almost entirely replaced the normal endometrium (Fig. 1C and inset). The bilateral ovarian cystic lesions measured 25.0 cm in the greatest dimension. Reportedly, one of the cystic lesions was ruptured during surgery. They had similar morphology with each other and to the cervical lesion. The gastrointestinal- type epithelium had minimal to moderate proliferation (Fig. 1D and inset). Based on morphologic features and ancillary studies a MDA in the background of gAIS diagnosis was rendered for the cervical lesion. The endometrial and ovarian lesions were interpreted as direct extension and metastatic carcinoma of the cervical tumor respectively.
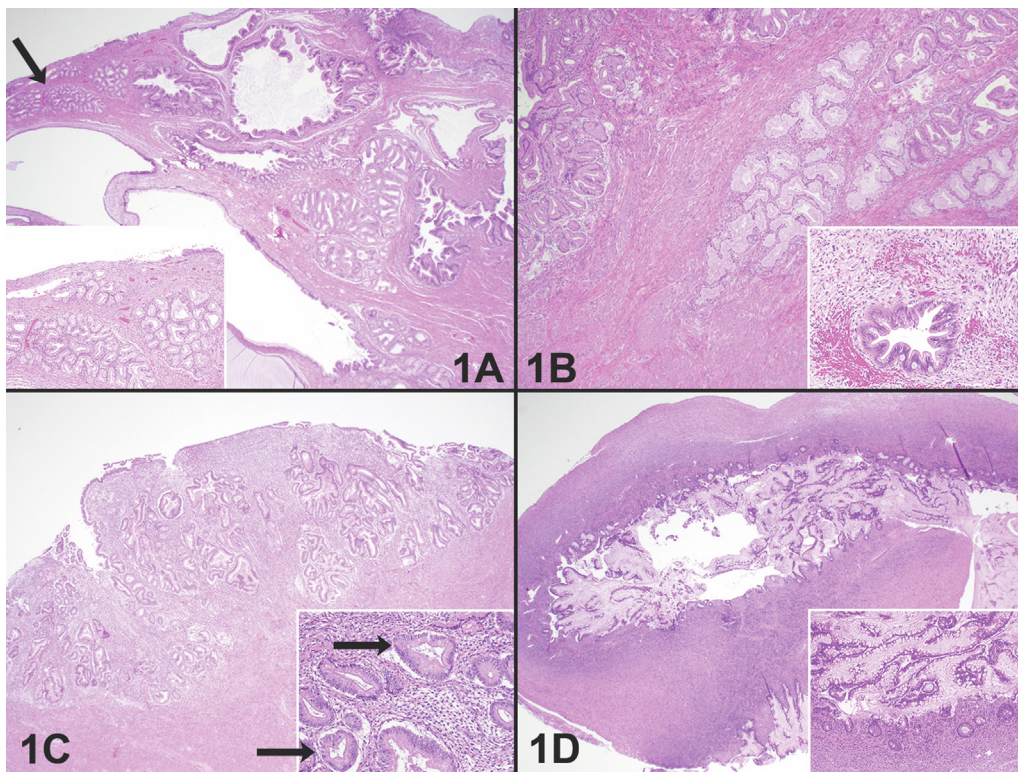
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Fig. 1. AEndocervical lesion. Lobular endocervical glandular hyperplasia (LEGH) is in close proximity of surface epithelium and invasive carcinoma, the arrow points LEGH (20x). Inset: LEGH has well-defined borders. The lining epithelium is bland and pyloric-type mucinous epithelium (200x). 1B: There is subtle reaction to invasive carcinoma. The glands are clustered in groups. The glandular branching and irregularities are observed. The cytological atypia is minimal. The nuclei are basally located and there is abundant pink cytoplasm (100x). Inset: Gastrointestinal-type endocervical adenocarcinoma in situ. There is prominent luminal infoldings. Rare mitotic figures are present (200x). 1C: Endometrial section. The normal endometrium is replaced by gastrointestinal type epithelium. The stromal reaction is minimal (20x). Inset: Higher power view of endometrial lesions. Arrows indicate goblet-type intestinal epithelium (200x). 1D: The left ovarian cystic lesion (40x). Higher power view of lining epithelium (200x).

Table 1

Comparative genomic profiling of cervical and ovarian tumors. MAF: Mutation Allele Frequency. MSS: Microsatellite Stable. TMB: Tumor Burden.

	Cervix	Ovary
KRAS G13D	Present (8% MAF)	Present (5% MAF)
GNAS R201C	Present (6% MAF)	Present (5% MAF)
CDKN2A R87fs*59	Present (5% MAF)	Absent
MSI status	Cannot be determined	MSS
TMB	Cannot be determined	1 mut/Mb
HPV 16, 18	Negative	Negative

Representative tissue sections from cervical and ovarian lesions were evaluated by targeted next-generation sequencing by Foundation Medicine testing (Cambridge MA) which included comprehensive genomic profiling of 324 genes involved in tumorigenesis. HPV status was also determined via adaptor-ligation and hybrid capture next-generation sequencing using probes for low-risk HPV 6 and 11 and high-risk HPV 16 and 18 DNA. Following hybrid capture with specific HPV probes, patient samples were fully sequenced and evaluated for presence of viral HPV DNA reads. Genomic profiling revealed concordant activating *KRAS* G13D and a concordant pathogenic *GNAS* R201C alteration in both cervical and ovarian tumors (Table 1). These alterations were at low mutational allelic frequencies (< 10%), reflective of low tumor purity (< 30% tumor nuclei) relative to benign tissue of sequenced samples. Both tumors were negative for high-risk HPV 16 and 18. The cervical tumor exhibited *CDKN2A* R87fs*59, which was not identified in the ovarian tumor. The ovarian tumor was microsatellite stable and had low tumor mutational burden (1 mutations/Megabase), while these 2 biomarkers could not be determined on the cervical tumor due to low tumor purity. Finally, examination of copy number plots demonstrated comparable gains and losses across the genome, compatible with the notion that these tumors were of same origin (Fig. 2).

The patient was evaluated for inherited cancer predisposition in clinical genetic consultation. The patient denied a history of mucocutaneous macules or polyposis. She reported a history of several (less than five) benign polyps; however, pathology records of her polyp history were unavailable. Upon evaluation, she did not appear to have any abnormal mucocutaneous pigmentation. Family history was significant for a maternal history of breast and colon cancer. A blood sample was obtained and sent for germline genetic testing, specifically, an 84 -gene panel using next-generation sequencing technology. The panel included analysis of *STK11, MSH2, MSH6, PMS2 and MLH1* genes. Testing did not identify any pathogenic variants or variants of uncertain significance.

After a multidisciplinary conference review, a full staging procedure with extensive sampling and washings was performed with negative pathology results. Further chemotherapy options with their risks and uncertain but potential benefits were discussed with the patient and she chose surveillance without postoperative adjuvant therapy.

3. Discussion

Non-HPV associated adenocarcinomas of the uterine cervix makes about 10% of cervical adenocarcinoma in the United States. Among this group GAS is the most common subtype. It is an aggressive tumor with unusual metastatic sites including adnexa, peritoneal surfaces, liver brain and bone (Karamurzin et al., 2015). Recognizing GAS as a subtype of cervical cancer is significant for the disease prognosis and treatment options as well as ruling out potential genetic diseases. The survival studies demonstrated significantly worse 5 year disease-specific survival rates for GAS compared to non-gastric type cancers (30% compared to around 80%) (Kojima et al., 2007). The bland cytological features in well-differentiated GAS, i.e., MDA, localized atypia, low mitotic rates, minimal stromal reaction to invasive carcinoma and absence of specific marker expression contribute to diagnostic difficulties. Immunostain for gastric pyloric-type mucin was developed by Mikami et al (Mikami et al., 1999) in early 2000 s. However, HIK1083 antibody has limited availability in the United States. Identification of *TP53* mutation pattern staining can also support the diagnosis since usual-type endocervical adenocarcinoma does not express the mutation pattern immunostaining. *TP53* mutation rates are around 40% in GAS
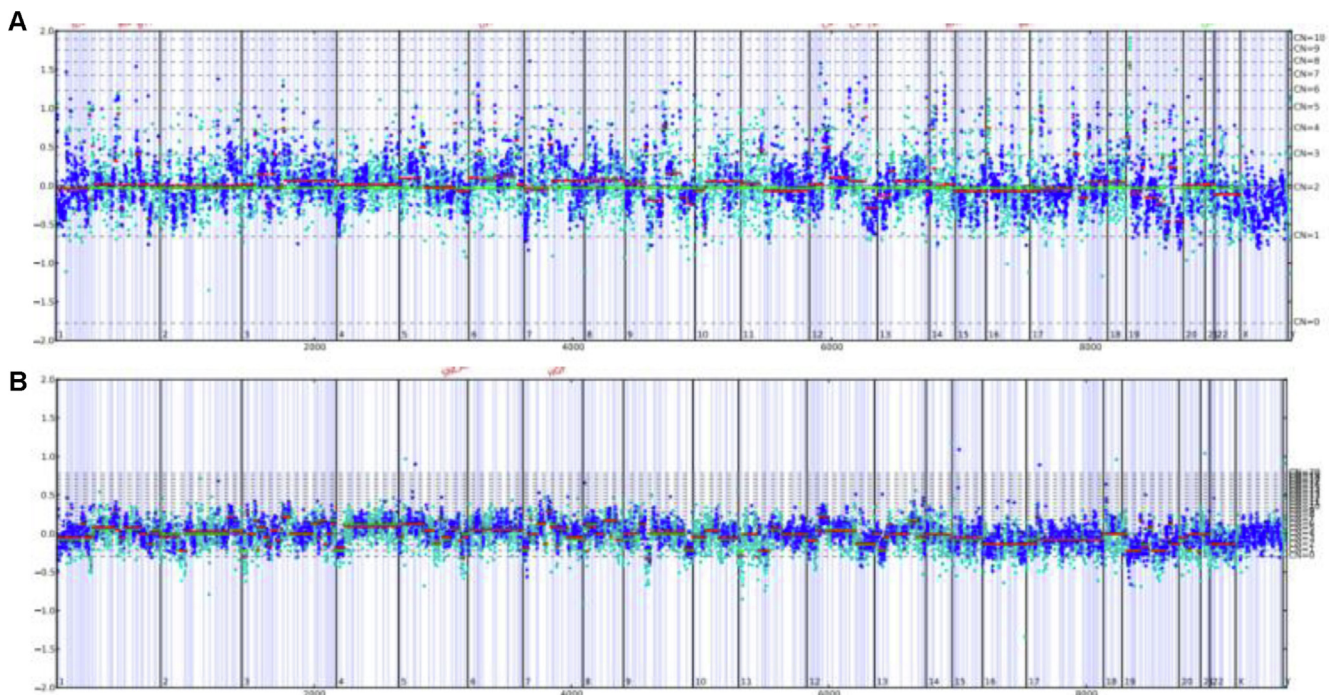
Fig. 2. Copy number plots of cervix (A, top) and ovary (B, bottom) tumors demonstrating overall similar copy number changes across the genome. Tumor purity of ovarian sample was lower, and therefore copy number changes are less pronounced.

(Carleton et al., 2016), therefore the normal expression does not rule out the disease. The presence of typical and atypical LEGH in close proximity of GAS is reported in the literature as it is seen in this case. A recent molecular study reported *GNAS, KRAS* and *STK11* mutations in LEGH (Matsubara et al., 2014), which might represent a precursor lesion for GAS. The major diagnostic challenge in our case was determining whether the ovarian lesions were primary or metastatic neoplasms. Synchronous mucinous metaplasia and neoplasia of the female genital tract can be difficult to separate as independent proliferations or metastatic carcinoma in syndromic and non-syndromic patients. The presence of endometrial extension with replacement of almost entire endometrial tissue by GAS with stromal reaction, bilateral ovarian disease and identical gastrointestinal type lining epithelium in all 3 anatomic sites were in favor of metastatic endocervical adenocarcinoma. In addition, molecular testing supported morphological interpretation. The sequencing showed concordant activating *KRAS G13D* and a concordant pathogenic *GNAS R201C* alteration in both cervical and ovarian tumors. The copy number analysis had also similar gains and losses across the genome.

The management of GAS is still controversial. The surgical removal of the uterus, adnexa, omentum, appendix, and gross tumor might be considered because of its tendency to spread along surfaces throughout the peritoneal cavity and the higher likelihood of presenting with advanced stage (Karamurzin et al., 2015). While GAS represents a rare disease in most populations, it is a common variant (20–25% of cervical adenocarcinomas) in Japanese women (Nishio et al., 2019). In a recently reported prospective study by the Japanese Clinical Oncology Group where stage I to II GAS was treated with radical hysterectomy and lymphadenectomy followed by tailored radiation based on pathologic features, metastatic disease was more common and progression-free and overall survivals were significantly worse. The role for chemotherapy and the optimal agents are unclear. GAS has been reported as relatively chemoresistant, with just under half of patients having a tumor response to combination platinum and taxane regimen (Kojima et al., 2018). Whether the addition of bevacizumab to GAS regimens improves outcomes, as with cervical adenocarcinomas, is unknown; but consideration of this and other novel approaches are reasonable given

the relative chemoresistance.

Finally identification of benign and malignant gastric-type endocervical lesions should trigger genetic testing. LEGH and GAS are associated with Peutz-Jeghers Syndrome (PJS). Approximately 10% of patients with GAS are the carrier of PJS and a single case of cervical GAS is reportedly associated with Lynch Syndrome. Currently there is no screening protocol for patients with PJS. The clinocopathologic correlation might have significant impact in patient's management.

CRediT authorship contribution statement

Ozlen Saglam: Conceptualization, Data curation, Writing - original draft. **Douglas I. Lin:** Data curation, Writing - original draft. **Christine B. Steele:** Data acquisition. **Jonathan K. Killian:** Data acquisition. **Robert M. Wenham:** Data acquisition, 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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